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Synthetic Approaches To Construct the 6,8-DOBCO Framework in Natural Products

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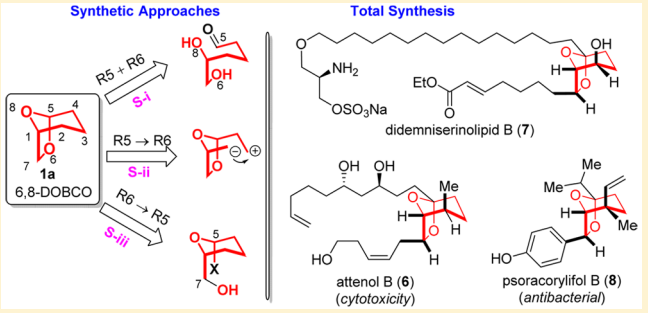
ABSTRACT: 6,8-Dioxabicyclo[3.2.1]octane skeleton (6,8-DOBCO) is a very common structural motif in many biologically active natural products. This synopsis surveys various approaches used to access the 6,8-DOBCO framework present in natural products and summarizes total syntheses of 6,8-DOBCO-containing psoracorylifol B, *ent*-psoracorylifol C, didemniserinolipid B, and attenol B from our laboratory and others.



Dioxabicyclo-[3.2.1]octane (DOBCO) is a structurally unique bridged fused ring system found in many natural products, featuring a one-atom bridge between the five- and six-membered rings. From the point of view of organic functional groups consisting of these two oxygen atoms, the nine known DOBCOs (**1a**–**i**, Figure 1) can be categorized as either bicyclic acetals (6,8-, 2,8-, 2,7-, and 2,4-DOBCOs; **1a**, **1b**, **1c**, and **1f**), ethers (3,8-, 2,6-, and 3,6-DOBCOs; **1d**, **1h**, and **1i**), or peroxides (2,3- and 6,7-DOBCOs; **1e** and **1g**). Although all types of DOBCOs except for 2,3-DOBCO exist as a subunit of complex natural products, the most common DOBCO found in various natural sources is the bicyclic acetal 6,8-DOBCO (**1a**), which usually adopts a six-membered chair conformation and seven-membered boat conformation[1] due to the inherent anomeric effect.[2] The 6,8-DOBCO-containing natural products (**2**-**9**)[3] exhibit various biological activities including cytotoxicity and antibacterial. Not surprisingly, the privileged intriguing 6,8-DOBCO structure embodied in many biologically active natural products has attracted extensive interest in the synthetic community, leading to the development of many efficient or interesting synthetic methods and strategies, which have not been reviewed or summarized to date. It would be of paramount importance and interest to synthetic chemists that different synthetic methods/strategies for preparation of 6,8-DOBCOs are summarized with selected examples highlighted in natural product synthesis. This Synopsis, therefore, will be focused on (i) a brief summary of the synthetic methods and strategies reported for preparation of 6,8-DOBCOs and (ii) recent advances in total syntheses of four 6,8-DOBCO-containing natural products psoracorylifol B,[4] *ent*-psoracorylifol C,[4] attenol B,[5] and didemniserinolipid B,[6] which have been accomplished recently in our laboratory. Readers who are interested in total synthesis of other 6,8-DOBCO-containing natural products such as pinnatoxin A[7] and trichodermatide A[8] are advised to refer to the other related references.

1.0. GENERAL STRATEGIES TOWARD 6,8-DOBCOS

Strategically, as depicted in Scheme 1, 6,8-DOBCOs could be constructed by (i) simultaneous formation of 5- and 6-membered rings in a single step (R5 + R6, S-i), (ii) formation of dioxolane derivatives followed by 6-membered ring annulation (R5 → R6, S-ii), and (iii) formation of tetrahydropyran derivatives and subsequent 5-membered ring cyclization (R6 → R5, S-iii). The most widely used strategy in total synthesis of complex natural products is S-i (R5 + R6): bicyclization of dihydroxycarbonyls or its chemical equivalents (such as dihydroxyalkene/alkyne, epoxycarbonyls, or even [3 + 2]-dipolar cycloaddition) due to its high efficiency and predictable stereochemistry outcome. However, the enantioselective preparation of the substrates often requires multiple steps with particularly sophisticated manipulations of functional groups. The second strategy (S-ii) features (i) facile and efficient formation of the dioxolanes from various diols and carbonyl compounds and (ii) many favorable cyclization methods (e.g., intramolecular S_N2 substitution and ring-closing metathesis) available for the subsequent 6-membered ring construction. Therefore, it has been employed for the synthesis of simple 6,8-DOBCO-containing natural products. The third strategy (S-iii) has also received much attention probably because the stereoselective construction of functionalized tetrahydropyrans is interesting and has been well established in the context of total synthesis of other complex natural products. The next section will summarize specific synthetic approaches based on these three general strategies. In addition, other interesting methods will be included at the end of this section.

1.1. (S-i) Intramolecular Cycloketalization (Or Cycloacetalization) of δ-Keto Diols and Its Chemical Equivalents. The most prevailing and straightforward method for

