Synthetic Utility of Sugar-Derived Cyclic Nitrones: A Diastereoselective Synthesis of Linear 4-Azatriquinanes

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Received: 02.02.2012; Accepted after revision: 12.04.2012

Abstract: A diastereoselective Pauson–Khand reaction has been utilized as the key step in the construction of azatriquinanes from sugar-derived nitrones.

Key words: diastereoselectivity, sugar derivatives, nitrones, Pauson–Khand reaction

Polyquinane[1] natural products and their analogues have attracted attention from the synthetic community owing to their unique molecular architecture and interesting biological activities. Among the polyquinanes, natural products containing the triquinanes, especially some linearly fused triquinanes, have elicited much interest due to their promising biological activities (Figure 1). For example, hirsutic acid (**1**) exhibits antibiotic activity, and coriolin (**3**) shows antibacterial and antitumor activities.[2] Deoxyhypnophilin (**4**) and hypnophilin (**5**) are active against the Gram-positive bacterium *Bacillus cereus*, and spores of *Aspergillus niger*, *Aspergillus flavus*, and *Mucorrouxii*, with MIC values of 1–5 μg/mL.[3] Moreover, highly functionalized and biologically active linear triquinane natural products are continuously being isolated from various sources. Recently, connatusins A (**6**) and B (**7**) have been isolated from the culture broth of the fungus *Lentinus conatus* BCC 8996.[4]

The hetero-analogues of carbocyclic triquinanes, namely azatriquinanes[5] and oxatriquinanes,[6] have shown promising biological activities. Although several methods[7] are known to construct oxatriquinanes utilizing a sugar template, to the best of our knowledge, there has been no report on the construction of linear azatriquinanes with an appended sugar unit. Furthermore, because of their known polyhydroxylated carbon framework with multiple avenues of chirality, sugar-derived nitrones[8] have been widely used as chiral building blocks in the synthesis of several biologically active compounds. Bearing in mind these findings, in continuation of our interest in the synthesis of natural-product-like molecular scaffolds,[9] we developed an interest in devising a simple and straightforward strategy to synthesize a small set of azatriquinane scaffolds **8** (Figure 1).

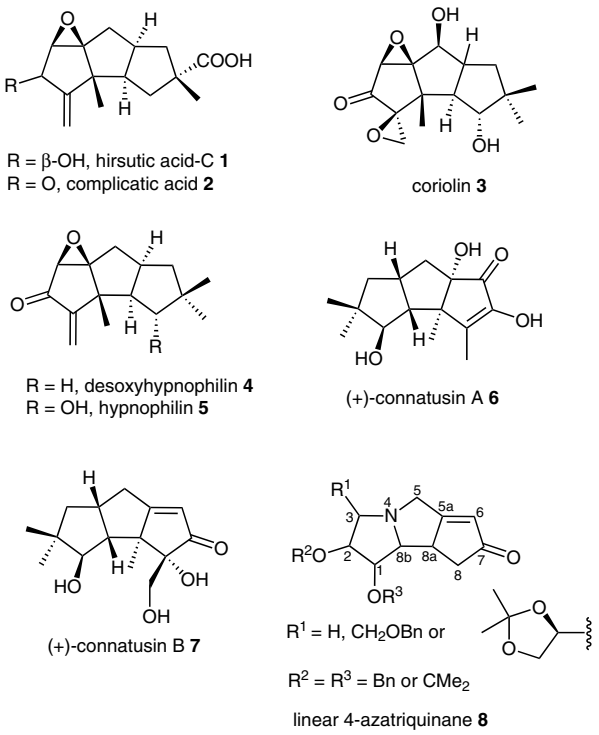
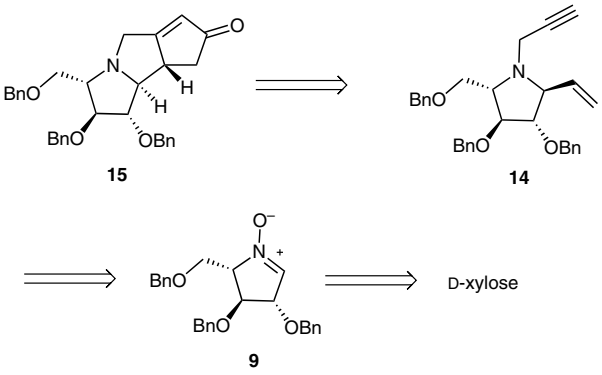


