Cascade Reactions

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

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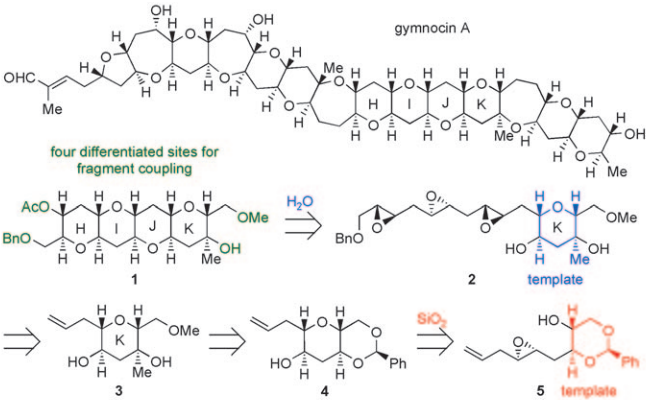
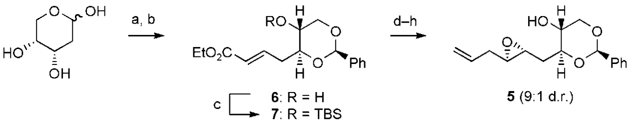
Epoxide-opening cascade reactions offer an attractive strategy for the construction of *trans-syn*-fused arrays of oxygen heterocycles, which are a hallmark of ladder-type polyether natural products such as gymnocin A.[1] We have previously described efficient water-promoted cascade reactions that are 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 (Scheme 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.



Scheme 1. Gymnocin A and the retrosynthetic analysis of rings HIJK. Bn = benzyl.

We envisioned that the HIJK-ring system (**1**) of gymnocin A could be constructed by a water-promoted cascade reaction of triepoxide **2**, where ring K of the natural product templates the reaction (Scheme 1). In turn, this triepoxide could be prepared through a cross-metathesis reaction involving olefin **4**, with the THP of **4** being assembled by 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**. 2-Deoxyribose was transformed into benzylidene acetal **7** and subsequent reduction and Sharpless epoxidation gave good yield and diastereoselectivity (Scheme 2).[3] Conversion of the alcohol into the iodide, a copper catalyzed displacement,[4] and cleavage of the silyl ether afforded multigram quantities of **5**.



Scheme 2. Reagents and conditions: a) Ph_3PCHCO_2Et, THF, reflux, 83:17 *E/Z*; b) $PhCH(OMe)_2$, CSA, CH_2Cl_2, 76% (over 2 steps); c) TBSCl, imid, DMF, 71%; d) DIBALH, CH_2Cl_2, 97%; e) D-(−)-DET, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, −25 °C, 95%, 9:1 d.r.; f) I_2, imid, PPh_3, Et_2O/CH_3CN, 83%; g) CuBr·DMS, $CH_2{=}CHMgBr$, HMPA, THF, −25 °C, 84%; h) TBAF, THF, 0 °C, 90%. CSA = 10-camphorsulfonic acid, DET = diethyl tartrate, DIBALH = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMS = dimethyl sulfide, HMPA = hexamethylphosphoramide, imid = imidazole, TBAF = tetra-*n*-butylammonium fluoride, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

It quickly became apparent that the behavior of the 1,3-dioxane template was markedly different than that of the THP templates we have previously reported.[2] Water, which proved effective for THP templates, did not promote the cyclization of **5** at ambient temperature and only hydrolyzed the acetal group at elevated temperatures (Table 1, entries 1–2). As both the solvent and promoter can significantly affect selectivity, we examined a variety of reaction conditions to identify an efficient promoter for this dioxane template (entries 3–8). Low selectivity or low conversion was generally observed, yet gratifyingly, the use of silica gel exhibited high *endo*-selectivity albeit in low yield (entry 9).[5] Recognizing that silica gel is hygroscopic, it was unclear to us whether trace H_2O or the silanol surface of the silica gel was promoting the reaction. Rigorous drying of the silica gel prior to use had no

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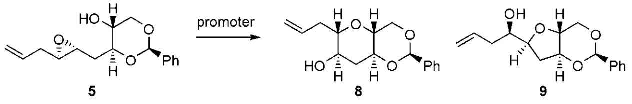
Table 1: Screen of promoters for *endo*-selective cyclization of **5**.



