



A Pd-mediated intramolecular ketalization of alkyne diols: construction of the central [3.2.1]-bicyclic ketal core of cyclodidemniserinol trisulfate

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ABSTRACT

A preliminary study dealing with the Pd-mediated alkyne diol cycloisomerization to construct the central bicyclic ketal core of cyclodidemniserinol trisulfate is documented.

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Cyclodidemniserinol trisulfate was isolated in 2000 by Faulkner and co-workers through a bioassay-guided fractionation of the methanol extract of Palauan ascidian *Didemnum guttatum* (Fig. 1).¹ Cyclodidemniserinol trisulfate inhibited the purified HIV integrase with an IC₅₀ of 60 µg/mL and also MCV topoisomerase with an IC₅₀ of 72 µg/mL. The complete constitution of cyclodidemniserinol trisulfate (**1**) was elucidated with the help of extensive NMR and mass spectral analyses, albeit with a partial assignment of relative/absolute stereochemistry. In continuation of our interest in the synthesis of bridged/spiro-bicyclic ketal skeletons,^{2–4} we were interested in exploring a Pd-mediated intramolecular ketalization of an alkyne diol for the synthesis of **1** (Fig. 1).

The alkyne **3** was identified as a model substrate for construction of the central [3.2.1]-bicyclic ketal unit through cycloisomerization.^{5,6} The positioning of the alkyne group was made in anticipation of a 6-*endo*-dig mode of cyclization. Indeed, such an exclusive 6-*endo*-dig cyclization (Fig. 1) was employed as the key reaction in our recent synthesis of didemniserinolipid B (**2**)^{4b} (a related natural product from an Indonesian *Didemnum* sp.⁷). The synthesis of the key ω-alkyne-1,2,4-triol **12** was intended through the coupling of aldehyde **6** and C₉-alkynol **5**.⁸ The synthesis of the alkyne **5** was a direct proposition from octane-1,8-diol. Considering the stereochemical similarity, the easily available D-gluconolactone was identified as the starting point for the synthesis of aldehyde **6**.

The synthesis of the 9-carbon alkyne fragment started from 1,8-octanediol (**7**). The 1,8-octanediol was converted to its mono benzyl ether **8** following the reported procedure.⁹ The oxidation of

alcohol under the Swern conditions followed by the Ohira–Bestmann alkynylation¹⁰ gave the alkyne fragment **5** in good yields. D-Gluconolactone was advanced to the known methyl ester **9** following the reported procedure.^{11,12} The controlled reduction of methyl ester **9** using DIBAL-H in toluene at –78 °C gave the aldehyde **6**. Initial attempts to directly add the lithiated alkyne **5** or the corresponding Grignard reagent to aldehyde **6** resulted mainly in the elimination product **10** along with the requisite alkyne **11**. The formation of **10** could be explained by the presence of a potential leaving group such as acetonide β to the carbonyl.¹² Following Carriera's protocol,⁸ that is, employing Et₂Zn, Ti(OⁱPr)₄ and (S)-BINOL, the elimination could be circumvented with good yields of the alkyne **11**. However, the diastereomeric ratio was poor (4:3). As the reaction without chiral ligand also gave a similar diastereomeric ratio, the alkynylation reaction has been optimized without the chiral ligand to afford a diastereomeric mixture (3:2) of **11** in 69% yields over two steps. Oxidation of the resulting propargylic alcohol with MnO₂ and the selective 1,3-*syn* reduction¹³ of the intermediate alkyne with LiI–LAH at –100 °C gave the alkyne **11β** with excellent diastereoselectivity (>20:1). The terminal isopropylidene group of **11β** was selectively deprotected by exposing it to 0.8% H₂SO₄ in MeOH. Perbenzylation of the resulting triol **12** using NaH and BnBr and subsequent acetonide hydrolysis completed the synthesis of alkyne **3** (Scheme 1).