Figure 1 Biologically active linear triquinanes and our designed linear 4-azatriquinanes

According to our retrosynthesis, as delineated in Scheme 1, we envisaged that the hexahydrocyclopenta[*a*]pyrrolizin-7-one (**15**) could be obtained by an intramolecular Pauson–Khand reaction[10] of enyne **14**, which, in turn, could be generated from sugar-derived nitrone **9**.[8]



Scheme 1 Retrosynthetic analysis

SYNLETT 2012, 23, 1473–1476
Advanced online publication: 29.05.2012
DOI: 10.1055/s-0031-1290375; Art ID: ST-2012-D0100-L

During the course of our synthetic studies, a report on the synthesis of hexahydrocyclopenta[*a*]pyrrolizin-7-one was published by Vicario, Badía and co-workers using an organocatalytic [3+2] cycloaddition of azomethine ylides with α,β-unsaturated aldehydes, and Pauson–Khand reaction as key steps.[11] An important advantage of our strategy is that the structurally intriguing linear azatriquinanes, in which the nitrogen atom is embedded in the cyclic framework, could be easily obtained by utilizing nitrones as appropriate precursors. Furthermore, the peripheral substitution around the cyclic nitrone governs the stereochemical outcome of further synthetic transformations. To this end, we selected a set of nitrones **9**, *ent*-**9**, **10**, **11**, **12**, and **13** as the basic building blocks, following literature procedures (Figure 2).[8]

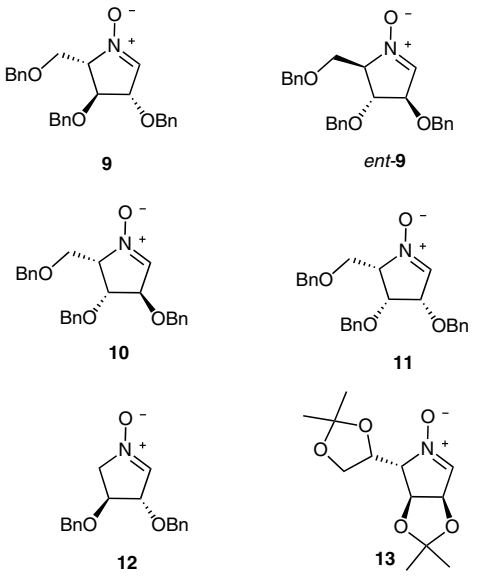
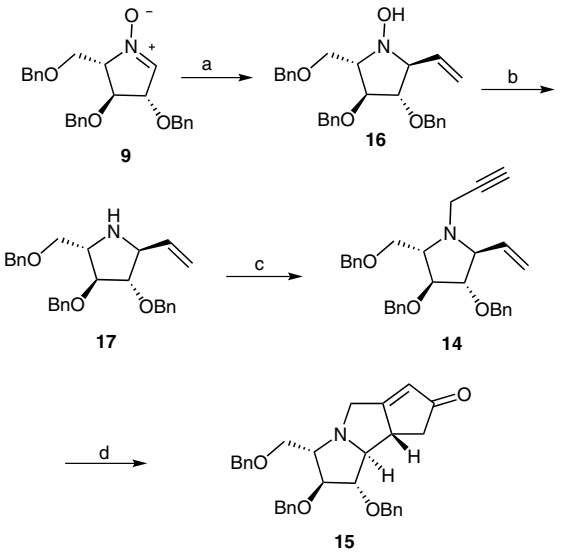


Figure 2 Sugar-derived nitrones

Thus, our synthesis of azatriquinanes as shown in Scheme 2, commenced with the addition of vinylmagnesium bromide to a previously cooled solution of nitrone **9** in tetrahydrofuran (THF) at –20 °C to furnish the hydroxylamine **16** as a single diastereoisomer.[8c–e] The diastereoselectivity of the reaction can easily be explained by *anti* attack of the organometallic reagent with respect to the adjacent benzyl ether, as a result of steric and stereoelectronic effects. Amine **17**, obtained through N–O bond cleavage of **16** with activated Zn (4 equiv) and saturated ammonium chloride solution in the presence of a catalytic amount of indium (18%),[12] was further treated with propargyl bromide in the presence of K_2CO_3,[11] to afford enyne **14**.

