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Recent topics of the stereodivergent synthesis of natural products

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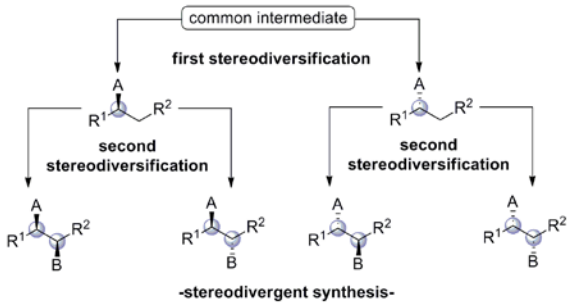

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Recent topics of the stereodivergent synthesis of natural products

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ABSTRACT

A variety of natural products, a valuable source of drug lead compounds, coexist with their stereoisomers as congeners. For pursuing the structural elucidation and the structure–activity relationship study of natural products, it is needed to establish the streamlined synthetic route to supply natural products and their stereoisomers. Divergent pathway is one of the synthetic strategies to deliver more than one target compound. In this digest, selected examples of the stereodivergent approach toward the synthesis of natural products are described. Especially, this digest focuses on common synthetic intermediates and stereodiversification steps from the common intermediates to reach the target compounds.

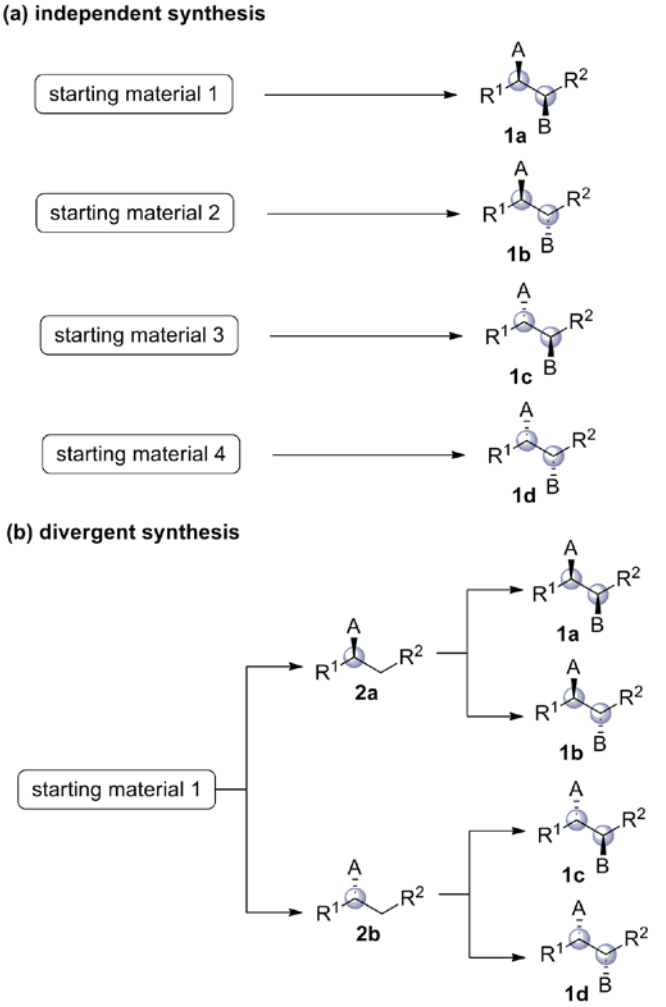
Contents

Introduction

Natural products have been a valuable source of lead compounds in the drug discovery and development process.[1] Research on the synthesis of a specific natural product as a target molecule, that is target-oriented synthesis (TOS), has a long history in organic chemistry.[2] In order to create the drugs based on the natural product structure, we need to synthesize structural analogues of the natural product, which cannot be obtained by the biosynthesis, and carry out the structure–activity relationship study. In this case, we have sometimes encountered a problem that we cannot supply the structural analogues from the natural product by the chemical synthesis, directly, due to its instability and incompatibility of its functional groups with the organic reaction conditions. The way to synthesize analogues of the natural product with avoiding the difficulty mentioned above is to derivatize the advanced intermediate in total synthesis of the natural product to the target analogues. This approach of preparing the analogues is called as diverted total synthesis (DTS), which was proposed by Danishefsky.[3] In contrast to TOS, diversity-oriented synthesis (DOS), which was proposed by Schreiber,[4] aims to populate chemical space broadly with small molecules having skeletal and stereochemical diversity. In the strategy of DOS, the structural complexity of each compounds and the structural diversity of the overall synthetic scheme are maximized, and the synthetic pathway is branched and divergent.