Our next concern was the Pd-mediated alkyne diol cycloisomerization reaction of triol **3**. With 10 mol % of Pd(CH₃CN)₂Cl₂ complex, the reaction advanced smoothly with the disappearance of **3** within 1 h and afforded **13**. The constitution of the bicyclic ketal unit present in **13** was investigated with the help of NMR spectral analysis. This turned out to be an undesired [2.2.1]-bicyclic ketal

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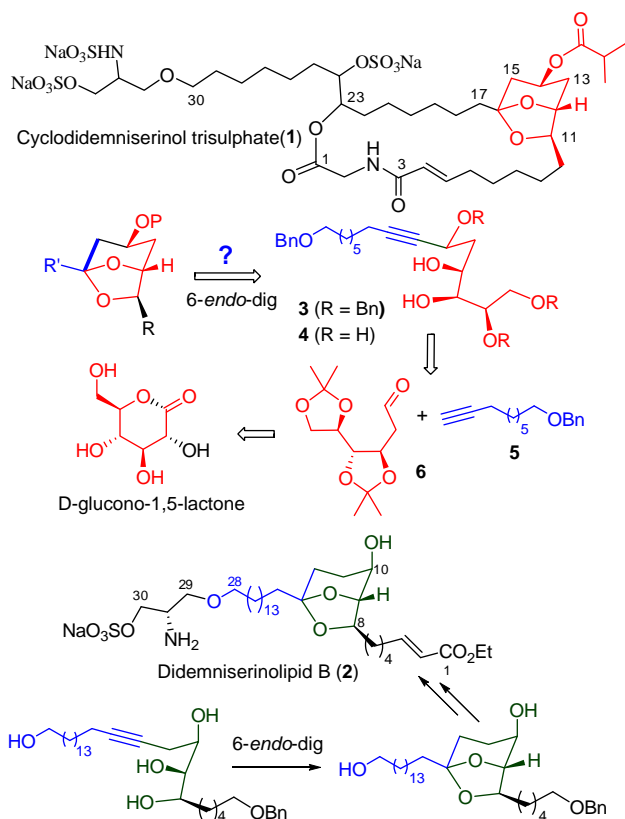


Figure 1. Structure of cyclodidemniserinol trisulfate (1) and the projected 6-endo-dig cyclization.

resulting from the unpredicted 5-*exo*-dig mode of cyclization.¹⁴ For example, in the ¹³C NMR spectrum of **13**, characteristic ketal car-

bon peak appeared at 110.7 ppm and a CH₂ triplet resonating at 37.2 ppm was noticed. The appearance of the other CH₂ triplets below 30 ppm clearly indicated the presence of a single methylene carbon inside the bicyclic ring. The undesired cycloisomerization of **3** led us to do some experimentation with this model system to understand the mode of cyclization.

The pentitol **4** was prepared either by the acetonide deprotection of **12** or by the global deprotection of **11β**. Cycloisomerization of **4** with Pd(CH₃CN)₂Cl₂ proceeded smoothly in CH₃CN–THF and gave exclusively **14** which was characterized as its triacetate **15**. Structural analysis of compound **15** using COSY, NOESY and HMBC spectra indicated the presence of an undesired 2,8-dioxabicyclo [3.2.1]-octane skeleton (Supplementary data).¹⁵ Although there was a scope for 6-*endo*-cyclization with both the substrates **3** and **4**, the exclusive formation of 5-*exo*-cyclization product indicates a dominant acyclic stereocontrol over the regiochemistry of this cycloisomerization reaction.¹⁶

As the above strategy led to the products resulting from the undesired 5-*exo*-cyclization, we revised the strategy by choosing the diol **17** that has an extra carbon in between the alkyne and the next chiral centre. The competition is now between 6-*exo*-dig and 7-*endo*-dig, the latter being energetically more demanding. The key retrosynthetic disconnections for the preparation of **17** are given in Figure 2. The synthesis began with the known

