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 \(\alpha\)-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 NCT’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 \(\alpha\)-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 with photoactive \(\alpha\)-aminoketones and aldehydes.

RESULTS AND DISCUSSION

As shown in Figure 1 such preassembly of the furan-bearing azadienophiles requires three components, the \(\beta\)-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 \(\alpha\)-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

dx.doi.org/10.1021/co3001296 | ACS Comb. Sci. 2013, 15, 73–76
Preassembly of the azadienophile furoyl pendant with oxo- or thioproline linker 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—syn stereoisomers were not detected at all in the NMR of reaction mixture. The minor [4 + 2] dihydroquinolinones 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 s-system hovering over the aromatic moiety of azaxylylene (biased by the secondary s-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, preventing wasteful back proton transfer. In azaxylylenes derived from benzaldehydes, the bulky HMPA ether increases the lifetime of azaxylylene. The addition of HMPA is expected to increase the lifetime of azaxylylenes because of hydrogen bonding, preventing wasteful back proton transfer. In azaxylylenes derived from benzaldehydes, the bulky HMPA ether increases the lifetime of azaxylylene.

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 thioproline 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.

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.
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 OsO₄ 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

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

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<tr>
<td>2a X=O, R'=H, R=H</td>
<td>5a 57% (xray)</td>
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<td>2b X=O, R'=Me, R=H</td>
<td>5b 63%</td>
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<td>2c X=O, R'=Me, R=t-Bu</td>
<td>5c 68% (xray)</td>
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<tr>
<td>2d X=O, R'=H, R=Ph</td>
<td>5d (xray)</td>
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<tr>
<td>2e X=S, R'=H, R=t-Bu</td>
<td>5e 66% (xray)</td>
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<td>3a R'=H</td>
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<td>4b X=O, R'=Me</td>
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<td>6d 7% (xray)</td>
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<td>7a 13%</td>
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"Isolated yields, after column chromatography. The minor syn-[4 + 2] was detected in the reaction mixture but not isolated. 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. Stereoisomers are tentatively assigned by NMR. Observed as a minor product in the reaction mixture, not isolated."
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 (Jexp < 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 OsO4/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