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Strategies toward the Biomimetic Syntheses of Oligomeric Sesquiterpenoids

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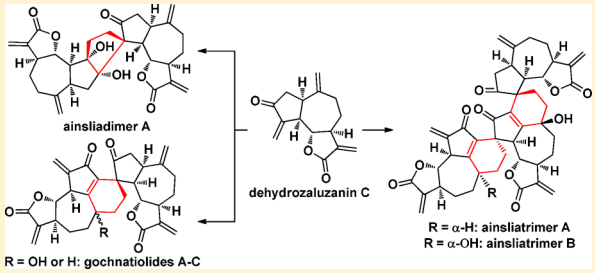
ABSTRACT: Oligomeric sesquiterpenoids, biogenetically assembled from two or three monomeric sesquiterpenoid units via diverse pathways, represent a unique class of natural products. The synthetic studies inspired by their biogenesis have offered significant impetus for the efficient construction of these architecturally complex frameworks. Here we provide an overview for the biomimetic syntheses of these dimeric and trimeric molecules based on the different strategies of bond formation, including Diels–Alder reaction, hetero-Diels–Alder reaction, [2 + 2] cycloaddition, and C–C bond coupling.



Oligomeric natural products with a great variety of architectures have evoked a wide interest in the synthetic community and resulted in a number of elegant total syntheses.[1] Within the terpenoid family, hundreds of disesquiterpenoids (or sesquiterpenoid dimers), which are biosynthetically originated from two sesquiterpenoid molecules, have been isolated to date. Most of these natural products displayed a host of important biological activities including anti-inflammation, anticancer, and anti-HIV activities.[2] Another rare class of terpenoid is the trimeric sesquiterpenoid. Until now, only four naturally occurring trimeric sesquiterpenoids have been reported: (−)-trishizukaol A,[3] (−)-cinnafragrin C,[4] as well as (−)-ainsliatrimers A and B (Figure 1).[5]

Most dimeric sesquiterpenoids are featured on the direct connection between two different or identical sesquiterpenoid monomers via one or two C–C bond formations such as Diels–Alder, hetero-Diels–Alder, [2 + 2] cycloaddition, or C–C coupling reactions.[2] Because three units and two connecting moieties are involved in the formation of trimers, a more complex connection paradigm is required. To this point, the conceivable biosynthetic pathway might inspire us to develop effective synthetic strategies to achieve the dimerization and trimerization. However, significant synthetic challenges for the "ideal synthesis" remain. For example, how to prepare the highly functionalized monomeric precursor in good yield, how to assemble the monomers effectively with good control of chemo- and regioselectivities, and how to convert the oligomeric precursors to the desired natural products always hamper the related synthetic work. Herein, this synopsis will provide a brief review for the recently reported intriguing biomimetic syntheses of complex oligomeric sesquiterpenoids. We will primarily highlight the biogenesis-inspired strategies for C–C bond formation.

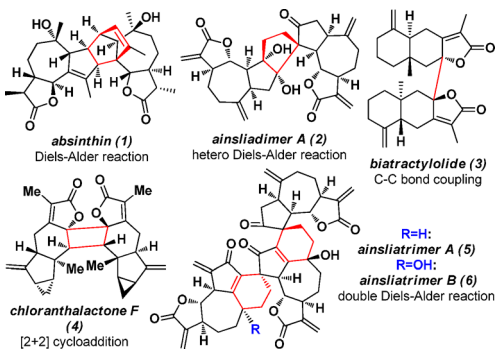


Figure 1. Representative oligomeric sesquiterpenoids.

■ DIELS–ALDER REACTION

The naturally occurring anti-inflammatory (+)-absinthin (**1**) was isolated from *Artemisia absinthium* in 1953.[6] After the structure was elucidated by NMR spectroscopic and X-ray crystallographic analyses in the 1980s,[7,8] the first total synthesis was accomplished by Zhai and co-workers in 2005 (Scheme 1).[9] This landmark synthesis began with the commercially available santonin (**7**), which was converted to a 5/7/5 tricyclic compound **8** via exposure to light in AcOH.[10] This effective photochemical transformation has served as the starting point for dozens of natural product syntheses.[11] After reduction of the ketone moiety of the five-membered ring, the newly generated alcohol was eliminated through a stepwise procedure including Mitsunobu arylselenulation and oxidative elimination.