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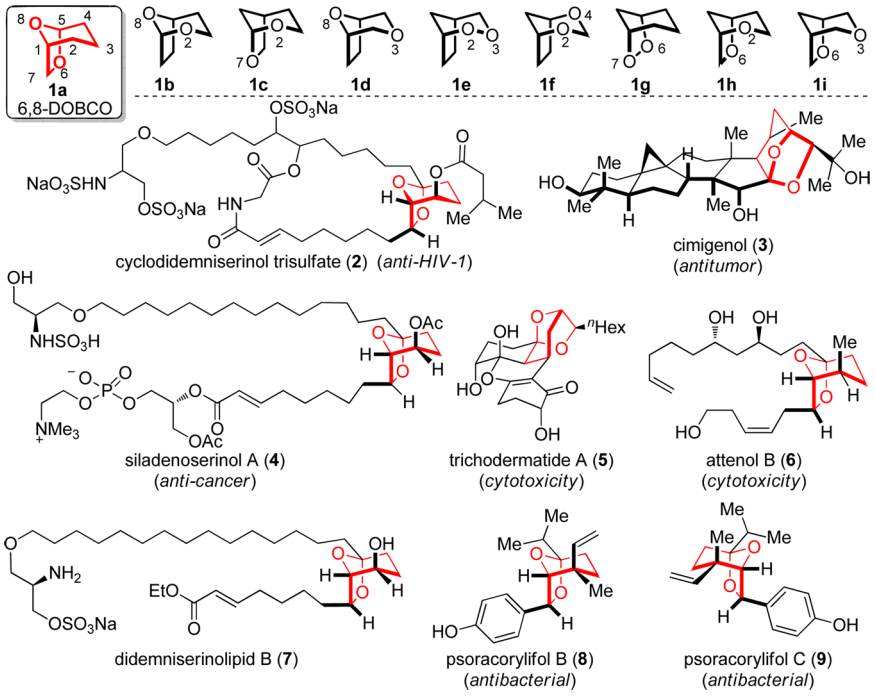
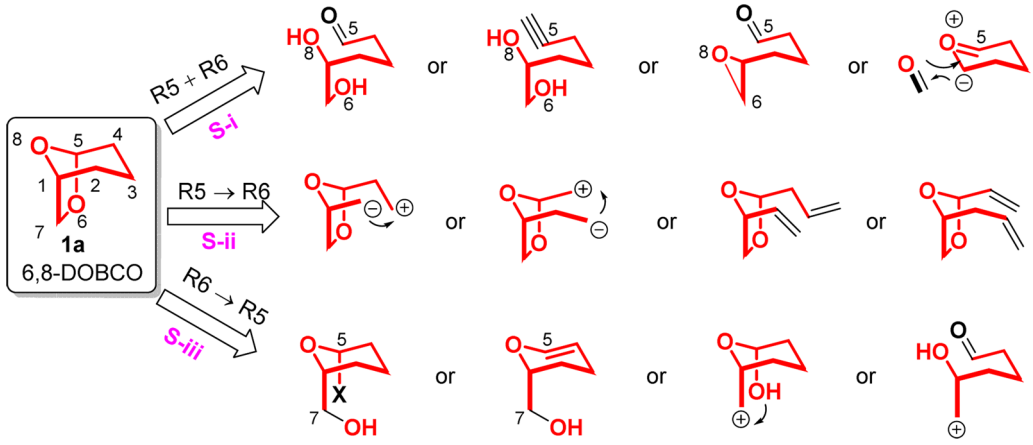
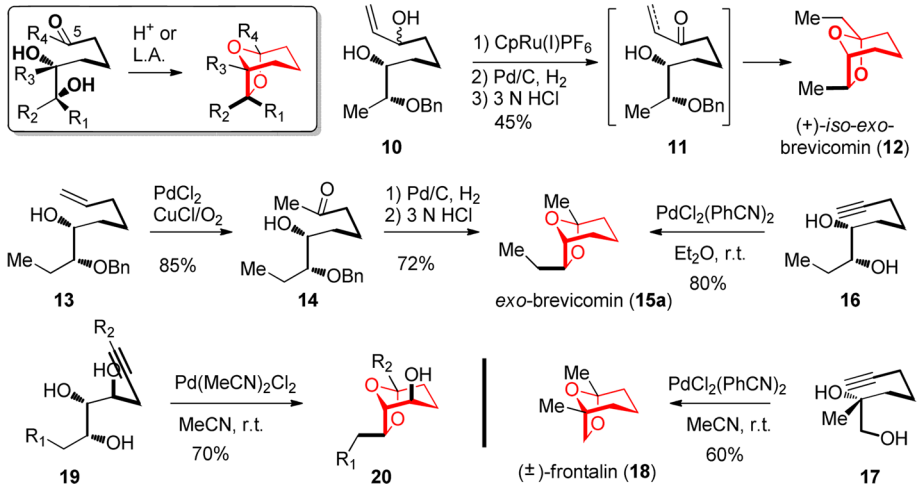


Figure 1. Examples of DOBCO skeletons and representative 6,8-DOBCO-containing natural products.

Scheme 1. Three General Strategies to 6,8-DOBCO



Scheme 2. Intramolecular Dehydrative Cycloketalization of *δ*-Keto Diols and Related Processes



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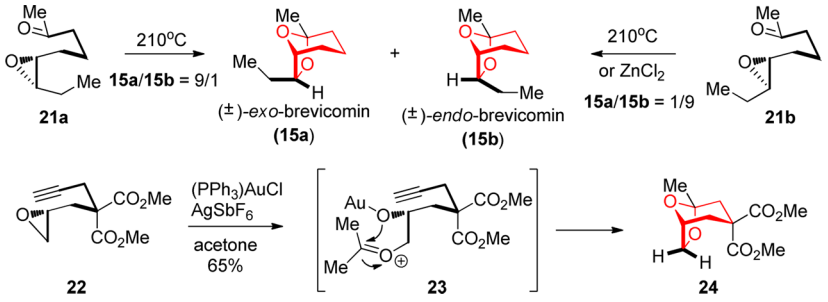
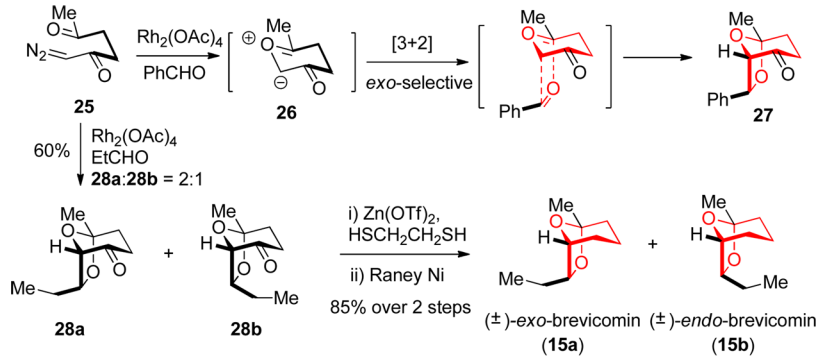
Scheme 3. Rearrangement of δ-Keto Epoxides and δ-Alkyne Epoxides



