DIRECT FORMATION OF VICINAL QUATERNARY CARBON STEREOCENTERS IN TOTAL SYNTHESIS OF NATURAL PRODUCT

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INTRODUCTION

Natural products are rich resources of intriguing questions for chemists. Not only the application of its function, but also the structural complexity and diversity of natural products inspired organic chemists. Vicinal quaternary carbon stereocenters (VQCS) is one of the most challenging structural features found frequently in natural products.\(^1\) Having two quaternary stereocenters directly attached to each other, VQCS shows highly congested structures. Direct construction of VQCS generates both of the quaternary stereocenters in single operation, making overall synthesis more efficient. Two major synthetic strategies will be discussed in this seminar, highlighting case studies for each strategy by total synthesis of natural products.

STRATEGY 1: DIMERIZATION OF TERTIARY RADICALS

Combining two tri-substituted carbons are one of the most straightforward ways to construct VQCS in single operation. Case studies were done on dimeric cyclotryptamine alkaloids by Movassaghi et al.\(^2\) The first generation approach is Co-mediated homodimerization of tertiary radicals. Co-mediated single electron reduction generates tertiary radical, which dimerizes to form VQCS. With the defined stereochemistry of the tertiary radical, combination should occur with one possibility, making diastereoselective construction of VQCS possible. They have also developed heterodimerization reaction for constructing VQCS, which utilizes directed diazene fragmentation. With the diazo bridge on the heterodimeric precursor, the resulting radicals will be in close proximity making selective synthesis of heterodimer possible. Case study for heterodimerization is represented in Scheme 1 on total synthesis of Communesin F.\(^3\)

Scheme 1. VQCS Construction via Radical Dimerization in Total Synthesis of Communesin F

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STRATEGY 2: TRANSFORMATION UTILIZING PI-BOND(S)

Strategy that is widely applied to synthesis of various natural products involves transformations of substituted pi-bonds. The flat nature of pi-bonds (e.g. olefin) makes the initial approach of reaction partners more likely, making VQCS formation feasible. Case studies are done on Crinippilins natural product, that bears highly congested structure with three contiguous VQCS.

Scheme 2. VQCS Construction via Tandem Cycloadditions in Total Synthesis of Crinippilins

Lee et al. utilized trimethylenemethane (TMM) diradical-mediated tandem cycloadditions to construct VQCS and tetraquinane core in single operation. The stereochemical outcome for the transformation is majorly controlled by chiral substituent (OTBDPS) on the carbon chain, which arranges the desired transition state structure for stereo-determining cycloaddition.

CONCLUSIONS AND OUTLOOK

Two major strategies to directly construct VQCS is shown, which are dimerization of tertiary radicals and transformation involving pi bonds. The two strategies are actually fall into one category, which is ‘substrate-controlled construction of stereocenters.’ Stereochemical outcome of both of the case studies are controlled by pre-installed chiral element in substrates. There are reactions constructing VQCS in catalytic enantioselective fashion. It is especially challenging because of the highly congested nature of transition state, having all the substrates and chiral catalyst at the reacting site. Generally, strategies developed to directly construct VQCS needs significant synthetic overhead before and after the VQCS forming step. It is highly desired to develop general (less substrate-dependent) and practical (tolerance to more functionalities) strategy to directly construct VQCS, to explore a new dimension of chemical space.

REFERENCES