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A Synthetic Route to Highly Substituted 1,2,3,4-Tetrahydroisoquinolines via $Yb(OTf)_3$-Catalyzed Diastereoselective Ring Opening of Bridged Oxazolidines: Asymmetric Synthesis of 2-Azapodophyllotoxin

Ajay Kumar Srivastava,[a] Minseob Koh,[a] and Seung Bum Park*[a, b]

Abstract: We herein report a robust and efficient synthetic route to highly functionalized enantiopure 1,2,3,4-tetrahydroisoquinolines (THIQs) from Garner aldehyde. We utilized the inherent chirality of Garner aldehyde through 1,2- and 1,3-/1,4-asymmetric inductions iteratively to obtain 1,2,3,4-tetrasubstitued THIQs using rigid and isolable bridged oxazolidines without any external chiral sources. All possible stereoisomers of bridged oxazoliodines were efficiently synthesized from L- and D-Garner aldehydes and transformed into fully functionalized THIQs via diastereoselective ring opening with various nucleophiles in the presence of $Yb(OTf)_3$. This methodology furnished four out of eight possible diastereomers of 1,2,3,4-tetrasubstituted THIQs despite the electronic nature of substituents on the aryl rings. Finally, the enantioselective synthesis of 2-azapodophyllotoxin was achieved with an overall yield of 35.4% (eight steps) from D-Garner aldehyde using this synthetic route.

Keywords: 2-azapodophyllotoxin · Garner aldehyde · natural products · tetrahydroisoquinoline · total synthesis

Introduction

Since completion of the human genome project in 2003, biomedical communities have focused on elucidation of the gene functions and associated control of gene products by small-molecule modulators.[1] The systematic perturbation of protein functions using bioactive small molecules,[2] which is also known as chemical genetics/genomics, is one of the major research areas in the new interdisciplinary field of chemical biology.[3] To enable discovery of novel small molecules that act as perturbing agents in biological systems, it is essential to construct a collection of drug-like small molecules with maximized molecular diversity. To accomplish this, we adopted a diversity-oriented synthesis (DOS) approach that focused on the development of new methods for synthesis of drug-like polyheterocycles and the efficient construction of small molecule libraries containing a large number of structurally diversified molecular frameworks.[4]

We then pursued the development of a novel route for the efficient synthesis of highly functionalized 1,2,3,4-tetrahydroisoquinolines (THIQs),[5] a privileged structural motif that is frequently found in bioactive natural products and therapeutic agents.[6] In particular, C-4-oxidized THIQs[7] exhibit a wide range of biological activities. For example, 2-azapodophyllotoxin (**1**), a nitrogen variant of podophyllotoxin, is a potent antitumor agent,[8] whereas 11-hydroxyerythratidine (**2**) exhibits curare-like, sedative, hypotensive, and central nerve system (CNS) depressant activities.[9] Simple C-4-hydroxy THIQ **3** possesses anti-inflammatory and anti-allergic properties,[10] while 8-*O*-methyl-dioncophyllinol D (**4**) and dioncophyllinol D (**5**), the naturally occurring naphthoisoquinolines, exhibit antimalarial and antiviral activities (Figure 1).[11]

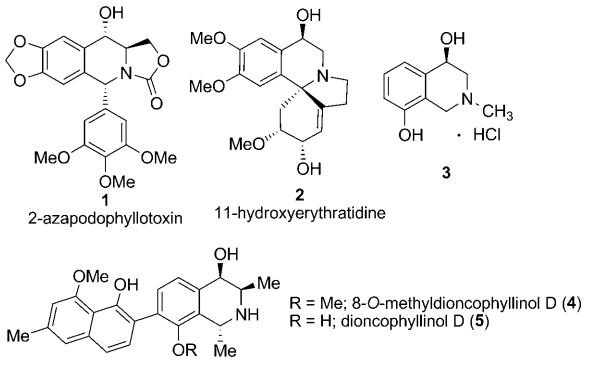

Figure 1. THIQ-containing natural products and bioactive analogues.

Because of the biomedical importance of THIQs, asymmetric strategies for the synthesis of 1-substituted or 1,3-/3,4-disubstituted THIQs have been developed.[12] However, a flexible and efficient synthetic route for all possible stereoisomers of C-1, C-3, and C-4 substituted THIQs has not yet been developed.[7,13] Most of the known asymmetric synthetic routes involve the Pictet–Spengler reaction or the Bis-

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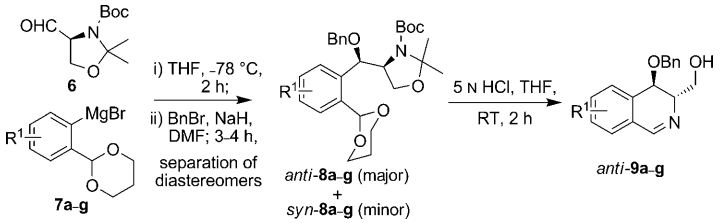
chler–Napieralski cyclization/reduction sequence of β-arylethylamines that undergo ring closure after condensation with aldehydes to produce only 1,3-*syn* isomers as the major product. These methods inevitably require electron-donating groups at the phenyl ring for successful cyclization,[14] and are therefore not applicable to electron-deficient aryl systems. Reported approaches for the synthesis of 1,3-*anti* THIQs involve nucleophilic addition to 3,4-dihydroisoquinoline (DHIQ) precursor as iminium intermediates at very low temperatures; however, these methods achieved a high level of diastereoselectivity via 1,3-asymmetric induction only when a bulky C-3 substituents was pre-installed on the DHIQ precursors.[15] Schreiber and coworkers also utilized DHIQ-derived iminium intermediates to synthesize 1-alkyne-substituted THIQs in the presence of CuBr/QUINAP as catalysts,[16] whereas Inomata et al. employed DHIQ-*N*-oxide for C-1 functionalization using a tartaric-acid-derived chiral auxiliary to obtain 1-substituted THIQs with poor to moderate enantioselectivity.[17] The direct alkylation of a C-1 lithiated THIQ offers an alternative route of synthesis, but this provides only modest diastereoselectivity.[18]

All these methods can access the enantiomerically enriched THIQs in various yields and diastereoselectivities in the presence of specific substituents on aryl systems, and the resulting THIQs are certain diastereomers without robustness for the synthesis of other diastereomers. Given the biomedical applications of THIQs and the limitation of current synthetic methodologies, there is a great need for the development of robust and modular synthesis for highly functionalized 1,2,3,4-THIQs without the limitation of electronic characteristics on the aromatic ring. In addition, the synthetic method should allow for stereochemical diversification of THIQ with a high degree of diastereoselectivity, and yet should be efficient enough to be applied for the total synthesis of complex bioactive THIQs. To address this unmet need, we synthesized a series of enantiopure bridged oxazolidine intermediates starting from Garner aldehyde[19] through internal asymmetric inductions and envisioned utilization of these bridged oxazolidines for C-1 functionalization with various nucleophiles, which allows an expeditious synthetic route for the stereodiversification of fully functionalized 1,2,3,4-THIQs.

