ACS Combinatorial Science

Research Article

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Photoassisted Access to Enantiopure Conformationally Locked Ribofuranosylamines Spiro-Linked to Oxazolidino-Diketopiperazines.

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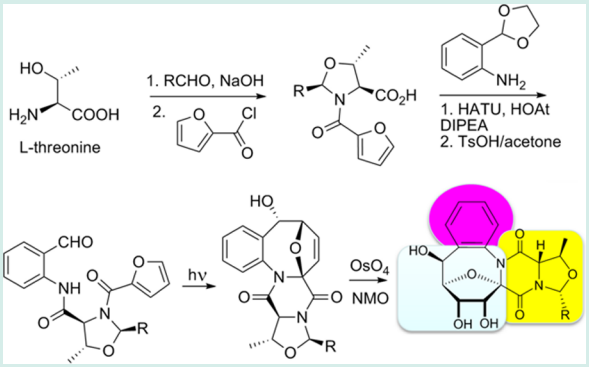
Supporting Information

ABSTRACT: N-Furoylated L-threonine-, serine-, or cysteine-based aminoacetals are coupled with *o*-aminoketones or aldehydes to offer rapid access to diverse enantiopure polyheterocycles possessing conformationally locked aminoglycoside-containing molecular scaffolds. The key step involves photogeneration of azaxylylenes which undergo [4 + 4] or [4 + 2] cycloadditions to the tethered furoyl pendants.



KEYWORDS: *conformationally locked ribofuranosylamines, enantiopure polyheterocycles, molecular scaffolds, photogeneration of azaxylylenes, [4 + 2] and [4 + 4] photocycloadditions*

INTRODUCTION

Conformational flexibility of potential therapeutic agents has always been one of the critical properties in drug design and discovery. The relationship between the promiscuity of binding due to a large number of rotatable bonds and the associated entropic penalty attenuating the relevant K_D's is generally well understood and taken into consideration when modeling molecular recognition events.[1] Even the properties such as oral bioavailability of drug candidates, which normally are not associated with conformational flexibility, in fact correlate strongly with the number of rotatable bonds.[2] Smythe and coauthors of a review[3] prominently referenced on the NCI's Screening Services Web site *Selection guidelines for small molecule structures for screening*[4] believe that "bicyclic and tricyclic scaffolds are ... an ideal size for library synthesis" because "they provide molecular rigidity allowing less entropic energy to be lost upon binding and also provide better bioavailability".

Thus, synthetic methods to access new relatively rigid and diverse poly(hetero)cyclic core scaffolds decorated with biorelevant functional groups are always sought after. We have been developing[5] such methods for diversity-oriented synthesis based on a synthetic paradigm which involves modular synthesis of photochemical precursors and their subsequent photoassisted transformations, for example, intramolecular [4 + 4] or [4 + 2] cycloadditions. Modular assembly of photoprecursors renders this methodology suitable for combinatorial chemistry, while the photochemical step allows for a dramatic increase in molecular complexity, generally not available for chemical transformations in the ground state.

Earlier we found that short-lived azaxylylenes, generated via the excited state intramolecular proton transfer (ESIPT[6]) in aromatic *o*-aminoketones and aldehydes, undergo intramolecular cycloaddition reactions with the appropriately tethered unsaturated pendants, including alkenes, thiophenes, and furans.[7]

In this paper we report on a new photoassisted synthesis of enantiopure conformationally locked ribofuranosylamines possessing a spiro-diketopiperazine moiety which are derived from a straightforward modular preassembly of N-furoylated L-threonine, serine, or cysteine-based aminoacetals **1a**–**f**[8] with photoactive *o*-aminoketones and aldehydes.

RESULTS AND DISCUSSION

As shown in Figure 1 such preassembly of the furan-bearing azadienophiles requires three components, the *β*–OH or SH amino acid, an aldehyde, and furoyl chloride, which in the combinatorial context constitute three diversity inputs. The acetal formation is stereospecific. X-ray structure of oxaproline **1c**, based on threonine and pivalic aldehyde, reveals that the *tert*-butyl group is *cis* to the carboxylate (and *trans* to the methyl).

These furan-containing azadienophile modules, outfitted with the carboxylate *handle*, are readily coupled with the photoactive *o*-aminoketone pendants via the well-developed amide bond-forming chemistry as shown in Figure 2.

