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Calyciphylline A-型虎皮楠生物碱himalensine A的全合成研究进展

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摘要 虎皮楠生物碱自从1909年被首次分离报道至今, 已有300多个已知家族成员. 它们具有广泛的生物活性以及复杂多变的多环骨架结构, 其独特的氮杂笼状稠环结构以及骨架中包含季碳中心的多个手性中心使得其合成极具挑战性. 在虎皮楠生物碱的众多家族中, 含有20多个成员的calyciphylline A-型虎皮楠生物碱是具有代表性的家族之一, 而himalensine A则是calyciphylline A-型虎皮楠生物碱的代表性成员之一. 该分子被岳建民课题组分离报道以来受到了众多合成化学家的关注, 迄今已有多篇合成研究与全合成工作报道. 本文主要介绍关于calyciphylline A-型虎皮楠生物碱himalensine A近期的全合成研究进展. 这些工作为虎皮楠生物碱的全合成研究贡献了宝贵的经验, 并展示了许多开拓性的思路.

关键词 虎皮楠生物碱, 天然产物全合成, calyciphylline A, himalensine A

虎皮楠是广泛分布于环太平洋地区的一种常绿乔木, 在我国主要分布于长江以南地区. 传统中医理论中, 一些虎皮楠科植物具有清热解毒、活血化瘀等功效. 虎皮楠生物碱是虎皮楠植物的特征化学成分. 自1909年日本化学家Yagi[1]首次分离得到虎皮楠生物碱daphnimacrine以来, 该家族已经拥有300多个已知成员. 根据它们的化学结构特征, 这些生物碱骨架可分为13~35种类型[2~4]. 同时, 该类天然产物也具有广泛的生物活性[2~4], 如2014年, 岳建民课题组[5]报道的虎皮楠生物碱二聚体logeracemin A就表现出显著的抗HIV活性.

在众多虎皮楠生物碱家族中, calyciphylline A-型虎皮楠生物碱是具有代表性的一类(图1). 2003年, Morita和Kobayashi[6]从*D. calycinum*的叶子中分离出calyciphylline A. 此后, 更多结构相似的虎皮楠生物碱, 如daphnilongeranin B、daphniyunnine C(longeracinphyllin A)、daphenylline、hybridaphniphylline B、longeracemin A、himalensine A等约20个成员被陆续分离报道[5~12]. 该类天然产物复杂的结构为它们的化学合成带来了巨大的挑战, 李昂课题组[13~16]、Fukuyama/Yokoshima课题组[17]、翟宏斌课题组[18]和邱发洋课题组[19]等先后报道了多个含相邻双季碳及含苯环结构的calyciphylline A-型虎皮楠生物碱的精彩全合成. 2016

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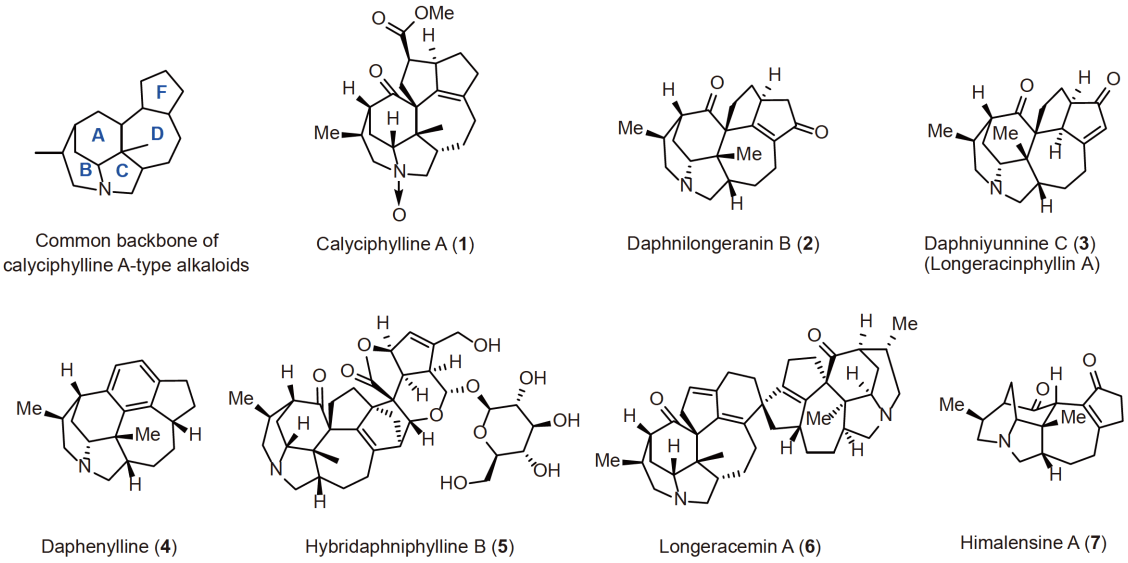