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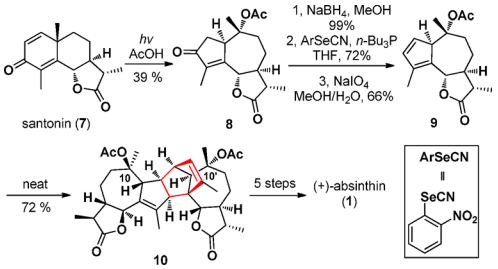
Scheme 1. Biomimetic Total Synthesis of (+)-Absinthin (1)



Remarkably, diene **9** underwent a spontaneous homodimerization via a highly regio- and stereospecific [4 + 2] cycloaddition to assemble the desired skeleton of **1** in 72% yield. The late-stage inversion of the configuration of the tertiary alcohols at C10/C10′ was realized in 5 steps to afford (+)-absinthin (**1**).

Other representative and structurally related classes of oligomeric sesquiterpenoids are the gochnatiolides, ainsliadimers, and ainsliatrimers. Gochnatiolides were first isolated by Robinson and co-workers from *Gochnatia* species in the 1980s.[12] Recently, ainsliadimers A (**2**) and B (**11**), along with two sesquiterpene trimers ainsliatrimers A (**5**) and B (**6**), were isolated by Zhang and co-workers from *Ainsliaea* species.[5,13] (−)-Gochnatiolides A−C, (−)-ainsliadimer B, as well as (−)-ainsliatrimers A and B all possess the intriguing spiro-[4,5]decane moiety which might be biosynthetically originated from the same precursor, the monomeric natural product dehydrozaluzanin C (**15**), through [4 + 2] cycloaddition (Figure 2).[5] The intriguing chemical structures and the

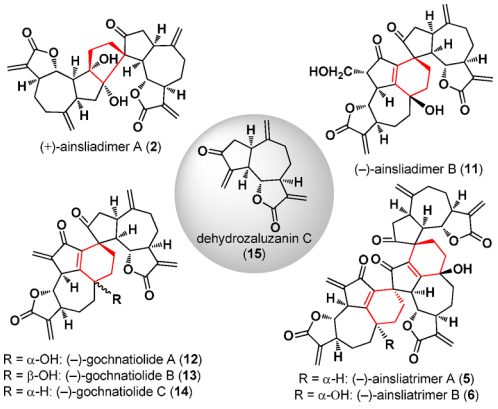
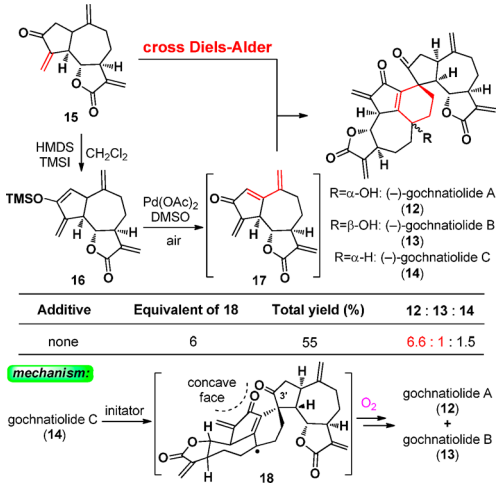


Figure 2. Structures of dehydrozaluzanin C and its oligomers.

promising anti-inflammation and anticancer activities aroused our interest. For the past four years, our group has systematically investigated the biomimetic total syntheses of this unique family of natural products, which has led to the development of a number of new synthetic strategies and methodologies.

