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A Pd-mediated intramolecular ketalization of alkynediols: 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 alkynediol cycloisomerization to construct the central bicyclic ketal core of cyclodidemniserinol trisulfate is documented.

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 IC_{50} of 60 μg/mL and also MCV topoisomerase with an IC_{50} 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 alkynediol for the synthesis of **1** (Fig. 1).

The alkynol **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 C_9-alkynol **5**.[8] The synthesis of the alkynol **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 alkynylation[10] gave the alkynol 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 alkynols **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 Et_2Zn, $Ti(O^iPr)_4$ and (*S*)-BINOL, the elimination could be circumvented with good yields of the alkynols **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 MnO_2 and the selective 1,3-*syn* reduction[13] of the intermediate alkynone with LiI–LAH at −100 °C gave the alkynol **11β** with excellent diastereoselectivity (>20:1). The terminal isopropylidene group of **11β** was selectively deprotected by exposing it to 0.8% H_2SO_4 in MeOH. Perbenzylation of the resulting triol **12** using NaH and BnBr and subsequent acetonide hydrolysis completed the synthesis of alkynol **3** (Scheme 1).

Our next concern was the Pd-mediated alkynol cycloisomerization reaction of triol **3**. With 10 mol % of $Pd(CH_3CN)_2Cl_2$ 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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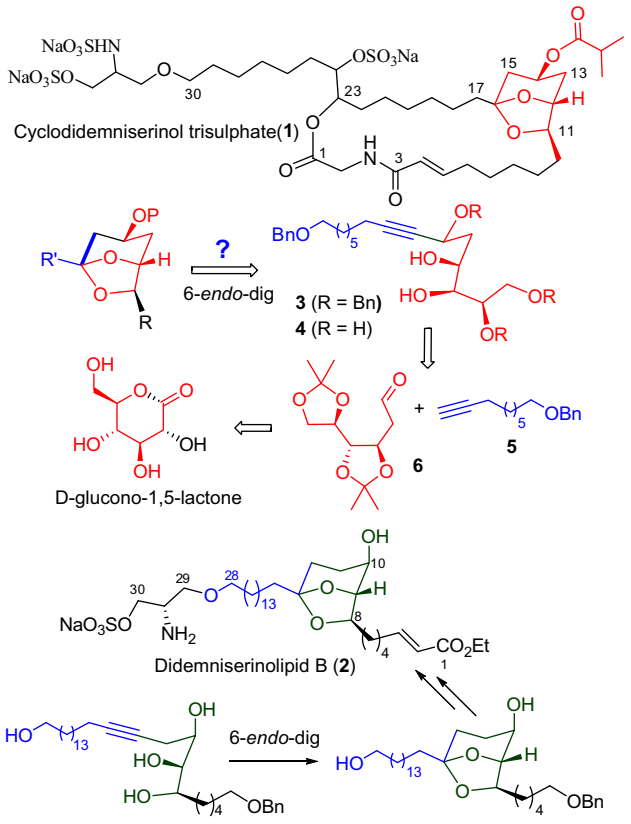


Figure 1. Structure of cyclodidemniserinol trisulfate (**1**) and the projected 6-*endo*-dig cyclization.

resulting from the unpredicted 5-*exo*-dig mode of cyclization.[14] For example, in the ^{13}C NMR spectrum of **13**, characteristic ketal carbon peak appeared at 110.7 ppm and a CH_2 triplet resonating at 37.2 ppm was noticed. The appearance of the other CH_2 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 $Pd(CH_3CN)_2Cl_2$ proceeded smoothly in CH_3CN–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*-cyclizaton 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

