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Studies toward the total synthesis of cyclodidemniserinol trisulfate. Part II: 3,5,7-Trisubstituted 6,8-dioxabicyclo [3.2.1] octane core structure construction via I_2-mediated deprotection and ring closure tandem reaction

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ABSTRACT

The 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane core structure was synthesized by employing a chiral pool convergent synthesis strategy and the I_2-mediated simultaneous deprotection and ring closure reaction as the key step, providing a practical and efficient synthetic approach applicable to the further total synthesis of the natural product cyclodidemniserinol trisulfate.

Cyclodidemniserinol trisulfate (Fig 1), known as a natural product HIV-1 integrase inhibitor, was isolated and characterized from extracts of marine invertebrates, the Palauan ascidian *Didemnum guttatum* by Faulkner et al. in 2000.[1] Undetermined absolute configuration and the low content in nature hampered its further biological studies. In order to determine the absolute stereochemistry and to establish synthetic methodology for further structural derivatization and medicinal chemistry study, we initiated the project of total synthesis of the natural HIV-1 integrase inhibitor, cyclodidemniserinol trisulfate.

On the basis of the retrosynthetic analysis of the molecule, we decided to start the total synthesis from constructing the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane, the core structure of the natural marine product. Furthermore, the 6,8-dioxabicyclo [3.2.1] octane is an attractive structure embedded in many biologically active molecules.[2] The study of its synthesis will be beneficial for developing the active structure into promising pharmaceutical candidates.

In our previous efforts, we tried a stereoselective convergent synthesis strategy and a linear synthesis strategy to construct the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane by employing intramolecular ketal formation as the key step.[3] However, the stereoselective convergent synthesis resulted in a very low overall yield, inappropriate for the total synthesis. And the linear synthesis consisted of too many steps, not convenient for the further total synthesis and structural elaboration either. So, for the purpose of future applicability, we needed to develop another efficient and convenient strategy to synthesize the core structure.

Herein, we report a chiral pool convergent synthesis toward the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane structure with fewer steps, acceptable yield, and with flexible substitution in proper positions. More significantly, the application of I_2-mediated ketal and thioketal deprotection reaction accomplished the simultaneous removal of the ketal and thioketal groups and the formation of intramolecular ketal in one pot, greatly improving the synthesis efficiency.

The retrosynthetic analysis of the target molecule is outlined in Scheme 1. After several steps of functional group conversion, with the chirality at 3-position being kept intact, a thioacetal fragment and an epoxide fragment were selected as the starting materials. Furthermore, considering the 3-substituent elimination issue,[3] the protecting group of the 3-hydroxy on the dioxabicyclo skeleton was designed as isovalerate. The isovalerate group naturally occurs in the product as well as is less liable to eliminate during the synthesis.

The dithioacetal fragment **2** was easily synthesized from 1,4-butandiol (Scheme 2). Oxidation of monobenzyl derivative **1** via Swern oxidation followed by treatment with 1,3-propanedithol resulted in the dithioacetal **2** in 87% yield.

The epoxide fragment was synthesized from D-tartaric acid, which served as a chiral pool. The esterification with ethanol followed by diol protecting as acetonide furnished the fully protected

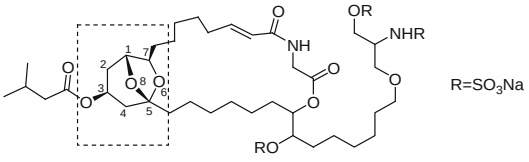

Figure 1. The structure of cyclodidemniserinol trisulfate. The dashed circle indicates the core structure of 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane.