Results and Discussion

Preparation of bridged oxazolidines: On the basis of our proposed method for asymmetric synthesis of fully functionalized THIQs via bridged oxazolidine intermediates, our study commenced with the addition of L-Garner aldehyde **6** with properly functionalized Grignard reagents **7a–g** at −78 °C, which was followed by benzylation of the resulting alcohols to obtain *anti*-**8a–g** as the major products. Deprotection reaction of **8a–g** with 5 N HCl in THF produced corresponding 3,4-dihydroisoquinolines *anti*-**9a–g** (Table 1), which were readily converted to the desired bridged oxazolidines **10a–o** upon treatment with various *N*-modifying agents, such as acyl halides, anhydrides, sulphonyl chlorides, and alkyl halides via iminium formation and subsequent intramolecular nucleophilic addition of C-3′-OH (Table 2). The absolute stereochemistry at the C-4 position of *anti*-**9a** was confirmed by the observed coupling constant between C-3 and C-4 protons, which was found to be 8.0 Hz.

Table 1. Diastereoselective Synthesis of intermediates **8** and DHIQs **9** from L-Garner aldehyde.



Entry	R^1	Intermediate (**8a–g**)	Yield [%] (d.r.[a])	DHIQ (**9a–g**)	Yield [%]
1	H	*anti*-**8a**	78 (9:1)	*anti*-**9a**	83
2	5-F	*anti*-**8b**	83 (14:1)	*anti*-**9b**	89
3	4-F	*anti*-**8c**	81 (16:1)	*anti*-**9c**	85
4	4-Cl	*anti*-**8d**	76 (9:1)	*anti*-**9d**	80
5	4-OMe	*anti*-**8e**	73 (12:1)	*anti*-**9e**	73
6	4,5-OMe	*anti*-**8f**	64 (21:1)	*anti*-**9f**	65
7	4,5-dioxole	*anti*-**8g**	86 (>99:1)	*anti*-**9g**	79

[a] Diastereomeric ratio was determined by isolated yields.

As shown in Table 2, we successfully synthesized a series of bridged oxazolidines with various N-substituents as single diastereomers in good yields. The formation of enantiopure bridged oxazolidine was confirmed by $^1H/^{13}C$ NMR spectroscopy and crystallographic analysis of compound **10h** (Figure 2). Therefore, we were confident that we could generate a series of highly diversified and enantiomerically pure key intermediates, bridged oxazolidines **10**, with the flexible modification potential at the bridged nitrogen.

Screening of catalysts for nucleophilic addition: After the successful construction of bridged oxazolidines, we examined their reactivity toward the diastereoselective addition of various nucleophiles at the C-1 position. The use of allyltrimethylsilane (allyl TMS), a silane-based carbon nucleophile, was particularly interesting because of its neutral nature and mild reactivity along with its high-yielding and irreversible reactions.[20] Along with these advantages, the steric interactions are also minimized with this small nucleophile.[21] Initially, we pursued the stereoselective nucleophilic opening of Fmoc-protected bridged oxazolidine **10b** with allyl TMS in the presence of Brønsted–Lowry acids. How-

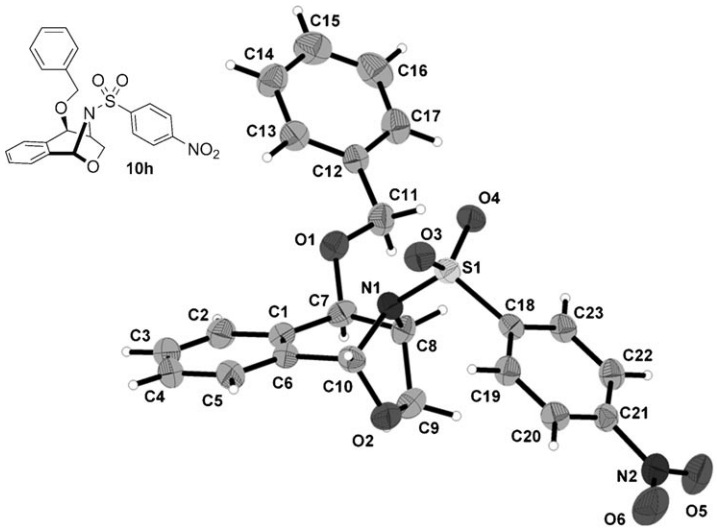
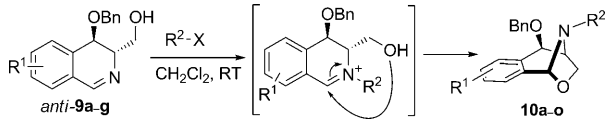


Figure 2. Chemical structure and ORTEP diagram of bridged oxazolidine **10h**.

Table 2. Preparation of enantiopure bridged oxazolidines with various N-modifications.