With enyne **14** in hand, the stage was set for the execution of the Pauson–Khand reaction.[13] Initially, when enyne **14** was treated with $[Co_2(CO)_8]$ and subsequent treatment with *N*-methylmorpholine *N*-oxide (NMO), an unidentified complex mixture was obtained. Pleasingly, replacement of NMO with DMSO led to exclusive formation of the desired azatriquinane **15** as a single diastereoisomer in excellent yield.[14] The observed diastereoselectivity can be



Scheme 2 *Reagents and conditions*: (a) CH_2=CHMgBr, THF, 0 °C, 4 h, 97%; (b) Zn, In (cat.), MeOH, sat. NH_4Cl, reflux, 12 h, 84%; (c) 3-bromoprop-1-yne, K_2CO_3, acetone, 92%; (d) i. $[Co_2(CO)_8]$, CH_2Cl_2; ii. toluene, DMSO, 80 °C, 69% (2 steps).

rationalized on the basis of the approach of the alkene from the less hindered side of the $[Co_2(CO)_6]$–alkyne complex. The configuration of the newly generated stereocenter was confirmed by COSY and NOESY experiments (Figure 3).

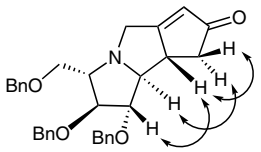


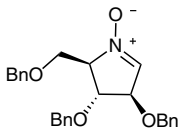
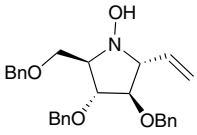
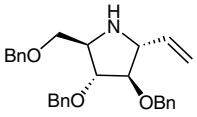
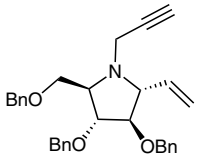
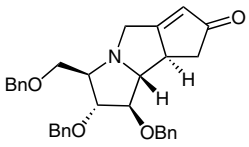
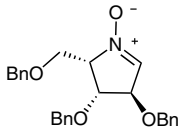
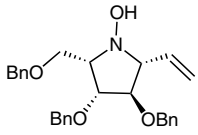
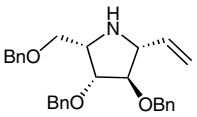
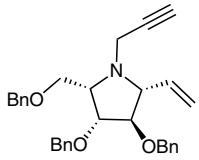
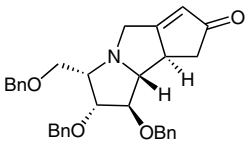
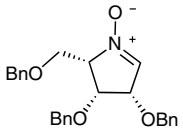
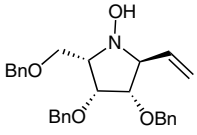
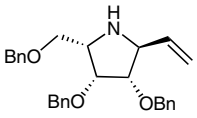
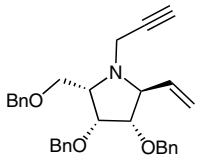
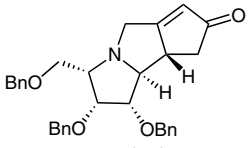
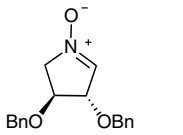
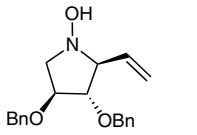
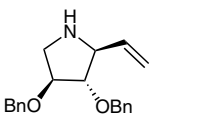
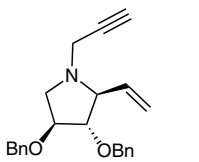
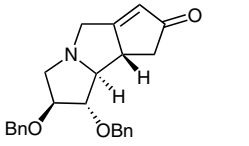
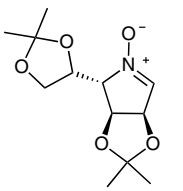
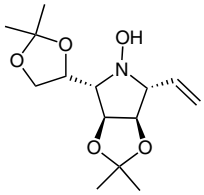
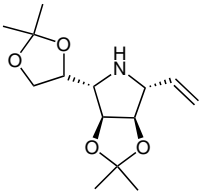
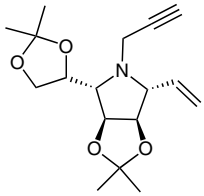
Figure 3 NOE interactions between protons of **15**

To expand the scope of our strategy, the sugar-derived nitrones *ent*-**9**, **10**, **11**, **12**, and **13** (Figure 2) were then subjected to the same synthetic sequence, which allowed the efficient preparation of enyne **14** through vinyl Grignard addition, N–O bond cleavage and *N*-propargylation, to provide the enynes *ent*-**14**, **20**, **24**, **28**, and **32**, respectively, in excellent yields (Table 1).