图 1 一些代表性的calyciphylline A-型生物碱
Figure 1 Representative calyciphylline A-type alkaloids

年, 岳建民课题组[12]从喜马拉雅地区的*Daphniphyllum* himalense中分离得到一种特殊的calyciphylline A-型虎皮楠生物碱himalensine A. 它是目前已知的唯一含19个碳的虎皮楠生物碱. 该分子自报道以来迅速得到了国际上多个有机合成小组的关注. 鉴于本课题组[20~35]长期以来对复杂笼状天然产物全合成的兴趣, 我们完成了包括himalensine A在内的一系列分子的全合成工作. Dixon课题组[36]和高栓虎课题组[37]也先后完成了himalensine A的全合成工作. 此外, Bonjoch课题组[38,39]、Stockdill课题组[40]、Hudlicky课题组[41]等也先后开展了一系列适用于himalensine A全合成的关键骨架构筑探索. 下面将聚焦于介绍2017~2020年针对himalensine A及相关结构的合成研究进展.

1 Himalensine A的ABC三环骨架合成研究

2018年, Stockdill课题组[40]提出了一个新颖的ABC三环体系的构筑策略(图2). 他们以内半缩醛**8**为起始原料, 与叠氮化合物**9**发生氮杂Wittig反应并原位还原亚胺引入氨基侧链得到化合物**10**. 随后, 利用*N*-氯代琥珀酰亚胺(NCS)实现了氯代, 并将烯丙醇氧化成α,β-不饱和酮, 成功得到串联自由基反应的中间体. 在无金属锡参与的自由基关环(AIBN, iPr$_3$SiH)条件下, 得到期望的三环产物及部分氯代产物. 然后, 在二氧化铂催化氢化条件下都还原为同一产物**11**, 这为接下来的Knoevenagel缩合作好准备. 氧化态调整并经Roskamp偶联可得β-羰基酯**12**. 然而, 大量尝试证实化合物**12**无法被转化得到期望的七元环关环产物, 而仅得到五元环化合物**13**. 该路线利用了硅烷参与的自由基串联关环反应一步同时构筑了BC环, 颇为高效.

2019年, Bonjoch课题组[38]实现了calyciphylline A-型虎皮楠生物碱ABC三环体系的构筑(图3). 从环己酮**14**开始, 与苄胺缩合并酰胺化得到化合物**15**. 然后, 在偶氮二异丁腈(AIBN)和三丁基锡氢(nBu$_3$SnH)的条件下发生环化, 得到含有一个全碳季碳的二环中间体, 并通过烷基化引入烯丙基片段得到化合物**16**. 利用氰基硼氢化钠还原烯胺得到化合物**17**, 双键经过氧化裂解(NaIO$_4$, OsO$_4$)得到醛**18**. 接着将酰胺和醛同时还原得到氨基醇**19**并脱除苄基保护生成胺**20**. 然后, 氨基上引入侧链得到化合物**21**, 并在酸性条件下脱除缩酮保护基得到酮**22**. 随后, 三环中间体**23**可由钯催化的分子内偶联反应关环得到. 最后, 在Crabtree催化剂条件下, 双键异构化得到化合物**24**. 他们的尝试为himalensine A及其同系物的合成提供了颇为有益的思路.

2019年, Hudlicky课题组[41]发表了calyciphylline A-型生物碱三环骨架的合成研究工作(图4). 以(*S*)-香芹酮(**25**)为手性源, 一锅法通过烯丙位氯代和对不饱和酮的Luche还原后得到氯代香芹醇**26**. 其被转化为氨基甲酸酯**27**后, 脱水并迁移形成异氰酸酯中间体, 一锅法与炔烃片段**28**连接得到酰胺**29**. 再经过Finkelstein类型的取代反应使之关环得到AB二环化合物**30**. 接下来, 通过