Initially, we completed the synthesis of the monomeric natural product dehydrozaluzanin C (**15**) from the photolysis product of santonin in 10 steps in 17% overall yield.[14] With the monomer in hand, we set out to explore different pathways to achieve the biomimetic syntheses of these intriguing dimers and trimers. At the outset, we hypothesized two biogenetic pathways for gochnatiolides, but neither of them was realized in practice. Ultimately, we found (−)-gochnatiolides A−C could be generated in a collective manner using one-pot cascade transformations including Saegusa oxidation, intermolecular Diels−Alder reaction, and radical-mediated allylic oxidation (Scheme 2).[15] Our synthesis also enabled the

Scheme 2. Biomimetic Syntheses of (−)-Gochnatiolides A−C and the Proposed Reaction Mechanism

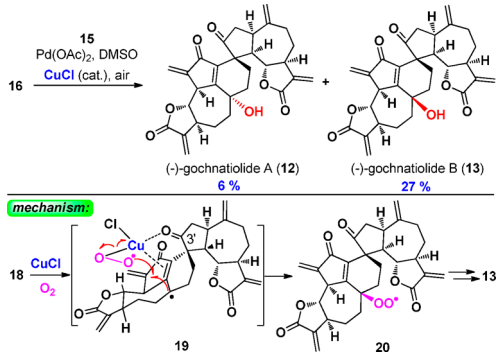


Additive	Equivalent of 18	Total yield (%)	12 : 13 : 14
none	6	55	6.6 : 1 : 1.5

structural reassignment of gochnatiolide B (**13**), which was a crucial precursor for the syntheses of ainsliadimer B and ainsliatrimers A and B. We also investigated the reaction mechanism for the remarkable one-pot cascade transformation. We proposed that the tertiary radical **18** was initially generated from gochnatiolide C (**14**), and then radical **18** reacted with oxygen to afford two peroxyl radicals as diastereomers. The two peroxyl radicals could be transformed to hydroperoxides through hydrogen abstraction from **14**. Finally, hydroperoxides were reduced in situ to afford **12** and **13**. The more favored production of gochnatiolide A (**12**) was attributed to the steric effect of the radical intermediate **18**.

In the allylic oxidation process, we also uncovered an unprecedented "copper effect" to control the stereochemical outcome of the newly formed hydroxyl group.[15] As shown in Scheme 3, the addition of a catalytic amount of CuCl

Scheme 3. "Copper Effect": Improved Synthesis of (−)-Gochnatiolide B (13)



remarkably facilitated the generation of gochnatiolide B (**13**). The mechanism we proposed was that radical intermediate **18** reacted with a monomeric Cu(II) peroxo species generated from the reaction of CuCl with oxygen. Due to the chelate effect between Cu and carbonyl at C3′, the peroxide radical was delivered from the *β*-face to generate **20**, which was further reduced to afford **13**.

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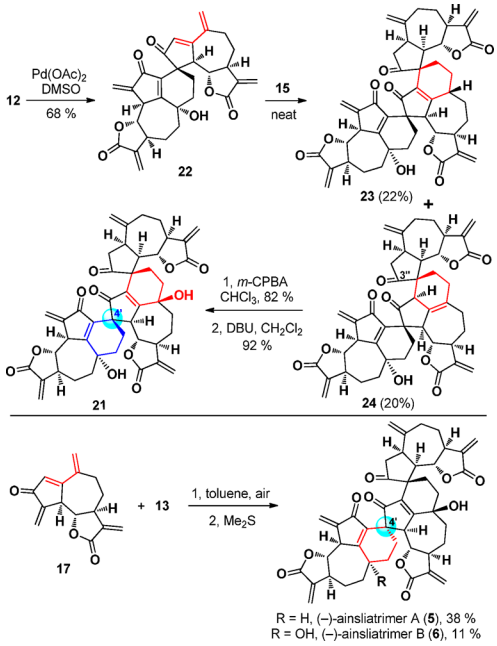
Having accomplished the biomimetic syntheses of gochnatiolides A–C as well as ainsliadimer B, we set to investigate the biomimetic synthesis of the stunningly complex trimeric sesquiterpenoids (−)-ainsliatrimers A and B.[16] One of the major synthetic challenges exhibited by ainsliatrimers A and B was the ambiguous configuration of the two intriguing spiro[4,5]decane moieties. Accordingly, we decided to construct the two spiro[4,5]decane moieties via different pathways, which might provide us insightful information for the structural elucidation.