Many natural products coexist with their stereoisomers as congeners to each other. It is significant to develop the efficient synthetic route to access to all stereoisomers of the natural product from the point of view of both structural confirmation/elucidation and structure–activity relationship study. There are mainly two kinds of synthetic strategy to reach the target compounds **1a**–**1d** possessing two chiral centers, as described in Scheme 1.[5] In the independent pathway (a), four target compounds **1a**–**1d** are synthesized from the different

starting materials, independently and respectively. In the divergent pathway (b),[6] **1a**–**1d** are synthesized from the same starting material. In this synthetic route, **2a** and **2b** are synthesized by branching from the common intermediate (first stereodiversification). In addition, **1a**,**1b** and **1c**,**1d** are synthesized from the common intermediates prepared from **2a** and **2b**, respectively (second stereodiversification). In this stereodivergent synthesis, all four target compounds **1a**–**1d** are supplied in a unified manner, and setting the branching point from the common synthetic intermediates at the late-stage of synthesis makes the whole synthetic scheme more efficient because of decreasing the number of overall steps. In this digest, selected examples of the stereodivergent approach toward the synthesis of natural products, which were published during the past five years, are presented. This digest focuses on common synthetic intermediates and stereodiversification steps from the common intermediates for delivering stereoisomers.



Scheme 1. Two kinds of synthetic strategy toward **1a**–**1d** bearing two chiral centers.

Breit's synthesis of helicascolides A, B, and C[7]

In addition to the lactonization by activation of hydroxycarboxylic acids,[8] transition metal-catalyzed addition reaction,[9] halo- and selenolactonization,[10] and ring-closing metathesis[11] have been reported as the synthetic methods for the five- or six-membered lactones. Breit and co-workers developed regio- and enantioselective rhodium-catalyzed addition of carboxylic acids to allenes in 2011.[12] This research group investigated the protecting-group-free synthesis of six-membered lactone natural products, helicascolide A (**3a**, Figure 1),[13a] its C3 epimer helicascolide B (**3b**),[13a] and C3 ketone helicascolide C (**4**).[7,13b]

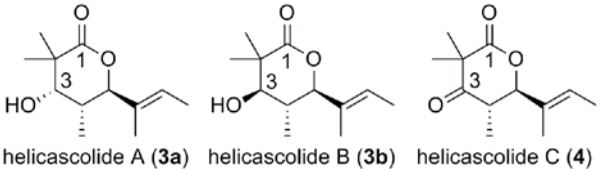
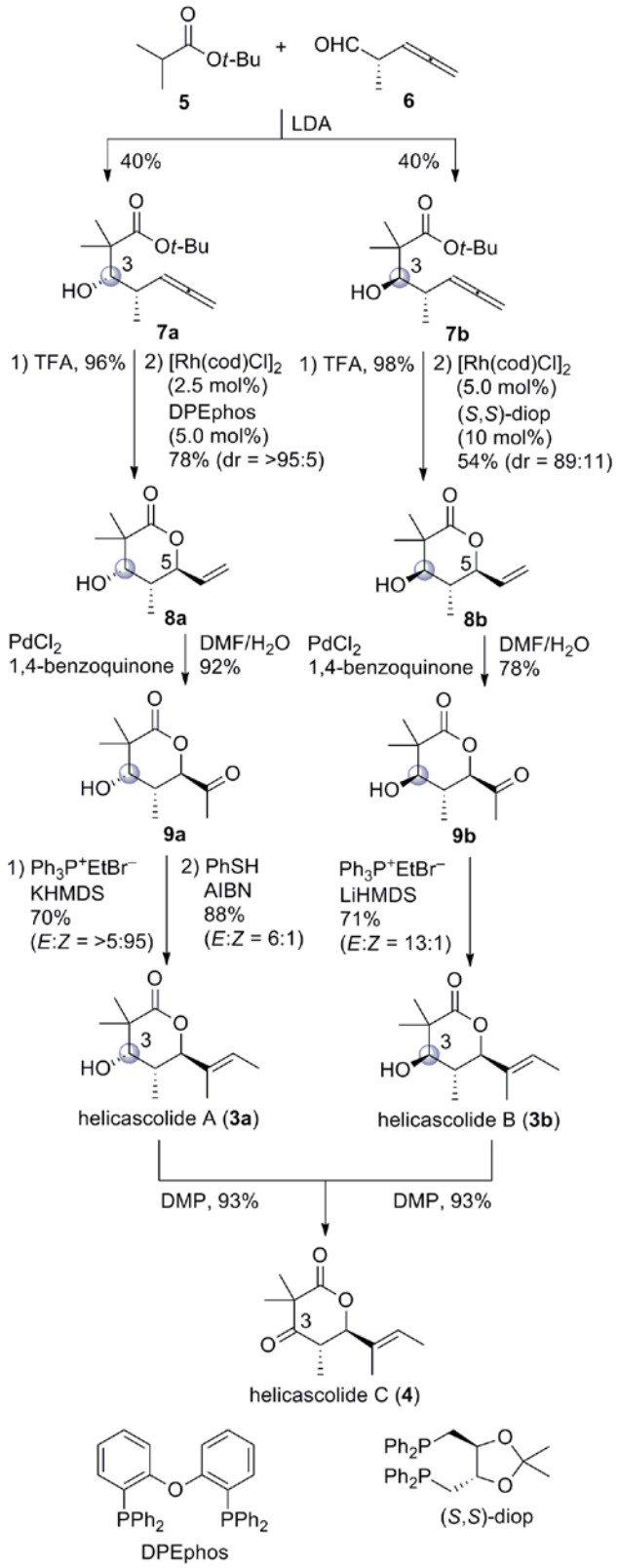


