Radical Cyclization

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Synthesis of Bridged Diketopiperazines by Using the Persistent Radical Effect and a Formal Synthesis of Bicyclomycin

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In memory of Ekkehard Winterfeldt

Abstract: *A conceptually new and unified approach to diverse bridged diketopiperazines (DKPs) with widely variable ring sizes was developed by taking advantage of the persistent radical effect. This method enables synthesis of the core structures of bridged DKP alkaloids and was applied to a formal synthesis of the antibiotic bicyclomycin.*

Natural products are a very important driving force and a source of inspiration for organic chemistry and drug discovery. Developed by evolutionary selection for optimal interactions with biological targets, the majority of them bear complex three-dimensional structures.[1] Bridged diketopiperazine (DKP) alkaloids such as **1**–**3**, which contain a bicyclo-[*n*.2.2]piperazinedione ring system ($n \geq 2$), constitute a growing class of peptide-derived secondary metabolites, and they demonstrate nature's chemical craftsmanship in generating diverse and complex architectures (Figure 1 A).[2]

Unnatural bioactive bridged DKPs have also been discovered as important scaffolds. The highly selective inhibition of α-glucosidase over β-glucosidase exhibited by compounds **4** and **5** might be useful for the design of small-molecule antidiabetic medications (Figure 1 B).[3] Bridged DKPs are also precursors for conformationally locked bridged piperazines (**6**–**7**), another class of privileged structures, many of which have been reported to be strong ligands for CNS receptors.[4]

A number of approaches to the diazabicyclo[2.2.2]octane system present in numerous prenylated indole alkaloids such as stephacidin A (**1**) have been developed.[5,6] However, approaches to bridged DKP systems with larger bridges, and especially to heteroatom-bridged DKPs such as bicyclomycin (**2**) and cottoquinazoline D (**3**), are very rare. They capitalized on polar reactions like intramolecular alkylations of DKP enolates that contain a pendant side chain bearing a good leaving group[4a,7] or cyclization to *N*-acyliminium intermediates, which are limited to bicyclomycin-type compounds (Scheme 1).[6j,8,9]

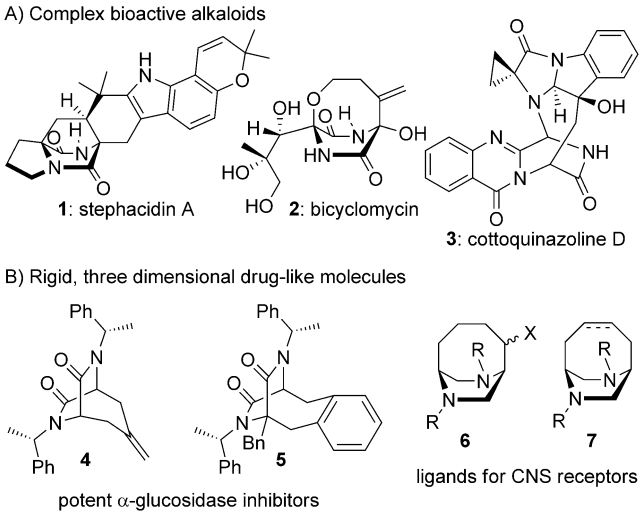
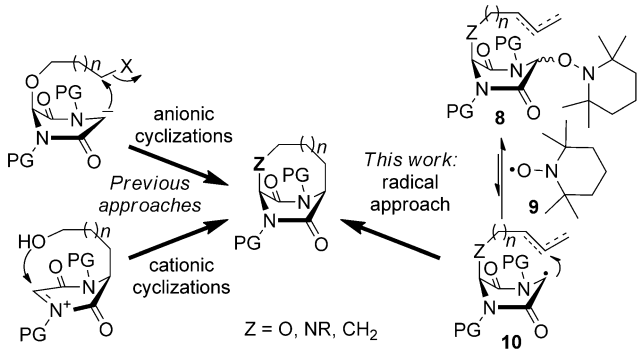


Figure 1. Bioactive bridged DKPs and piperazines.



Scheme 1. Known polar approaches to the bridged DKP core of **2** and a new radical approach based on the persistent radical effect (PRE).