Entry	Solvent	Promoter	T [°C]	t	**8**/**9**[a]	Yield of **8** [%]
1	H_2O	none	23	13 d	–[b]	–
2	H_2O	none	60	3 d	–[c]	–
3	H_2O	NaOH	23	12 h	2.0:1	58
4	MeOH	Cs_2CO_3	23	12 h	1.2:1	45
5	MeOH	imidazole	23	12 h	–[b]	–
6	MeOH	none	23	9 d	–[b]	–
7	C_6H_6	CSA	23	1 h	1.9:1[c]	51
8	CH_2Cl_2	none	40	2 d	–[b]	–
9	CH_2Cl_2	SiO_2(35)[d]	40	2 d	>9:1[e]	45
10	CH_2Cl_2	SiO_2(35)[d,f]	40	2 d	>9:1[e]	47
11	CH_2Cl_2	SiO_2(90)[d,f]	40	2 d	>9:1	78
12	CH_2Cl_2	SiO_3H_2(90)[d,f]	40	2 d	>9:1	75
13	CH_2Cl_2	SiO_3H_2(90)[d,f]	135	0.2 h	>9:1	72

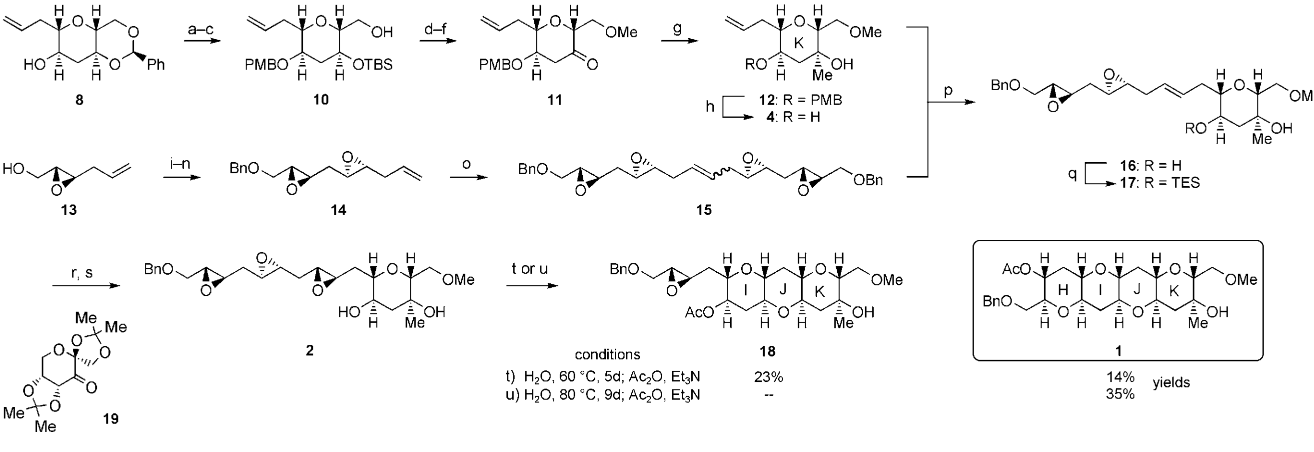
[a] Determined by ^{1}H NMR spectroscopy. [b] <5% cyclization of **5**. [c] 1,3-Dioxane cleaved. [d] mg of silica promoter per mg of **5**. [e] 50–60% cyclization of **5** was observed. [f] Promoter was dried at 140 °C for 12 hours prior to use.

effect on conversion or selectivity (entry 10), thus suggesting that indeed the silanol was the promoting species.[6] Complete conversion was obtained by simply increasing the promoter loading (entry 11). Silicic acid (SiO_3H_2) also promoted the cyclization (entry 12). Owing to the mild nature of silica promoters, only the major diastereomer of **5** cyclized at 40 °C, thus 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 reaction. Protection of alcohol **8** as a PMB ether and subsequent acetal solvolysis provided a diol, the secondary alcohol of which was protected as a silyl ether (Scheme 3).[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 reaction. Cleavage of the silyl group, oxidation, and a stereoselective addition of methyl Grignard reagent[9] afforded **12**, ring K of the natural product, in 38% overall yield from **8**.

