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Digest Paper

Catalytic asymmetric reactions in alkaloid and terpenoid syntheses

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ABSTRACT

Catalytic asymmetric induction is one of the most important methods in current synthetic organic chemistry for designing efficient and attractive synthetic routes. The efficient total synthesis of a natural product can be achieved through the identification of appropriate method and strategy. This Letter introduces the catalytic asymmetric syntheses of alkaloids and terpenoids based on an overview of four recently reported types of asymmetric reaction: (1) asymmetric decarboxylative allylation, (2) organocatalytic cascade reaction, (3) polyene cyclization, and (4) asymmetric [2+2]-photocycloaddition catalyzed by a chiral Lewis acid.

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Introduction

Novel natural products that display attractive bioactivities have been isolated from a variety of natural resources. The structural determination of these natural products has been accelerated recently through the development of a range of instrumental and analytical techniques. Natural resources play an important role in the search for biologically active compounds in the field of pharmaceuticals and agrochemicals;[1] however, the isolation of an attractive bioactive compound as a minor component in nature typically does not allow for the elucidation of its biological mode of action or for the development of a pharmaceutical or agrochemical product without the establishment of a supply method. One solution to this problem is presented by natural product synthesis methods using synthetic organic chemistry. Such methods are an indispensable research field.

In the past, the efficiency of a target molecule synthesis tended to receive little attention as researchers worked toward the fastest route to total synthesis; however, the realization of a sustainable society[2] requires the development of effective synthetic routes to natural products that utilize limited resources efficiently in addition to achieving total synthesis. Several measures of a synthetic route's efficiency have been proposed, including the atom economy,[3] redox economy,[4] and step economy,[5] and several total syntheses focusing on efficiency have been reported.[6] In general, synthetic strategies are planned using a retrosynthetic analysis upon initiating the total synthesis of a target molecule. When considering a synthetic route for a complex natural product, many possible retrosynthetic analyses are available. The key to achieving an efficient total synthesis lies in selecting the most appropriate synthetic route based on a variety of retrosynthetic considerations. Asymmetric reactions are indispensable when the selective preparation of one enantiomer of a target molecule must be performed. Because each enantiomer of a certain biologically active compound

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can display distinct effects, new methods for asymmetric synthesis have remained under active development. Asymmetric synthesis may be divided roughly into four categories:[7] the chiral pool method;[8] optical resolution;[9] the use of chiral auxiliaries;[10] and the use of a chiral catalyst.[11] Recently, asymmetric reactions that rely on the memory of chirality (MOC), in which asymmetric induction occurs via a chiral enolate intermediate with a lifetime in its chirality, have been applied in natural product synthesis.[12] These reactions play significantly important roles in the total synthesis of natural products. Among these reactions, the catalytic asymmetric reactions have several advantages for natural product synthesis: compared to the chiral pool method, any starting materials may be selected because an achiral compound can be used. Catalytic asymmetric reactions can shorten a synthetic route relative to a route based on the use of chiral auxiliaries because asymmetric induction proceeds from the chirality of the catalysis reaction. Theoretically, a chiral compound may be obtained in quantitative chemical yield compared to the optical resolution. However, in some cases, catalytic asymmetric reactions put synthetic chemists into trouble if the asymmetric induction cannot occur efficiently due to the narrow and limited scope of the catalyst's substrates, due to reconsideration of the substrates or the synthetic route, or due to the inability to improve the enantioselectivity. In these cases, strict optimization of reaction conditions is then required to improve the enantiomeric excess. Synthetic chemists must choose an appropriate catalytic asymmetric reaction to achieve the effective total synthesis of a natural product by assessing these merits and drawbacks.

This review provides an overview of recent attractive and interesting reports of catalytic asymmetric total syntheses of alkaloids and terpenoids. Asymmetric dihydroxylation,[13] asymmetric epoxidation,[14] and asymmetric hydrogenation[15] are frequently applied to enantioselective total synthesis of natural products not only because their experimental procedures are simple and versatile, but also because the chemical yield and optical purity resulting from these reactions are relatively highly reproducible. This discussion will focus on enantioselective total syntheses using several recently developed asymmetric catalytic reactions that are distinct from these famous reactions.

Total synthesis of aspidosperma alkaloids using asymmetric decarboxylative allylation