Scheme 4. [3 + 2] Cycloaddition of α-Diazo Ketone with Aldehyde



the construction of the 6,8-DOBCO framework is intramolecular dehydrative ketalization (or acetalization) of δ-keto diols and its chemical equivalents (Scheme 2). Most 6,8-DOBCO-containing natural products have been synthesized by this strategy. There are also several reviews summarizing the syntheses of pheromones[9] and marine natural products[10] containing the 6,8-DOBCO motif. In addition, Ley and co-workers employed this strategy for divergent syntheses of natural-product-like derivatives with a 6,8-DOBCO scaffold for bioactivity evaluation.[11] One of the most interesting applications of this strategy is the combination of a metal-catalyzed reaction with cycloketalization. For example, Carreaux[12] reported the synthesis of (+)-iso-*exo*-brevicomin (**12**) using ruthenium-catalyzed isomerization (or oxidation) of allylic alcohol **10** to provide the necessary keto-diol precursor (**11**) for subsequent hydrogenation and HCl-promoted dehydrative cycloketalization. Similarly, Mori[13] et al. devised a Wacker oxidation and hydrogenation/cycloketalization for the enantioselective synthesis of the pheromone (+)-*exo*-brevicomin (**15a**) and Kongkathip[14] and co-workers employed Wacker oxidation and simultaneous cycloketalization for the total synthesis of amberketal. Alternatively, metal-mediated cycloisomerization of alkynediols has been recognized as an effective method for the construction of 6,8-DOBCO frameworks. In this regard, Utimoto[15] and co-workers reported the pioneering work on syntheses of racemic *exo*-brevicomin (**15a**) and frontalin (**18**) through palladium-catalyzed cycloisomerization of alkyne-δ,ε-diol **16** and **17**, respectively (Scheme 2). One key issue for cycloisomerization of γ-hydroxyalkyne is the mode of cyclization: 5-*exo*-*dig* versus 6-*endo*-*dig*. The systematic investigation by Ramana[16] et al. revealed that the regioselectivity in general was influenced by the electronic nature of the alkyne substituents. A preference of 6-*endo*-*dig* fashion over the 5-*exo*-*dig* mode was noted, provided the alkyne substituents are not sufficiently electron-withdrawing. Based on this finding, Ramana[17] et al. documented an exclusive 6-*endo*-*dig* cyclization of the ω-alkyne-1,2,3-triol **19** to forge the 6,8-DOBCO core **20** of didemniserinolipid B. In addition, platinum could also catalyze this cycloisomerization reaction.[18]

1.2. (S-i) Rearrangement of δ-Keto Epoxides and δ-Alkyne Epoxides. In 1969, Wassermann[19] and co-workers found that the δ-keto epoxides **21a** and **21b** underwent thermal rearrangement at 210 °C to generate a mixture of *exo*-brevicomin (**15a**) and *endo*-brevicomin (**15b**) (Scheme 3). Interestingly, the rearrangement was highly stereoselective: the *cis*-epoxide **21a** could deliver the *exo*-brevicomin (**15a**) as a major product with 90% yield and the *endo*-isomer **15b** with 10% yield; the *trans*-epoxide **21b** gave the opposite ratio of **15b** and **15a** with similar yield. Importantly, the rearrangement could also be promoted by Brønsted acid[20] (H_2SO_4, $HClO_4$, *p*-TsOH), Lewis acid[21] (e.g., $ZnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$), or activated microporous solids[22] under mild conditions. Yadav[23] and Boeckman[24] exploited this interesting transformation in the total synthesis of amberketal and saudin, respectively. In addition, on the basis of Shi's pioneering work on gold-catalyzed cascade cyclization of epoxyalkynes,[25] Balamurugan[26] reported that the gold activation of both epoxide and alkyne (e.g., **22**) could be exploited for the synthesis of 6,8-DOBCO **24**.

1.3. (S-i) [3 + 2]-Dipolar Cycloaddition of Diazo Ketones with Aldehyde. In 1988, Padwa[27] et al. found that carbonyl ylide **26** generated by rhodium-induced reaction of α-diazo carbonyl compound **25** could undergo regioselective 1,3-dipolar cycloaddition with benzaldehyde to afford *exo*-6,8-DOBCO **27** in high yield (Scheme 4). This initial discovery was exploited subsequently in the total synthesis of racemic *exo*-brevicomin (**15a**) and *endo*-brevicomin (**15b**).[28] Significant levels of enantioselectivity could be achieved by using chiral Pybox-rare earth metal triflate complexes as chiral Lewis acid catalysts.[29] Hashimoto[30] et al. employed a similar catalytic

