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First Total Synthesis of (+)-Podophyllic Aldehydes

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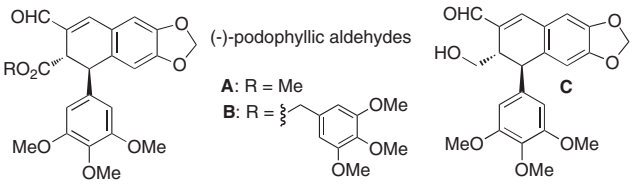
The first total synthesis of three (+)-podophyllic aldehydes was achieved in a highly enantiocontrolled manner. Key steps include the organocatalyzed highly enantioselective cyclopropanation and Lewis acid-mediated chiral transfer ring expansion with excellent level of stereoinduction. This method can alternatively provide (+)- and (−)-podophyllic aldehydes by switching the organocatalyst in the asymmetric cyclopropanation.

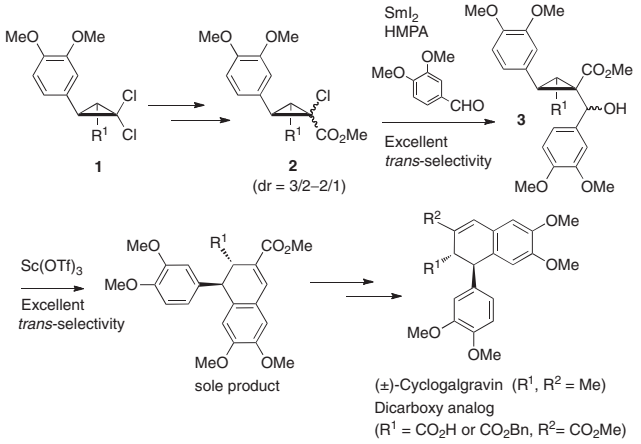
Dihydronaphthalene-type lignans are attracting considerable attention because of their widespread distribution in nature and multiple, significant biological activities.[1,2] Among them, (−)-podophyllic aldehydes **A**, **B**, and **C** exhibit notable antineoplastic cytotoxicity and apoptosis-inducing activities (Scheme 1).[3] The first reported synthesis of (−)-podophyllic aldehydes **A**, **B**, and **C** was started from natural (−)-podophyllotoxin.[3c,3d] Although the asymmetric synthesis of both enantiomers is necessary for investigating their structure and activity relationship, the (+)-podophyllic aldehydes have not been synthesized. Here, we disclose the first total synthesis of (+)-podophyllic aldehydes **A**, **B**, and **C** utilizing organocatalyzed asymmetric cyclopropanation and Lewis acid-mediated chiral transfer ring expansion as key reactions.

During the course of our synthetic studies on the transformation of dichlorocyclopropanes,[4–6] Recently, we reported the diastereoselective total synthesis of (±)-cyclogalgravin and its dicarboxy analog utilizing the SmI_2-promoted Reformatsky-type addition of ester **2** to aldehyde and the $Sc(OTf)_3$-mediated ring expansion of key intermediate **3** (Scheme 2).[6b] However, the enantioselectivity of the ring expansion of alcohol **3** to afford dihydronaphthalene has not been investigated. In addition, highly enantioselective dichlorocyclopropanation has not yet been achieved. Therefore, we attempted to synthesize **7a** using the asymmetric cyclopropanation of aldehyde **5** with dimethyl α-bromomalonate (**4**) under the presence of organocatalyst **6**.[7] Fortunately, the cyclopropanation proceeded to afford the desired optically active diester **7a** in 91% yield with 95% ee (Scheme 3).[8] The same cyclopropanation using organocatalyst **D-6** provided the enantiomer **7b** in 88% yield with 95% ee. We used diester **7a** for the total synthesis of (+)-podophyllic aldehydes.