We initially set to synthesize ainsliatrimer B (**21**) from gochnatiolide A in order to generate the upside spiro[4,5]-decane motif (Scheme 4). Gochnatiolide A (**12**) was converted

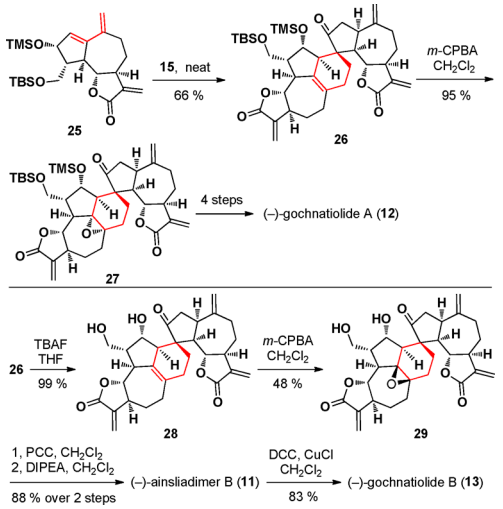
Scheme 4. Biomimetic Syntheses and Structure Elucidation of (−)-Ainsliatrimers A (5) and B (6)



to diene **22** via a direct palladium-mediated dehydrogenation. When diene **22** and dehydrozaluzanin C (**15**) were combined in neat conditions, we obtained a mixture of alkene-isomerized product (**23**) and Diels–Alder cycloadduct (**24**) in 22% and 20% yield, respectively. Selective epoxidation of **24** followed by DBU-mediated epoxide opening proceeded smoothly to afford trimer **21** as a single diastereomer. Unfortunately, the NMR data of **21** did not fully match with the reported data of natural ainsliatrimer B. We then turned our attention to an alternative pathway in which the downside spiro[4,5]decane motif was constructed. After extensive exploration, we developed cascade transformations involving the Diels–Alder reaction of gochnatiolide B (**13**) with the purified diene **17** in toluene under air followed by reduction using Me_2S to afford both (−)-ainsliatrimers A (**5**) and B (**6**) in 38% and 11% yield, respectively. The spectral data of these synthetic samples fully matched with the natural ones. Therefore, through total synthesis we ultimately confirmed the structures of (−)-ainsliatrimers A (**5**) and B (**6**) unambiguously.

Qin and co-workers also reported an alternative strategy for the total syntheses of (−)-ainsliadimer B, (−)-gochnatiolides A and B.[17] As shown in Scheme 5, silyl-protected diene **25** derived from santonin (**7**) via 19 steps underwent a [4 + 2]

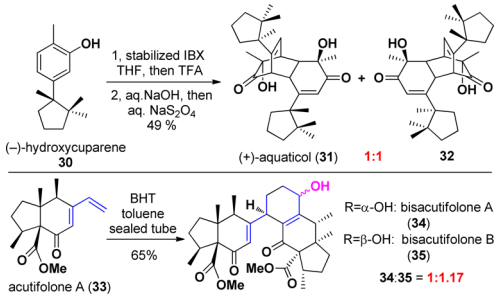
Scheme 5. Total Syntheses of (−)-Ainsliadimer B (11) and (−)-Gochnatiolides A (12) and B (13)



cycloaddition with **15** in neat conditions to afford the endo product **26** with a high diastereoselectivity. Epoxidation of **26** produced epoxide **27** as a single stereoisomer which was further transformed to gochnatiolide A (**12**) in four steps including deprotection of silyl groups, selective oxidation, epoxide opening, and hydroxyl elimination. When the silyl groups in dimer **26** were removed, the epoxidation generated a mixture of α and β-epoxide with a 1:1 ratio. The β-epoxide **29** was converted to ainsliadimer B (**11**) via selective oxidation of the secondary alcohol followed by epoxide opening. Finally, dehydration of ainsliadimer B (**11**) with DCC/CuCl furnished the synthesis of gochnatiolide B (**13**).