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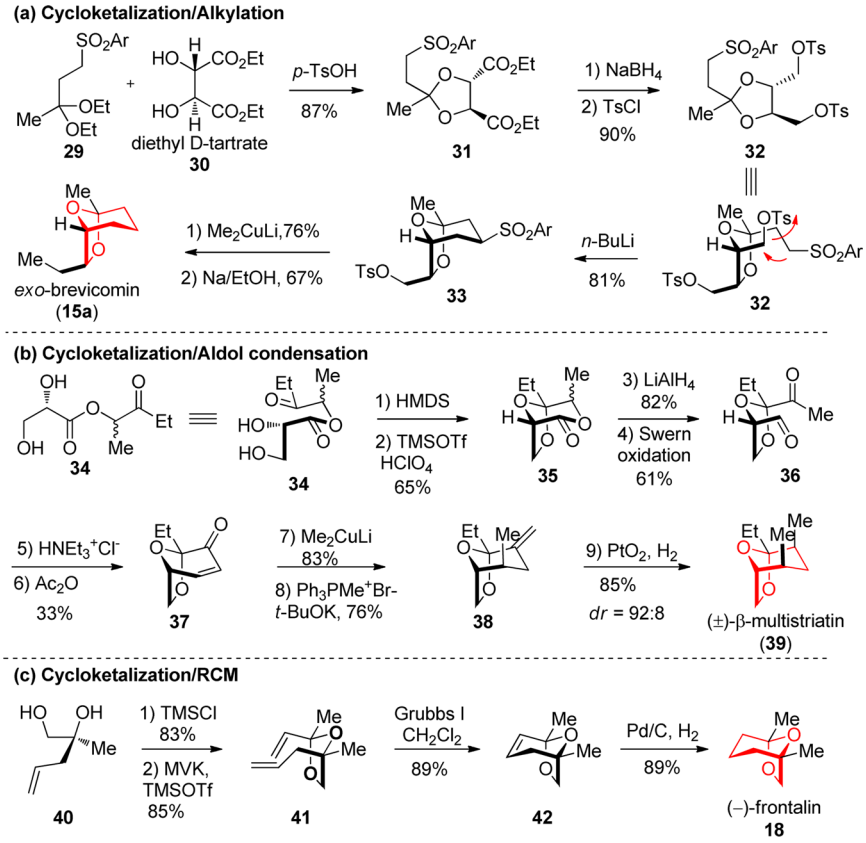
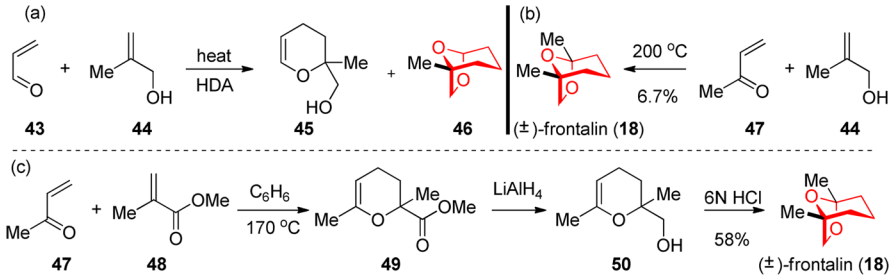
Scheme 5. Cycloketalization/6-Membered Ring Formation



Scheme 6. Oxa-Diels−Alder Reaction/Cycloketalization



asymmetric [3 + 2] cycloaddition for the construction of the 6,8-DOBCO framework of psoracorylifols B and C.

1.4. (S-ii) Cycloketalization/6-Membered Ring Formation. The second strategy for synthesis of the 6,8-DOBCO framework primarily revolves on dioxolane formation via cycloketalization followed by (i) intramolecular S_N2 substitution, (ii) intramolecular aldol reaction, and (iii) olefin ring-closing metathesis (Scheme 5). In 1982, Masaki[31] et al. reported the total synthesis of (+)-*exo*-brevicomin (**15a**) via dioxolane formation (**29** + **30** → **31**) and intramolecular S_N2 substitution (**32** → **33**) as the key steps for the 6,8-DOBCO framework (Scheme 5a). Subsequently, Scharf[32] et al. employed the similar strategy for total syntheses of several 6,8-DOBCO pheromones. In 1995, Sharf[33] achieved the first total synthesis of racemic *β*-multistriatin by a new tactic for the 6,8-DOBCO: an intramolecular cycloketalization for the dioxolane formation (**34** → **35**) and intramolecular aldol condensation (**35** → **36**), to avoid the facile epimerization of C-2 axial methyl group under mild acidic condition (Scheme 5b). The first intermolecular cycloketalization/ring-closing metathesis strategy to 6,8-DOBCO was reported by Grubbs[34] and co-workers in the total synthesis of (−)-frontalin ((−)-**18**, Scheme 5c). Later, Burke had fully exploited this efficient and concise strategy for the total syntheses of many natural products including brevicomin,[35] didemniserinolipid B,[36] Neu5Ac,[37] and KDN.[38]

1.5. (S-iii) Oxa-Diels−Alder Reaction/Cycloketalization. The third synthetic strategy (S-iii) has also been widely used in the synthesis of 6,8-DOBCO and related natural products, and only some of them will be included in Schemes 6−8. In 1951, Smith[39] reported the isolation of an unexpected bicyclic acetal **46** from the thermal reaction of acrolein (**43**) and methallyl alcohol (**44**) (Scheme 6a). In 1969, Kinzer[40] employed this type of oxa-Diels−Alder reaction/cycloketalization for the first synthesis of frontalin (**18**) (no yield or experimental details) (Scheme 6b). Mundy repeated Kinzer's work and only obtained 6.7% overall yield.[41] It is of interest to note that the oxa-Diels−Alder reaction of methyl vinyl ketone (MVK, **47**) and excess methyl methacrylate (**48**) proceeded much better and after reduction and cycloketalization provided