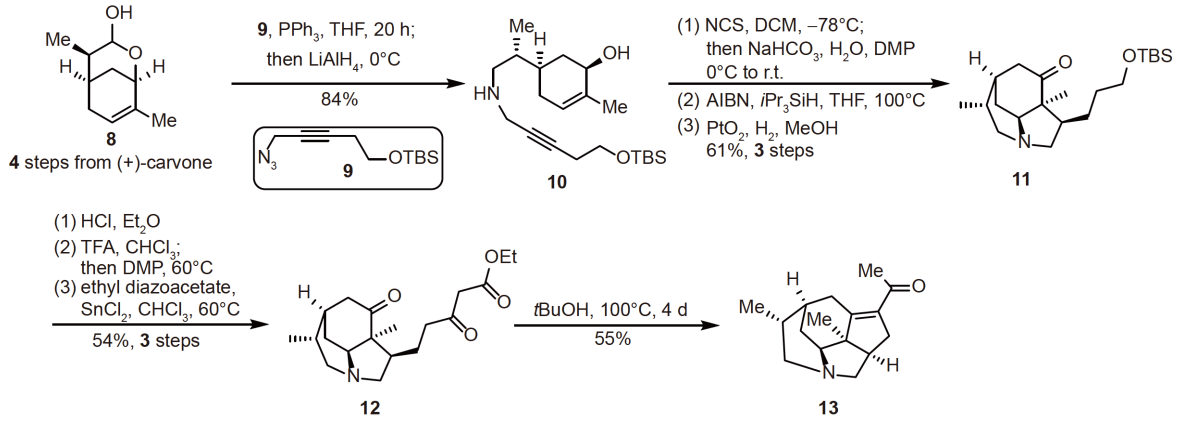

图 2 Stockdill课题组[40]对于ABC三环骨架的合成研究
Figure 2 Synthesis of the ABC tricyclic ring system by the Stockdill group[40]

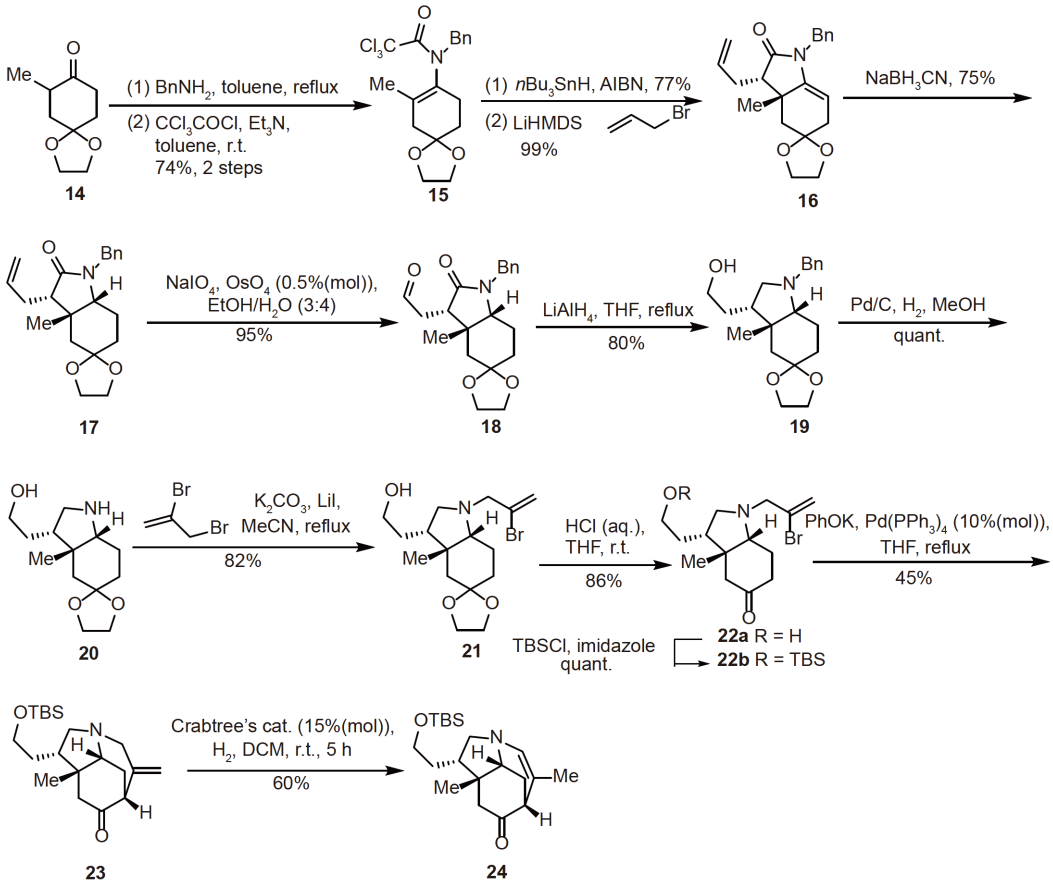

图 3 Bonjoch课题组[38]对于ABC三环骨架的合成研究
Figure 3 Synthesis of ABC tricyclic ring system by the Bonjoch group[38]

钯催化化学选择性及区域选择性的锡氢化反应得到乙烯基锡, 碘代后得到化合物**31**. 再经过Heck偶联顺利关上四氢吡咯环得到**32**. 最终, 选择性氢化C6~C12位双键及脱除硅醚保护得到醇**33**. 该路线巧妙地利用了[1,3]-Ichikawa迁移作为关键反应来完成关键三环骨架的构筑, 进一步丰富了虎皮楠生物碱的合成研究.