Olefin metathesis to couple the template and epoxide-bearing fragment **14** (prepared from known epoxy alcohol **13**[10] in six 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 occurred. We suspected that the PMB ether of **12** may be interfering with the desired reaction;[11] thus this group was removed, and under reaction conditions identical to those used for **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 unchanged **15** was recovered and could be reused in the metathesis reaction without event. Even though the cross-metathesis reaction proceeded with moderate *E*/*Z* selectivity, the olefin isomers were separable thus allowing us to recycle the undesired *Z* olefin by resubjection 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 assembled polyepoxide **2** in a convergent manner, we were eager to explore the water-promoted cascade reaction. 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 methoxy-



Scheme 3. Reagents and conditions: a) KH; then PMBCl, THF, 94%; b) CSA, MeOH/THF (3:1), 90%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2; then CSA, MeOH, 91%; d) Ag_2O, MeI, CH_3CN, 60 °C, 76%; e) TBAF, THF, 98%; f) Dess–Martin periodinane, CH_2Cl_2, 96%; g) MeMgBr, toluene, −78 °C, 75%; h) DDQ, CH_2Cl_2/H_2O (20:1), 0 °C, 93%; i) NaH; then BnBr, THF, 87%; j) $CH_2{=}CHCHO$, Hoveyda–Grubbs cat. (2nd generation), CH_2Cl_2, 40 °C, 83%, >10:1 *E*/*Z*; k) $NaBH_4$, MeOH; l) D-(−)-DET, Ti(O*i*Pr)$_4$, TBHP, CH_2Cl_2, −25 °C, (64% over 2 steps), 5:1 d.r.; m) I_2, imid, PPh_3, Et_2O/CH_3CN (3:1), 87%; n) CuBr·DMS, $CH_2{=}CHMgBr$, HMPA, THF, −25 °C, 84%; o) Hoveyda–Grubbs cat. (2nd generation), CH_2Cl_2, 40 °C, 85%; p) Hoveyda–Grubbs cat. (2nd generation), CH_2Cl_2, 40 °C, 74%, 2.6:1 *E*/*Z*; q) TESCl, imid, DMF, 82%; r) **19**, Oxone, Bu_4NHSO_4, K_2CO_3, pH 10.5, DMM/CH_3CN (2:1), 82%, 93:7 d.r.; s) TBAF, THF, 77%; t) H_2O, 60 °C, 5 days; then Ac_2O, Et_3N; u) H_2O, 80 °C, 9 days; then Ac_2O, Et_3N. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinine, DMM = dimethoxymethane, PMB = *para*-methoxybenzyl, TES = triethylsilyl.

methyl 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. Heating of **2** in H_2O at 60 °C for 5 days and subsequent acetylation afforded a mixture of the desired tetrad **1** and **18,** in which rings IJ had formed but the final epoxide had remained intact. This triad **18** intrigued us for two reasons. Firstly, in previous cascade reactions complete conversion was typically observed after 3 days at 60 °C. Secondly, 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 to result from the presence of the electron-withdrawing oxygen atom in the benzyl ether. A higher temperature and longer reaction time (80 °C, 9 days) surmounted this stalled cascade reaction, and after acetylation afforded **1**, the desired HIJK fragment of gymnocin A in 35 % overall yield, which corresponds 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 elaborated in a facile manner into a second template (ring K of gymnocin A) and facilitated a water-promoted cascade reaction of triepoxide **2** into tetrad **1**. Noteworthy is that this polyether subunit enjoys a total of four differentiated functional groups—two at each end—thus allowing for elaboration of both termini and significantly increasing the synthetic utility of products obtained from epoxide-opening cascade reactions. The use of dioxane and other functionalized templates towards the total synthesis of ladder polyether natural products is under investigation.

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Keywords: cascade reactions · metathesis · natural products · polyethers · template synthesis

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[1] For an excellent and recent review of the ladder polyether natural products, see: a) K. C. Nicolaou, M. O. Frederick, R. J. Aversa, *Angew. Chem.* **2008**, *120*, 7292 – 7335; *Angew. Chem. Int. Ed.* **2008**, *47*, 7182 – 7225.

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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: G. Adiwidjaja, H. Flörke, A. Kirschning, E. Schaumann, *Tetrahedron Lett.* **1995**, *36*, 8771 – 8774.

[6] The concentration of **5** in the reaction solution dropped by an order of magnitude after the addition of silica gel (UV analysis), thus indicating significant adsorption onto SiO_2.

[7] Given the mildly acidic nature of silica gel, we did not predict it would be an effective promoter for an epoxide-opening cascade reaction. Indeed, in studies of templates bearing two epoxide groups, silica-based promoters led to the formation of undesired oxetane and tetrahydrofuran rings.

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[13] Although cross-metathesis afforded ample quantities of **16** to evaluate ring K as a template in epoxide-opening cascade reactions, we are investigating other more general strategies for the construction of similar "skipped" polyepoxides.

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