Two topics on the synthesis of biologically important compounds will be described.

(1) Enantiodivergent Synthesis of Cyclic Amino Acids with a Tetrasubstituted Stereo-Center via Memory of Chirality

Cyclic amino acids are of increasing interest in the life-science industry. Incorporation of these compounds into peptides induces conformational constraint, and it provides an important tool for studying the relationships between peptide conformation and biological activity and for probing biological processes including protein folding. Cyclic amino acids with a tetrasubstituted stereo-center constitute a new class of non-natural amino acids with an even more constrained conformation. The lack of availability of these unusual amino acids from natural sources necessitates the development of the efficient methods for their synthesis. The simplest and ideal access to these molecules seems to involve direct intramolecular alkylation of α-amino acid derivatives. Here, enantiodivergent asymmetric cyclization of N-Boc-N-ω-bromoalkyl-α-amino acid derivatives via memory of chirality is to be discussed. With potassium hexamethyldisilazide (KHMDS) in DMF, cyclization proceeds in up to 98% ee with retention of configuration, while inversion of configuration was observed with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF in up to 91% ee. Thus, each of the enantiomers of cyclic amino acids with a tetrasubstituted stereo-center was prepared in high enantiomeric purity from readily available L-α-amino acids without the aid of external chiral sources such as chiral auxiliaries and chiral catalysts.

(2) Catalytic One-Step Process for the Chemo- and Regioselective Acylation of Carbohydrates

Carbohydrates play key roles in intercellular processes including infection, metastasis, differentiation, regulation of signaling, and so on. In order to clarify the mechanisms of these events and to develop new therapeutics, chemical synthesis of carbohydrates is indispensable. However, synthetic methods of carbohydrates have been relatively unexplored. Multistep protection/deprotection procedures are usually required for their synthesis because of the lack
of a direct method for the chemo- and regioselective manipulation of one of the multiple hydroxyl groups of carbohydrates. Here, a catalytic one-step process for the chemo- and regioselective acylation of monosaccharides is to be discussed. With catalyst 1, acylation of the secondary hydroxyl group at C(4) of octyl β-D-glucopyranoside proceeded in up to >99% selectivity in the presence of a primary hydroxyl group at C(6) and two other secondary hydroxyl groups at C(2) and C(3). Competitive acylation between the primary and secondary hydroxyl groups usually takes place chemoselectively at the primary one. On the other hand, with catalyst 1, chemoselective acylation in favor of a secondary hydroxyl group and regioselective acylation in favor of one out of three secondary hydroxyl groups took place with perfect selectivity. The same molecular transformation could be alternatively achieved by the conventional protection/deprotection procedure via five steps in 46% overall yield.

(a) catalytic one-step process

(b) conventional protection/deprotection procedure

1. TBDMSI / imidazole
2. 2-methoxypropene / PPTS
3. (i-PrCO)₂O / DMAP
4. CSA / MeOH
5. separation of regioisomers

46% overall

>99% selective
98% yield