Having generated sufficient amounts of these enynes, they were subjected to the Pauson–Khand reaction as described for **14**,[14] and, pleasingly, we could isolate the desired azatriquinanes *ent*-**14**, **21**, **25**, and **29** as single diastereoisomers in all cases except for enyne **32**, wherein a separable mixture of diastereoisomers **33** and **34** was obtained in a 4:1 ratio (Figure 4).

In conclusion, we have disclosed a simple approach to the synthesis of a set of linear azatriquinanes from sugar-derived nitrones using a diastereoselective Pauson–Khand reaction as the key step. The requisite nitrones have been prepared easily from inexpensive carbohydrate starting materials. Using this approach, the desired linear azatriquinanes could be synthesized in good yields; the ste-

Table 1 Synthesis of Azatriquinanes[a]

Sugar-derived nitrone	Hydroxylamine	Amine	Enyne	Azatriquinane
				
ent-**9**	*ent*-**16** (94)	*ent*-**17** (80)	*ent*-**14** (91)	*ent*-**15** (66)
				
10	**18** (92)	**19** (78)	**20** (89)	**21** (70)
				
11	**22** (97)	**23** (81)	**24** (90)	**25** (68)
				
12	**26** (95)	**27** (82)	**28** (89)	**29** (71)
				**33**/**34** 4:1
13	**30** (87)	**31** (72)	**32** (89)	

[a] Yield given in parenthesis.

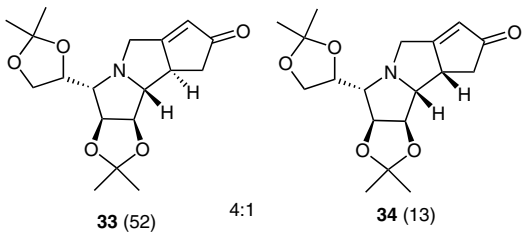


Figure 4

reochemistry of the newly formed stereocenter was confirmed by COSY and NOESY experiments. The described approach should open the way for the synthesis of a library of linear azatriquinanes from a variety of appropriately functionalized sugar templates.

Acknowledgment

We thank DST, New Delhi for financial support. K.P.K. thanks DST for the Swarnajayanti fellowship. A.B. thanks CSIR, New Delhi for a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Genaral Procedure for Pauson–Khand Reaction**: To a stirred solution of enyne (1 mmol) in CH_2Cl_2 (30 mL), $[Co_2(CO)_8]$ (1.2 mmol) was added under a nitrogen atmosphere at 25 °C. After stirring at 25 °C for 1 h, the solvent was removed to obtain the crude product. To a solution of the above crude product in toluene (20 mL), DMSO (10 mmol) was added and the solution was heated at reflux overnight at 80 °C. After completion, the reaction mixture was quenched with 1% HCl (50 mL) (except for compounds **33** and **34**, which were quenched with water) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by basic alumina column chromatography. Data for (1*S*,2*S*,3*S*,8a*S*,8b*S*)-1,2-bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,8,8a,8b-hexahydrocyclopenta[*a*]pyrrolizin-7(5*H*)-one (**15**): R_f = 0.4 (EtOAc–hexanes, 50%); $[\alpha]_D^{20}$ –9.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.26 (m, 15 H), 6.0–5.99 (m, 1 H), 4.69–4.44 (m, 6 H), 4.08–4.02 (m, 3 H), 3.71 (d, *J* = 16.9 Hz, 1 H), 3.62 (dd, *J* = 9.4, 4.5 Hz, 1 H), 3.52 (dd, *J* = 9.4, 6.5 Hz, 1 H), 3.29–3.24 (m, 1 H), 3.19 (dd, *J* = 10.5, 3.3 Hz, 1 H), 3.12–3.08 (m, 1 H), 2.60 (dd, *J* = 17.6, 6.2 Hz, 1 H), 2.10 (dd, *J* = 17.6, 3.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 186.9, 138.4, 138.1, 137.7, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 125.1, 86.8, 86.1, 73.6, 73.0, 72.7, 72.5, 72.3, 70.2, 54.2, 48.5, 40.6; IR (neat): 3872, 3030, 2924, 2854, 2109, 1966, 1703, 1646, 1454, 1367, 1306, 1215, 1106, 1028, 754, 698 cm^{-1}; HRMS (ESI): calcd for $C_{32}H_{34}NO_4$ $[M + 1]^+$ 496.2488; found 496.2469.

