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Photoreductive β -aminoalkylation with amino acids affords functionalized γ -aminoketones for nucleoside mimics†

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We developed a facile photoreductive and stereoselective β -aminoalkylation of a crowded enone by blue LED light irradiation using a wide variety of α -amino acids in order to access 5'-amino substituted carbasugar nucleosides for SAM-based methyltransferase inhibitors. This photochemical method provides highly functionalized carbasugar mimics for nucleoside analogue synthesis.

S-Adenosyl methionine (SAM) is the second most abundant cosubstrate in the human body. It is the major methyl-donor reagent for essential methylation reactions.¹ The methyl group is transferred by methyltransferases which exhibit their catalytic activity in a multitude of biological substrates *e.g.* DNA, RNA, neurotransmitters, and proteins.² As such methyltransferases play a pivotal role in many biological processes they were recognized as interesting and promising drug targets. Over the past decades the FDA approved several methyltransferase-inhibitors³ *e.g.* azacytidine (2005)⁴ and tazemetostat (2020).⁵ Moreover, the PRMT5-inhibitor onametostat and the DOT1L inhibitor pinometostat are clinical candidates.⁶ This shows the significant therapeutic potential of methyltransferase inhibitors.⁷ Moreover, 5'-substituted carbocyclic nucleosides received much attention in the development of new antitumor and antiviral therapeutic agents.⁸ For instance, the natural occurring carbocyclic nucleosides (–)-aristeromycin and (–)-neplanocin A led to the design of the antiviral agents carbavir and abacavir.⁹ In addition, carbocyclic nucleosides such as 8-azapurine carbocyclic hydrazones¹⁰ and fluorocyclopentenyl cytosines¹¹ have anticancer activity.^{12,13}

In this regard, SAM-derived nucleosides represent a promising scaffold. Hence, an efficient synthetic pathway is desirable as the current synthesis for functionalized 5'-amino substituted

carbasugar nucleosides involves multistep synthesis.^{6,14,15} Within this work, we report an innovative and highly efficient 5-step synthesis approach for the design of 5'-substituted carbasugar nucleoside analogues. This approach is amenable to diverse alterations towards promising biological active compounds, *e.g.* the DOT1L inhibitor pinometostat⁶ or its recent derived analogue MU1656 (Fig. 1).⁶ Carbasugar nucleosides were chosen due to their higher lipophilicity and metabolic stability as compared to the natural ribose.⁸

Akita and co-worker as well as Ronghua and co-workers showed the successful photochemical addition of organoborates and α -amino acids to cyclopentenone with a yield of up to 54%, respectively.^{16,17} Using chiral Lewis acids as a catalyst, Yoon and colleagues were able to demonstrate the effective efficient enantioselective addition of photogenerated α -amino radicals to Michael acceptors¹⁸ while our approach was substrate induced diastereoselectivity (Scheme 1).

We herein describe the highly efficient photochemical redox reaction between various α -amino acids and an α - β -unsaturated carbasugar mimic driven by blue LED light leading to Boc-protected primary amines. These intermediates can serve for further applications such as the design of 5'-amino carbasugar nucleosides. First Boc-protected glycine was tested in the presence of 3 mol% of the photocatalyst Ir[dF(CF₃)ppy]₂(dtbpy)PF₆, KH₂PO₄ in DMF at rt under blue LED light irradiation (*via* a 40W A160WE Tuna Blue lamp from Kessil).¹⁹ In this case we achieved the desired coupling product with high efficiency (example **3a**, yield 93%), while switching to

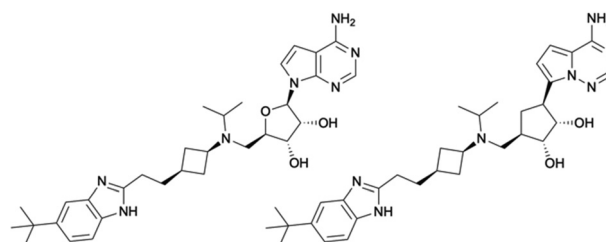


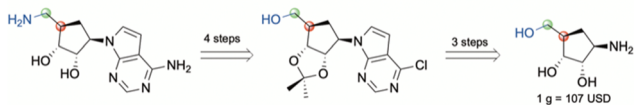
Fig. 1 Structures of the DOT1L-inhibitors pinometostat and MU1656.