In 2007, Quideau and co-workers described a biomimetic synthesis of (+)-aquaticol (**31**), which was the first example of using Diels–Alder reaction of orthoquinol-derived monomeric sesquiterpenoid (Scheme 6).[18] They applied a one-pot cascade

Scheme 6. Biomimetic Syntheses of (+)-Aquaticol (31) and Bisacutifolones A (34) and B (35)



reaction including dearomatizing hydroxylation and intermolecular Diels–Alder reaction to construct the highly functionalized framework. In the same year, Nishiyama's group reported the syntheses of bisacutifolones A (**34**) and B (**35**) using [4 + 2] cycloaddition as a central strategy.[19] Interestingly, the authors observed a rapid autoxidation to install the required hydroxyl group within the natural products **34** and **35**.

Other excellent synthetic endeavors in biomimetic syntheses of disesquiterpenoids using [4 + 2] cycloaddition strategy include the syntheses of bacchopetiolone (**38**) and chloraholide A (**42**) (Scheme 7).[20,21] Wood and co-workers

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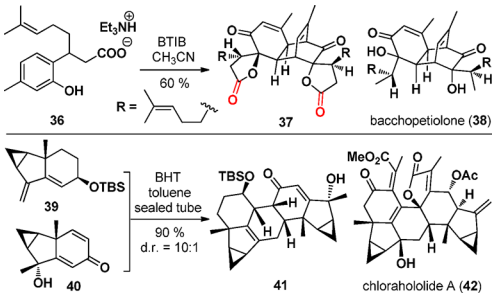
Scheme 7. Studies toward the Total Syntheses of Bacchopetiolone (38) and Chlorahololide A (42)

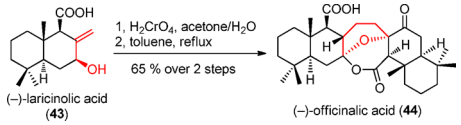


developed an efficient tandem phenolic oxidation/Diels–Alder reaction strategy to furnish the synthesis of **37**, which was an advanced intermediate for **38**. Unfortunately, the further synthetic elaboration of **37** like the bis-decarbonylation was proved to be problematic. Recently, Peng et al. reported the synthesis of the heptacyclic core **41** for **42** using a biomimetic endoselective Diels–Alder reaction as the key step.

■ HETERO-DIELS–ALDER REACTION

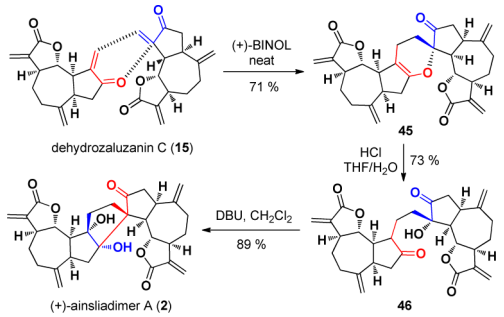
Although a large number of disesquiterpenoid natural products derived from hetero-Diels–Alder reactions exist, only a handful of them have been synthesized. (−)-Officinalic acid (**44**), a metabolite of fungus, was first isolated by Jahns in the 1890s,[22] but the structure was not fully elucidated until 1979. Recently, Arigoni and co-workers completed the partial synthesis of **44** from the naturally occurring (−)-laricinolic acid (**43**).[23] As shown in Scheme 8, the alcohol in **43** was initially oxidized by Jones' reagent, and the product was subsequently heated in toluene to give **44** via a two-step cascade reaction.

