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Digest Paper

Total synthesis of natural and pharmaceutical products powered by organocatalytic reactions

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ABSTRACT

Organocatalysis has emerged as the third pillar of modern asymmetric catalysis in the past two decades. Applying organocatalytic reactions in total synthesis is currently a highly dynamic research area. This Digest focuses on selected recent examples of total synthesis of natural and pharmaceutical products enabled by organocatalytic reactions, highlighting the importance of organocatalytic reactions in fostering structures of biological importance.

Contents

Introduction

Natural products play pivotal roles in drug discovery. Approximately two thirds of all small-molecule drugs approved during 1981–2010 have their origins in natural products.[1] In the process of drug discovery, organic synthesis provides the most transformative power that can build natural or designed molecules of interest. The art and science of organic synthesis have evolved tremendously since its inception.[2] 'Can we synthesize the molecule?' is no longer the question. Nowadays, armed with the strategies and methodologies developed over the past decades, synthetic chemists have been endowed with the capability to

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conquer almost any known natural product if given sufficient resources, efforts, and time. The ideal synthesis is gaining increasing attention from synthetic chemists to confront the demand from interdisciplinary scientific community as well as industry to produce sufficient amount of desired compounds in sustainable ways.[3]

Organocatalysis has emerged as the third pillar of modern asymmetric catalysis, along with metal catalysis and biocatalysis.[4] Organocatalytic reactions usually feature mild reaction conditions, adequate functional group tolerance, insensitivity toward air and moisture, as well as their diverse catalytic mechanisms.[5] The metal-free nature of organocatalytic reactions meets the demands of green chemistry. The ability of organocatalysis to effect cascade reactions and one-pot tandem transformations is of particular importance and has attracted significant attention from the chemical synthesis community. To combine organocatalysis with metal catalysis is a highly dynamic arena. These efforts have culminated in a number of elegant total syntheses of natural products with biological significance. A number of elegant reviews have appeared highlighting respective topics in this research area.[6] This Digest focuses on selected recent examples of total synthesis of natural and pharmaceutical products enabled by organocatalytic reactions. These examples are grouped in terms of the mechanisms of the organocatalytic reactions applied in the total syntheses, including general base catalysis,[5a] enamine catalysis,[5b] iminium catalysis,[5c] and Brønsted acid catalysis.[5d]

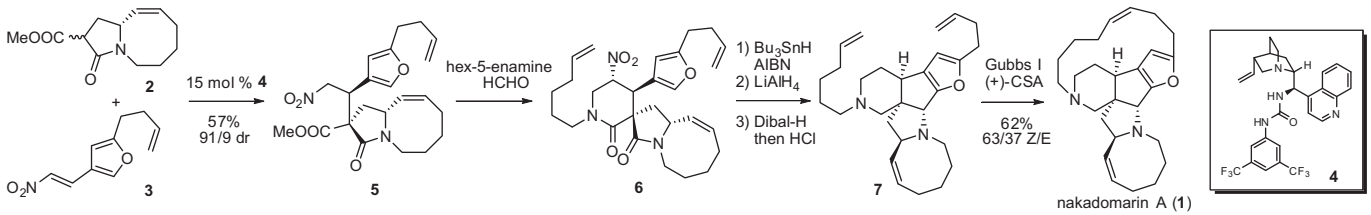
Total syntheses enabled by general base catalysis

Dixon's synthesis of nakadomarin A[7]