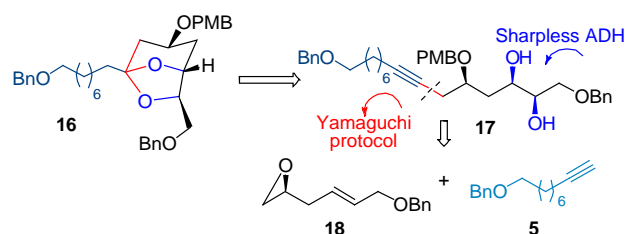
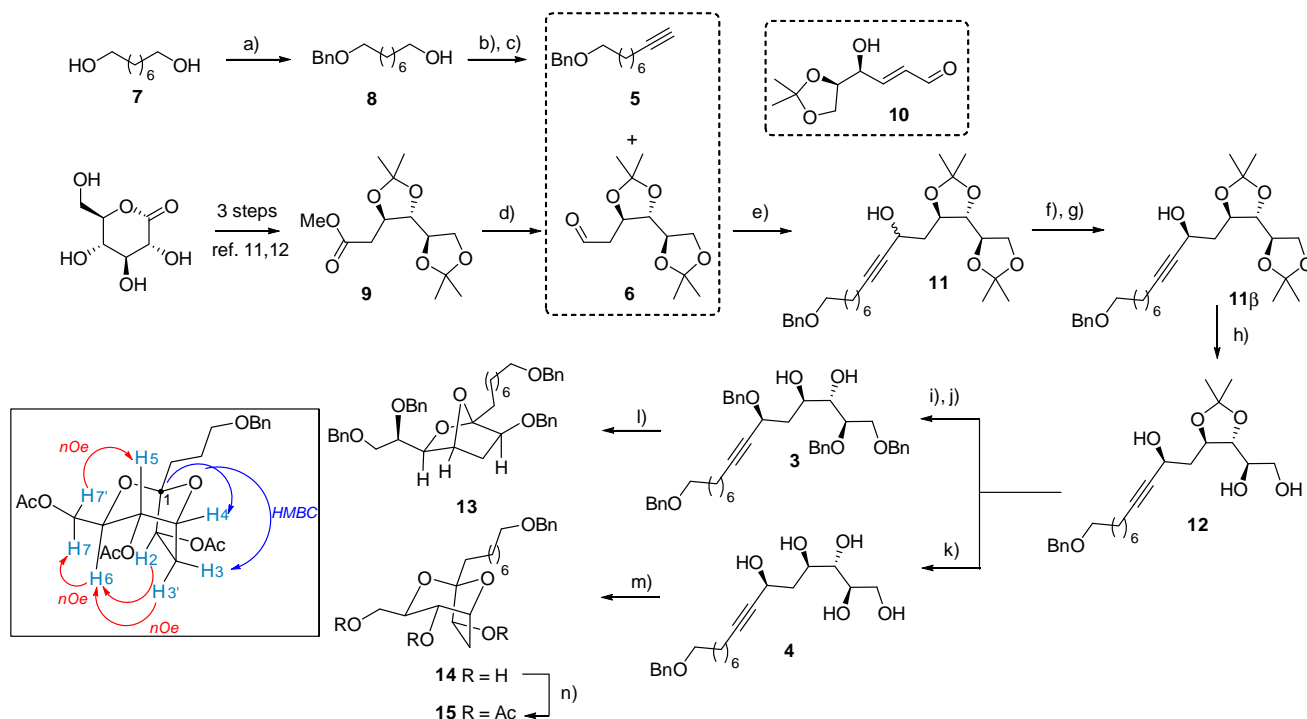
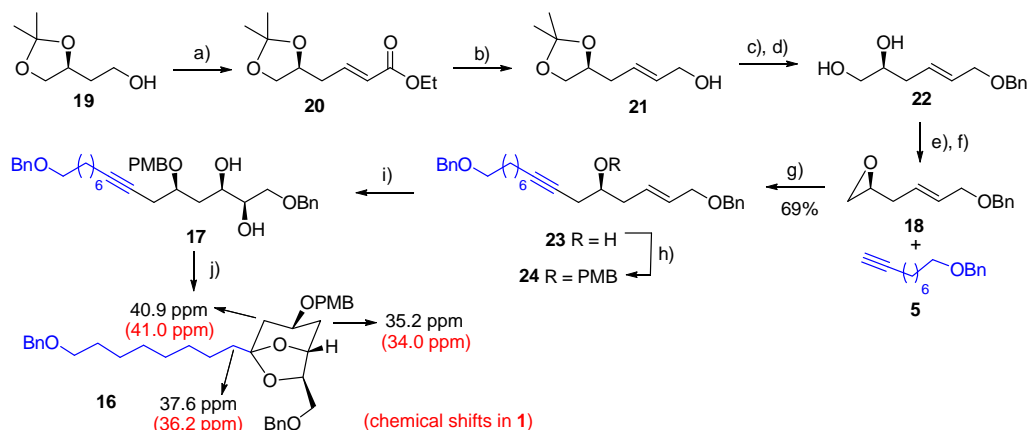