Received: October 27, 2012
Revised: November 6, 2012
Published: November 19, 2012

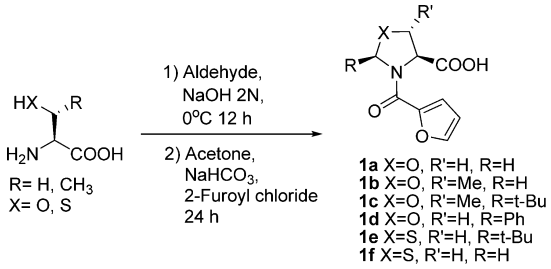


Figure 1. Preassembly of the azadienophile furoyl pendant with oxa- or thioproline tether from three components (i) β-XH aminoacid, (ii) aldehyde R′CHO, and (iii) 2-furoyl chloride.

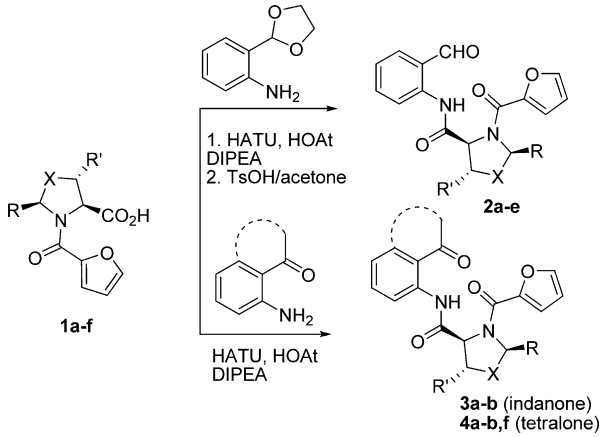
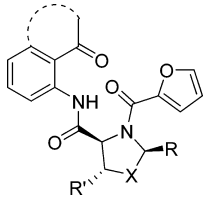


Figure 2. Coupling of furoyl azadienophiles with the photoactive aminoketone moiety.

o-Aminobenzaldehyde was protected as a cyclic acetal before coupling.

Table 1 gives the matrix of photoprecursors which were synthesized to probe the generality of photoinduced cyclization reactions of azaxylylenes tethered to the furan moiety via a substituted thia- or oxaproline linker, Table 2.

Table 1. Matrix of Photoprecursors Assembled in This Study with *o*-Aminobenzaldehyde and *o*-Amino Ketones, Indanone, and Tetralone



	serine (X=O, R′=H)	threonine (X=O, R′=Me)	cysteine (X=S, R′=H)
benzaldehyde	**2a**, R=H **2d**, R=Ph	**2b**, R=H **2c**, R=*t*-Bu	**2e**, R=*t*-Bu
indanone	**3a**, R=H	**3b**, R=H	
tetralone	**4a**, R=H	**4b**, R=H	**4f**, R=H

Precursors **2**−**4** were all found to be photoactive. Upon irradiation with an in-house built UV LED illuminator (five 365 nm Nichia LEDs @ 250mW each) in acetonitrile in the presence of HMPA, they underwent photoinduced cycloaddition yielding enantiopure polyheterocycles **5**−**11**.

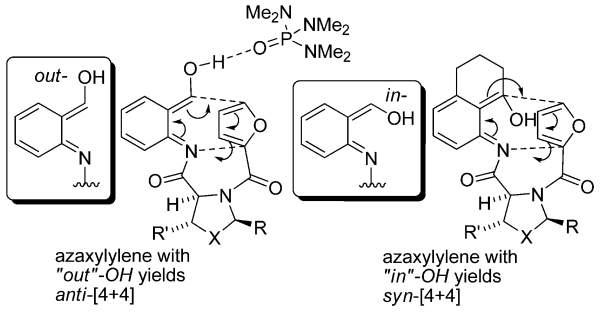


Figure 3. Stereochemistry of the OH group in photoproducts **5**−**11** depends on whether the initial carbonyl is rotatable.

The benzaldehyde-based precursors yielded [4 + 4] cycloadducts as major products, whereas the indanone- and tetralone-based precursors **3**−**4** predominantly gave the [4 + 2] products, with the exception of the tetralone-based thiaproline **4f** which did not require addition of HMPA and gave 11:1 ratio of [4 + 4] to [4 + 2] products. These results show that the variations in the structure of the starting materials and the presence of HMPA additive affect the regiochemistry, that is, the [4 + 4] to [4 + 2] ratio, of this photoinduced transformation.