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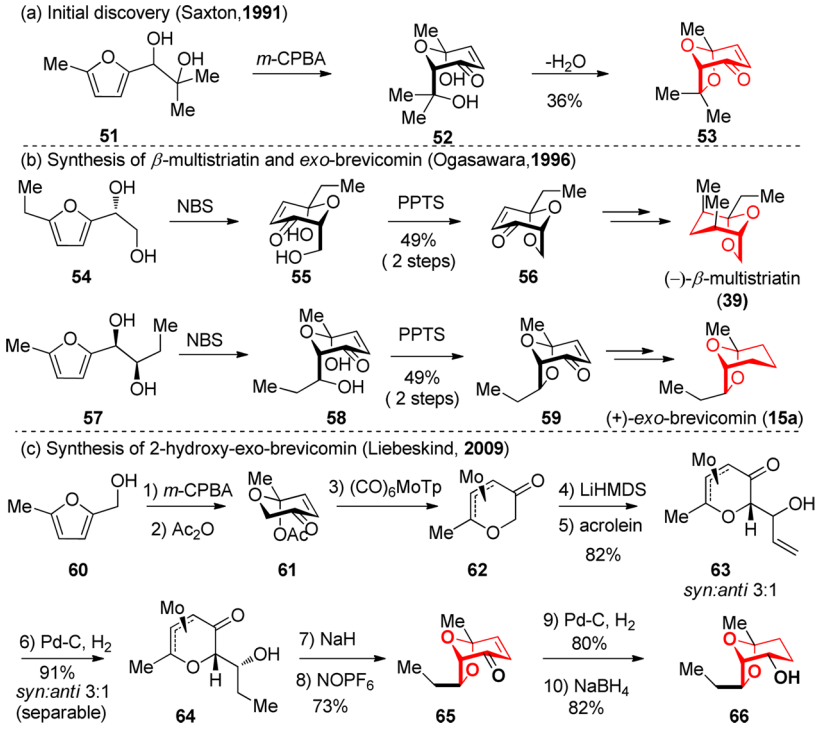
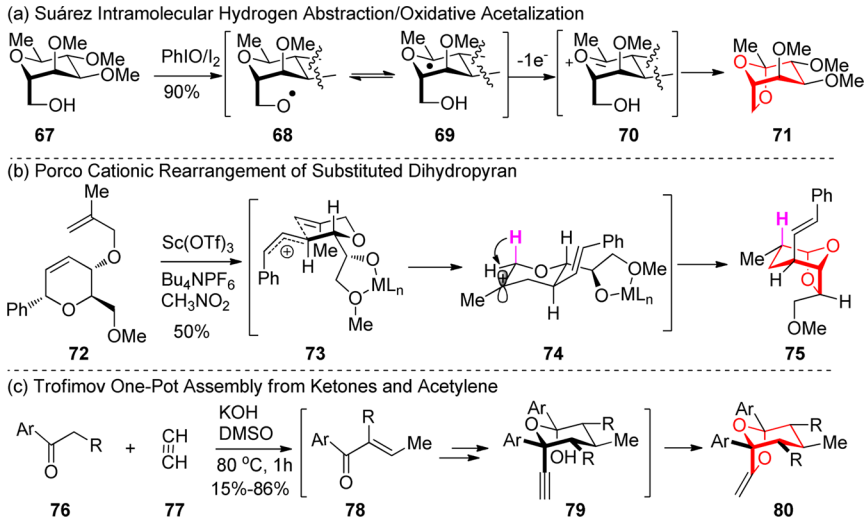
Scheme 7. Achmatowicz Rearrangement/Cycloketalization



Scheme 8. Synthetic Methods Based on Pyran Derivatives (Suarez, Porco, and Trofimov)



40−58% yield of frontalin (**18**) (Scheme 6c).[42] Recently, Maignan[43] and Carreaux[12] reported asymmetric versions of oxa-Diels−Alder reaction for the enantioselective synthesis of 6,8-DOBCO natural products.

1.6. (S-iii) Achmatowicz Rearrangement/Cycloketalization. The construction of the 6,8-DOBCO framework through Achmatowicz rearrangement/cycloketalization was first reported by Saxton[44] and co-workers in 1991 (Scheme 7a). Achmatowicz rearrangement of furfuryl diol **51** was readily promoted with *m*-CPBA to provide the dihydropyranone acetal **52** (a mixture of two isomers), which underwent spontaneous dehydrative ketalization to afford 6,8-DOBCO **53** in 36% yield. In 1996, Ogasawara[45] employed this strategy to complete the enantioselective synthesis of (−)-*β*-multistriatin (**39**) and (+)-*exo*-brevicomin (**15a**) (Scheme 7b). In 2009, Liebeskind[46] developed a new method to rapidly generate the 6,8-DOBCO framework through Achmatowicz rearrangement/organometallic enantiomeric scaffold-based aldol reaction/nucleophilic ketalization/demetalation sequence with high enantiopurity. The method was conceptually an equivalent of intermolecular oxa-[5 + 2] cycloaddition and showcased by an effective enantioselective total synthesis of (+)-2-hydroxy-*exo*-brevicomin (**66**) (Scheme 7c). In 2011, Vassilikogiannakis[47] and co-workers employed similar but photopromoted Achmatowicz rearrangement/cycloketalization for the synthesis of 2-hydroxy-*exo*-brevicomin (**66**).

1.7. (S-iii) Some Unusual and Interesting Methods Based on Pyran Derivatives. Levoglucosans, the most representative examples of 6,8-DOBCO compounds, are generally formed by acid-promoted dehydration of the

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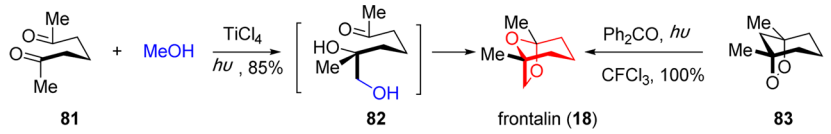
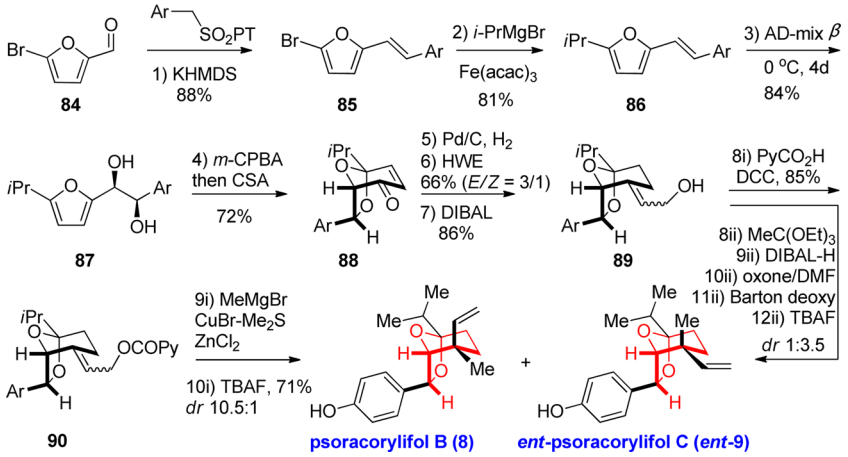
Scheme 9. Photopromoted Rearrangement



Scheme 10. Total Syntheses of Psoracorylifol B and *ent*-Psoracorylifol C



corresponding carbohydrates, thermal depolymerization of some polysaccharides, or by specific intramolecular glycosylation reactions. In 2000, Suárez and Francisco[48] reported an interesting method for the synthesis of levoglucosans under neutral conditions (Scheme 8a). This reaction of tetrahydropyran **67** was initiated by treatment of (diacetoxyiodo)benzene (DIB) or iodosylbenzene in the presence of iodine to generate the alkoxy radical (**68**), which underwent intramolecular hydrogen abstraction (IHA) to generate the *C*-radical (**69**). Subsequent oxidation to the oxycarbenium ion (**70**) and cycloketalization gave the levoglucosan **71**. Another interesting unexpected formation of the 6,8-DOBCO framework observed by Porco[49] and co-workers involved $Sc(OTf)_3$-mediated cation−olefin cyclization of dihydropyran **72**, 1,2-hydride shift, and cycloketalization (Scheme 8b). Recently, Trofimov[50] et al. discovered a one-pot reaction of aromatic ketone and acetylene to afford 7-methylene-6,8-DOBCOs (e.g., **80**) with high regio- and stereoselectivity in good to excellent yield. They proposed a plausible thought-provoking mechanism to rationalize the formation of the 6,8-DOBCO **80** (Scheme 8c).