Scheme 8. Biomimetic Synthesis of (−)-Officinalic Acid (44)



(+)-Ainsliadimer A (**2**) was isolated by Zhang and co-workers from a traditional Chinese medicine *Ainsliaea macrocephala* recently.[13] The structure of **2** features a cyclopentane system connecting the two monomeric sesquiterpene lactone units. According to the biogenetic proposal, the full carbon cyclopentane system would be constructed in a three-step sequence involving hetero-Diels–Alder reaction, hydrolysis, and intramolecular aldol reaction. We initiated the synthetic studies toward (+)-ainsliadimer A (**2**) in 2009. We first developed an efficient route to access dehydrozaluzanin C (**15**) from santonin (**7**).[14] With dehydrozaluzanin C in hand, we examined the key hetero-Diels–Alder reaction. Initial attempts to use a number of different conditions including Lewis acids, different solvents, or temperature unfortunately failed. We then shifted our focus to the hydrogen-bonding catalysis. Ultimately, we observed that BINOL effectively mediated the hetero-[4 + 2] cycloaddition to afford dimer **45** as a single stereoisomer in 71% yield (Scheme 9). Hydrolysis of dimer **45** under mild acidic conditions afforded compound **46**, which could further undergo an intramolecular aldol reaction to furnish (+)-ainsliadimer A (**2**) efficiently. Notably, this synthetic work presented the first example of hydrogen-bonding-mediated

Scheme 9. Biomimetic Total Synthesis of (+)-Ainsliadimer A (2)

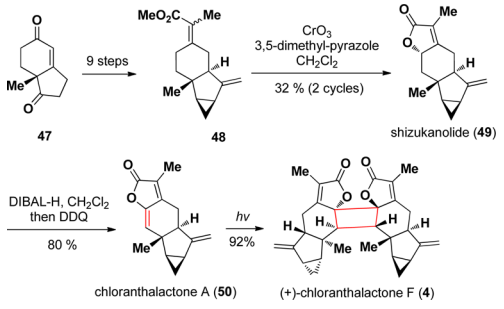


hetero-Diels–Alder reaction of both electron-deficient diene and dienophile.

■ [2 + 2] CYCLOADDITION

[2 + 2] cycloaddition is also involved in the biosynthesis of a number of disesquiterpenoids. Surprisingly, until now only one total synthesis has been reported. (+)-Chloranthalactone F (**4**) was initially isolated from *Chloranthus glaber* by Takeda and co-workers in 1993.[24] However, the structure of **4** was initially misassigned as a monomeric lindenane sesquiterpenoid due to the highly axial symmetry. Nakatani's group disclosed the structural revision of chloranthalactone F in 1995, indicating the natural product possessed a dimeric structure.[25] Very recently, Zhao and co-workers completed the first total synthesis of **4** using a biomimetic strategy.[26] They also unambiguously confirmed the structure of **4** by X-ray crystallography. As shown in Scheme 10, the key intermediate

Scheme 10. Biomimetic Total Synthesis of (+)-Chloranthalactone F (4)



48 was synthesized from (*R*)-Hajos–Wiechert ketone (**47**) in nine steps. The following conversion of **48** to shizukanolide (**49**) was achieved by a CrO_3-mediated allylic oxidation/lactonization process. Sequential treatment of **49** with DIBAL-H and DDQ led to a reductive/oxidative enol–lactonization cascade and afforded the desired monomer chloranthalactone **A** (**50**). Exposure of **50** to a high-pressure Hg lamp furnished **4** smoothly in high yield as a single diastereoisomer.

■ C–C BOND COUPLING

Biosynthetically, most of disesquiterpenoids with one C–C bond to link two monomeric units are formed through a radical coupling pathway. Biatractylolide (**3**) and biepiasterolide (**55**), containing two identical units linked by a bond between carbon atoms C8 and C8′, were isolated from a traditional Chinese medicinal plant *Atractylodes macrocephala*.[27] Baldwin and co-