One aspect of the stereochemical outcome is the stereochemistry of the OH group, which can be either *syn* or *anti* to dihydrofuran's oxygen. In the presence of HMPA the benzaldehyde-based *anti*-[4 + 4] cycloadducts **5** were formed with high selectivity—the *syn* stereoisomers were not detected at all in the NMR of reaction mixture. The minor [4 + 2] dihydroquinolinoles **6** (*anti*) and **7** (*syn*) were both observed in the reaction, albeit in low amounts, 5−10%. In contrast, photoprecursors **3** and **4** based on cyclic ketones produced only *anti*-[4 + 2] and *syn*-[4 + 4] adducts. The OH-epimers, *syn*-[4 + 2] or *anti*-[4 + 4] were not observed.

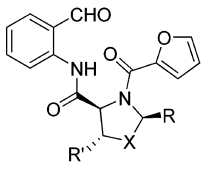
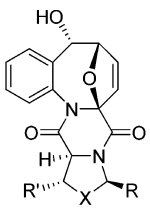
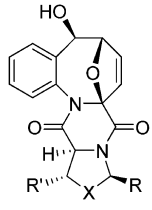
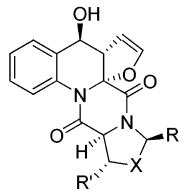
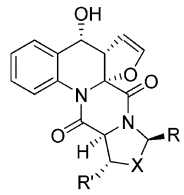
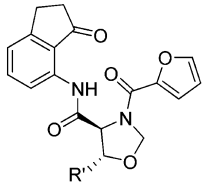
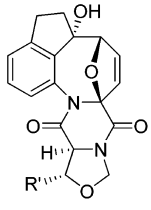
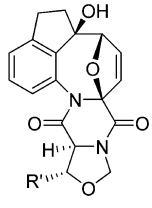
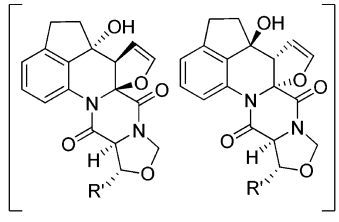
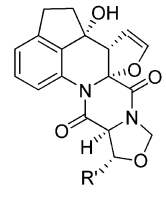
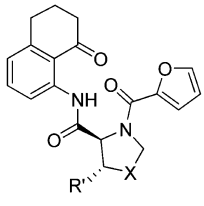
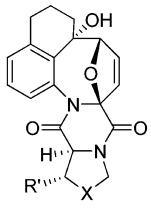
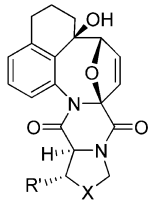
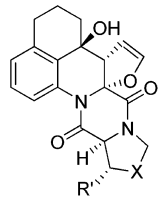
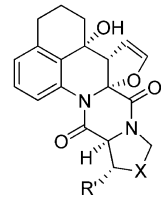
Our rationale is that in all cases the *endo* transition state is involved, with the furan's π-system hovering over the aromatic moiety of azaxylylene (biased by the secondary π-overlap). Figure 3 illustrates that the resulting stereochemistry of the hydroxy group thus depends on whether it is "*out*" or "*in*" in the photogenerated azaxylylene. The addition of HMPA is expected to increase the lifetime of azaxylylenes because of hydrogen bonding,[9] preventing wasteful back proton transfer. In azaxylylenes derived from benzaldehydes, the bulky HMPA ensures the *out* configuration of the rotatable OH, which yields the *anti*-[4 + 4] adducts. Such rotation is not possible in indanone or tetralone and precursors **3**,**4** yield only the *syn*-[4 + 4] products.

The second stereochemical aspect of these reactions is the folding of the chiral oxa/thiaproline tether which, depending on the furoyl approach from "above" or from "under", can produce two diastereomeric cores. We classify the two by their epimeric aminoacetal carbons. In most of the cases studied this aminal carbon has the *S* configuration for the [4 + 4] and *R* configuration for the [4 + 2] products, as shown in Table 2.