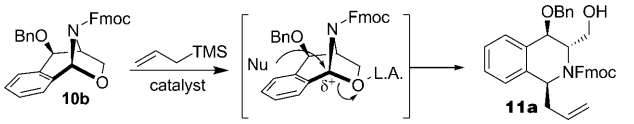
Entry	Substrate	R^2-X	R^1	R^2	Product	Yield [%]
1	*anti*-**9a**	$(Boc)_2O$	H	Boc	**10a**	88
2	*anti*-**9a**	FmocCl	H	Fmoc	**10b**	78
3	*anti*-**9a**	CbzCl	H	Cbz	**10c**	81
4	*anti*-**9a**	BzCl	H	Bz	**10d**	73
5	*anti*-**9a**	*p*-MeOBzCl	H	*p*-MeOBz	**10e**	76
6	*anti*-**9a**	*p*-NO_2BzCl	H	*p*-NO_2Bz	**10f**	68
7	*anti*-**9a**	TsCl	H	Ts	**10g**	89
8	*anti*-**9a**	NsCl	H	Ns	**10h**	91
9	*anti*-**9a**	BnBr	H	Bn	**10i**	92[a]
10	*anti*-**9b**	FmocCl	6-F	Fmoc	**10j**	91
11	*anti*-**9c**	FmocCl	7-F	Fmoc	**10k**	93
12	*anti*-**9d**	FmocCl	7-Cl	Fmoc	**10l**	92
13	*anti*-**9e**	FmocCl	7-OMe	Fmoc	**10m**	83
14	*anti*-**9f**	FmocCl	6,7-OMe	Fmoc	**10n**	72
15	*anti*-**9g**	FmocCl	6,7-dioxole	Fmoc	**10o**	73

[a] The reaction was carried out overnight in refluxing diethyl ether.

ever, this condition yielded THIQs in moderate yields with no diastereoselectivity (data not shown). Therefore, we turned our attention to Lewis acids for the activation of bridged oxazolidines.

To our delight, the Lewis acid-catalyzed allylation provided the desired THIQ **11a** in high yields with 91–99% diastereoselectivity (Table 3), which confirmed that chiral enrichment of nucleophilic ring opening is caused by the unique structural elements of key bridged oxazolidine intermediates and not the presence of Lewis acids. The remarkable efficiency of lanthanide triflates is noteworthy as the reaction

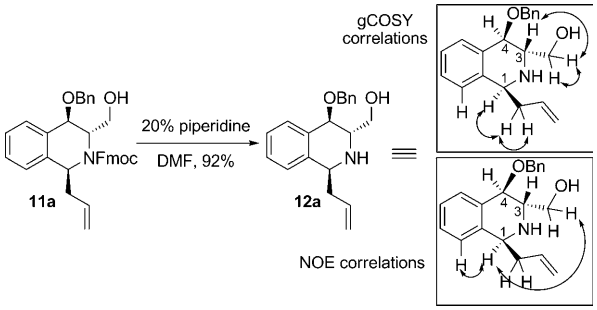
Table 3. Reaction optimization on diastereoselective nucleophilic opening of bridged oxazolidine **10b** through the activation with various Lewis acids for asymmetric synthesis of 1,2,3,4-tetrasubstituted THIQ **11a**.



Entry	Lewis acid	T [°C]	t	d.r.[a] 1β/1α
1	no catalyst	35	1 d	NR[b]
2	$Yb(OTf)_3$	−20	1 h	98:2
3	$BF_3{\cdot}OEt_2$	−78	10 min	99:1
4	$TiCl_4$	−20	15 min	97:3
5	$Cu(OTf)_2$	−20	10 min	91:9
6	TMSOTf	25	30 min	97:3
7	AgOTf	−20	10 min	95:5
8	$Er(OTf)_3$	−20	3 h	96:4
9	$Ho(OTf)_3$	−20	3 h	95:5
10	$In(OTf)_3$	−20	3 h	94:6
11	$Sm(OTf)_3$	−20	3 h	96:4
12	$Tm(OTf)_3$	−20	3 h	97:3
13	$Sn(OTf)_2$	−20	3 h	96:4
14	$Zn(OTf)_2$	−20	3 h	97:3
15	$Sc(OTf)_3$	−20	3 h	96:4

[a] Diastereomeric ratio was determined by HPLC analysis. [b] NR = no reaction.

can be carried out in the air without the need to provide an inert atmosphere. Thus, we selected $Yb(OTf)_3$[22] as the optimized Lewis acid catalyst on the basis of its excellent yield and diastereoselectivity, which is presumably a result of its strong oxophilicity[23] and high coordination number.[24] The acid-sensitive carbamate-based bridged oxazolidines (**10a**, **10c**) provided deprotected DHIQ *anti*-**9a** as the major product along with a small amount of desired THIQs under the identical reaction condition. In the case of N-modified bridged oxazolidines with benzoyl (**10d**), substituted benzoyl (**10e–f**), substituted sulfonyl (**10g–h**) and benzyl (**10i**), we did not observe any chemical conversion under the optimized reaction condition with $Yb(OTf)_3$, or even at the elevated temperature. Therefore, we selected Fmoc-protected bridged oxazolidine **10b** as a model system for further study due to its acid-stability and synthetic versatility. The stereochemistries of **11a** and its deprotected **12a** were verified by ^1H NMR analyses.[25] We also performed NOE and gradient-selected COSY (gCOSY) correlations to confirm the relative stereochemistry at the C-1 position of **12a** (Scheme 1

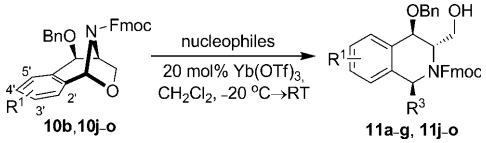


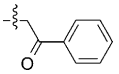
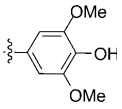
Scheme 1. Spectroscopic confirmation of the stereochemical outcomes of THIQs **12a** via Fmoc deprotection of **11a**.

and Figure S2). Strong signals were found to indicate cross-talk between the C-1 proton and C-3-CH_2 in **12a**; however, there was no NOE correlation between the C-1 and C-3 protons, which confirms the 1,3-*anti* stereochemistry.

To examine the general scope of the stereoselective ring opening of bridged oxazolidines (**10b**, **10j–o**), the reaction was tested with various nucleophiles in the presence of Yb(OTf)$_3$. As shown in Table 4, a wide variety of substituents can be introduced at the C-1 position of THIQ via asymmetric nucleophilic ring opening of **10b** (entries 1–7, Table 4). It should be noted that the 4-hydroxy-3,5-dimethoxyphenyl moiety was introduced via *p*-C attack. The resulting fully functionalized THIQs (**11a–g**, **11j–o**) were isolated in good to excellent yields and diastereoselectivity. However, the introduction of a CN group at the C-1 position caused a significant decrease in diastereoselectivity, presumably because of the increased acidity of the C-1 hydrogen owing to the introduction of nitrile (entry 4, Table 4).[26] In the case of polar silane-based nucleophiles such as $TMSN_3$, TMSCN, and TMS-morpholine, the addition products underwent TMS protection on C-3-CH_2OH. We then examined the scope of this transformation with various bridged oxazolidine intermediates **10j–l** and **10m–o** containing electron-poor and electron-rich aryl rings, respectively. As shown in entries 8–13 of Table 4, the corresponding THIQs were successfully produced through the addition of allyl TMS in excellent yields with high diastereoselectivity, irrespective of the electronic character of the substituents on the aryl rings. It is worth noting that our synthetic method is general enough to access highly functionalized enantiopure THIQs with both electron-donating and electron-withdrawing substituents, in contrast to reported methods for asymmetric synthesis of THIQs that are applicable only to electron-rich aryl systems. One additional feature was that we observed the slightly extended reaction time with electron-rich bridged oxazolidine intermediates (**10m–o**) compared to electron-poor counterpart (**10j–l**), which provides the evidence that the mechanism of this synthetic route for highly functionalized enantiopure THIQs is clearly different from the conventional methods.