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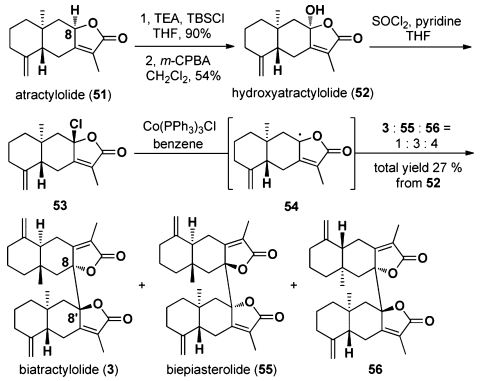
workers initially envisioned that both of the dimers might be biosynthetically generated by the dimerization of atractylolide (**51**) via a radical intermediate **54**.[28] However, the direct dimerization of **51** using DTBP (di-*tert*-butyl peroxide) as a radical initiator did not produce the desired **3** or **55** (Scheme 11). The following mechanistic studies revealed that the steric

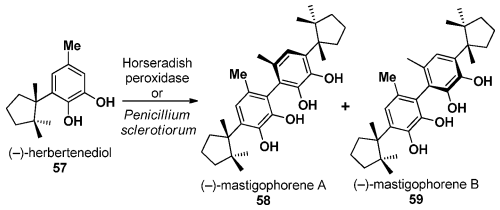
Scheme 11. Biomimetic Syntheses of Biatractylolide (3) and Biepiasterolide (55)



hindrance between C8−H in **51** and the *t*-BuO radical might prevent the dimerization. Nevertheless, after **51** was converted to hydroxyatractylolide (**52**) via a stepwise vinylogous Rubottom oxidation, and the newly generated hydroxyl group was substituted by a chlorine atom to afford chloroatractylolide (**53**), the key dimerization was accomplished by the treatment of **53** with $Co(PPh_3)_3Cl$. As a result, biatractylolide (**3**) and biepiasterolide (**55**) were afforded in one pot but along with another diastereoisomer **56**.

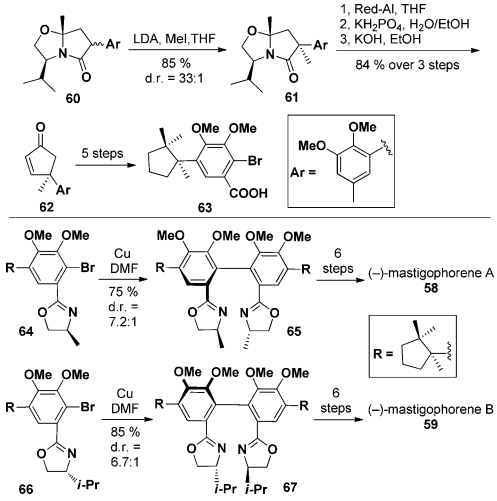
(−)-Mastigophorenes A (**58**) and B (**59**), two dimeric isocuparane sesquiterpenes, were isolated from the liverwort *Mastigophora diclados*. They showed potential neurotrophic properties,[29] As shown in Scheme 12, (−)-mastigophorenes A and B are biosynthetically generated from the oxidative dimerization of the naturally occurring (−)-herbertenediol (**57**).[30]

Scheme 12. Syntheses of (−)-Mastigophorenes A (58) and B (59)



The intriguing axially chiral architectures of mastigophorenes A (**58**) and B (**59**) attracted a number of synthetic studies.[31] The first total syntheses of **58** and **59** were accomplished by Meyers and co-workers (Scheme 13).[31a] The absolute configuration of cyclopentane was initially established by "deracemizing alkylation" of **60** to afford **61** with high diastereoselectivity. A sequence involving reduction, hydrolysis, and cyclization delivered cyclopentenone **62** in high yield. After the elaboration of **62** to generate acid **63** in five steps, two oxazoline auxiliaries were attached to **63** to afford compounds **64** and **66**. Interestingly, both **64** and **66** could be converted to

