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Functionalized Templates for the Convergent Assembly of Polyethers: Synthesis of *HIJK* Rings of Gymnocin A**

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Abstract

Epoxide-opening cascades offer an attractive strategy for the construction of *trans-syn*-fused arrays of oxygen heterocycles, a hallmark of ladder-type polyether natural products such as gymnocin A.

[1] We have previously described efficient water-promoted cascades templated by a minimally functionalized tetrahydropyran (THP) ring, the products of which were not directly amenable to further elaboration.[2] To expand the utility of this methodology in target-oriented synthesis, we have now developed two highly functionalized heterocycles that not only serve as templates but also possess differentiated functional groups for modification and fragment coupling. One of these templates (THP **2**), resembles ring K of the natural product gymnocin A (Figure 1). The other functionalized template (1,3-dioxane **5**), while not found in ladder polyethers, is synthetically versatile and can easily be transformed into rings present in gymnocin A. The reactivity and selectivity patterns of this novel dioxane template are significantly different from and thus complementary to those of THP-based templates in water.

Keywords

cascade; ladder polyether; metathesis; natural products; template

We envisioned the *HIJK* ring system (**1**) of gymnocin A could be constructed by a water-promoted cascade of triepoxide **2**, where ring *K* of the natural product templates the reaction. In turn, this triepoxide is prepared via a cross-metathesis involving olefin **4**, with the THP of **4** being assembled via an *endo*-selective cyclization of epoxy alcohol **5**. Having not previously examined such 1,3-dioxanes as templates, we began our studies with the synthesis and evaluation of **5** in this context. 2-Deoxyribose was transformed into benzylidene acetal **7** followed by reduction and Sharpless epoxidation in good yield and diastereoselectivity (Scheme 1). [3] Conversion of the alcohol to the iodide, a copper catalyzed displacement,[4] and cleavage of the silyl ether afforded multigram quantities of **5**.

We quickly discovered that the behavior of the 1,3-dioxane template is markedly different than that of the THP templates we have reported.[2] Water, which proved effective for THP templates, did not promote the cyclization of **5** at ambient temperature and only hydrolyzed the acetal at elevated temperatures (Table 1, entries 1–2). Since both solvent and promoter can significantly affect selectivity, we examined a variety of conditions in order to identify an efficient promoter for this dioxane template (entries 3–8). Low selectivity or low conversion

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was generally observed, yet gratifyingly, silica gel exhibited high *endo*-selectivity albeit in low yield (entry 9).[5] Recognizing that silica is hygroscopic, it was unclear to us whether trace H₂O or the silanol surface of the silica gel was promoting the reaction. Rigorous drying of the silica prior to use had no effect on conversion or selectivity (entry 10), suggesting that indeed the silanol was the promoting species.[6] Complete conversion was obtained by simply increasing the promoter loading (entry 11). Silicic acid (SiO₃H₂) also promoted the cyclization (entry 12). Due to the mild nature of silica promoters, only the major diastereomer of **5** cyclized at 40 °C, allowing for facile removal of the unwanted stereoisomer by chromatography. Conveniently, microwave heating reduced the reaction time from days to minutes with no appreciable drop in yield or selectivity (entry 13).

Having identified a new and efficient promoter for the cyclization of the 1,3-dioxane template onto a single epoxide,[7] we turned our attention towards elaboration of the newly formed THP in **8** into ring *K* of the natural product, and the template for the next cascade. Protection of alcohol **8** as a PMB ether was followed by acetal solvolysis to provide a diol, the secondary alcohol of which was protected as a silyl ether (Scheme 2).[8] At this stage we chose to protect primary alcohol **10** as a methyl ether which would serve as an orthogonally protected fragment coupling site following the epoxide-opening cascade. Silyl group cleavage, oxidation and a stereoselective addition of methyl Grignard[9] afforded **12**, ring *K* of the natural product, in 38% overall yield from **8**.