Radical cyclizations using traditional methods have only been reported in the context of total syntheses of alkaloids containing the diazabicyclo[2.2.2]octane core by the Myers,[10] Trost,[11] and Simpkins groups.[6c–e] An oxidative enolate coupling was used by Baran and co-workers to achieve the total synthesis of **1**.[12]

Radical approaches to alkaloids such as **2** and **3** and unnatural bridged DKPs with longer bridges are absent in the literature. This is not surprising, since the inherently short life

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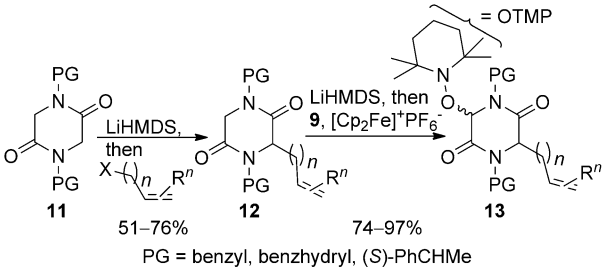
times of the generated radical species do not favor cyclization to medium-sized bridged ring systems under conventional conditions. Premature radical coupling reactions, radical quenching by hydrogen atom abstraction from solvent molecules or reaction mediators such as metal hydrides, and intramolecular 1,*n*-H transfer processes often outcompete the slow cyclization step.

We hypothesized that application of the persistent radical effect (PRE) would be an attractive atom-economic solution to these shortcomings.[13] This powerful principle governs the selective cross-coupling of two different radical species that are produced at equal rates, where one is transient and the other persistent. Although the utility of the PRE was recognized from the onset in polymer research, its application in organic chemistry was neglected until Studer's seminal studies a decade ago.[14,15] The first application of the PRE as a key step in total synthesis was only recently reported by Theodorakis and co-workers, who used a 5-*exo*-trig cyclization toward fusarisetin A.[16]

Given the importance of bridged DKPs and the recent growth of interest in three-dimensional heterocyclic architectures in medicinal chemistry,[1,17] methods that allow rapid access to diverse bridged DKP motives are highly desired. Herein, we present a unified, practical, general, and conceptually new radical approach to diverse bridged DKPs. Central is the facile and reversible thermal bond homolysis of hitherto unknown alkoxyamines **8** to generate captodatively stabilized transient DKP radicals **10** and the persistent radical TEMPO (**9**; Scheme 1).[18] This degenerative process confers a sufficiently long lifetime for radical **10** to undergo irreversible *endo* or *exo* cyclizations to pendant alkene units depending on the tether length and substitution pattern, thereby steering the equilibrium to the bridged DKP products.

To test these hypotheses, several alkoxyamines **13** were synthesized through alkylation of DKPs **11** followed by oxidative enolate oxyamination in good to high overall yields (Scheme 2).[19] Products **13** were isolated as 1:1 to 1:10 *cis*/*trans* diastereomeric mixtures or as single *trans* isomers (see the Supporting Information for details).

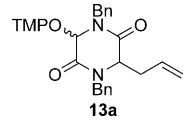
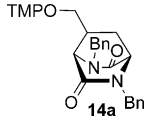
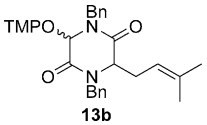
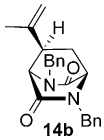
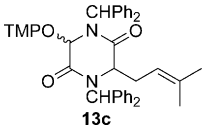
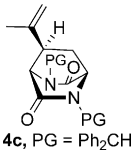
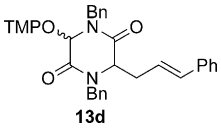
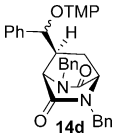
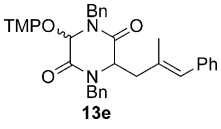
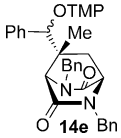
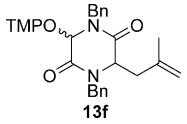
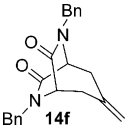
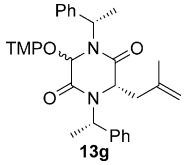
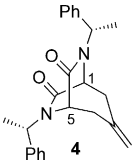
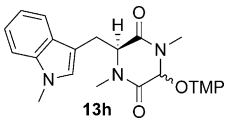
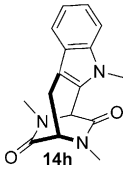
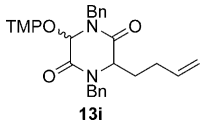
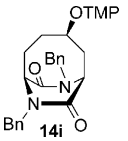


Scheme 2. Synthesis of DKP alkoxyamines **13**.