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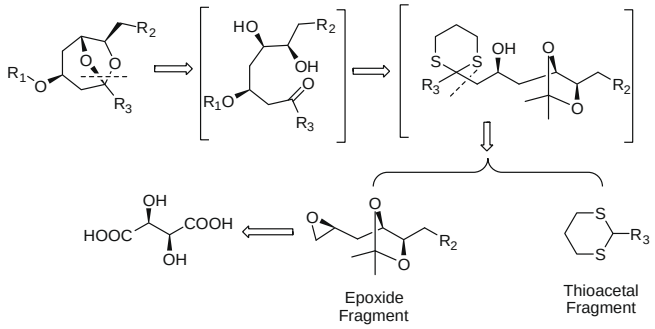
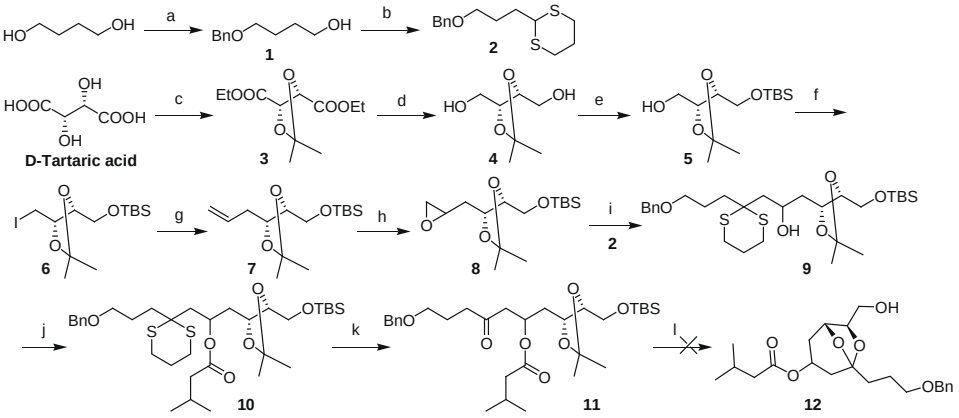


Scheme 1. The retrosynthetic analysis of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane via a chiral pool convergent synthesis approach.

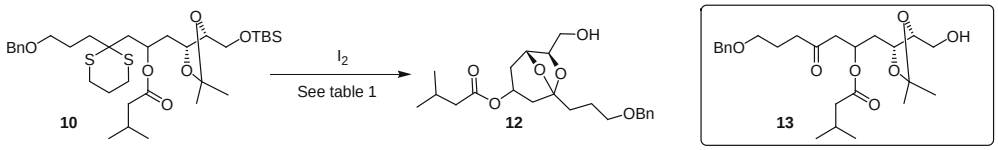
in Et_2O, *p*TsOH in MeOH, 6 N HCl in H_2O, and $TiCl_4$ in CH_2Cl_2 all failed, even 5.0 equiv of $BF_3{\cdot}Et_2O$ produced the deprotected compound **13** only. So, we had to explore other reaction conditions to promote the intramolecular ketal formation reaction instead of proton or Lewis acid catalysis.

It was reported in the literature that iodine reagent could remove both thioketal group and ketal group.[7] It occurred to us that the thioketal group and ketal group in compound **10** might be removed simultaneously when treating with iodine, then the resulting ketone could further react with the generated diol group to achieve intramolecular ketal formation in situ.

Therefore, we investigated the reaction of compound **10** with iodine (Scheme 3) under different conditions (Table 1). When MeOH was used as the solvent, no reaction occurred. When H_2O



Scheme 2. The fragments synthesis and the first trial of Lewis acid-mediated construction of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane. Reagents and conditions: (a) NaH, BrBn, THF, reflux, 80%; (b) (1) Swern oxidation, (2) $HS(CH_2)_3SH$,$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 87% for two steps; (c) (1) EtOH, toluene, reflux, (2) $CH(OEt)_3$, acetone, *p*-TsOH, 82% for two steps; (d) LAH, THF, reflux, 80%; (e)NaH, TBSCl, DME, 0 °C, 82%; (f) Ph_3P, imidazole, I_2, toluene, rt, 87%; (g) vinylmagnesium bromide, CuI, THF–HMPA, −78 °C, 71%; (h) *m*CPBA, CH_2Cl_2, rt, 69%; (i) *n*-BuLi, THF–HMPA, −78 °C then rt, 65%, (j) isovaleric acid, DCC, CH_2Cl_2, rt, 80%; (k) MeI, K_2CO_3, MeCN/THF/H_2O, reflux, 71%; (l) H^+ or Lewis acid, see text.



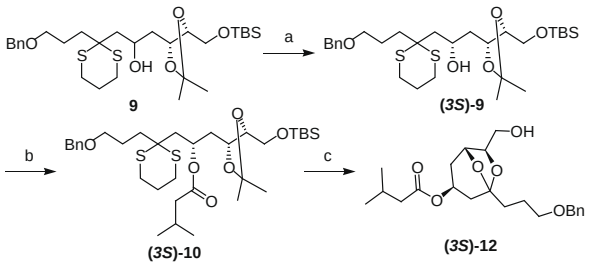
Scheme 3. I_2-mediated tandem reaction of deprotection and ring closure via intramolecular ketal formation.

D-tartaric acid derivative **3** in an overall yield of 82%. The ester **3** was reduced by LAH into the 1,4-diol **4**. Mono-protection of **4** with TBSCl was achieved in the solvent DME in 81% yield.[4] Iodination of the resulting alcohol **5**[5] followed by coupling with vinyl magnesium bromide in the presence of catalytic CuI afforded terminal alkene **7** in 71% yield. Subsequent oxidation with *m*CPBA yielded epoxide **8** non-stereoselectively.