Olefin metathesis to join the template and epoxide-bearing fragment **14** (prepared from known epoxy alcohol **13**[10] in 6 steps) initially proved challenging. Attempts to couple olefins **12** and **14** with ruthenium-based catalysts gave mainly the self-metathesis product (**15**) of **14** and minimal cross-metathesis. Suspecting that the PMB ether of **12** may be interfering with the desired reaction,[11] this group was removed, and under reaction conditions identical to those investigated with **12**, diol **4** underwent cross-metathesis to give **16** in moderate yield and *E*:*Z* selectivity. The yield was improved significantly by replacing olefin **14** with an excess of self-metathesis product **15**. [12] Greater than 90% of unreacted **15** was recovered and could be reused in the metathesis reaction without event. Furthermore, while the cross-metathesis proceeds with moderate *E*:*Z* selectivity, the olefin isomers are separable allowing for recycling of the undesired *Z*-olefin by re-subjection to the metathesis reaction. In all, this metathesis strategy afforded several hundred milligrams of **16**. [13] Finally, protection of alcohol **16** prevented undesired cyclization during the subsequent asymmetric epoxidation with fructose-derived ketone **19**. [14]

Having convergently assembled polyepoxide **2**, we were eager to explore the water-promoted cascade. Cognizant of how changes to the template composition can radically affect *endo*-selectivity,[15] it was challenging to predict a priori whether ring *K*, bearing a methoxymethyl substituent at the 2-position as well as a tertiary alcohol and axial methyl group at the 3-position, would template the reaction in the desired fashion. Incubation of **2** in H₂O at 60 °C for 5 days followed by acetylation afforded a mixture of the desired tetrad (**1**) and a compound in which rings *IJ* had formed, but the final epoxide had remained intact. This triad (**18**) intrigued us for two reasons. In previous cascades, complete conversion was typically observed after 3 days at 60 °C. Second, we had not previously isolated an epoxide-containing intermediate *en route* to the final cascade product. The attenuated reactivity of the remaining epoxide is likely due to the presence of the electron-withdrawing oxygen atom in the benzyl ether. A higher temperature and longer reaction time (80 °C, 9 d) surmounted this stalled cascade and after acetylation afforded **1**, the desired *HIJK* fragment of gymnocin A in 35% overall yield, corresponding to approximately 70% yield per newly formed ring.

In summary, we have employed two different functionalized templates for the synthesis of the *HIJK* rings of gymnocin A. The *first* template (1,3-dioxane of **5**) provides high *endo*-selectivity

in the presence of silicon dioxide-based promoters. The product (**8**) of this cyclization, a synthetically versatile intermediate, was facilely elaborated into a *second* template (ring *K* of gymnocin A) facilitating a water-promoted cascade of triepoxide **2** into tetrad **1**. Noteworthy is that this polyether subunit enjoys a total of 4 differentiated functional groups, 2 at each end, thus allowing for elaboration of both termini and significantly increasing the synthetic utility of products obtained from epoxide-opening cascades. The use of dioxane and other functionalized templates towards the total synthesis of ladder polyether natural products is under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

