Department of Synthetic Medicinal Chemistry

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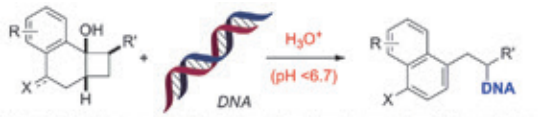
Research Projects:

Generation of new organic molecules is essential to develop new medicines and medical substances. Organic chemists can create novel organic molecules (drug candidates and nano-machines) with chemical reactions. We must think over "What molecules do we design?", "How do we synthesize them?" and "How do we analyze their actions?" Our groups aim to contribute for the life sciences through discovery of new reactions and molecular structures.

1) Development of new synthetic methodology towards rapid molecular construction: A variety of natural and non-natural substances that contain polycyclic rings and an assortment of stereogenic centers have been found to exhibit attractive and specific biological activities. Owing to this, synthetic organic chemists are constantly confronted with the task of developing new reactions that can be used to prepare these complex targets in concise fashions starting from simple and readily available materials. An innovative strategy developed for this purpose relies on the use of highly convergent domino reactions. Major advantages of these, in which multiple covalent bonds are formed in single steps, include operational simplicity, time- and cost-saving, atom economy, environmental benignancy, and applicability to diversity-oriented synthesis and combinatorial chemistry.

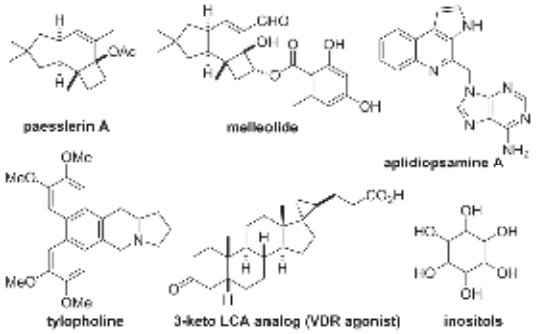
We have explored several classes of domino reactions using anionic, cationic, radical and pericylic chemistry. We recently focus on "tandem catalysis" in domino reactions, in which catalyst(s) promote more than two fundamentally different reactions in a single reactor. We have achieved rapid syntheses of structurally complex molecules including antitumor active natural products and anti-trypanosomal compounds.

2) Design and Synthesis of Artificially Useful Molecules and Materials: When we wish to design artificial biologically active molecules, it is necessary to grasp their dynamic behavior and to imagine their specific interaction with biomolecules. We are now challenging to develop original biofunctional molecules based on fine organic chemistry. Recently, we developed low-pH sensitive DNA cleaving agents based on originally developed organic reactions.

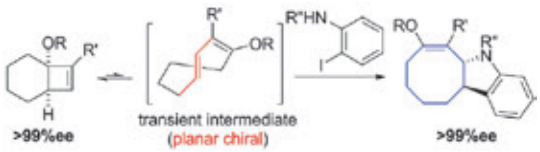


Plasmid DNAs are nicked by the molecule under weak acidic condition

3) Total Synthesis of Biologically Active Compounds: Synthesis of natural products needs comprehensive power of organic chemistry, including knowledge of a variety of organic reactions, reaction mechanism as well as structural organic chemistry. We continuously concentrate on the synthesis of natural products possessing novel chemical structure as well as potent and/or unique biological activities.



4) New Frontier of Strained Molecules: Small and medium-sized cyclic molecules show unique three-dimensional structure, unique chemical reactivity and biological activity owing to their ring strain. However, the chemistry has not been sufficiently explored. We are investigating the methodology for the synthesis of the strained molecules and molecular transformation into organic materials showing unique characters.



Recent publications

- Mogi, Y.; Inanaga, K.; Tokuyama, H.; Ihara, M.; Yamaoka, Y.; Yamada, K.; Takasu, K Rapid Assembly of Protoilludane Skeleton through Tandem Catalysis; Total Synthesis of Paesslerin A and Its Structural Revision. *Org. Lett.* **2019**, *21*, 3954–3958.
- Ogawa, N.; Yamaoka, Y.; Takikawa, H.; Tsubaki, K.; Takasu, K. Synthesis and Properties of Tribenzocarbazoles via an Acid-Promoted Retro (2+2)-Cycloaddition of Azapropellanes. *J. Org. Chem.* **2018**, *83*, 7994–8002.
- Ogawa, N.; Yamaoka, Y.; Yamada, K.; Takasu, K. Synthesis of π-Extended Fluoranthenes via a KHMDS-Promoted Anion and Radical Reaction Cascade. *Org. Lett.* **2017**, *19*, 3327–3330.
- Kuroda, Y.; Harada, S.; Oonishi, A.; Kiyama, H.; Yamaoka, Y.; Yamada, K.; Takasu, K. Use of a Catalytic Chiral Leaving Group for Asymmetric Substitutions at sp3-Hybridized Carbon Atoms: Kinetic Resolution of β-Amino Alcohols by *p*-Methoxybenzylation. *Angew. Chem. Int. Ed.* **2016**, *55*, 13137–13141.