Table 4. Diastereoselective ring opening of enantiopure bridged oxazolidines with various nucleophiles in the presence of Yb(OTf)$_3$ for asymmetric synthesis of 1,2,3,4-tetrasubstituted THIQs.



Entry	Substrate	Nu	R^1	R^3	Product	Yield [%] (1β/1α)[a]
1	**10b**	allyl-TMS	H		**11a**	95 (98:2)
2	**10b**	1-phenyl-1-trimethylsilyloxyethylene	H		**11b**	84 (96:4)
3	**10b**	$TMSN_3$	H	N_3	**11c**[b]	86 (92:8)
4	**10b**	TMSCN	H	CN	**11d**[b]	67 (58:42)
5	**10b**	TMS-morpholine	H		**11e**[b]	84 (>99:1)
6	**10b**	indole	H		**11f**	89 (80:20)
7	**10b**	2,6-dimethoxyphenol	H		**11g**	89 (92:8)
8	**10j**	allyl-TMS	4′-F		**11j**	86 (>99:1)
9	**10k**	allyl-TMS	3′-F		**11k**	89 (>99:1)
10	**10l**	allyl-TMS	3′-Cl		**11l**	91 (>99:1)
11	**10m**	allyl-TMS	3′-OMe		**11m**	81 (>99:1)
12	**10n**	allyl-TMS	3′,4′-OMe		**11n**	72 (>96:4)
13	**10o**	allyl-TMS	3′,4′-dioxole		**11o**	64 (>99:1)

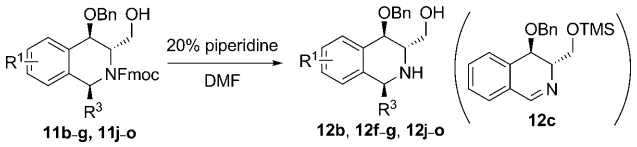
[a] Diastereomeric ratio was determined by HPLC analysis. [b] Product contains C3′-OTMS.

The subsequent Fmoc deprotection was carried out to obtain a clear spectrum and confirm the exact structure and relative stereochemistry of the compound. The base-promoted Fmoc deprotection of **11c**, **11d**, and **11e** unexpectedly led to the formation of C-1-unmodified DHIQ **12c** via elimination of the azide, cyanide, and morpholine moieties, respectively (Table 5). This elimination can be prevented by modification of the functional groups of these newly introduced C-1 groups in **11c–e** prior to Fmoc deprotection.

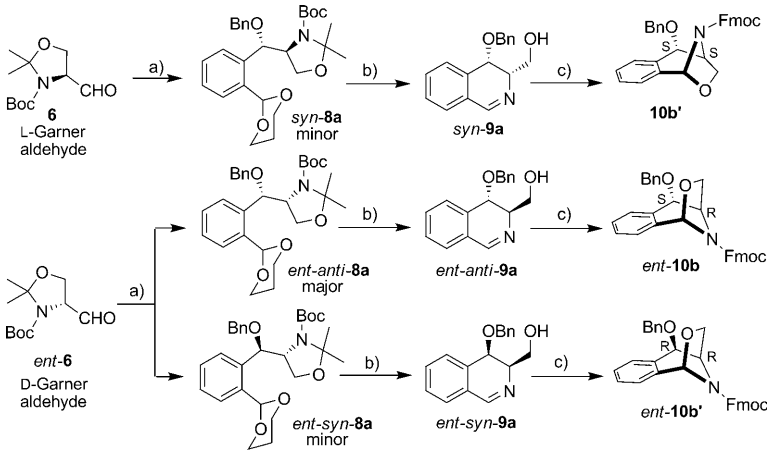
Synthesis of other possible stereoisomers of THIQs and effect of C-4 stereochemistry: We next attempted the asymmetric synthesis of other possible stereoisomers of THIQs to investigate the effect of C-4 configuration on the stereochemical outcome of the nucleophilic ring opening of bridged oxazolidines. Thus, we synthesized all possible stereoisomeric bridged oxazolidines. First, compound **10b′** was prepared as a diastereomeric counterpart of **10b**, from *syn*-**8a**. We also synthesized enantiopure bridged oxazolidines *ent*-**10b** and *ent*-**10b′**, as enantiomeric counterparts of **10b** and **10b′**, from D-serine-derived Garner aldehyde using a similar synthetic procedure as described for **10b** (Scheme 2). The absolute stereochemistry at the C-4 position of *syn*-**9a** was confirmed by the observed coupling constant between C-3 and C-4 protons, which was found to be 1.5 Hz.

These newly synthesized bridged oxazolidines (**10b′**, *ent*-**10b**, and *ent*-**10b′**) were further treated with allyl TMS

Table 5. Fmoc deprotection of 1,2,3,4-tetrasubstituted THIQs.