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5. Silica gel has been used for endo-selective epoxysilane opening but not, to our knowledge, for electronically unbiased epoxides such as **5**. We confirmed that the allyl substituent was not electronically biasing the epoxide as studies with fully saturated analogues gave comparable results. See: Adiwidjaja G, Florke H, Kirschning A, Schaumann E. *Tetrahedron Lett* 1995;36:8771–8774.
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7. Given the mildly acidic nature of silica, we did not predict it would be an effective promoter for an epoxide-opening *cascade*. Indeed, in studies of templates bearing *two* epoxides, silica-based promoters led to the formation of undesired oxetane and tetrahydrofuran rings.
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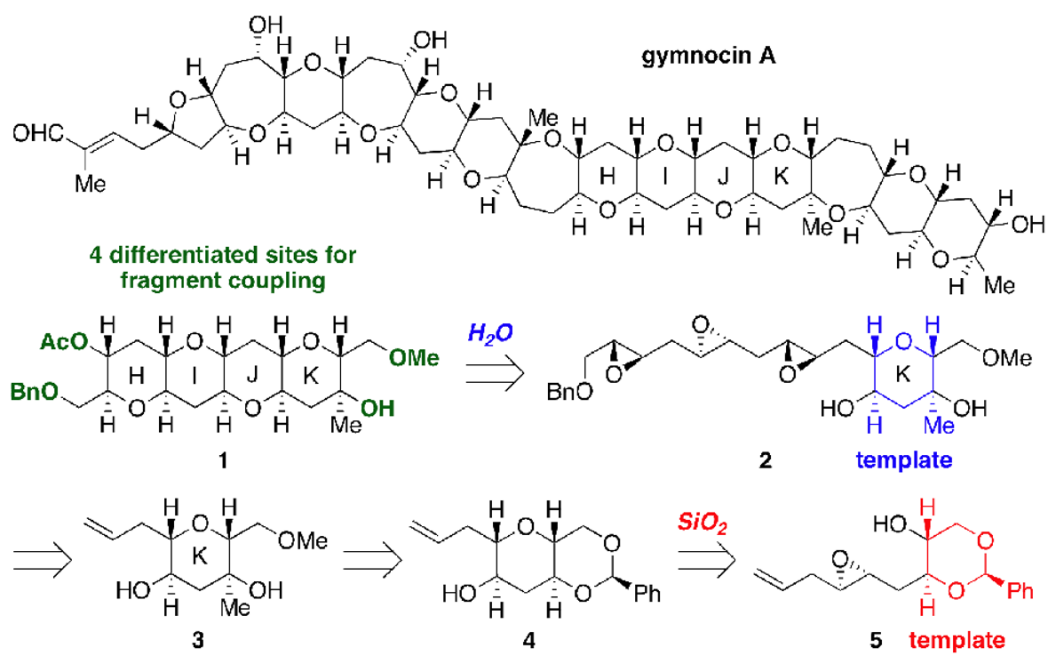
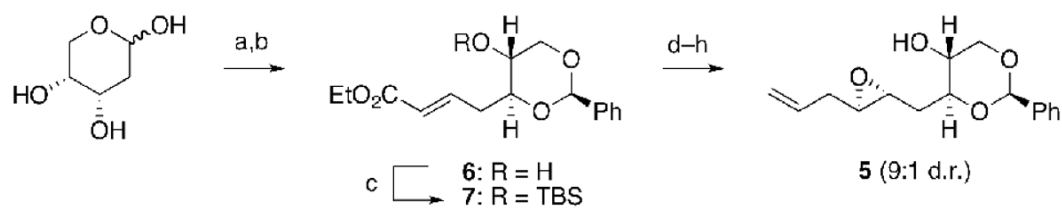


Figure 1.
Gymnocin A and retrosynthetic analysis of rings *HIJK*.

**Scheme 1.**

Reagents and conditions: a) $\text{Ph}_3\text{PCHCO}_2\text{Et}$, THF, reflux, 83:17 *E:Z*; b) PhCH(OMe)_2 , CSA, DCM, 76% (2 steps); c) TBSCl, imid, DMF, 71%; d) DIBALH, DCM, 97%; e) D-(–)-DET, $\text{Ti(O}i\text{Pr)}_4$, TBHP, DCM, -25°C , 95%, 9:1 d.r.; f) I_2 , imid, PPh_3 , $\text{Et}_2\text{O/CH}_3\text{CN}$, 83%; g) $\text{CuBr}\cdot\text{DMS}$, $\text{CH}_2=\text{CHMgBr}$, HMPA, THF, -25°C , 84%; h) TBAF, THF, 0°C , 90%.

Table 1

Screen of promoters for *endo*-selective cyclization of **5**.

entry	solvent	promoter	T (°C)	t	8 : 9 ^d	yield 8
1	H ₂ O	none	23	13 d	-- ^b	--
2	H ₂ O	none	60	3 d	-- ^c	--
3	H ₂ O	NaOH	23	12 h	2.0:1	58%
4	MeOH	Cs ₂ CO ₃	23	12 h	1.2:1	45%
5	MeOH	imidazole	23	12 h	-- ^b	--
6	MeOH	none	23	9 d	-- ^b	--
7	C ₆ H ₆	CSA	23	1 h	1.9:1 ^c	51%
8	CH ₂ Cl ₂	none	40	2 d	-- ^b	--
9	CH ₂ Cl ₂	SiO ₂ (35) ^d	40	2 d	>9:1 ^e	45%
10	CH ₂ Cl ₂	SiO ₂ (35) ^{d,f}	40	2 d	>9:1 ^e	47%
11	CH ₂ Cl ₂	SiO ₂ (90) ^{d,f}	40	2 d	>9:1	78%
12	CH ₂ Cl ₂	SiO ₃ H ₂ (90) ^{d,f}	40	2 d	>9:1	75%
13	CH ₂ Cl ₂	SiO ₃ H ₄ (90) ^{d,f}	135	0.2 h	>9:1	72%

^aDetermined by ¹H-NMR.^b<5% cyclization of **5**.^c1,3-dioxane cleaved.^dmg silica promoter/mg **5**.^e50–60% cyclization of **5** observed.

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f Promoter dried at 140 °C for 12 h prior to use.