Figure 2. Revised strategy for the central [3.2.1]-bicyclic ketal core.



Scheme 1. Reagents and conditions: (a) Ref. 9, 80%; (b) oxalyl chloride, DMSO, Et₃N; (c) Ohira–Bestmann reagent, K₂CO₃, MeOH, rt, 14 h, 79% in two steps; (d) DIBAL-H, toluene, –78 °C, 20 min; (e) **5**, Et₂Zn, toluene, reflux, 1 h, **6**, rt, 14 h, 69% in two steps; (f) MnO₂, CH₂Cl₂, rt, 24 h, 70%; (g) LiI, THF, –40 °C, 30 min, LAH, –100 °C, 1 h, 82%; (h) MeOH, 0.8% aq H₂SO₄, rt, 8 h, 75%; (i) NaH, BnBr, DMF, 0 °C→rt, 10 h, 83%; (j) MeOH, *p*-TSA, rt, 2 h, 87%; (k) MeOH, *p*-TSA, rt, 18 h, 88%; (l) 10 mol % Pd(CH₃CN)₂Cl₂, CH₃CN/THF (6:2), rt, 30 min, 67%; (m) 10 mol % Pd(CH₃CN)₂Cl₂, CH₃CN/THF (6:2), rt, 30 min, 67%; (n) Ac₂O, Et₃N, DMAP, rt, 4 h, 87%.



Scheme 2. Reagents and conditions: (a) (i) IBX, DMSO, rt, 2 h, (ii) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, 5 h, 85% in two steps; (b) DIBAL-H, CH_2Cl_2 , -78°C , 2 h, 86%; (c) NaH, BnBr, DMF, 0°C \rightarrow rt, 4 h, 95%; (d) MeOH, *p*-TSA, rt, 8 h, 98%; (e) *n*-Bu₂SnO, TsCl, Et₃N, CH_2Cl_2 , rt, 2 h, 89%; (f) NaH, DMF, 0°C \rightarrow rt, 4 h, 82%; (g) **5**, *n*-BuLi, $\text{BF}_3\cdot\text{Et}_2\text{O}$, THF, -78°C , 1 h, 77%; (h) NaH, PMBCl, DMF, 0°C \rightarrow rt, 8 h, 75%; (i) AD-mix- β , MeSO_2NH_2 , *t*-BuOH/ H_2O (1:1), $0 \rightarrow 10^\circ\text{C}$, 48 h, 73%, (dr 7:3); (j) 10 mol % $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, CH_3CN , rt, 1 h, 51%.