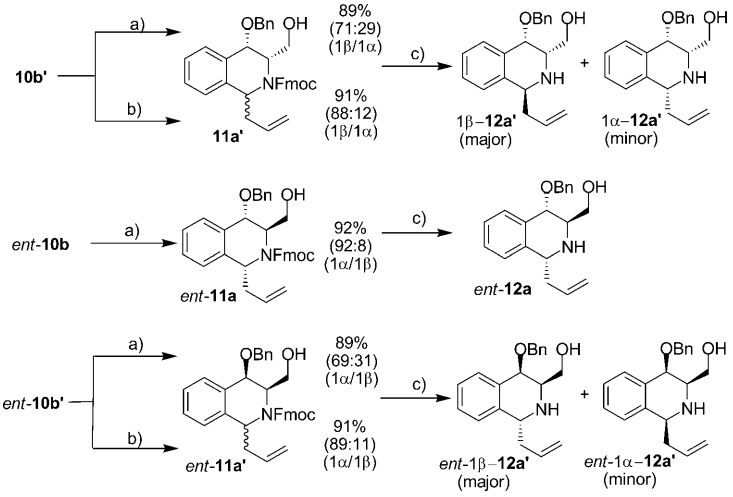


Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1	**11b**	**12b**	94	7	**11j**	**12j**	93
2	**11c**	**12c**	83	8	**11k**	**12k**	96
3	**11d**	**12c**	89	9	**11l**	**12l**	98
4	**11e**	**12c**	80	10	**11m**	**12m**	92
5	**11f**	**12f**	91	11	**11n**	**12n**	84
6	**11g**	**12g**	86	12	**11o**	**12o**	89



Scheme 2. Synthesis of all possible stereoisomeric bridged oxazolidines. a) i) **7a**, THF, −78 °C, ii) BnBr, NaH, DMF; b) 5 N HCl, THF, RT, 2 h; c) FmocCl, CH_2Cl_2, RT, 3–4 h.

under optimized reaction conditions. Surprisingly, **10b′** and *ent*-**10b′** required more time for completion of the reaction and with deterioration of diastereoselectivity, while *ent*-**10b** provided the desired THIQ with a high degree of diastereoselectivity similar to **10b** (Scheme 3). This significant loss of diastereoselectivity with substrates **10b′** and *ent*-**10b′** at the C-1 position of the resulting THIQs was strongly correlated with the orientation of C-4-OBn.[27] This deterioration of diastereoselectivity was presumably a result of the extended reaction time of less reactive substrate **10b′** and *ent*-**10b′** under mild activation by $Yb(OTf)_3$, which might lead to the undesired reaction path through iminium intermediates. When the reaction of **10b′** was carried out at −78 °C in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid with a single coordination site,[28] we observed the restoration of diastereoselectivity for the formation of enantiopure THIQs **11a′** and *ent*-**11a′**.



Scheme 3. Effect of C-4 stereochemistry on 1,3-/1,4-asymmetric induction at C-1 position of THIQs. a) 20 mol% $Yb(OTf)_3$, CH_2Cl_2, −20 °C→RT; b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; c) 20% piperidine, DMF.

Mechanistic investigations: The different stereochemical outcomes found in the nucleophilic ring opening of two diastereomeric bridged oxazolidines (**10b** and **10b′**) led us to study the mechanism of this transformation. As mentioned earlier, the poor diastereoselectivity of **10b′** was presumably caused by the bypassed formation of iminium intermediate, which has no major control on the facial selectivity of nucleophilic attacks on iminium and generates THIQs without good diastereoselectivity. These results indicate that C-4-OBn plays a role in the reaction.[28]

To prove this hypothesis, we performed time-dependent monitoring of this chemical transformation using ^{1}H NMR analysis for both diastereomers **10b** and **10b′**. In the case of **10b**, the reaction was completed within 35 min without any formation of iminium intermediate as we did not observe any signal in the region of δ 8.0–12.0 ppm (Figure 3), while its diastereomeric bridged oxazolidine, **10b′**, required the extended time for the reaction completion. More importantly, we observed a small peak at δ 9.24 ppm, which is a firm indication for the formation of iminium intermediate during the reaction (Figure 4). The presence of C-4-OBn on the same face of the nucleophilic attack in **10b** probably provides assistance through an electronic effect, while the opposite is true for diastereomeric **10b′** making it less reactive and leading to the partial conversion of **10b′** to iminium intermediate, which causes a loss in diastereoselectivity. In order to ex-

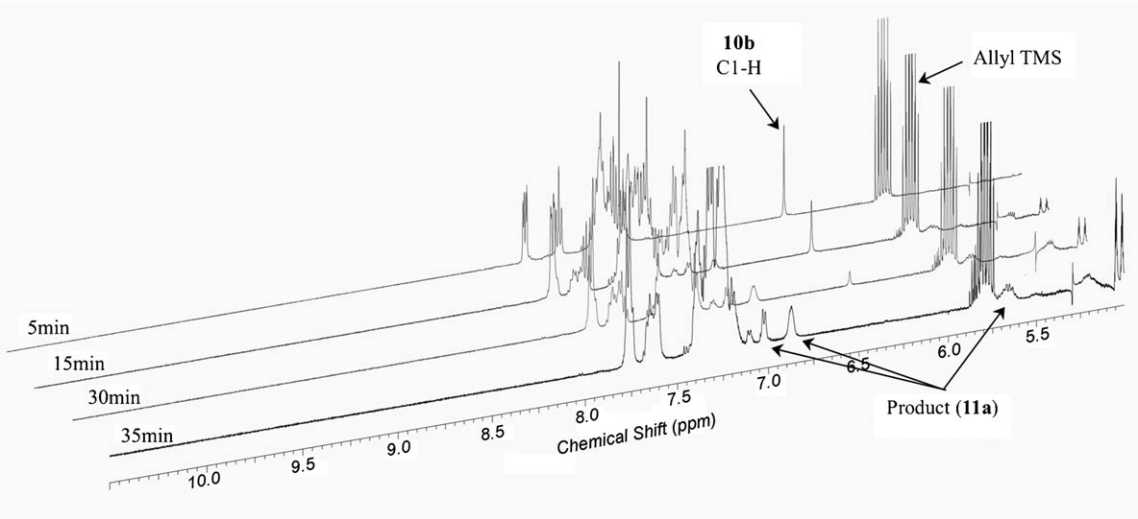


Figure 3. Time-dependent ^{1}H NMR spectra of diastereoselective ring opening of bridged oxazolidine **10b** with allyl TMS in the presence of $Yb(OTf)_3$. The region of δ 5.0–10.5 ppm in ^{1}H NMR spectra is shown only for clarification.