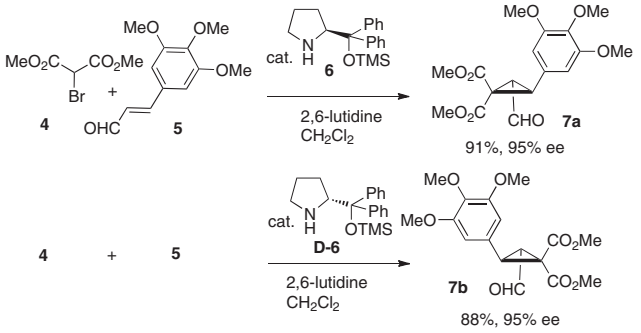
Scheme 4 outlines the asymmetric synthesis of dihydronaphthalene **12** from diester **7a**. After the reduction of the



Scheme 1. (−)-Podophyllic aldehydes.

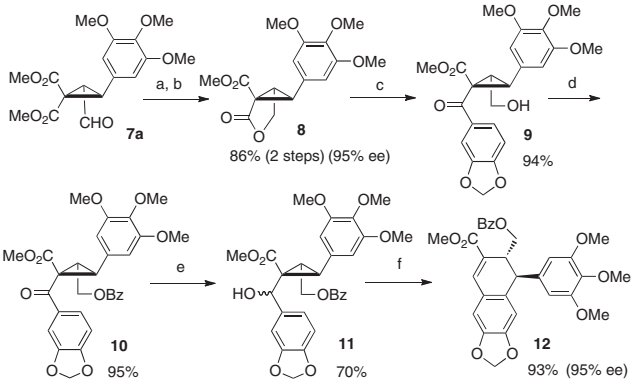


Scheme 2. Diastereoselective total synthesis of (±)-cyclogalgravin and its analog form dichlorocyclopropane **1**.

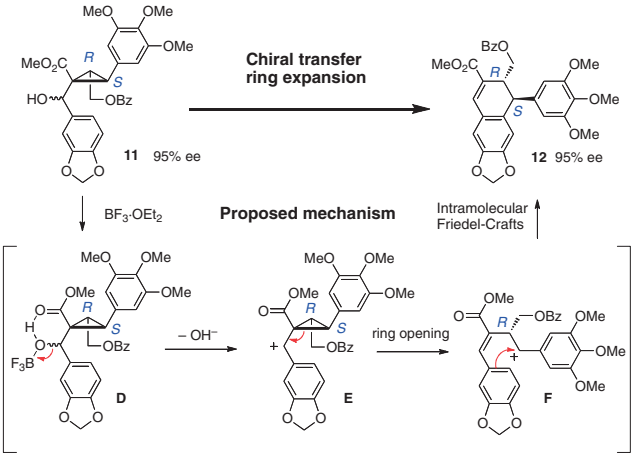


Scheme 3. Organocatalyzed asymmetric cyclopropanations.

aldehyde group in diester **7a** using $NaBH_4$, the lactonization of the resulting alcohol with a catalytic amount of *p*-toluenesulfonic acid (PTS) in $CHCl_3$ gave γ-lactone **8** in 86% yield (2 steps) with 95% ee.[8] Optical purity of lactone **8** was observed by HPLC analysis using a chiral column. The ee of the aforementioned asymmetric cyclopropanation was estimated based on the HPLC analysis of lactone **8**. Treatment of γ-lactone **8** with 3,4-methylenedioxyphenylmagnesium bromide in THF resulted in a highly regioselective Grignard reaction on a slightly strained lactone ring to give β-ketoester **9** in 94% yield. After benzoyl protection of the hydroxy group in β-ketoester **9**, the reduction of the resulting benzoyl-protected β-ketoester **10** (95% yield from **9**) with $NaBH_4$ afforded hydroxyester **11** in 70% yield (dr = 6/1, 95% ee). Although the stereochemistry of the newly formed benzylic alcohol was in a 6:1 ratio, both diastereomers were converted into the same enantiomer of dihydronaphthalene **12**. Treatment of the diastereoisomeric mixture of hydroxyester **11** with $BF_3 \cdot OEt_2$[6a,9] in 1,2-dichloroethane (EDC) at 83 °C resulted in a chiral transfer ring expansion to provide dihydro-