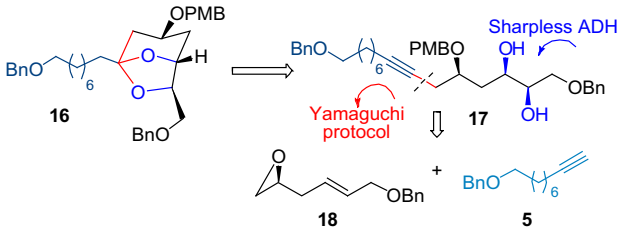
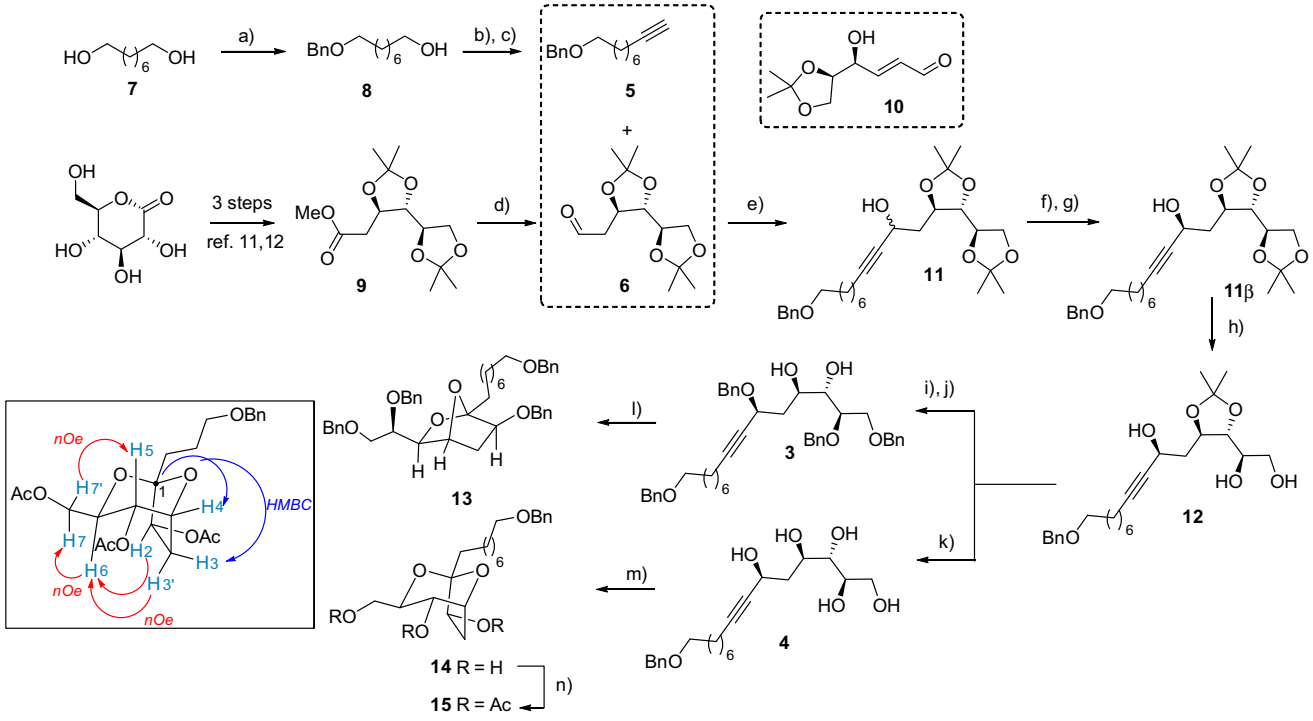
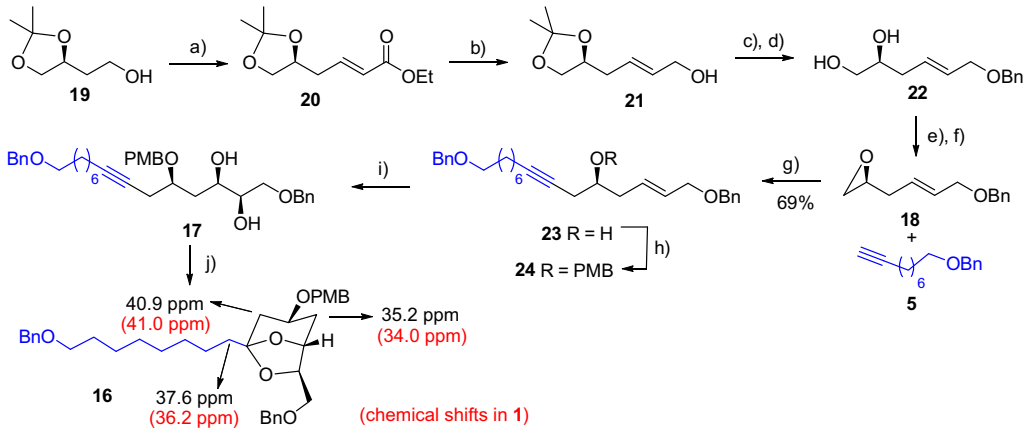


Figure 2. Revised strategy for the central [3.2.1]-bicyclic ketal core.



Scheme 1. Reagents and conditions: (a) Ref. 9, 80%; (b) oxalyl chloride, DMSO, Et_3N; (c) Ohira–Bestmann reagent, K_2CO_3, MeOH, rt, 14 h, 79% in two steps; (d) DIBAL-H, toluene, −78 °C, 20 min; (e) **5**, Et_2Zn, toluene, reflux, 1 h, **6**, rt, 14 h, 69% in two steps; (f) MnO_2, CH_2Cl_2, rt, 24 h, 70%; (g) LiI, THF, −40 °C, 30 min, LAH, −100 °C, 1 h, 82%; (h) MeOH, 0.8% aq H_2SO_4, 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 % $Pd(CH_3CN)_2Cl_2$, CH_3CN, rt, 1 h, 59%; (m) 10 mol % $Pd(CH_3CN)_2Cl_2$, CH_3CN/THF (6:2), rt, 30 min, 67%; (n) Ac_2O, Et_3N, DMAP, rt, 4 h, 87%.