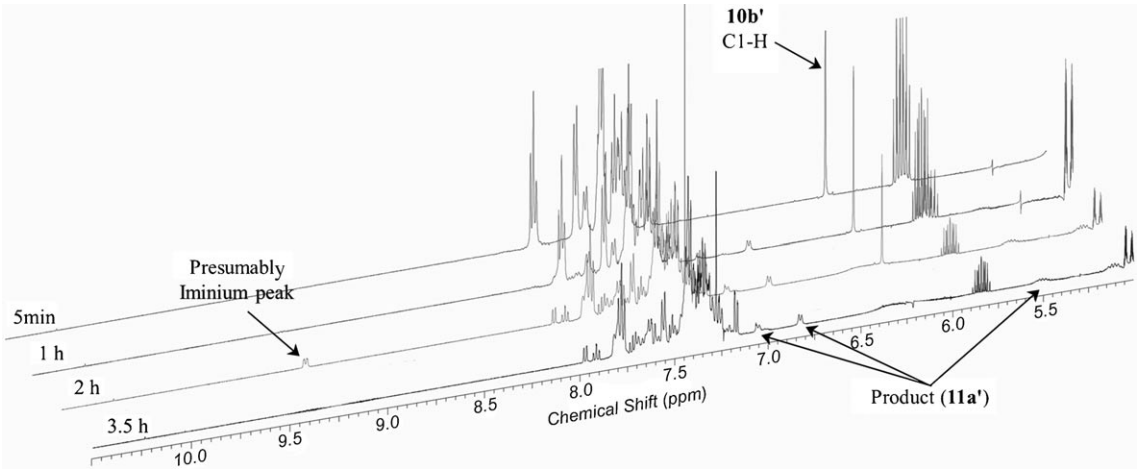
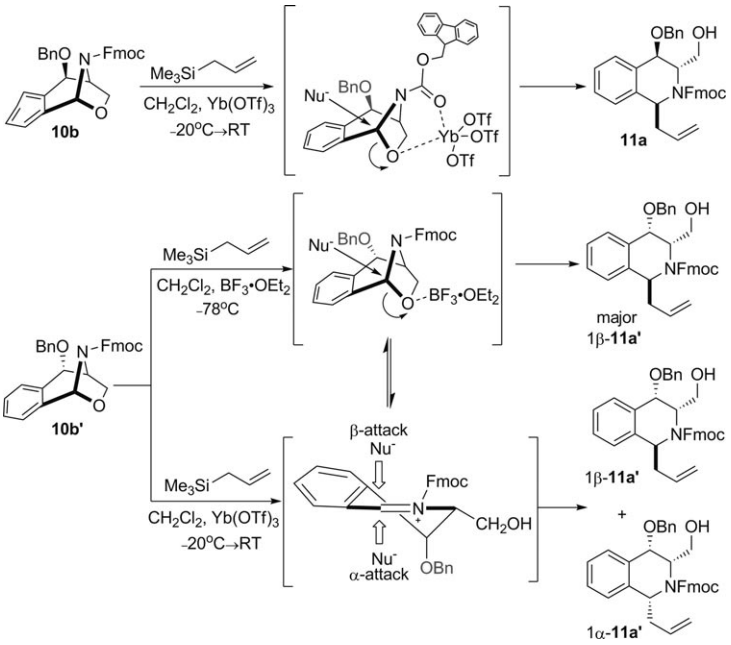


Figure 4. Time-dependent ^{1}H NMR spectra of diastereoselective ring opening of epimeric bridged oxazolidine **10b′** with allyl TMS in the presence of $Yb(OTf)_3$. The region of δ 5.0–10.5 ppm in ^{1}H NMR spectra is shown only for clarification.

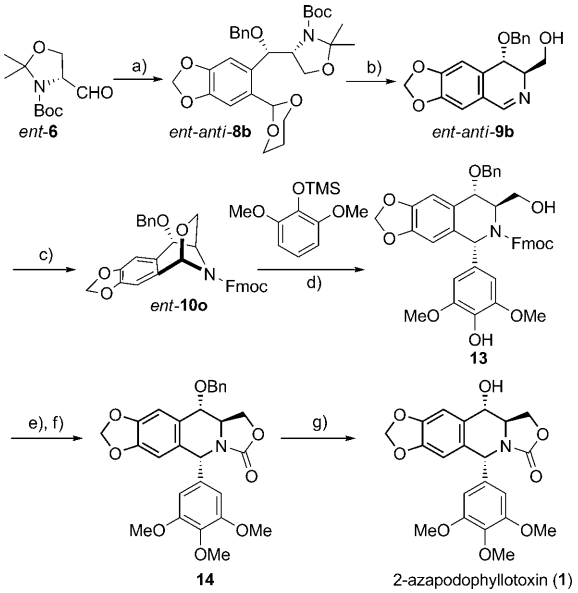
plain the deterioration in the stereochemical outcome of substrate **10b′**, we investigated probable conformations of the transition state of **10b′** and their reactivity towards the nucleophilic addition via iminium intermediates, unlike the case of substrate **10b**.

Considering the stereoelectronic aspects, the C4-substituent bearing electronegative oxygen prefers to occupy the pseudoaxial position of DHIQ intermediate to maximize the electrostatic interactions with iminium carbocation.[29] Along with this, allylic strains also play a pivotal role in determining the facial selectivity of nucleophilic addition toward its cyclic iminium.[30] Therefore, the extended reaction time in the presence of $Yb(OTf)_3$ allows the formation of cyclic iminium intermediate of **10b′**, whose transition state might adopt C4-OBn at the pseudoaxial orientation and make both α- and β-faces equally approachable by the nucleophile. In contrast, the activation of $BF_3{\cdot}OEt_2$ at the lower temperature can preserve the bridged oxazolidine **10b′** and allow the β-face attack to produce 1β-**11a′** as the major product (Scheme 4).

Enantioselective total synthesis of 2-azapodophyllotoxin: Having a facile methodology for the asymmetric synthesis of fully functionalized THIQs, we focused on the enantioselective total synthesis of 2-azapodophyllotoxin (**1**). This 2-aza analogue of podophyllotoxin, which is a potential anticancer agent, became an important target as it showed similar cytotoxic properties to podophyllotoxin without the possibility of epimerization at the C-2 center, thereby facilitating the natural transformation of podophyllotoxin to inactive picropodophyllin under physiological conditions.[31] The reported syntheses of azapodophyllotoxin were accomplished by the Pictet–Spengler reaction or via metal-assisted reduction of DHIQ precursors.[32] However, these routes lack synthetic



Scheme 4. Plausible reaction mechanism for the diastereoselective ring opening of bridged oxazolidines **10b** and **10b′**.