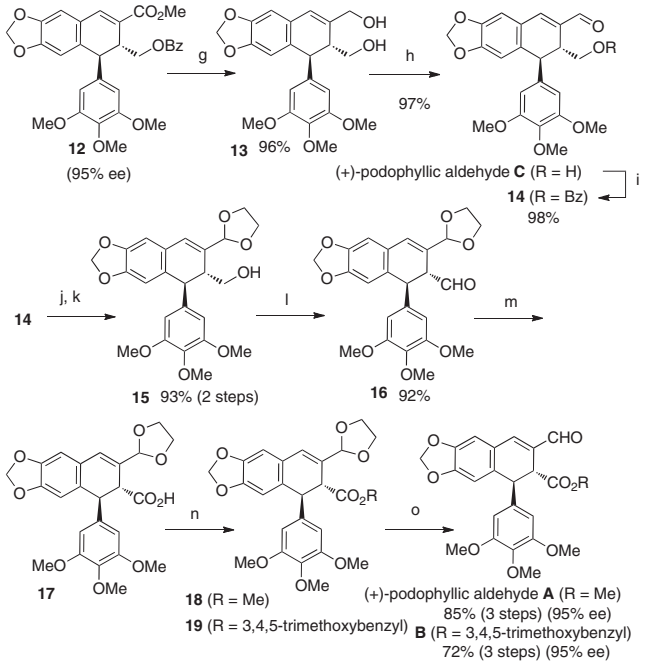
Scheme 4. Reagents and conditions: (a) $NaBH_4$, THF, MeOH; (b) cat. PTS, $CHCl_3$; (c) 3,4-methylenedioxyphenylmagnesium bromide, THF; (d) BzCl, Et_3N, CH_2Cl_2; (e) $NaBH_4$, THF, MeOH; (f) $BF_3 \cdot OEt_2$, EDC.



Scheme 5. Proposed mechanism for the Lewis acid-mediated chiral transfer ring expansion.

naphthalene **12** in 93% yield with 95% ee. The ee of dihydronaphthalene **12** was determined by HPLC analysis using a chiral column. Thus, almost complete stereoinduction from cyclopropane (95% ee) to dihydronaphthalene (95% ee) was performed. The same reaction using $Sc(OTf)_3$,[6] which was used in the diastereoselective synthesis of (±)-cyclogalgravin (Scheme 2), gave dihydronaphthalene **12** (59% yield, 95% ee) with inseparable complex mixtures.

The proposed mechanism of chirality transfer mediated by $BF_3 \cdot OEt_2$ is as follows (Scheme 5). First, $BF_3 \cdot OEt_2$ coordinates to the oxygen of the OH in alcohol **11** to give an intermediate **D**. The hydrogen bond between OH and the carbonyl group should play a chelation-like role in the intermediate **D**. Successive BF_3-promoted elimination of the OH group affords the cationic intermediate **E**. A highly regioselective ring-opening occurs to give cationic intermediate **F**, and then the Friedel–Crafts-type cyclization sequentially proceeds to afford dihydronaphthalene **12**.[10] Although the chirality of the 3,4,5-trimethoxybenzyl position of the cationic intermediate **E** disappears and changes to sp^2-carbocation in the intermediate **F**, after the cyclopropane-ring opening, the chirality is reconstructed as *S* in the 1 position



Scheme 6. Reagents and conditions: (g) DIBAH, CH_2Cl_2; (h) MnO_2, CH_2Cl_2; (i) BzCl, Et_3N, CH_2Cl_2; (j) cat. PTS, ethylene glycol, benzene; (k) KOH, MeOH; (l) Et_3N, $(COCl)_2$, DMSO, CH_2Cl_2; (m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (n) RX, K_2CO_3, DMF; (o) 4 M aqueous HCl solution, THF.

of dihydronaphthalene **12** with excellent stereoinduction in the following Friedel–Crafts-type cyclization.