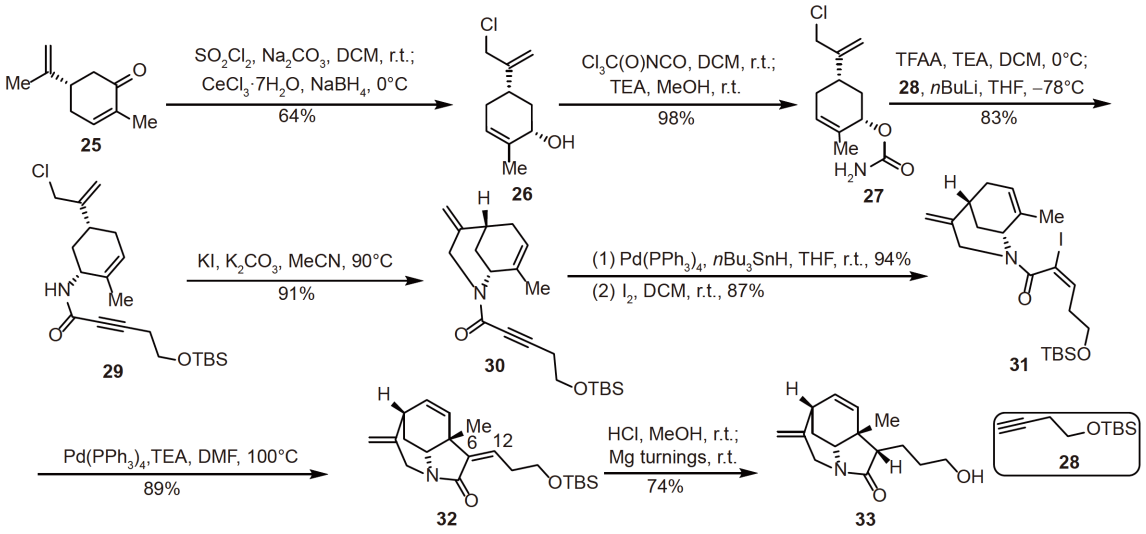

图 4 Hudlicky课题组[41]对于ABC三环骨架的合成研究
Figure 4 Synthesis of ABC tricyclic ring system by the Hudlicky group[41]

2 Himalensine A的ABCD四环骨架合成研究

2017年, Bonjoch课题组[39]报道了himalensine A中ABCD四环骨架的合成(图5). 该合成路线以消旋的环己酮**14**为起始原料, 经过5步反应得到化合物**17**(图3), 然后通过烯烃复分解反应延碳得到α,β-不饱和醛**34**. 随后双键还原并缩酮水解后, 利用对甲苯磺酸促进的羟醛缩合构筑七元环, 接着在酸性条件下保护羰基的同时得到双键迁移的化合物**35**. 苄基脱除并将酰胺还原得到化合物**36**之后, 再次引入三氯乙酰基并脱除缩酮以及双键迁移, 得到不饱和酮**37**. 接下来利用三氯乙酰胺对乙酰烯醇酯的自由基加成, 成功构筑himalensine A的B环得到化合物**38**. 然后该化合物经过烷基化得到**39**. 最后再经α-羟基化和脱水得到化合物**40**. 该路线利用19步构造出了himalensine A的四环骨架, 其中两次利用AIBN、nBu$_3$SnH介导的自由基关环策略分别构筑C环和B环, 在酸性条件下通过羟醛缩合构筑七元D环, 为himalensine A及其同系物的合成提供了有趣的思路.

3 Himalensine A的全合成

2017年, Dixon课题组[36]首次完成了himalensine A的不对称全合成(图6). 他们从β-羰基酯**41**作为起始原料, 通过7步反应得到化合物**42**. 在催化剂**43**作用下发生不对称Diels-Alder反应, 对映选择性构筑出ACD三环化合物**44**. 在三氟乙酸条件下, 打开氧桥键并经过催化氢化得到烯醇**45**. 氮上引入炔丙基后对氧化态进行调整得到不饱和酮**46**. 将羰基转化成烯醇硅醚后发生自由基环化反应(AIBN, nBu$_3$SnH)顺利构筑桥环得到四环中间体, 在酸性条件下脱除烷基锡得到酰胺化合物**47**. 随后该化合物在Crabtree催化剂存在下被高非对映选择性氢化, 并经溴代得到化合物**48**. 接下来, **48**在碱性条件下被氧化得到二酮**49**. 随后, 把七元环上的羰基转化为三氟甲磺酸酯后, 再经Negishi偶联可得共轭二烯酮**51**. 酸性条件下脱除醛基保护后进行Stetter反应并发生双键迁移, 成功构筑出himalensine A的骨架**53**. 最终, 利用Vaska催化剂对酰胺进行选择性还原, 并完成了himalensine A的首次全合成. 他们以分子内不对称Diels-Alder反应为关键步骤, 高效构建了三环骨架和手性季碳中心, 再利用自由基环化和卡宾催化的Stetter反应顺利构筑剩余两个环, 从而精彩地完成了himalensine A的首次全合成工作.