Terpenoid indole alkaloids make up a major fraction of the alkaloids present in plants, and more than 3000 such alkaloids have been recognized.[16] Several synthetic studies of these alkaloids have been reported because most of them have complex and interesting chemical structures and show attractive biological activities.[16] One such class of alkaloids, the aspidosperma alkaloids, includes a quaternary carbon in their ring-fused structure. A key to the successful achievement of an effective total synthesis of the aspidosperma alkaloids is to select an appropriate strategy for constructing the quaternary stereogenic center. Catalytic asymmetric decarboxylative allylation is often applied in the total synthesis of natural products bearing a quaternary carbon[17] because these reactions present a powerful tool for the effective and highly enantioselective construction of quaternary stereogenic centers. Recently, Shao and co-workers reported the total syntheses of aspidosperma alkaloids using a key intermediate prepared by the asymmetric decarboxylative allylation of carbazolone derivatives.[18a–c] The decarboxylative allylation of carbazolone derivatives presents a significant challenge, unlike the corresponding reaction of the β-ketoester derivatives, because the nucleophilicity at the indole C(3) can affect the decarboxylative allylation. Shao and co-workers investigated a catalytic asymmetric decarboxylative allylation using carbazolone derivative **1** (Scheme 1, Eq. 1).[18a] While investigating the optimized conditions through the use of a variety of chiral ligands, they found that treatment of **1** in the presence of $Pd_2(dba)_3$ and phosphinooxazoline ligand **L1** in toluene gave desired compound **2a** in 93% yield and in 92% ee with the concomitant formation of small amounts of **2a′** as a side product of the deallyloxycarbonyl reaction. The optimal conditions provided carbazole derivatives containing a variety of substituents at the quaternary stereogenic center α to the ketone in up to 97% ee. The total syntheses of (−)-aspidospermidine (**3**), (+)-kopsihainanine A (**4**), and (−)-limaspermidine (**5**), and the formal total synthesis of (−)-1-acetylaspidoalbidine (**6**) were accomplished from **2a** (Scheme 1, Eqs. 2–4).[18a,b] The conversion of **2a** into amide **7** under acidic conditions, followed by the chemoselective reduction at the keto carbonyl group and the intramolecular cyclization under acidic conditions, between the benzylic secondary alcohol and amide, gave **8** (Scheme 1, Eq. 2). Oxidative degradation at the vinyl group led to aldehyde **9** and its thioacetal formation followed by desulfurization in the presence of a Raney-Ni catalyst under hydrogen provided **10**. The reduction of **10** with $LiAlH_4$ and debenzylation under Birch conditions gave the key intermediate **11**, which was converted to (−)-aspidospermidine (**3**) in three steps, as reported by Heathcock and co-workers:[19] (1) *N*-chloroacetylation, (2) formation of the γ-lactam, and (3) reduction of amide. Synthesis of (+)-kopsihainanine A (**4**) was commenced from **8** (Scheme 1, Eq. 3). Hydroboration of **8** and oxidative treatment gave alcohol **12**. *O*-mesylation of **12** followed by intramolecular *N*-alkylation under basic conditions led to **13**. Amide **13** was converted into (+)-kopsihainanine A (**4**) through known methods, a stereoselective α-hydroxylation followed by *N*-debenzylation, as reported by Xie, She, and co-workers;[20] however, it was not clear whether the synthetic **4** was identical to the natural compound because the synthetic **4** was not soluble in chloroform (although it was soluble in DMSO), whereas the natural **4** was soluble in chloroform. After several analyses and investigations, they speculated that the product of the debenzylation of **14** with aluminum chloride was the chelate compound **A** in complex with aluminum. The pure synthetic **4** was obtained through the addition of Rochelle salt in a workup of the debenzylation with aluminum chloride. The synthesis of (−)-limaspermidine (**5**) was begun from **9** (Scheme 1, Eq. 4).[18c] The reduction of aldehyde and amide moieties in **9**, followed by the debenzylation and protection of the primary alcohol with a *tert*-butyldiphenylsilyl group, gave **15**, which led to **5** using a sequence similar to those applied to obtain **3** from **11** in the (−)-aspidospermidine synthesis. The conversion of **5** into **6** was reported in two steps,[21] so the formal synthesis of **6** was also achieved. Using catalytic asymmetric decarboxylative allylation, Shao and co-workers recently reported the total syntheses of (+)-10-oxocylindrocarpidine, (+)-cylindrocarpidine, (−)-*N*-acetylcylindrocarpinol, and (+)-aspidospermine.[18c]

Zhu and co-workers reported the total syntheses of five terpenoid indole alkaloids:[22] (−)-mersicarpine (**18**), (−)-scholarisine G (**19**), (+)-melodinine E (**20**), (−)-leuconoxine (**21**), and (−)-leuconolam (**22**), from the key intermediate **17** (90% yield, 92% ee), which was prepared from β-ketoester **16** using a catalytic asymmetric decarboxylative allylation developed by Stoltz (Scheme 2).[23] The key to these total syntheses was that the nucleophilic addition of the nitrogen (N(4)) residue occurred selectively via discrimination between the two carbonyl carbons (C(7) and C(21) positions) in **23**, thereby controlling their electrophilicities. Ozonolysis of cyclohexenone **24**, which was converted from **17** in four steps, including functionalization at the residual chain and α-arylation, gave α-diketone **23**. Hydrogenolysis in the presence of Pd/C under a H_2 atmosphere, followed by the sequential treatment with KOH in ethanol, with molecular oxygen, and with dimethyl sulfide in the same flask, gave (−)-mersicarpine (**18**) in 75% yield (Scheme 2, Eq. 1). In this one-pot reaction, it was assumed that the sequential