Further functional transformations leading to target compounds were performed as follows (Scheme 6). The reduction of **12** with DIBAH (excess) in CH_2Cl_2 gave diol **13** in 96% yield. Treatment of diol **13** with activated MnO_2 resulted in the regioselective oxidation of the allylic alcohol to afford (+)-podophyllic aldehyde **C** in 97% yield with 95% ee. Benzoyl protection of (+)-podophyllic aldehyde **C** with BzCl and Et_3N in CH_2Cl_2 provided aldehyde **14** in 98% yield. After acetal protection of aldehyde **14** with ethylene glycol, the hydrolysis of the resulting acetal with KOH yielded alcohol **15** in 93% yield (2 steps). Swern oxidation of alcohol **15** afforded aldehyde **16** in 92% yield.[11] The Pinnick (Kraus) oxidation of aldehyde **16** provided carboxylic acid **17**.[12] Thus, carboxylic acid **17** was obtained through the stepwise oxidation of alcohol under mild conditions. Other direct oxidations such as the Jones oxidation of alcohol provided naphthalenes. The methylation of acid **17** using MeI with K_2CO_3 in DMF to yield ester **18**, followed by treatment of ester **18** with a 4 M aqueous HCl solution in THF resulted in the removal of the acetal to furnish (+)-podophyllic aldehyde **A** in 85% (three steps overall yield from **16**) with 95% ee.

Similarly, after the benzylation of acid **17** using 3,4,5-trimethoxybenzyl bromide, deprotection of the acetal in the resulting ester **19**, using diluted aqueous HCl solution in THF, produced (+)-podophyllic aldehyde **B** in 72% yield (3 steps overall yield from **16**) with 95% ee. The ^1H- and ^{13}C NMR spectral data for the synthesized (+)-podophyllic aldehydes **A**, **B**, and **C** were in agreement with those reported for (−)-podophyllic aldehydes[3] derived from podophyllotoxin. Optical

purities (95% to 96% ee) of the synthesized (+)-podophyllic aldehydes **A**, **B**, and **C** were observed by HPLC analysis using a chiral column.[8]

In conclusion, the first total synthesis of (+)-podophyllic aldehydes **A**, **B**, and **C** with high ee was achieved using the organocatalyzed asymmetric cyclopropanation and Lewis acid-mediated chiral transfer ring expansion of the cyclopropane to give the optically active dihydronaphthalenes with excellent level of stereoinduction. Finally, (+)-podophyllic aldehydes **A**, **B**, and **C** were obtained in 30% (16 steps), 26% (16 steps), and 43% overall yield (8 steps), respectively. This method can provide (−)-podophyllic aldehydes using diester **7b** instead of **7a**.[13]

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Supporting Information is available electronically on J-STAGE.

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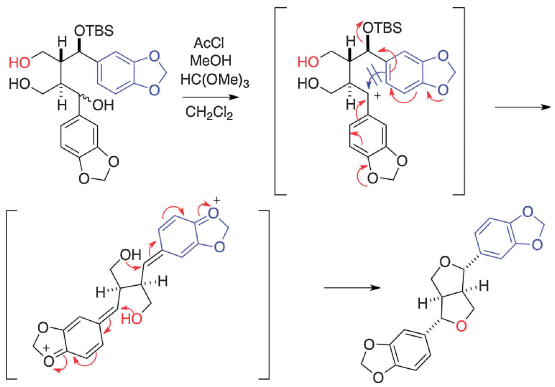

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13 We also synthesized (−)-podophyllic aldehydes **A**, **B**, and **C** starting from **7b**. See Supporting Information.