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State of the art for aminomethyl nucleoside analogues

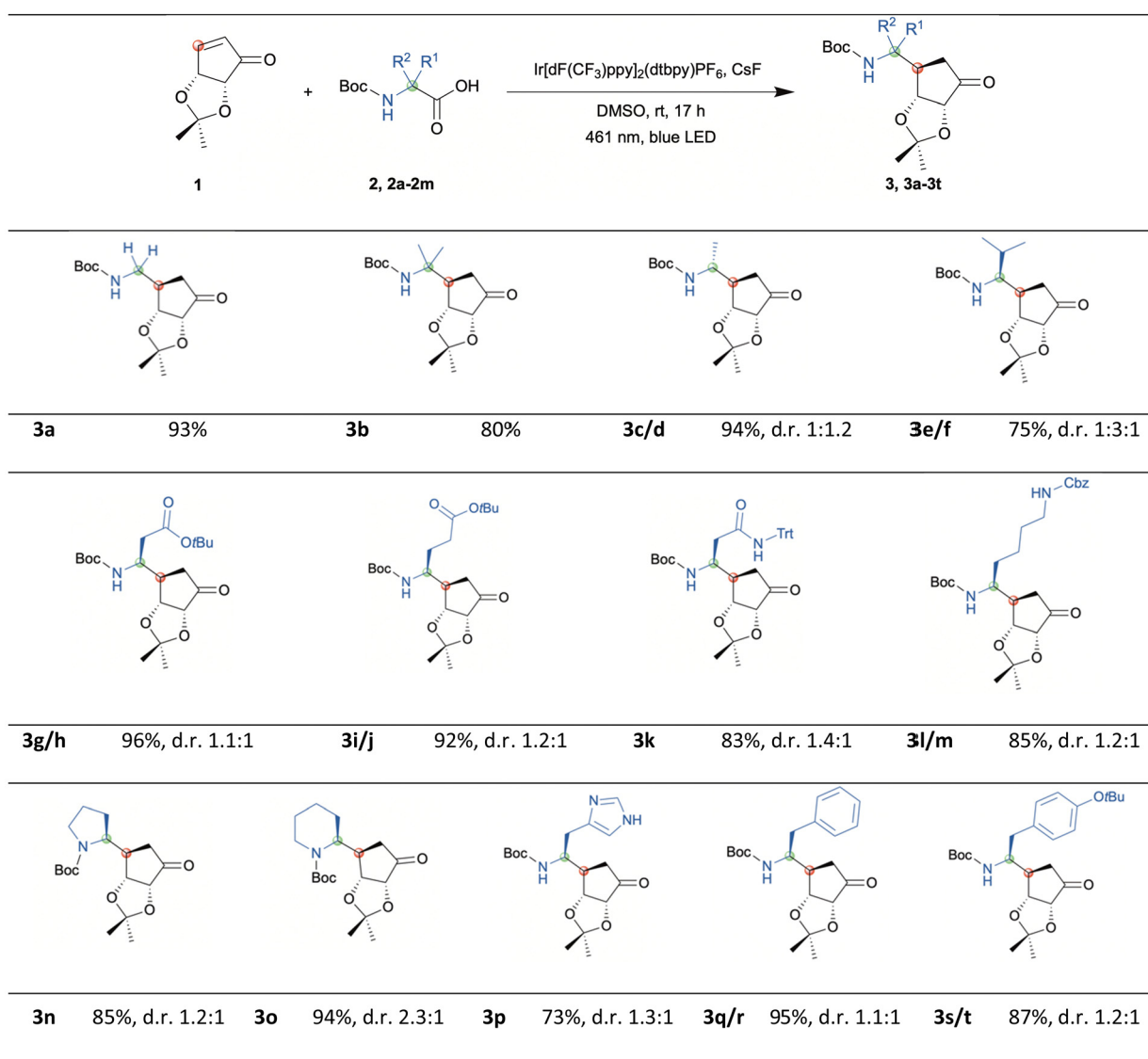


Our route, also for branched aminomethyl cyclopentanes



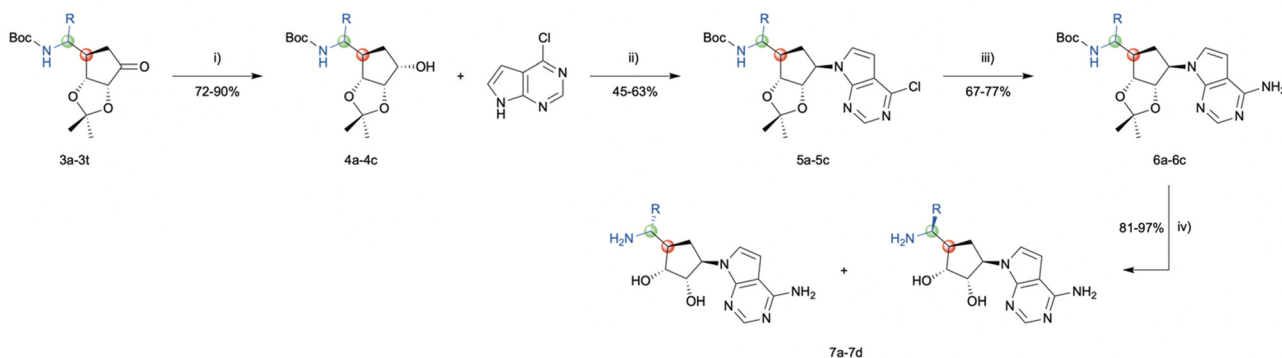
Scheme 1 State of the art for retrosynthetic analysis for nucleoside analogues which does not allow branching between amino group and cyclopentane (top). Our new route is shorter of lower cost and allows easy access to branched nucleoside analogues (bottom).