Scheme 5. Enantioselective synthesis of 2-azapodophyllotoxin **1**. a) i) **7g**, THF, −78 °C→RT, 2 h; ii) BnBr, NaH, DMF, 0 °C→RT, 4 h, 79 % (after two steps); b) 5 N HCl, THF, RT, 3 h, 80 %; c) FmocCl, THF, reflux, 3.5 h, 91 %; d) $Yb(OTf)_3$, CH_2Cl_2, RT, 28 h, d.r. 93:7, 83 %; e) i) 20 % piperidine, DMF, 10 min; ii) $(Boc)_2O$, THF, RT, 30 min; iii) Me_2SO_4, K_2CO_3, acetone, reflux, 1 h, 85 % (after three steps); f) NaH, THF, RT, 5 h, 91 %; g) H_2, 10 % Pd/C, THF, 1 atm, 3 h, 96 %.

generality and failed to provide enantiopure 2-azapodophyllotoxin (**1**) through direct enantioselective synthesis. Therefore, we envisioned enantioselective synthesis of 2-azapodophyllotoxin (**1**) using our bridged oxazolidine intermediate *ent*-**10o**, which was obtained from D-Garner aldehyde in four steps. The resulting *ent*-**10o** was subjected to diastereoselective ring opening with 2,6-dimethoxy-1-silyloxybenzene[33] in the presence of $Yb(OTf)_3$ at room temperature to give the desired THIQ **13** in 83 % yield with excellent diastereoselectivity. Compound **13** was then converted to compound **14** via one-pot transformation: Fmoc deprotection, and subsequent Boc protection and methylation of the phenol using dimethyl sulfate and K_2CO_3 in acetone. The treatment of resulting methylated compound with NaH in THF yielded **14**, and the subsequent debenzylation of **14** using catalytic hydrogenation furnished 2-azapodophyllotoxin **1** with an overall yield of 35.4 % (eight steps) from D-Garner aldehyde (Scheme 5). The spectroscopic data were in accordance with the reported one.[32b]

Conclusion

In summary, we developed a concise and highly diastereoselective synthetic route for the construction of fully functionalized THIQs. We introduced a new series of bridged oxazolidines from Garner aldehydes as key intermediates with exceptional potential for the asymmetric synthesis of various THIQs. The inherent chirality of Garner aldehyde was utilized through 1,2- and 1,3-/1,4-asymmetric inductions iteratively to obtain 1,2,3,4-tetrasubstitued THIQs using rigid and isolable bridged oxazolidines. The methodology is robust enough to produce a diverse collection of biologically relevant 1,2,3,4-tetrasubstituted THIQs, despite the electronic nature of the substituents on the aryl rings, which clearly differentiates this methodology from other reported routes for the synthesis of THIQs, such as the Pictet–Spengler reaction and the Bischler–Napieralski cyclization/reduction. We demonstrated the stereodiversification of THIQs through the synthesis of all four possible diastereomers of bridged oxazolidines in a highly efficient manner. In addition, we proposed a plausible mechanism on the basis of our time-dependent ^{1}H NMR study with two diastereomeric bridged oxazolidines. Finally, we successfully accomplished the first enantioselective total synthesis of 2-azapodophyllotoxin **1** with an overall yield of 35.4 % (eight steps) from D-Garner aldehyde for validation of our synthetic methodology. Application of this method to the construction of various chiral THIQ-based natural products and their analogs and the subsequent biological evaluation of the synthesized THIQs are currently underway and will be reported in due course.

Experimental Section

General methods: See Supporting Information.

General procedure for the preparation of 3,4-dihydroisoquinolines: 5 N HCl (1 mL) was added to a solution of **8** (1.03 mmol) in THF (5 mL) and the reaction mixture was then stirred at room temperature for 2 h. After complete disappearance of the starting material, the reaction mixture was diluted with CH_2Cl_2 and washed with water (2×5 mL). The aqueous layer was then basified by the addition of saturated $NaHCO_3$ and extract-

ed by CH_2Cl_2 (3×10 mL), after which the combined organic extract was dried over anhydrous Na_2SO_4(s). The filtrate was then condensed under reduced pressure and the crude mixture was recrystallized using ethyl acetate/hexane to obtain the pure DHIQs.

General procedure for the preparation of bridged oxazolidines: Acyl chloride/sulphonyl chloride/alkyl halide (1.5 mmol) was added to a solution of DHIQ (1 mmol) in dry CH_2Cl_2 (5 mL) and the reaction mixture was then stirred until all of the starting material was converted to the products. The solvent was then evaporated and the crude was purified by silica-gel flash column chromatography. Anhydrous THF and diethyl ether were used as a solvent for the preparation of **10a** with $(Boc)_2O$ and **10i** with benzylbromide, respectively.

General procedure for the nucleophilic addition

Using Yb(OTf)$_3$: Nucleophile (2 equiv) was added to a solution of bridged oxazolidine (1 equiv) in dry CH_2Cl_2 at −20 °C followed by Yb(OTf)$_3$ (20 mol %). The reaction mixture was then stirred until all of the starting material were consumed which was monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2, after which the organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extract was then washed with brine and dried over anhydrous Na_2SO_4(s), after which the solvent was evaporated and the crude product was purified by silica-gel flash column chromatography.

Using BF$_3$·OEt$_2$: Nucleophile (2 equiv) was added to a cooled solution of bridged oxazolidine (1 equiv) in dry CH_2Cl_2 at −78 °C followed by a 1 M solution (1.3 equiv) of BF_3·OEt_2 in CH_2Cl_2. The reaction was monitored by TLC. After completion of the reaction, saturated $NaHCO_3$ was added and the reaction mixture warmed to room temperature. The organic phase was then separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4(s), after which the solvent was evaporated and the crude product was purified by silica-gel flash column chromatography.