Alkoxyamines **13** are stable to chromatography and can be stored at room temperature and in daylight for at least a year when they are purified and properly dried. They are often crystalline, which allows confirmation of their structures by X-ray crystallography (Figure 2).

Heating solutions of alkoxyamines **13a–e**, which bear terminal 1,2-di- or trisubstituted olefinic acceptors, in degassed *t*BuOH at 130 °C in a sealed tube for 1.5–2 h afforded diazabicyclo[2.2.2]octan-3,6-diones **14a–e** resulting from 6-*exo*-trig cyclization in high yields (Table 1, entries 1–5).[20] The diastereoselectivity was low with *N*-benzyl groups, but was significantly improved when using the more bulky *N*-benzhydryl group (entry 3). Substrates **13f,g**, which contain

Table 1: Synthesis of diverse diazabicyclo[n.2.2]alkanediones **14a–i** from alkoxyamines **13a–i**.[a]

Entry	13	14[b]	Yield [%][c] (d.r.)[d]
1	 **13a**	 **14a**	79 (1:1)[e]
2	 **13b**	 **14b**	88 (2:1)
3	 **13c**	 **14c**, PG = Ph_2CH	97 (5.6:1)
4	 **13d**	 **14d**	97[f]
5	 **13e**	 **14e**	92[g]
6	 **13f**	 **14f**	96
7	 **13g**	 **4**	89 (4.6:1)[h]
8	 **13h**	 **14h**	72[i]
9	 **13i**	 **14i**	94 (3.3:1)

[a] General conditions: 0.02 M **13** in *t*BuOH, 130 °C, 1.5–2 h. [b] Only the major diastereomer is shown. [c] Yield of isolated product. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] Additionally, 10% of the 7-*endo*-trig cyclization product was isolated (see the Supporting information). [f] Overall ratio 3.4:2:2:1.[20] [g] The ratio at the exocyclic stereocenter could not be determined.[20] [h] (1*S*,5*S*)/(1*R*,5*R*) (see Supporting information for details). [i] At 170 °C. Bn = benzyl.

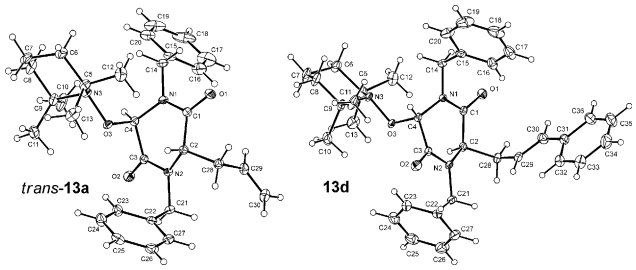


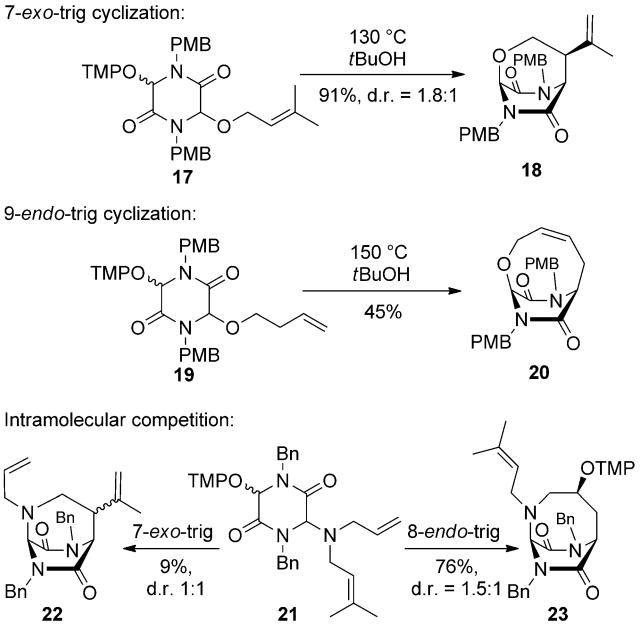
Figure 2. X-ray structures of alkoxyamines *trans*-**13a** and **13d**.