1.8. (Others) Photopromoted Synthesis of 6,8-DOBCO. There are some other synthetic methods/strategies that could not be classified as Scheme 1 and are not included in this section. One important consideration to select these methods is the possible/proven application in natural product synthesis. Therefore, we add two more intriguing examples of the synthesis of frontalin (**18**) via photopromoted rearrangement (Scheme 9). In 1980, Sato[51] et al. found that irradiation of the solution of heptane-2,6-dione (**81**) in $MeOH/CH_2Cl_2$ with high pressure mercury lamp in the presence of $TiCl_4$ could gave the racemic frontalin **18** in gram scale. In 1981, Wilson and Rekers[52] studied the decomposition of bicyclic endoperoxide under various conditions and found that benzophenone-sensitized photodecomposition of **83** could lead to the quantitative formation of frontalin (**18**).

2.0. TOTAL SYNTHESES OF 6,8-DOBCO-CONTAINING NATURAL PRODUCTS

Many synthetic methods described in the previous section have been used in the total synthesis of simple 6,8-DOBCO-containing natural products such as the pheromones frontalin, brevicomin, and multistriatin. Except for intramolecular dehydrative cycloketalization of δ-keto diols (S-i, Scheme 2) being widely used in the total synthesis of pinnatoxin A, the utility of these methods has rarely been demonstrated in the total synthesis of complex natural products. This would arouse wide concern on employment of these methods when designing a synthetic route for a complex molecule. In this section, we selected and highlighted some recent total synthesis of 6,8-DOBCO-containing natural products, which have also been achieved in our laboratory. In particular, three different strategies as depicted in Scheme 1 were demonstrated in these synthetic achievements. It is of importance to witness the application of these methods and strategies in the complex natural product synthesis, shedding some light on their powerfulness as well as potential limitations.

2.1. Total Syntheses of Psoracorylifol B and *ent*-Psoracorylifol C (Tong, 2014). Psoracorylifols B and C (**8** and **9**, Figure 1) were isolated in 2006 by Yue[3c] and co-workers from the seeds of *Psoralea corylifolia L.* (buguchi, a well-known traditional Chinese medicine for treatment and cure of gynecological bleeding, vitiligo, psoriasis, and bone fractures).[53] The first synthetic effort toward these natural products was made in 2010 by Hashimoto[30] and co-workers, who employed an efficient Rh-catalyzed 1,3-dipolar cycloaddition of α-diazo carbonyl compounds with aldehydes to prepare the common 6,8-DOBCO framework of **8** and **9**. In 2014, we achieved the first, asymmetric total synthesis of psoracorylifol B (**8**) and *ent*-psoracorylifol C (*ent*-**9**) by using Achmatowicz rearrangement/cycloketalization of the third strategy (S-iii) for the construction of the 6,8-DOBCO framework[4] (Scheme 10). A straightforward high-yielding three-step sequence, Julia−Kocienski olefination, iron-catalyzed Kochi cross-coupling

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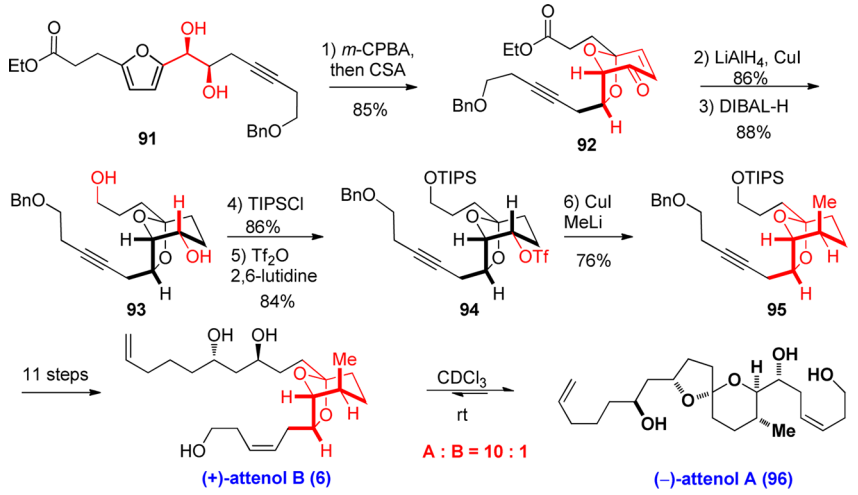
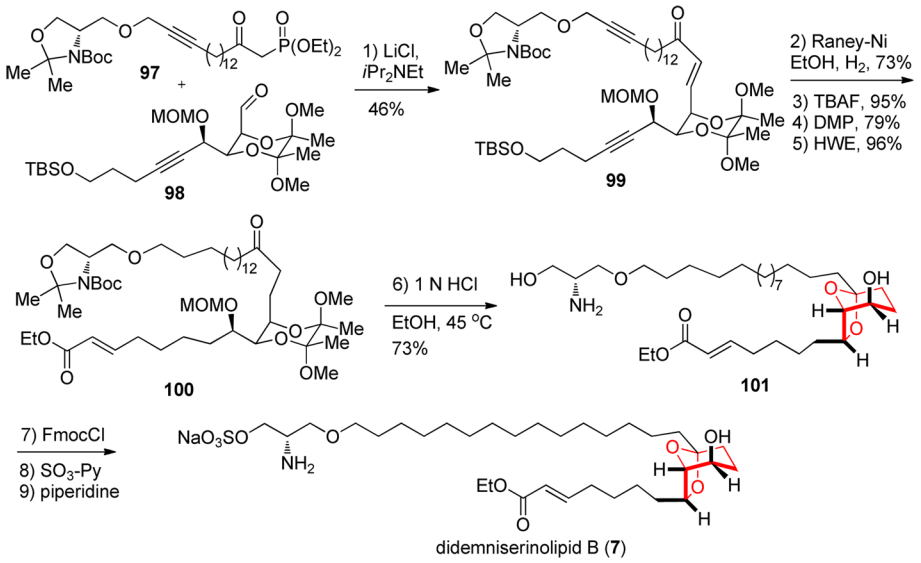
Scheme 11. Total Synthesis of Attenols A and B