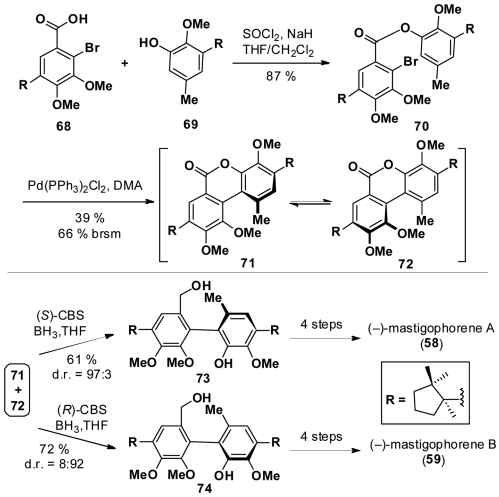
Scheme 13. Meyers's Syntheses of (−)-Mastigophorenes A (58) and B (59)



biaryl **65** and **67**, respectively, via Ullmann coupling in good diastereoselectivities. Finally, **65** and **67** were transformed to (−)-mastigophorenes A and B, respectively, in 6 steps. Applying a similar approach, Meyers' group also completed the synthesis of a structurally related cadinane sesquiterpenoid dimer (+)-gossypol.[32]

As a complementary approach to the enantioselective total syntheses of **58** and **59** described above, Bringmann's group reported a strategy that featured Pd(0)-catalyzed intramolecular biaryl coupling and Corey−Bakshi−Shibata (CBS) reduction mediated resolution (Scheme 14).[31b] The dimerization

Scheme 14. Bringmann's Syntheses of (−)-Mastigophorenes A (58) and B (59)



commenced with an intermolecular esterification between **68** and **69**, which were derived from the optically pure *O,O*-dimethylated herbertenediol and herbertenediol, respectively. Subsequent treatment of bromo ester **70** with a Pd(0) catalyst for an intramolecular coupling afforded the two rapidly interconverting atropo-diastereomers **71** and **72** in moderate yield. Notably, this mixture could be converted to **73** or **74** directly with high diastereoselectivity by employing different oxazaborolidine-mediated CBS reductions. As a result, the enantiomerically pure **73** and **74** were transformed to **58** and

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59, respectively, in four steps. Using this established methodology, Bringmann and co-workers also completed the first total syntheses of (−)-mastigophorenes C and D,[33] which were structurally related dimeric isocuparane sesquiterpenes to **58** and **59**.

■ CONCLUSIONS

The stunningly complex and diverse structures as well as significant biological activities exhibited by the oligomeric sesquiterpenoids have long established this unique family of natural products as fascinating targets for synthetic studies. Remarkably, the dimeric or trimeric sesquiterpenoids have inspired the development of a number of elegant biomimetic strategies for the total synthesis. Despite a large variety of biomimetic bond formations, including Diels−Alder reaction, hetero-Diels−Alder reaction, [2 + 2] cycloaddition, and C−C bond coupling, significant synthetic challenges remain regarding the control of regio-, chemo-, and stereoselectivities. A large number of highly functionalized oligomeric sesquiterpenoids have yet to be synthesized efficiently. These unmet synthetic challenges demonstrate the urgent need for new methodologies which might provide an inspiration for future research in organic synthesis. Moreover, the efficient syntheses of bioactive oligomeric sesquiterpenoids will ultimately pave the way for the subsequent chemical biology studies as well as drug discovery endeavors.

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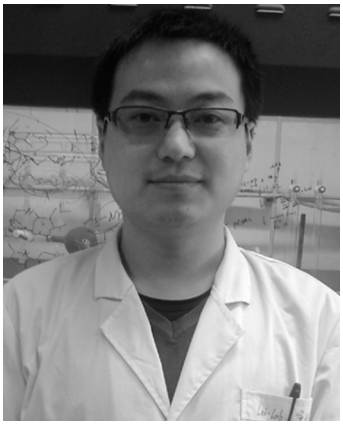
Notes

The authors declare no competing financial interest.

Biographies



Chao Li earned his B.S. from Qingdao University of Science and Technology in 2008 and completed his Ph.D. in Organic Synthesis in 2013 under the supervision of Prof. Xiaoguang Lei at Tianjin University and National Institute of Biological Sciences (NIBS), China. He will join Prof. Phil S. Baran's group at Scripps Research Institute as a postdoctoral fellow in the summer of 2014.

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