2019年, 本课题组[28]发表了(−)-himalensine A的全合成工作, 这是继Dixon之后又一项关于(−)-himalensine A的全合成工作(图7). 该工作从手性二环化合物**54**出发, 首先转化为烯醇甲醚, 然后通过Van Leusen反应发生还原氰基化反应得到化合物**55**. 再对烯醇甲醚进行γ-氧化在骨架中引入关键的二级羟基. 之后的Saegusa-Ito氧化反应顺利得到二烯酮中间体. 随后, 氰基的温和水解被证实颇为困难, 但通过大量探索, 最终发现可以利用一个非常温和的铜/羟胺促进的氰基水解反应成功得到伯酰胺, 并且可一锅继续在碱促进下发

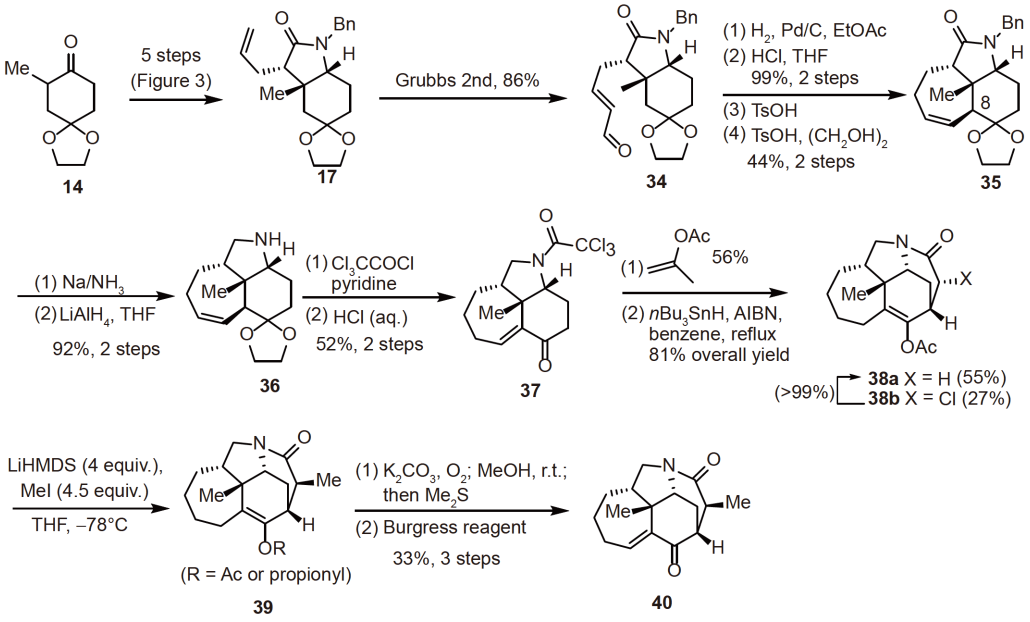

图 5 Bonjoch课题组[39]对于ABCD四环骨架的合成研究

Figure 5 Synthesis of ABCD tetracyclic ring system by the Bonjoch group[39]