However, in the case of indanones **3** the diastereomers possessing the *S* configuration of the aminal carbon in [4 + 2] cycloadducts **8a** and **8b** were the major products. In fact, diastereomer **8b** with an "inverted" tether fold was the sole product isolated from **3b**. Its structure was proven by X-ray crystallographic analysis, and the structures of **8a** and **9a** were inferred based on the analysis of their NMR spectra relative to **8b**.

dx.doi.org/10.1021/co3001296 | *ACS Comb. Sci.* 2013, 15, 73−76

Table 2. Enantiopure [4 + 4] and [4 + 2] Products Resulting from the Intramolecular Cycloadditions of Photogenerated Azaxylylenes[a]

Photo precursor	[4+4] *anti*-OH	[4+4] *syn*-OH	[4+2] *anti*-OH	[4+2] *syn*-OH
				
2a X=O, R'=H, R=H	**5a** 57% (xray)	-	-	-
2b X=O, R'=Me, R=H	**5b** 63%	-	-	-
2c X=O, R'=Me, R=t-Bu	**5c** 68% (xray)	-	**6c** 5%	**7c**[b]
2d X=O, R'=H, R=Ph	**5d**[c] (xray)	-	-	**7d** 7% (xray)
2e X=S, R'=H, R=t-Bu	**5e** 66% (xray)	-	**6e** 9%	**7e**[b]
				
3a R'=H	-	-	**8a** 37%[d]	**9a** 13%[d]	-
3b R'=Me	-	-	**8b** 40% (xray)	-	-
				
4a X=O, R'=H	-	**10a**[e]	**11a** 43%	-
4b X=O, R'=Me	-	**10b** 13% (xray)	**11b** 57%	-
4f X=S, R'=H	-	**10f** 67% (xray)	**11f**[e]	-

[a]Isolated yields, after column chromatography. [b]The minor *syn*-[4 + 2] was detected in the reaction mixture but not isolated. [c]The major product in the reaction mixture (>80% by NMR), mostly degraded during chromatographic purification, although enough was collected to crystallize and obtain X-ray structure. [d]Stereoisomers are tentatively assigned by NMR. [e]Observed as a minor product in the reaction mixture, not isolated.

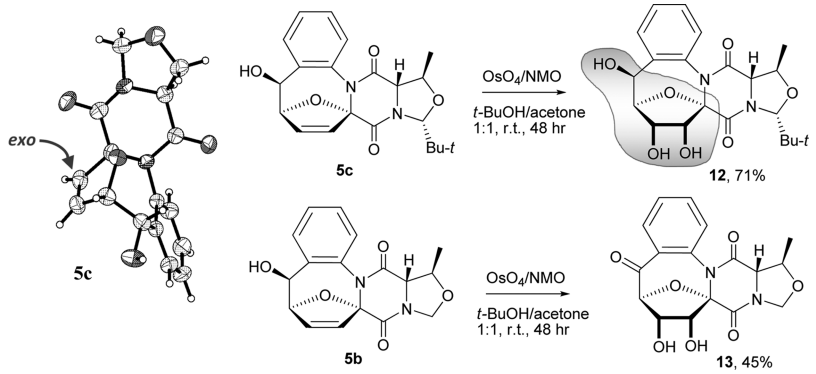


Figure 4. *exo-cis*-Dihydroxylation of double bonds in **5c** and **5b**; shown at left is the ORTEP drawing of X-ray structure of **5c** illustrating the exo approach.

The [4 + 4] cycloadducts possess a 2,5-dihydrofuran moiety, which lends itself to dihydroxylation from the *exo*-face. Inspection of the X-ray structure of the benzaldehyde-based *anti*-[4 + 4] cycloadduct **5c** indicates that the *exo*-approach is less sterically hindered. We proceeded to dihydroxylate it using OsO_4 and N-methylmorpholine oxide (NMO) as shown in Figure 4.

Dihydroxylation was carried out at ambient temperature in wet 1:1 *t*-butanol/acetone and required extended time (48 h) for completion. Under these conditions dihydrofuran **5b** undergoes further oxidation of its benzylic hydroxy group to yield ketone **13**. In both cases the reaction yielded a single stereoisomer for which we assigned the *exo*-configuration of the two hydroxy groups based on their NMR spectra. The

dx.doi.org/10.1021/co3001296 | *ACS Comb. Sci.* 2013, 15, 73−76

experimental data were augmented with density functional theory (DFT) NMR calculations: the Fermi contact terms were computed and scaled by 0.9155 as described by Bally and Rablen,[10] (see Supporting Information).