Boc-protected alanine resulted in a poor reaction efficiency where only traces could be detected presumably due to poor solubility of α -amino acids in DMF. Hence, KH_2PO_4 was exchanged to CsF and DMSO was chosen as solvent since high-dielectric solvents are required.²⁰ With this new setup the desired coupling product with Boc-Ala-OH was obtained with high yield (examples **3c** & **3d**, yield 94%). Based on the newly applied protocol, we next explored the scope of the α -amino acid component. As shown in Scheme 2 the reaction was performed for all entries at room temperature and the desired products were obtained with high yields. In addition, two negative experiments using Boc-Phe-OH were performed to rule out the possibility of a solely thermally driven reaction. For this purpose, a reaction was carried out with photocatalyst and without the use of irradiation. Another negative experiment was conducted



Scheme 2 α -Amino acid scope of photocoupled products. ^aReaction conditions: **1** (0.62–4.62 mmol, 1.00 eq.), **2, 2a–2m** (1.85–6.47 mmol, 3.00 eq.), CsF (1.85–6.47 mmol, 3.00 eq.), Ir[d(CF₃)ppy]₂(dtbbpy)PF₆ (0.02–0.04 mmol, 0.03 eq.), degassed DMSO (6.20–10.80 mL), rt (20–25 °C), under blue LED light irradiation. ^bYields are based on isolated material by column chromatography. ^cDiastereomeric ratio determined from isolated material or ¹H NMR. ^dUnder standard purification conditions the diastereomers for the examples **3c–3j**, **3l**, **3m**, and **3q–3t** could be separated.





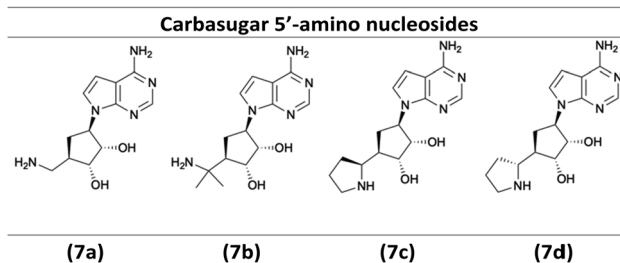
Scheme 3 Reagents and conditions: (i) NaBH₄, MeOH, 0 °C, 1 h; (ii) PPh₃, DBAD, PhMe, 0–60 °C, 17 h; (iii) NH₃, 1,4-dioxane, 100 °C, 17 h; (iv) TFA/H₂O, rt, 3 h.

with irradiation but no photocatalyst present. HPLC analysis of both trials revealed no conversion (depicted in ESI[†]).

The photocatalytic decarboxylation of α -amino acids generates radicals mediated by a single-electron transfer mechanism.¹⁶ Those α -amino radicals undergo conjugate addition on the convex side of the carbasugar mimic. Only one diastereomer was found regarding the newly formed chiral center at the carbasugar mimic. However, by this radical formation the stereocenter at the former α -amino acid site generates the product as mixture of two diastereomers except for the achiral examples **3a** & **3b** of course. For the examples **3c–3j**, **3l**, **3m**, and **3q–3t** the diastereomers were separated by flash column chromatography and the diastereomeric ratio was determined by isolated yields. Under standard conditions examples **3k** and **3n–3p** were isolated as mixtures, thus the diastereomeric ratio was determined by NMR-experiments of the purified material. With the help of 2D-NOESY experiments (shown in ESI[†]) for examples **3e** & **3f** we were able to assign the diastereomers. With these mild conditions a broad range of functional groups was accepted including esters, amides, and carbamates. The benzyl carbamate (CBz-NR₂) is tolerated as well and can be used in alternative to *tert*-butyloxycarbonyl (Boc) protected amino acids. In addition, the successful application could be demonstrated for various acyclic α -amino acids with aliphatic and aryl side chains as well as for the non-proteinogenic acyclic α -amino acid Boc-methylalanine. Moreover, excellent results were achieved for the cyclic amino acids proline and pipercolic acid. In the next step, the products were converted to nucleosides as potential starting point towards potent biologically active compounds.