Scheme 2. Reagents and conditions: (a) (i) IBX, DMSO, rt, 2 h, (ii) $Ph_3P{=}CHCO_2Et$, 5 h, 85% in two steps; (b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 86%; (c) NaH, BnBr, DMF, 0 °C→rt, 4 h, 95%; (d) MeOH, *p*-TSA, rt, 8 h, 98%; (e) *n*-Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, rt, 2 h, 89%; (f) NaH, DMF, 0 °C→rt, 4 h, 82%; (g) **5**, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 1 h, 77%; (h) NaH, PMBCl, DMF, 0 °C→rt, 8 h, 75%; (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0→10 °C, 48 h, 73%, (dr 7:3); (j) 10 mol % $Pd(CH_3CN)_2Cl_2$, CH_3CN, rt, 1 h, 51%.

acetonide **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 ally 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 C_9-alkynol fragment **5** was coupled with the oxirane **18** following the Yamaguchi protocol.[18] The resulting alkynol **23** was treated with NaH and PMBCl to afford the corresponding PMB ether **24**. As the Sharpless asymmetric dihydroxylation[19] of **24** using AD-mix-β at 0→4 °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 alkynediol **17** was carried out under optimized conditions (10 mol % of $Pd[CH_3CN]_2Cl_2/CH_3CN$, 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 ^{13}C 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 cyclodidemniserniol trisulfate was executed by employing a Pd-mediated intramolecular ketalization of an alkynediol. 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 cyclodidemniserinol 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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14. *Spectral data of bicyclic ketal* **13**: Colorless oil. $[\alpha]_D^{25}$ +26.5 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3412, 3011, 2929, 2856,1645, 1496, 1454, 1401, 1363, 1027, 971, 912, 697, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30–1.45 (m, 10H), 1.58–1.63 (m, 2H), 1.75 (ddd, *J* = 2.7, 5.5, 12.6 Hz, 1H), 1.86–1.94 (m, 1H), 1.96–2.01 (m, 2H), 3.37 (ddd, *J* = 1.9, 4.7, 9.0 Hz, 1H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.53 (d, *J* = 9.2 Hz, 1H), 3.55 (dd, *J* = 4.7, 10.7 Hz, 1H), 3.67 (dd, *J* = 2.7, 6.6 Hz, 1H), 3.75 (dd, *J* = 1.9, 10.7 Hz, 1H), 4.38 (d, *J* = 12.1 Hz, 1H), 4.49–4.61 (m, 6H), 4.70–4.75 (m, 2H), 7.26–7.34 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (t), 26.2 (t), 28.2 (t), 29.4 (t), 29.5 (t), 29.8 (t), 29.9 (t), 37.2 (t), 68.7 (t), 70.5 (t), 70.6 (t), 72.5 (t), 72.8 (t), 73.3 (t), 76.0 (d), 78.3 (d), 78.4 (d), 80.0 (d), 110.7 (s), 127.4 (d), 127.5 (d), 127.6

(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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20. *Spectral data of bicyclic ketal* ***16***: Colorless oil. $[\alpha]_D^{25}$ +11.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3445, 3251, 3020, 2941, 1603, 1386, 1166, 1107, 1072, 1017, 874, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.36 (m, 10H), 1.53 (dd, *J* = 10.3, 12.5 Hz, 1H), 1.62–1.76 (m, 5H), 2.05 (dd, *J* = 5.8, 13.0 Hz, 1H), 2.20 (dd, *J* = 6.1, 12.5 Hz, 1H), 3.28 (t, *J* = 8.6 Hz, 1H), 3.37 (dd, *J* = 5.5, 9.1 Hz, 1H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.86–3.94 (m, 1H), 3.98 (dd, *J* = 5.7, 7.6 Hz, 1H), 4.40 (br s, 1H), 4.44 (s, 2H), 4.50 (s, 2H), 4.52 (s, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.28–7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (t), 26.2 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 35.2 (t), 37.6 (t), 40.9 (t), 55.3 (q), 69.7 (t), 70.0 (d), 70.5 (t), 71.4 (t), 72.8 (t), 73.4 (t), 75.7 (d), 77.6 (d), 109.1 (s), 113.7 (d), 113.8 (d), 127.4 (d), 127.6 (d, 2C), 127.7 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.0 (d), 129.2 (d, 2C), 130.5 (s), 138.0 (s), 138.7 (s), 159.2 (s) ppm; ESI-MS: *m/z* 611.7 (100%, [M+Na]); Anal. Calcd for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.29; H, 8.36.