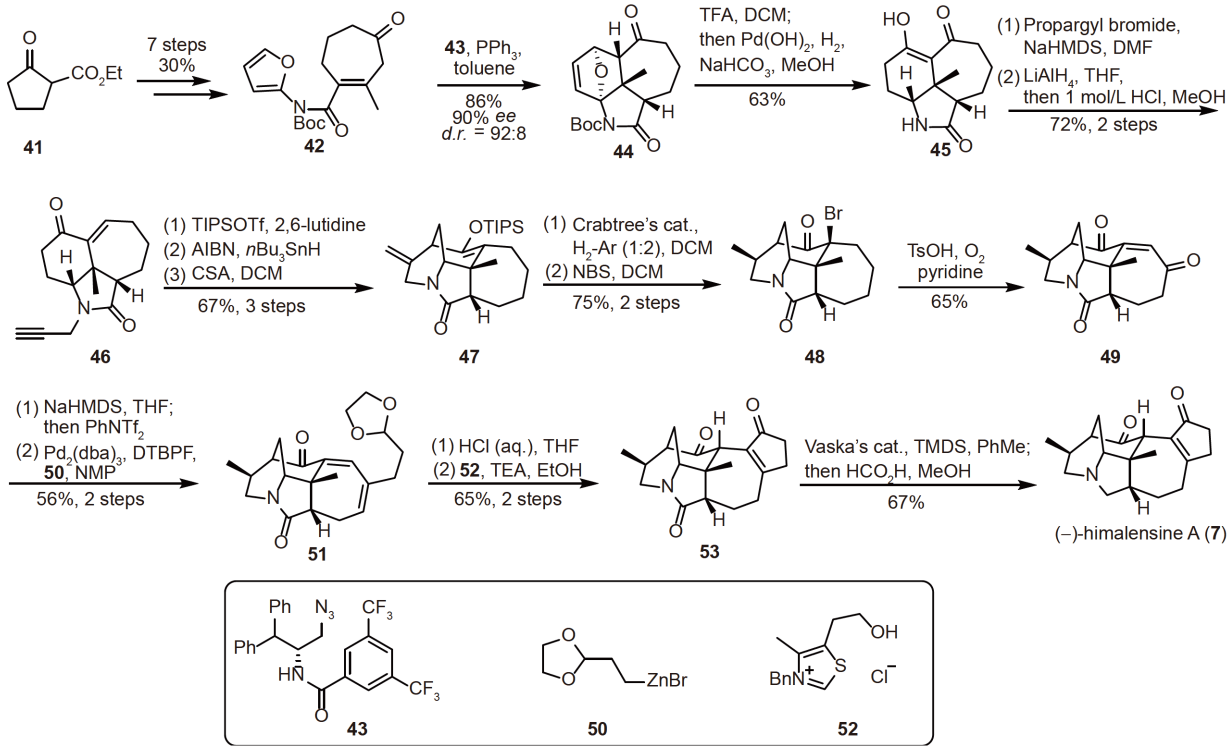

图 6 Dixon课题组[36]对于(–)-himalensine A的全合成

Figure 6 Total synthesis of (–)-himalensine A by the Dixon group[36]

生氮杂Michael加成关环, 得到三环产物**56**. 随后一锅法将不饱和酮转化为烯烃**57**. 该反应不仅使双键重排, 而且得到了C-8位构型正确的产物. 在氮上引入烯基溴侧链之后, 利用分子内的Heck偶联反应成功地构建出四环化合物**58**. 随后经过氧化态调整得到α,β-不饱和酮**59**. 之后, 利用Nazarov环化反应构筑出himalensine A

的完整骨架**60**. C-1位的羰基可以利用Meinwald重排反应快速引入, 得到化合物**53**. 最后, 他们参考Dixon课题组[36]的工作, 选择性将酰胺还原, 最终仅以14步路线完成了(−)-himalensine A的不对称全合成工作. 该路线利用了较为高效的分子骨架构建策略, 并在最大程度上避免了保护基的使用[42]. 该工作为复杂虎皮楠生物碱的全合成提供了新颖的策略思路.

同样在2019年, 高栓虎课题组[37]也精彩地完成了(±)-himalensine A的全合成工作(图8). 他们从二噻烷和溴代物出发, 经过5步反应得到不饱和酯**61**. 接着通过

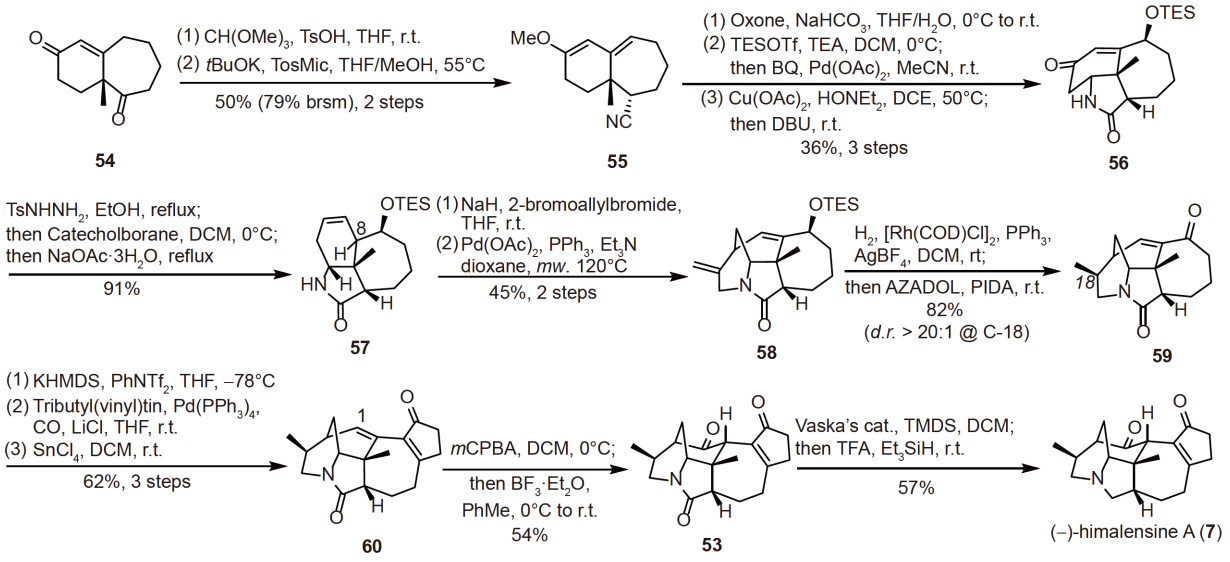

图 7 徐晶课题组[28]对于(−)-himalensine A的全合成
Figure 7 Total synthesis of (−)-himalensine A by the Xu group[28]