Scheme 12. Ley Synthesis of Didemniserinolipid B



with *i*-PrMgBr, and Sharpless asymmetric dihydroxylation with AD-mix β, provided the desired furfuryl diol **87**, which upon treatment with *m*-CPBA underwent Achmatowicz rearrangement and subsequent CSA-promoted dehydrative cycloketalization in one pot to give the 6,8-DOBCO **88** in 72% yield, corresponding to the core bicyclic skeleton of **8** and *ent*-**9**. Installation of the all-carbon quaternary center on the 6,8-DOBCO **88** was accomplished either by Kobayashi's Cu-mediated S_N2' methylation of allyl picolinate **90** derived from hydrogenation of **88**, Horner–Wadsworth–Emmons (HWE) olefination, DIBAL reduction, and DCC-mediated esterification or by Johnson–Claisen rearrangement of the allylic alcohol **89**, followed by DIBAL reduction, oxone/DMF oxidation, and Barton deoxygenation.

2.2. Total Synthesis of Attenols A and B (Tong, 2015). Attenols A and B isolated in 1999 by Uemura[3d] and co-workers from the Chinese bivalve *Pinna attenuate* as structurally novel bicyclic ethereal compounds have shown moderate cytotoxicity against P388 cell lines (IC_{50} = 24 and 12 μg/mL, respectively). The more cytotoxic, thermodynamically less stable (+)-attenol B (**6**) has been previously synthesized as a minor product via acid-catalyzed (spiro-)ketalization and/or isomerization of attenol A.[54] In 2015, we reported the total synthesis of (+)-attenol B as the exclusive product (no isomeric attenol A) for the first time using the similar Achmatowicz rearrangement/cycloketalization (S-iii) as the key method to construct the fully functionalized 6,8-DOBCO core (Scheme 11).[5] Specifically, the diol **91** derived from Sharpless asymmetric dihydroxylation with AD-mix β underwent smoothly Achmatowicz rearrangement/cycloketalization to provide the 6,8-DOBCO **92** in 85% yield. The axial methyl group on the 6,8-DOBCO core of attenol B was installed by the direct S_N2 substitution of the corresponding triflate **94**, which could be readily prepared from **92** through $LiAlH_4$/CuI reduction, DIBAL-H reduction, regioselective silylation and triflation. Notably, attenol A (**96**) could also be obtained by isomerization of attenol B under mild acidic condition, although our synthetic effort was directed to the synthesis of attenol B.

2.3. Total Synthesis of Didemniserinolipid B (Ley, 2002; Burke, 2007; Tong, 2014). Didemniserinolipids B (**7**) was isolated in 1999 by Jiménez[3e] and co-workers from the methanol extract of marine tunicate *Didemnum* sp. Ley's pioneering synthetic studies culminated in the first total synthesis and structural revision of didemniserinolipid B, in

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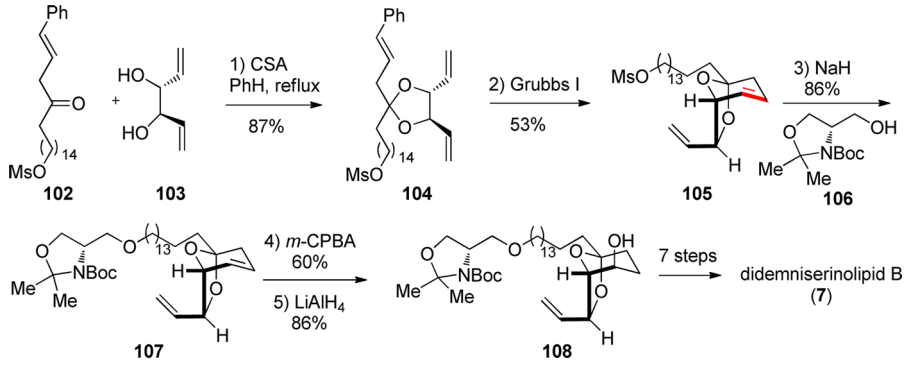
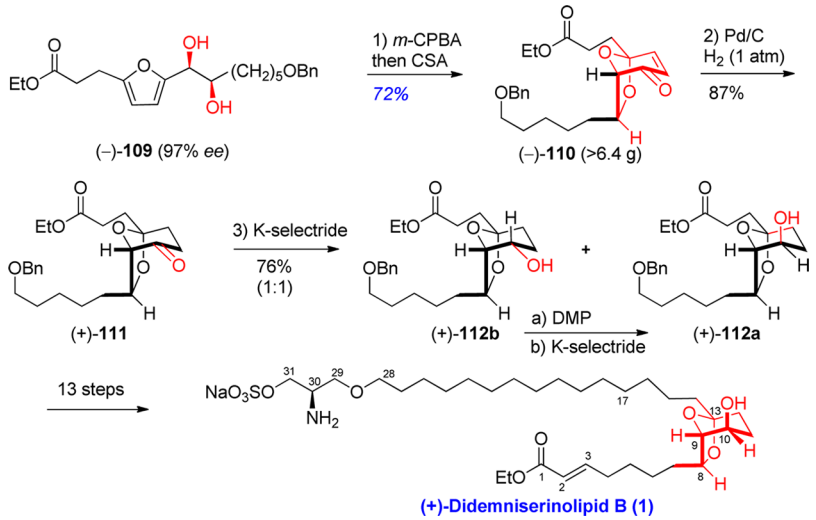
Scheme 13. Burke Synthesis of Didemniserinolipid B