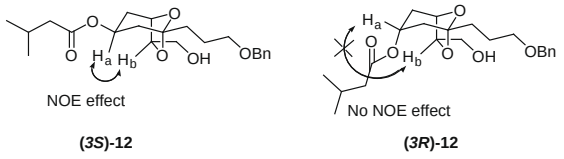
The coupling of the two fragments **2** and **8** proceeded smoothly via an S_N2 epoxide opening reaction in 65% yield. The hydroxyl group in the resulting compound **9** was protected with isovaleric acid in the presence of DCC to produce compound **10** in 80% yield. Removal of the thioketal group in **10** with CH_3I[6] produced the ring-closure precursor **11** in 71% yield. However, treatment of compound **11** with $BF_3{\cdot}Et_2O$ in ether system failed to generate the desired product, although this reaction worked well in our previous system.[3] Various reaction conditions were investigated with respect to the optimal acid-solvent combination. However, 1 N HCl was added as co-solvent, only deprotected compound **13** was obtained. Other solvents such as DMSO, THF, MeCN, and $CHCl_3$ were tested further. DMSO and THF proved not to be effective for

Table 1
Condition optimization for the I_2-mediated deprotection and intramolecular ketal formation reaction conducted on compound **10**

Entry	Solvent (equiv of I_2)	Conditions	Result
1	MeOH (6 equiv)	rt, 40 min	No reaction
2	MeOH–H_2O (6 equiv)	rt, 2 h	**13**
3	MeCN (6 equiv)	rt, 6 min	By-products
4	MeCN (2 equiv)	rt, 5 min	**12** (48%)
5	MeCN (cat.)	rt, 5 h	No reaction
6	MeCN (1 equiv)	0 °C, 15 min	By-products
7	DMSO (2 equiv)	rt 1 h	By-products
8	THF (2 equiv)	rt, 2 h	By-products
9	$CHCl_3$ (2 equiv)	rt, 15 min	**12** (30%)



Scheme 4. I_2-mediated deprotection and ring closure tandem reaction applied to the optically pure compound. Reagents and conditions: (a) Chromatograph; (b) isovaleric acid, DCC, CH_2Cl_2, rt, 80%; (c) I_2, MeCN, 30%.



Scheme 5. The NOE analysis of compounds (**3*S***)-**12** and (**3*R***)-**12**.

the production of the desired product, just producing side-products instead. However, when compound **10** was treated with I_2 in acetonitrile (2 equiv, 0.01 N in MeCN) at rt for 5 min, the target molecule **12** was harvested in 48% yield. And $CHCl_3$ behaved as effective as MeCN, affording the product **12** in 30% yield. After the success of the template reaction concerning I_2-mediated intramolecular ketal formation, we applied the optimized reaction condition to the optically pure compound. Compound **9** was separated by silica gel column chromatography to provide (**3*S***)-**9** and (**3*R***)-**9** in almost equal amount. Compound (**3*S***)-**9** was transformed into the isovalerate (**3*S***)-**10** according to the procedure mentioned above. Treatment of compound (**3*S***)-**10** with iodine in MeCN furnished the desired product (**3*S***)-**12** in 30% yield, without the formation of its diastereomer (**3*R***)-**12** (Scheme 4). The chirality of 3-position in compounds (**3*S***)-**12** and (**3*R***)-**12** was determined with NOESY (Scheme 5). The NOE between H_a and H_b in compound (**3*S***)-**12** revealed the *S* configuration of 3-position, while in compound (**3*R***)-**12**, such NOE was not observed.

In conclusion, we established a convenient and efficient synthetic route to achieve the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane core of cyclodidemniserinol trisulfate, by employing a chiral pool convergent synthesis strategy. This strategy was featured with an I_2-mediated deprotection and ring closure tandem reaction, including thioketal deprotection, acetonide deprotection, and intramolecular ketal formation in one pot. Thus the whole synthesis was accomplished with 13 reactions and 10 steps in nearly 3% overall yield (according to the longest route), with an unambiguous chiral center at 3-position. Definitely, the fewer steps, mild conditions, and acceptable overall yield will make this synthetic approach promising and applicable for the further total synthesis and the structural derivatization.

Acknowledgement

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Supplementary data

Synthetic procedure, NMR data and HRMS data of all new compounds; and ^1H and ^{13}CNMR spectra of important compounds, including the gCOSY and NOESY spectrum of (**3*S***)-**12** and (**3*R***)-**12**, are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.088.

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