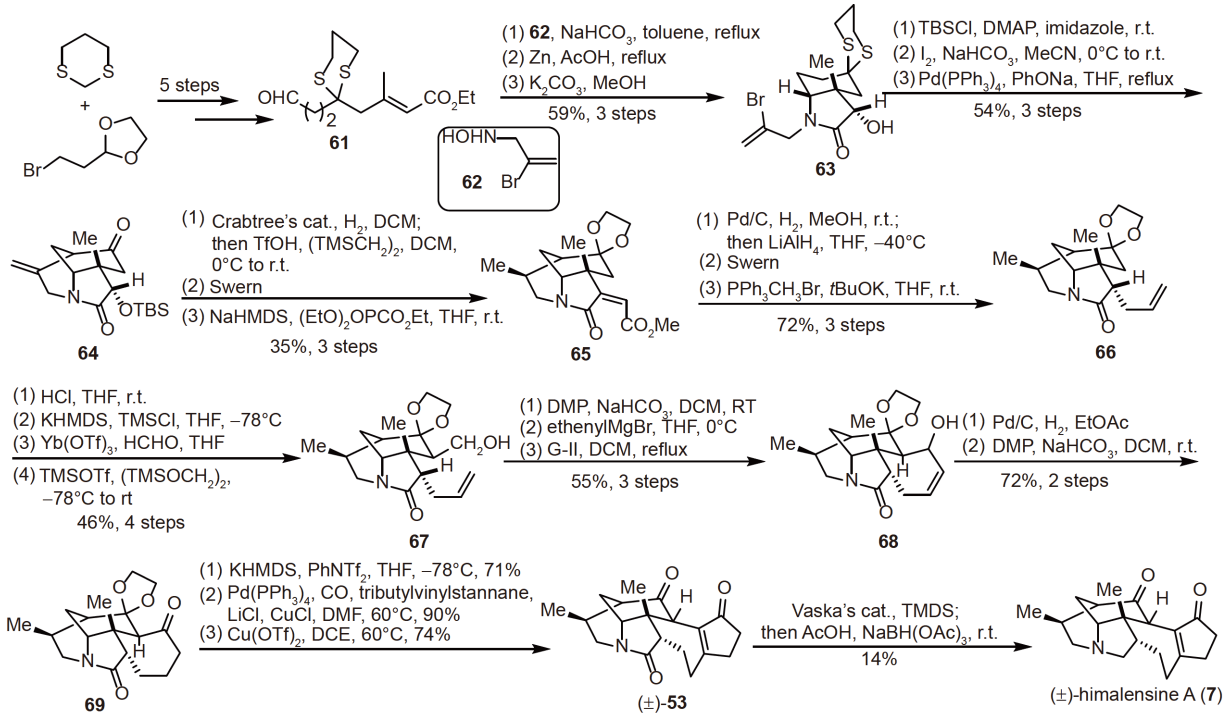

图 8 高栓虎课题组[37]对于(±)-himalensine A的全合成
Figure 8 Total synthesis of (±)-himalensine A by the Gao group[37]

1,3-偶极环加成反应得到化合物**63**. 脱除二噻烷保护后, 利用钯催化的分子内偶联反应, 成功构建三环化合物**64**. 然后将末端烯烃氢化并且羰基保护, 将脱除硅醚保护的羟基氧化, 再通过Horner-Wadsworth-Emmons (HWE)反应得到不饱和酯**65**. 将三取代双键氢化后, 一锅法还原酯得到醇, 并将其氧化后再发生Wittig反应得到烯烃**66**. 缩酮保护脱除后, 在羰基α位引入羟甲基后再次保护羰基得到化合物**67**. 羟基氧化得到醛, 乙烯基格氏试剂进攻醛基得到二烯化合物, 再进行烯烃复分解反应得到七元环化合物**68**. 随后, 将双键氢化并羟基氧化得到酮**69.** 接下来, 通过Nazarov环化反应, 并在酸性条件下将羰基保护基脱除, 成功构筑出himalensine A的完整骨架**53**. 最后, 选择性将酰胺还原完成了himalensine A的全合成工作. 纵观整条路线, 他们对于1,3-偶极环加成反应的巧妙应用是整个合成中的精彩之笔.