acetone **19**.¹⁷ One-pot sequential oxidation of alcohol **19** with IBX in DMSO, followed by a 2-carbon Wittig homologation furnished the *trans*-olefin **20**. Reduction of **20** with DIBAL-H gave the allylic alcohol **21**. Protection of the free -OH group in **21** as its benzyl ether followed by acetonide hydrolysis gave the diol **22**. The diol **22** was transformed to the oxirane fragment **18** following selective 1°-OH tosylation and base treatment. The readily available C₉-alkynol fragment **5** was coupled with the oxirane **18** following the Yamaguchi protocol.¹⁸ The resulting alkyne **23** was treated with NaH and PMBCl to afford the corresponding PMB ether **24**. As the Sharpless asymmetric dihydroxylation¹⁹ of **24** using AD-mix- β at $0 \rightarrow 4^\circ\text{C}$ was found to be sluggish, the reaction was carried out at 10°C , which resulted in a moderate diastereoselective (7:3). The cycloisomerization reaction of the resulting alkyne **17** was carried out under optimized conditions (10 mol % $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2/\text{CH}_3\text{CN}$, rt, 1 h) and the desired bicyclic ketal was obtained in 51% yield (Scheme 2). The constitution and the stereochemistry of the isolated bicyclic product **16** were established with the help of COSY and NOESY spectra.²⁰ For example, in the ¹³C NMR spectrum of the **16**, three methylene carbons appeared at δ 35.2, 40.9 and 37.6 ppm and were comparable with the chemical shifts of the C13 (34.0 ppm), C15 (41.0 ppm) and C17 (36.2 ppm), respectively, of the natural product **1**. As it was noticed with **1**, there was no cross-peak between H-C(3) and H-C(2) in the COSY of **16**, indicating a dihedral angle of 90° between them.¹ The other spectral data were in accordance with the assigned structure.

To conclude, synthesis of the bicyclic ketal core of the cyclodimniserinol trisulfate was executed by employing a Pd-mediated intramolecular ketalization of an alkyne. Contrary to our expectations, the initial design projecting a 6-*endo*-dig mode of cyclization resulted in an exclusive 5-*exo*-dig cyclization. By positioning the central alkyne for a 6-*exo*-dig mode, the required [3.2.1]-bicyclic ketal could be realized with the desired constitution. Application of this methodology to the synthesis of cyclodimniserinol is progressing in our laboratory.

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Supplementary data

Supplementary data (The NMR spectra of the bicyclic ketals **13**, **15** and **16**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.023.

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- (d, 2C), 127.6 (d, 2C), 127.7 (d), 127.9 (d, 2C), 128.0 (d, 2C), 128.3 (d, 2C), 128.4 (d, 5C), 128.4 (d, 2C), 137.9 (s), 138.3 (s), 138.4 (s), 138.7 (s) ppm; ESI-MS: m/z 687.9 (100%, [M+Na]); Anal. Calcd for $C_{43}H_{52}O_6$: C, 77.68; H, 7.88. Found: C, 77.39; H, 8.03.
15. *Spectral data of triacetate 15*: Colorless liquid. $[\alpha]_D^{25} +61.0$ (c 1, $CHCl_3$); IR ($CHCl_3$) 3391, 2931, 2851, 1745, 1648, 1402, 1231, 1045, 755, 602 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 1.29–1.40 (m, 9H), 1.44–1.52 (m, 1H), 1.59–1.62 (m, 2H), 1.71–1.79 (m, 2H), 1.84 (ddd, $J = 3.1, 7.5, 14.4$ Hz, 1H), 2.06 (s, 3H), 2.08 (s, 6H), 2.61 (dd, $J = 7.5, 14.4$ Hz, 1H), 3.46 (t, $J = 6.6$ Hz, 2H), 3.78 (ddd, $J = 2.6, 5.0, 9.5$ Hz, 1H), 4.05 (dd, $J = 5.0, 12.1$ Hz, 1H), 4.20 (dd, $J = 2.5, 12.1$ Hz, 1H), 4.50 (s, 2H), 4.60 (dd, $J = 4.0, 7.5$ Hz, 1H), 4.82 (dd, $J = 4.0, 9.5$ Hz, 1H), 5.22 (dd, $J = 3.1, 7.5$ Hz, 1H), 7.27–7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8 (q, 2C), 21.0 (q), 23.0 (t), 26.2 (t), 29.4 (t), 29.4 (t), 29.8 (t, 2C), 32.4 (t), 33.5 (t), 63.4 (t), 65.0 (d), 70.0 (d), 70.5 (t), 72.8 (t), 73.6 (d), 75.7 (d), 107.1 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.7 (s), 169.5 (s), 170.0 (s), 170.8 (s) ppm; ESI-MS: m/z 543.1 (100%, [M+Na]); Anal. Calcd for $C_{28}H_{40}O_9$: C, 64.60; H, 7.74. Found: C, 64.86; H, 7.35.
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