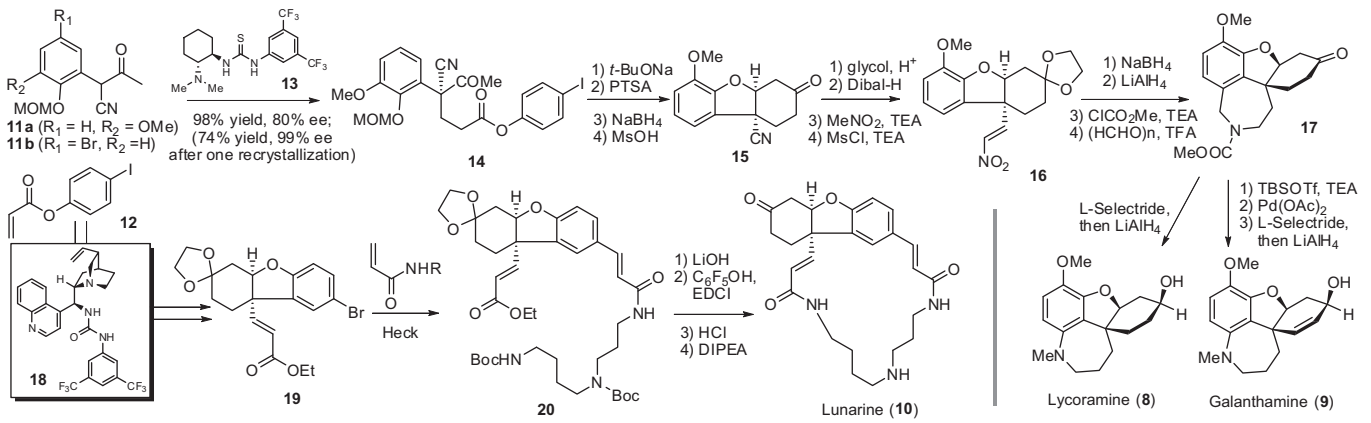
Construction of an all-carbon quaternary center usually constitutes a significant challenge in total synthesis, especially when the quaternary stereogenic carbon is surrounded by ring systems. This is the case in the total synthesis of nakadomarin A (**1**). Nakadomarin A was isolated by Kobayashi and co-workers in 1997 from a sponge collected off the coast of the Kerama Islands, Okinawa, and exhibits significant bioactivities. This molecule contains a synthetically challenging 8/5/5/5/15/6 hexacyclic ring system containing a quaternary carbon. Prior to Dixon's synthesis, the average step count of the three total syntheses of nakadomarin A reached 34. In 2009, Dixon's total synthesis reshaped the landscape. Pivoting on an organocatalytic diastereoselective Michael addition reaction, Dixon and co-workers amazingly telescoped the total synthesis of nakadomarin A into less than fifteen steps (longest linear sequence) (Scheme 1). The Michael reaction between **2** and **3** under the action of 15 mol % of **4** delivered a 91/9 diastereomeric mixture favoring the desired **5** in 57% yield. When LHMDS or KHMDS was employed in the place of the catalyst **4** to promote this reaction, a diastereoselectivity of 1.5/1 was observed. Notably, the configuration of the nascent quaternary carbon was dictated by the strong facial bias of the enolate of the 5/8 bicyclic framework. It was through the hydrogen bonding interactions between the thiourea catalyst **4** and the nitroalkene **3** that the stereochemistry of the newly generated tertiary carbon was effectively controlled. The subsequent nitro-Mannich/lactamization cascade formed the piperidone ring of **6**. Selective reductions transformed **6** to aminol which underwent furan/iminium cyclization to pentacyclic **7**. The camphorsulfonic acid-assisted Z-selective RCM reaction annulated the 16-membered macrocycle and finalized the total synthesis. This synthesis formed the basis of Dixon's second generation route for nakadomarin A, where the geometric selectivity issue in the formation of the macrocycle was addressed by virtue of alkyne metathesis.[8]

Fan's synthesis of lycoramine, galanthamine, and lunarine[9]

Lycoramine (**8**), galanthamine (**9**) and lunarine (**10**) are hydrodibenzofuran alkaloids with biological significance. In particular, galanthamine possesses acetylcholinesterase inhibitive activity, and is clinically used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments. In 2011, Fan and co-workers reported the collective total synthesis of these three molecules (Scheme 2). The stereochemistry-defining step is the asymmetric Michael addition reaction of **11** and **12**



Scheme 1. Dixon's synthesis of nakadomarin A (**1**).



Scheme 2. Fan's syntheses of lycoramine (**8**), galanthamine (**9**), and lunarine (**10**).