As illustrated in Scheme 3, the diastereoselective reduction of compounds **3a**, **3b**, and **3n** with NaBH₄ in MeOH yielded the desired alcohols **4a–4c** (72–90%). Then, a Mitsunobu-reaction was employed to introduce the base for the target nucleoside analogues shown in Scheme 4.²¹ Aromatic substitution with ammonia in 1,4-dioxane at 100 °C afforded the products **5a–5c** with a yield of 67–75%.²² Subsequently, acidic treatment with TFA afforded the desired 5'-amino carbasugar nucleoside analogues **7a–7d** shown in Scheme 4.

In conclusion, we were able to demonstrate the first efficient and versatile photochemical decarboxylative coupling between readily available α -amino acids and a highly crowded



Scheme 4 Synthesized 5'-aminonucleosides.

enone. This mild protocol affords rapidly functionalized carbasugar mimics for the design of 5'-amino carbasugar nucleosides which can serve as a starting point towards biologically active compounds, *e.g.* for protein lysine and arginine methyltransferases.

All experimental and characterization data are available in the ESI.[†]

S. O. K.: conceptualization, investigation, methodology, writing – original draft; A. A. B.: methodology, investigation, writing – review & editing; M. J.: conceptualization, funding acquisition, supervision, writing – review & editing.

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Conflicts of interest

There are no conflicts to declare.

References

- M. Fontecave, M. Atta and E. Mulliez, *Trends Biochem. Sci.*, 2004, **29**, 243–249.
- P. A. Frey, *Chem. Rev.*, 2003, **103**, 2129–2148.
- K. Nepali and J.-P. Liou, *J. Biomed. Sci.*, 2021, **28**, 27.
- E. Kaminskis, A. T. Farrell, Y.-C. Wang, R. Sridhara and R. Pazdur, *Oncologist*, 2005, **10**, 176–182.
- A. Mullard, *Nat. Rev. Drug Discovery*, 2020, **19**, 156.



- 6 P. Khirsariya, P. Pospíšil, L. Maier, M. Boudný, M. Babáš, O. Kroutil, M. Mráz, R. Vácha and K. Paruch, *J. Med. Chem.*, 2022, **65**, 5701–5723.
- 7 R. Ferreira de Freitas, D. Ivanochko and M. Schapira, *Molecules*, 2019, **24**, 4492.
- 8 L. S. Jeong and J. A. Lee, *Antiviral Chem. Chemother.*, 2004, **15**, 235–250.
- 9 H. R. Moon, W. J. Choi, H. O. Kim and L. S. Jeong, *Tetrahedron: Asymmetry*, 2002, **13**, 1189–1193.
- 10 Y. Wang, H. Yan, C. Ma and D. Lu, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4461–4463.
- 11 W. J. Choi, H.-J. Chung, G. Chandra, A. Varughese, L. X. Zhao, H. W. Lee, A. Nayak, M. S. Majik, H. O. Kim, J.-H. Kim, Y. B. Lee, C. H. Ahn, S. K. Lee and L. S. Jeong, *J. Med. Chem.*, 2012, **55**, 4521–4525.
- 12 V. P. Rajappan and S. W. Schneller, *Bioorg. Med. Chem.*, 2003, **11**, 5199–5201.
- 13 J. A. S. Iii, R. N. Comber, R. J. Gray, R. B. Gilroy and J. A. Montgomery, *J. Med. Chem.*, 1993, **36**, 2102–2106.
- 14 R. Schüle, E. Metzger, S. Wang, M. Jung, N. Barthes, B. Breit and D. Sarraf, WO2020/058358A1, 2020.
- 15 E. J. Olhava, R. Chesworth, K. W. Kuntz, V. M. Richon, R. M. Pollock and S. R. Daigle, WO2012/075381A1, 2012.
- 16 K. Miyazawa, T. Koike and M. Akita, *Adv. Synth. Catal.*, 2014, **356**, 2749–2755.
- 17 Z. R. Shi Zhifang, *Guangdong Chem. Ind.*, 2014, **4**, 2–3.
- 18 L. Ruiz Espelt, I. S. McPherson, E. M. Wiensch and T. P. Yoon, *J. Am. Chem. Soc.*, 2015, **137**, 2452–2455.
- 19 J. C. Deforest, R. A. Samame, G. Suryan, A. Burtea and S. D. Rychnovsky, *J. Org. Chem.*, 2018, **83**, 8914–8925.
- 20 Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 5257–5260.
- 21 J. Luengo, R. A. Leal and H. Lin, WO2018/085818A1, 2018.
- 22 P. Naus, O. Caletkova, P. Konec and M. Hocek, *J. Med. Chem.*, 2014, **57**, 1097–1110.