Scheme 14. Tong Synthesis of Didemniserinolipid B



which the *O*-sulfate at C31 was identified and the stereochemistry at C30 was unambiguously determined by chemical synthesis.[55] The key strategy to the synthesis of the 6,8-DOBCO core of didemniserinolipid B is S-i: simultaneous formation of 5- and 6-membered rings via dehydrative cycloketalization of a keto diol (Scheme 12). Specifically, HWE olefination coupled the fully functionalized phosphonate **97** and aldehyde **98**, yielding the complex ketone **99**. Raney-Ni-mediated hydrogenation of **99** followed by desilylation, DMP oxidation, and HWE olefination provided the diol-masked ketone **100**, which upon treatment of 1 N HCl in EtOH at 45 °C removed all of the alcohol protecting groups and underwent dehydrative cycloketalization to produce the 6,8-DOBCO **101** in a remarkably high yield (73%). Chemoselective sulfonylation of the alcohol over amine of **101** was achieved by temporary Fmoc protection of amine and sulfonylation and deprotection of Fmoc, leading to the first total synthesis of didemniserinolipid B (**7**). Recently, Chandrasekhar[56] and Prasad[57] used this strategy in the formal total synthesis of **7**. These syntheses clearly attested the effectiveness and robustness of dehydrative cycloketalization of functionalized δ-keto diol for the synthesis of 6,8-DOBCO. A related formal synthesis of **7** using the similar strategy (S-i) was reported by Ramana[58] through metal-mediated alkynediol cycloisomerization.

The second total synthesis of didemniserinolipid B was elegantly achieved by Burke[36] and co-workers through full exploitation of an efficient intermolecular cycloketalization/ring-closing metathesis (RCM) strategy (S-ii) to construct the 6,8-DOBCO moiety (Scheme 13). The obvious advantages of this method over the more conventional intramolecular dehydrative cycloketalization of a keto diol are the minimal use of protecting groups and stereoselective functional group introduction on the chiral rigid 6,8-DOBCO core. The union of the well-designed ketone **102** and C2-symmetric diene diol **103** provided diene ketal **104**, which underwent RCM in the presence of Grubbs I catalyst to produce the 6,8-DOBCO **105** in 53% yield. Notably, the C_2-symmetric diene **103** was desymmetrized through this cycloketalization/RCM sequence. Williamson etherification of **105** followed by chemo- and stereoselective epoxidation with *m*-CPBA and *trans*-diaxial reductive epoxide opening with $LiAlH_4$ provided the fully functionalized 6,8-DOBCO of didemniserinolipid B. This total synthesis fully demonstrates the synthetic utility of cycloketalization/RCM (S-ii) in the construction of 6,8-DOBCOs.

In 2014, we achieved the third total synthesis of didemniserinolipid B using Achmatowicz rearrangement/cycloketalization (S-iii) (Scheme 14).[6] Strategically similar to our synthesis of psoracorylifols and attenols, the readily available enantiopure furfuryl diol (−)-**109** underwent efficient Achmatowicz rearrangement/cycloketalization upon sequential treatment of *m*-CPBA and CSA to afford the 6,8-DOBCO **110** in 72% yield on a multigram scale, which showcased the efficiency and robustness of the sequential protocol. However, the K-Selectride reduction of the resulting ketone **111** to the axial alcohol **112a** was nonstereoselective (other reducing agents resulted in exclusive formation of the equatorial

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alcohol). Nevertheless, two times recycling of the undesired **112b** (facile separation from **112a** by column chromatography on silica gel) through DMP oxidation/K-selectride reduction secured the supply of this fully functionalized 6,8-DOBCO material for subsequent 13-step elaboration to didemniserinolipid B. This total synthesis further attested and expanded the synthetic utility of Achmatowicz/cycloketalization (S-iii) strategy. In particular, three 6,8-DOBCO-containing natural products (psoracorylifol B, attenol B, and didemniserinol B) with different substitution patterns and functionalities on the 6,8-DOBCOs could be prepared by this unified strategy and we optimiztically projected that it could be applicable to any other 6,8-DOBCO-bearing natural products.

3.0. CONCLUSION

In summary, various synthetic approaches for the synthesis of the 6,8-DOBCO framework found in natural products were reviewed and classified as three different strategies according to the order of formation of the bicyclic core. Emphasis was placed on those approaches that have been used in the synthesis of 6,8-DOBCO-containing natural products. The second section summarized the recent application of these approaches and strategies in total synthesis of psoracorylifol B, *ent*-psoracorylifol C, attenol B, and didemniserinolipid B. Notably, three different approaches representing the three general strategies have been attested in the asymmetric total synthesis of didemniserinolipid B. These approaches would have found more applications in total synthesis of other complex 6,8-DOBCO-bearing natural products.

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Notes

The authors declare no competing financial interest.

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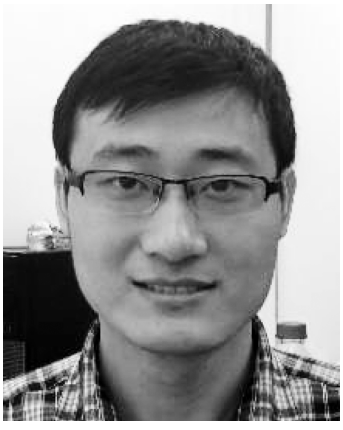

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Rongbiao Tong (right) received his B.Sc. in 2000 and M.Sc. in 2003 from Hunan University, Changsha, P. R. China, and Ph.D. degree in 2008 (advisor: Prof. Frank E. McDonald) from Emory University. After working with Prof. Amos B. Smith III at the University of Pennsylvania as a postdoc fellow (2008−2011), he started his independent research career in 2011 as assistant professor at the Hong Kong University of Science and Technology (HKUST). His current research interest focuses on total synthesis of complex biologically active natural products by exploitation of oxidative dearomatization of phenols and furfuryl alcohols.

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