The characteristic spin−spin coupling constant between the bridgehead proton and the adjacent CH−OH of the newly introduced *exo*-hydroxy group is calculated to be 0.3 Hz in **12** (J_{exp} < 0.5 Hz). For the *endo*-isomer (not observed) this constant is predicted to be much larger, 6.7 Hz. The same criterion is used for the stereochemical assignment of ketone **13**, where the calculated bridgehead to CH−OH coupling follows similar trend (0.4 Hz for the bridgehead proton's coupling with CH-*exo*-OH, and much larger, 8.0 Hz for the CH-*endo*-OH).

CONCLUSION

In conclusion, azaxylylenes photogenerated from modular photoprecursors **2**−**4** undergo intramolecular [4 + 4] or [4 + 2] cycloadditions with considerable selectivity, both in the folding of the chiral tether (to produce a single stereoisomer of the polyheterocyclic core) and in the diastereoselectivity of the resulting benzylic alcohol. The [4 + 4] photoadducts, possessing benzoazacane core, can be further *cis*-dihydroxylated with OsO_4/NMO to give novel enantiopure conformationally locked ribofuranosylamines spiro-connected to diketopiperazines.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and computational details (76 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

Support of this research by the NIH (GM-093930) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Erickson, J. A.; Jalaie, M.; Robertson, D. H.; Lewis, R. A.; Vieth, M. Lessons in Molecular Recognition: The Effects of Ligand and Protein Flexibility on Molecular Docking Accuracy. *J. Med. Chem.* **2004**, *47*, 45−55.

(2) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45*, 2615−2623.

(3) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chem. Rev.* **2003**, *103*, 893−930.

(4) http://dtp.nci.nih.gov/docs/misc/common_files/guidelines.html.

(5) (a) Valiulin, R. A.; Arisco, T. M.; Kutateladze, A. G. Double-tandem [4π+2π]-[2π+2π]-[4π+2π]-[2π+2π] Synthetic Sequence with Photoprotolytic Oxametathesis and Photoepoxidation in the Chromone Series. *J. Org. Chem.* **2011**, *76*, 1319−1332. (b) Valiulin, R. A.; Arisco, T. M.; Kutateladze, A. G. Strained to the Limit: When a Cyclobutyl Moiety Becomes a Thermodynamic Sink in a Protolytic Ring Opening of Photogenerated Oxetanes. *Org. Lett.* **2010**, *12*, 3398−3401. (c) Valiulin, R. A.; Kutateladze, A. G. First Example of Intramolecular [2π+2π] Alkene-Arene Photocyclization in the Chromone Series and its Synthetic Utility. *Tetrahedron Lett.* **2010**, *51*, 3803−3806. (d) Valiulin, R. A.; Kutateladze, A. G. Harvesting the Strain Installed by a Paternò-Büchi Step in a Synthetically Useful Way: High Yielding Photo-Protolytic Oxametathesis in Polycyclic Systems. *Org. Lett.* **2009**, *11*, 3886−3889.

(6) See Schmidtke, S.; Underwood, D. F.; Blank, D. A. Probing Excited-State Dynamics and Intramolecular Proton Transfer in 1-Acylaminoanthraquinones via the Intermolecular Solvent Response. *J. Phys. Chem. A* **2005**, *109*, 7033−7045 , and references therein.

(7) Mukhina, O. A.; Kumar, N. N. B.; Arisco, T. M.; Valiulin, R. A.; Metzel, G. A.; Kutateladze, A. G. Rapid Photoassisted Access to N,O,S-Polyheterocycles with Benzoazocine and Hydroquinoline Cores via Intramolecular Cycloadditions of Photogenerated Azaxylylenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 9423−9428.

(8) Aminoacetals **1a-e** were synthesized using a modified procedure from: Conti, S.; Cossu, S.; Giacomelli, G.; Falorni, M. Chiral ligands containing heteroatoms:13. Optically active 4-(2′-pyridyl)-1,3-oxazolidines: An improved synthesis of 2-(2′-pyridyl)-2-aminoalcohols. *Tetrahedron* **1994**, *50*, 13493−13500.

(9) By analogy to the reported effect of HMPA on lifetimes of all-carbon xylylenes: Haag, R.; Wirz, J.; Wagner, P. J. The Photoenolization of 2-Methylacetophenone and Related Compounds. *Helv. Chim. Acta* **1977**, *60*, 2595−2607.

(10) Bally, T.; Rablen, P. A. Quantum-Chemical Simulation of 1H NMR Spectra. 2. Comparison of DFT-Based Procedures for Computing Proton−Proton Coupling Constants in Organic Molecules. *J. Org. Chem.* **2011**, *76*, 4818−4830.