4 总结与展望

多年以来, 虎皮楠生物碱的分离、结构鉴定与活性测试和它们的合成一直吸引着众多科学家的关注. 它们多变的骨架以及复杂的多环结构, 多个手性中心与季碳中心的存在使得其全合成之路充满荆棘. 近年来, 在众多合成化学家的共同努力下, 虎皮楠生物碱全合成领域不断取得突破[4,43~59], 令人欣喜. 但显而易见的是, 仍有相当一部分虎皮楠生物碱的合成存在着巨大的挑战. 依我们的浅见, 将来针对虎皮楠生物碱的研究重点方向应是: (1) 针对此类生物碱多变的骨架, 继续探索构筑其环系结构的新颖高效策略, 如非仿生合成策略、仿生合成策略、酶催化与化学结合的策略等; (2) 依托多样复杂的底物结构体系, 探索并发展新颖高效的成键模式. 我们相信在可预见的将来, 复杂虎皮楠生物碱的全合成研究仍将是不断涌现精彩故事的前沿舞台.

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Summary for “Calyciphylline A-型虎皮楠生物碱himalensine A的全合成研究进展”

Recent progress in the total synthesis of calyciphylline A-type *Daphniphyllum* alkaloid himalensine A

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The evergreen plants of the genus *Daphniphyllum* are found mainly in the Asia-Pacific region and have played important roles in Traditional Chinese Medicine. Their leaves, barks and fruits have long been used to treat a variety of ailments including asthma, rheumatism, inflammation and fever. Since the isolation of daphnimacrine by the Yagi group in 1909, more than 330 structurally fascinating natural products, known as the *Daphniphyllum* alkaloids, have been isolated and structurally identified over the years. Owing to their unusual and disparate structural backbones, these alkaloids are highly attractive to synthetic chemists, spanning all around the world. Based on their distinct skeletons, these natural compounds can be categorized into 13−35 subfamilies. Among which, calyciphylline A-type is a particularly notable major subfamily that consists of approximately 20 members. These alkaloids show extensive physiological activities, such as anti-HIV and cytotoxicity and so on. Calyciphylline A-type alkaloids possess a characteristic structural backbone consisting of four fused rings [6-6-5-7] with one or more quaternary stereocenters. In 2016, a unique member of this family, namely himalensine A, was isolated from Nepalese *Daphniphyllum himalense* by Yue group. While its bioactivity remains unexplored, himalensine A possesses an unprecedented skeleton in the calyciphylline A-type alkaloids, which is the first natural C19 *Daphniphyllum* alkaloid isolated so far. Congested pentacyclic ring skeleton that includes a unique 2-azabicyclo[3.3.1] nonane motif, six stereogenic centers, and an all-carbon quaternary center, makes himalensine A a formidable synthetic challenge.

Since its isolation, three impressive total syntheses of himalensine A have been reported by Dixon, Xu and Gao groups, respectively. In 2017, the first enantioselective total synthesis of (−)-himalensine A was disclosed by Dixon and his co-workers. The total synthesis was elegantly accomplished in 22 linear steps. Enantioselective prototropic shift/furan Diels-Alder (IMDAF) cascade reaction to construct the ACD tricycle system and a reductive radical cyclization to build the B ring are notable highlights of Dixon’s synthesis. Other notable highlights include a molecular oxygen mediated γ-CH oxidation and a Stetter cyclization to access the critical cyclopentenone ring to achieve the full core of the natural product. Finally, a highly chemoselective lactam reduction delivered the target natural product. In 2019, Xu and co-workers accomplished an efficient total synthesis of (−)-himalensine A in 14 steps. Key features of this strategy include a Cu-catalyzed nitrile hydration and Michael addition to construct C ring, a Heck reaction to construct the challenging 2-azabicyclo[3.3.1]nonane motif, and a Meinwald rearrangement reaction to deliver the necessary carbonyl group, which significantly improved the overall synthetic efficiency. Concurrently, Gao and his co-workers reported the total synthesis of himalensine A in a new fashion. They developed a 1,3-dipolar nitrone [3+2] cycloaddition reaction to construct A ring. The Pd-catalyzed enolate alkenylation was employed to fabricate B ring, followed by the construction of the seven-membered ring via a ring closing metathesis reaction. Finally, a Lewis acid-promoted Nazarov cyclization successfully furnished the cyclopentanone F ring. Besides these total synthetic approaches, several other interesting synthetic studies along with noteworthy synthetic strategies reported by the Bonjoch, Stockdill and Hudlicky groups, have showcased valuable and pioneering strategies and methods for the synthesis of himalensine A and its related *Daphniphyllum* alkaloids. This review covers the efforts toward the synthesis of himalensine A spanning the period from 2017 to 2020. The innovative strategies and methods demonstrated in these impressive efforts are inspiring to the synthesis of various types of *Daphniphyllum* alkaloids and many other natural products.

***Daphniphyllum* alkaloids, natural product total synthesis, calyciphylline A, himalensine A**

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