Figure 1. Structures of helicascolides A (**3a**), B (**3b**), and C (**4**).

As shown in Scheme 2, addition reaction of enolate, derived from ester **5** with lithium diisopropylamide (LDA), and aldehyde **6** provided C3 stereoisomers **7a** and **7b**, divergently, in 80% combined yield with a 1:1 diastereomeric ratio. After the *tert*-butyl ester **7a** was transformed to the corresponding carboxylic acid with trifluoroacetic acid (TFA), intramolecular hydrooxycarbonylation of carboxylic acid to allene was investigated. Thus, when the carboxylic acid prepared from **7a** was subjected to the original reaction conditions,[12] the combination of $[Rh(cod)Cl]_2$ and DPEphos, the desired product **8a** was obtained in 78% yield as a single diastereomer. It is noteworthy that the hydroxy functional group at the C3 position was compatible with the reaction conditions and the C5 chiral center was installed by the substrate-control without adding the chiral ligand. When the intramolecular hydrooxycarbonylation of **7b** was carried out by using the same reaction system, six-membered lactone **8b** was produced as a major diastereomer (dr = 90:10), albeit in low chemical yield (20%). After the survey of reaction conditions for **7b**, it was found that the use of $[Rh(cod)Cl]_2$ and (*S*,*S*)-diop as a chiral ligand was effective and the product **8b** was obtained in 54% yield and diastereomeric ratio of 89:11. The alkenes **8a** and **8b** were oxidized to **9a** and **9b** in the presence of $PdCl_2$/1,4-benzoquinone, respectively.[14] The remaining task is to construct the trisubstituted alkene moieties. Treatment of the ketone **9a** with $Ph_3P^+EtBr^-$/potassium hexamethyldisilazide (KHMDS) gave the undesired (*Z*)-alkene as a single geometric isomer. Since attempts for the (*E*)-selective olefination of **9a** resulted in failure, one extra transformation was needed to obtain helicascolde A (**3a**). Thus, radical-mediated isomerization of double bond of the (*Z*)-alkene was performed with PhSH/2,2'-azobisisobutyronitrile (AIBN) to yield helicascolide A (**3a**) in an *E*/*Z* ratio of 6:1. In contrast, (*E*)-selective olefination of the ketone **9b** was achieved with $Ph_3P^+EtBr^-$/LiHMDS to give helicascolide B (**3b**) in an *E*/*Z* ratio of 13:1. Finally, stereoconvergent synthesis of helicascolide C (**4**) was achieved by oxidation of **3a** and **3b** with Dess–Martin periodinane (DMP).



Scheme 2. Stereodivergent synthesis of **3a** and **3b**, and stereoconvergent synthesis of **4**.