1,1-disubstituted alkene units, selectively provided the 7-*endo* cyclization product **14f** or the α-glucosidase inhibitor **4** (entries 6, 7). The radical cyclization can also be performed asymmetrically by using the 1-phenylethyl auxiliary or the enantiomerically pure substrate **13h** (entries 7, 8). Compound **13h**, which has an indole substituent, also reacted exclusively through 7-*endo*-trig cyclization to give diazabicyclo-[3.2.2]nonane **14h** (entry 8). However, an analogous substrate with a simple phenyl ring did not cyclize. Replacement of the allyl by a homoallyl unit in **13i** surprisingly resulted in an efficient and exclusive 8-*endo*-trig cyclization to provide the four-carbon-atom-bridged DKP **14i** in high yield with pronounced diastereoselectivity (entry 9).

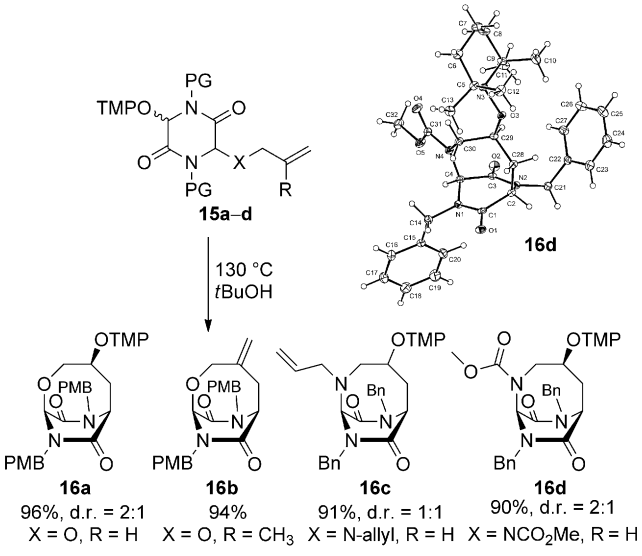
Cyclizations leading to primary and secondary radicals predictably gave the oxygenated products **14a**,**d**,**e**,**i**, whereas those generating tertiary radicals furnished the bridged DKPs **4** and **14b**,**c**,**f**,**h**, which bear alkene units because of TEMPOH elimination. The configurations of the products **14** were determined on the basis of ROESY spectra (see the Supporting Information).

The ease of the 8-*endo*-trig cyclization[21] of **13i** immediately called for the testing of heteroatom-bearing cyclization substrates **15**, which were easily accessible (Scheme 3, see the Supporting Information). Alkoxyamines **15a** and **15b**, which bear allyloxy and methallyloxy groups, performed well in thermal radical 8-*endo* cyclizations to give the oxa-DKPs **16a** and **16b**, the latter of which again has an *exo* methylene group. Their aza analogues **16c** and **16d**, which resemble the bridged core of cottoquinazoline D (**3**), were also very efficiently prepared. The structure of the major diastereomer of the carbamate-protected N-bridged DKP **16d** was confirmed by X-ray crystallography. To our knowledge, syntheses of such medium-sized bridged ring systems by using radical cyclization approaches have so far not been reported.

Other cyclization modes also worked well (Scheme 4). Precursor **17**, which bears a prenyloxy group, furnished the oxadiazabicyclo[3.2.2]nonanedione **18** through an efficient



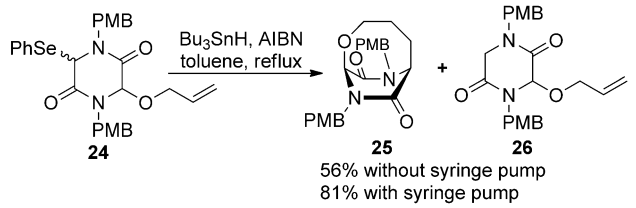
Scheme 4. Diverse cyclization modes with alkoxyamines **17**, **19**, and **21**.