(5*R*,7*R*,8*S*)-(9*H*-Fluoren-9-yl)methyl-8-(benzyloxy)-5-(4-hydroxy-3,5-dimethoxyphenyl)-7-(hydroxymethyl)-7,8-dihydro-[1,3]dioxolo[4,5*g*]isoquinoline-6(5*H*)-carboxylate (13): 2,6-Dimethoxy-1-trimethylsilyloxybenzene (210 mg, 0.9 mmol) was added to a solution of *ent*-**10o** (25 mg, 0.045 mmol) in dry CH_2Cl_2 (0.5 mL), followed by Yb(OTf)$_3$ (5 mg, 9 μmol). The reaction mixture was then stirred for 28 h at room temperature until all of the starting materials were consumed. The solvent was evaporated and the crude product was purified by silica-gel flash column chromatography to provide the desired product **13** (d.r. 93:7). Brown sticky solid (83 %, 270 mg); $[\alpha]_D^{28}=-17.36$ (c = 0.24, $CHCl_3$); R_f = 0.25 (50 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81–7.55 (m, 4H, ArH), 7.39–7.19 (m, 9H, ArH), 6.79–6.58 (m, 4H, ArH), 5.98–5.87 (m, 2H), 5.54–5.44 (m, 1H), 5.33–5.25 (m, 1H), 4.80–4.71 (m, 1H), 4.67–4.21 (m, 5H), 3.47 (s, 6H), 3.53–3.50 (m, 1H), 2.89–2.86 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 148.5, 146.9, 144.3, 143.7, 141.4, 138.0, 136.0, 133.7, 133.5, 131.3, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 125.4, 125.1, 124.9, 123.7, 122.4, 120.2, 110.4, 108.0, 104.1, 101.5, 74.7, 71.1, 68.1, 63.2, 58.7, 57.5, 56.5, 56.2, 47.5 ppm; HRMS (FAB): m/z: calcd for $C_{41}H_{37}NO_9$: 687.2468; found: 687.2474 $[M]^+$.

(5*R*,9a*R*,10*S*)-10-(Benzyloxy)-5-(3,4,5-trimethoxyphenyl)-9a,10-dihydro-5*H*-[1,3]dioxolo[4,5*g*]oxazolo[3,4-*b*]isoquinolin-7(9*H*)-one (14): Piperidine (0.400 mL) was added to a solution of **13** (150 mg, 0.22 mmol) in DMF (2.0 mL) and the reaction mixture was stirred for 10 min. DMF was then evaporated and the crude product was re-dissolved in THF (2.0 mL) before addition of $(Boc)_2O$ (57.0 mg, 0.26 mmol). The reaction mixture was stirred for 30 min at room temperature until all of the starting materials were consumed. The solvent was then evaporated and the crude mixture was diluted by dry acetone (3 mL), after which K_2CO_3 (138 mg, 1.0 mmol) was added along with the subsequent addition of dimethylsulfate (54 μL, 0.4 mmol). The reaction mixture was refluxed for 1 h, and the resulting mixture was filtered through celite and condensed under the reduced pressure. The crude product was purified by silica-gel flash column chromatography to obtain the methylated compound (102.8 mg, 85 %) as sticky solid. R_f = 0.48 40 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 5H, ArH), 6.82 (s, 2H, ArH), 6.78 (s, 1H, ArH), 6.64 (s, 2H), 5.97 (s, 1H), 5.92 (s, 1H), 5.58 (s, 1H), 5.02 (s, 1H), 4.62 (s, 1H), 4.58 (s, 2H), 3.74 (s, 3H), 3.54 (s, 6H), 3.51 (s. 1H), 3.42 (s, 1H), 2.21 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.1, 153.0, 148.5, 146.7, 138.0, 128.6, 128.3, 128.0, 123.3, 110.4, 104.0, 101.5, 81.0, 70.9, 68.1, 63.9, 60.9, 56.0, 48.7, 28.3; HRMS (FAB): m/z: calcd for: $C_{32}H_{37}NO_9$ 579.2468: found 579.2472 $[M^+]$.

The resulting methylated compound (60 mg, 0.10 mmol) was dissolved in anhydrous THF (1.5 mL) and cooled to 0 °C followed by the addition of NaH (4.9 mg, 0.020 mmol). After the reaction completion was monitored by TLC, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 twice. The combined organic layer was dried on anhydrous Na_2SO_4(s) and the filtrate was condensed under reduced pressure. The crude product was purified by silica-gel flash column chromatography to obtain **14** (47.6 mg, 91 %) as sticky solid. $[\alpha]_D^{28}=-93.69$ (c = 0.13, $CHCl_3$); R_f = 0.23 (40 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.37 (m, 5H, ArH), 7.06 (s, 1H, ArH), 6.49 (s, 2H, ArH), 6.46 (s, 1H, ArH), 5.99 (dd, J = 1.5, 5.0 Hz, 2H), 5.81 (s, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 8.5 Hz, 1H), 4.39 (t, J = 9.0 Hz, 1H), 4.17–4.14 (m, 1H), 3.98–3.94 (m, 1H), 3.84 (s, 3H), 3.79 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.4, 153.6, 148.0, 147.8, 138.2, 137.5, 136.7, 129.2, 129.1, 128.7, 128.0, 127.9, 107.9, 106.4, 106.1, 101.6, 76.9, 73.3, 67.6, 61.0, 56.6, 56.5, 52.7 ppm; HRMS (FAB): m/z: calcd for: $C_{28}H_{27}NO_8$: 505.1737; found 505.1736 $[M]^+$.

2-Azapodophylotoxin (1): 10 % Pd/C (10 mg) was added to a solution of compound **14** (25 mg, 0.001 mmol) in methanol (0.1 mL) and the reaction mixture was stirred for 3 h under the atmospheric pressure of hydrogen gas. Pd/C was removed by the filtration through celite and the filtrate was concentrated under reduced pressure to obtain 2-azapodophylotoxin **1** as a sticky solid (19.8 mg, 96 %). $[\alpha]_D^{28}=-89.68$ (c = 0.94, $CHCl_3$); R_f = 0.26 (60 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (s, 1H, ArH), 6.50 (s, 2H, ArH), 6.42 (s, 1H), 5.98 (s, 1H, ArH), 5.96 (s, 1H, ArH), 5.80 (s, 1H), 4.60 (t, J = 8.5 Hz, 1H), 4.51–4.45 (m, 2H), 3.84 (s, 3H), 3.79 (s, 6H), 3.80–3.75 (m, 1H), 3.03 ppm (d, J = 8.0 Hz, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 153.6, 148.0, 147.7, 138.2, 137.2, 131.1, 127.1, 107.9, 106.07, 105.7, 101.6, 69.6, 67.2, 61.1, 61.0, 56.9, 56.6, 56.5 ppm; HRMS (FAB): m/z: calcd for $C_{21}H_{21}NO_8$: 415.1267; found: 415.1270 $[M^+]$.

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[25] Due to rotameric signals in ^{1}H NMR spectrum of **11a**, it was difficult to assign all the protons and the C-1 stereochemistry, which was overcome by performing high-temperature ^{1}H NMR experiments of **11a** to obtain a clean spectrum with merged rotameric signals (see Supporting Information).

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