Scheme 3. 8-*endo*-trig cyclizations to give heteroatom-bridged DKPs **16** and an X-ray structure of **16d**.

and clean 7-*exo*-trig cyclization. Substrate **19**, which bears a homoallyloxy group, underwent a 9-*endo* cyclization at 150 °C to give DKP **20**, which has a five-atom bridge, in moderate yield.[22] Notably, the product did not contain the TEMPO fragment, which is unusual, since secondary alkoxyamines usually do not undergo homolysis at this temperature. Strong transannular strain in the 9-membered bridged system might be the reason for the facile TEMPOH elimination in this case. Alkoxyamine **21**, which bears both allyl and prenyl groups, was designed as a probe molecule to study the direct competition between the 7-*exo* and 8-*endo* cyclization modes. A 8.4:1 ratio of the 8-*endo*/7-*exo* cyclization products **23** and **22**, based on the yield of isolated products (9:1 by crude NMR measurement), speaks for the importance of strain in the transition state, which is more pronounced for the 7-*exo*-trig cyclization pathway.

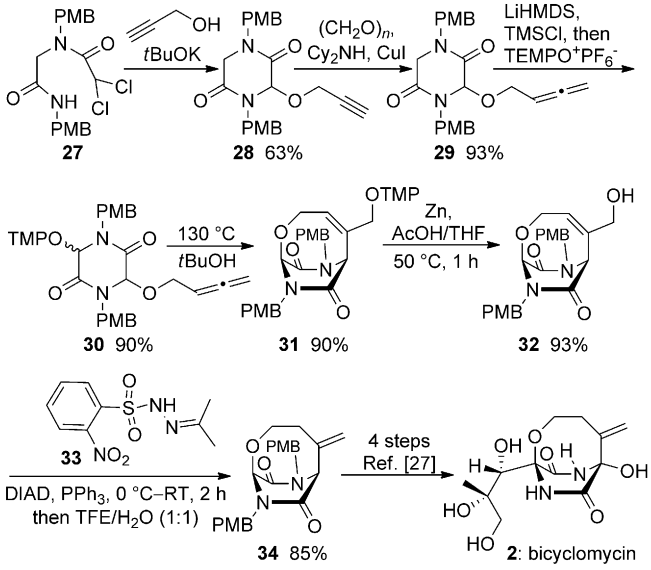
For direct comparison, the 8-*endo*-trig cyclization of unstable phenylselenide **24** was studied under conventional tributyltin hydride mediated conditions (Scheme 5). The desired cyclization product **25** was obtained in only 56%



Scheme 5. Conventional 8-*endo*-trig cyclizations.

yield under mix-and-heat conditions, together with 40% of the premature radical reduction product **26**. Slow addition of Bu_3SnH by syringe pump was necessary to increase the yield of the desired cyclization product **25** to 81%. These results clearly demonstrate the advantage of our method, which is simple to perform, tin-free, and atom-economic, since it retains the alkoxyamine functionality in the product.

Finally, the method was applied to the formal total synthesis of the antibiotic bicyclomycin (**2**; Scheme 6). To accomplish this, a precursor with a so far unused allene group as the radical acceptor was designed. The required alkoxyamine **30** was obtained in three steps from known dichloroacetamide **27**[7a] through oxygenative cyclization to give **28** under basic conditions, Crabbe homologation[23] to give **29**, and enolate oxygenation under internal quench conditions.[24] The key radical cycloisomerization took place very efficiently to provide the bridged DKP **31**, which has an internal double bond.[25] Reductive removal of the tetramethylpiperidinyl unit with zinc in acetic acid afforded allylic alcohol **32**. It is important to mention that the sensitive hemiaminal functionality at the bridgehead position survived the acidic and reductive conditions. A reductive transposition of the internal double bond to the *exo* position under the conditions developed by Movassaghi and Ahmad[26] furnished Williams' central intermediate **34** in 6 steps and 38% overall yield. Compound **34** was previously converted to bicyclomycin in four steps by Williams and co-workers.[27]



Scheme 6. Formal synthesis of bicyclomycin (**2**).

In conclusion, we have developed a conceptually new approach to diverse bridged diketopiperazines by introducing a novel class of amino acid derived alkoxyamines as radical surrogates and taking advantage of an inherently atom-economic cyclization that makes use of the PRE. This method provides efficient and practical access to diverse medium-ring bridged DKPs. Importantly, the reaction times are short compared to previously reported simple cyclizations,[15] which can be attributed to facile homolysis of the C–O bond to give captodatively stabilized DKP radicals. The excellent potential of the methodology was demonstrated in a formal total synthesis of the antibiotic bicyclomycin. Applications of this methodology to total syntheses of diverse alkaloid classes are ongoing.

Acknowledgements

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Keywords: alkaloids · bicyclomycin · bridged diketopiperazines · cyclization · radicals

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