Kim's synthesis of 2,5-*cis*- and *trans*-tetrahydrofuranoid oxylipids[15]

The marine oxylipids **10a** and **10b** (Figure 2) were isolated from the Australian brown algae *Notheia anomata*.[16] They have the 2,5-disubstituted-3-hydroxylated tetrahydrofuran (THF) unit as a common framework, furthermore, possess a structural diversity, that is, **10a** and **10b** bear the 2,5-*cis*- and *trans*-disubstituted THF moieties, respectively. Interestingly, both **10a** and **10b** exhibit the nematocidal activity with similar LD_{50} values without regard to the stereochemical difference. Kim's research group applied their originally developed stereodivergent intramolecular amide enolate alkylation (IAEA)[17] to the total synthesis of **10a** and **10b**.[15]

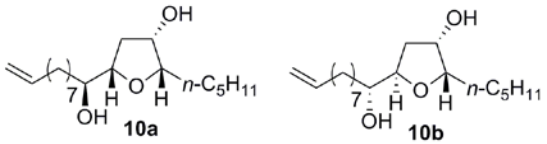
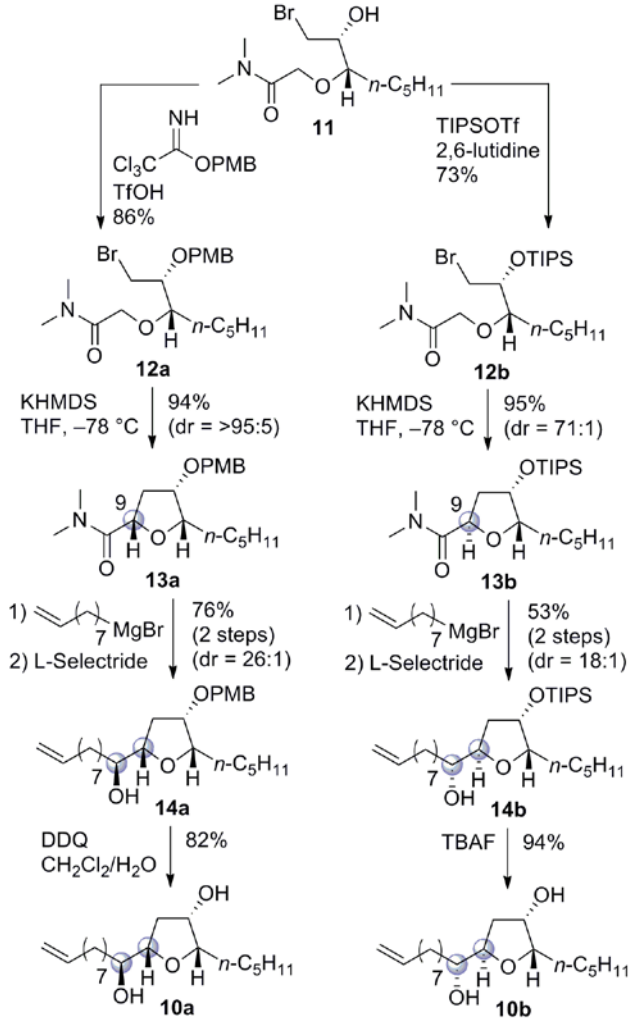
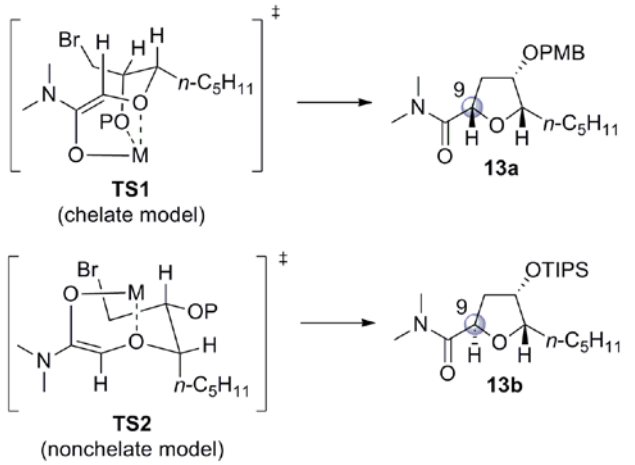


Figure 2. Structures of 2,5-disubstituted-3-hydroxylated tetrahydrofurans **10a** and **10b**.

First, alcohol **11**, which is the common intermediate toward the synthesis of **10a** and **10b**, was transformed to *p*-methoxy benzyl (PMB) ether **12a** and triisopropylsilyl (TIPS) ether **12b**, respectively (Scheme 3). Next, IAEA reaction of the PMB ether **12a**, leading to the *cis*-disubstituted THF **10a**, was examined in terms of base (LiHMDS, NaHMDS, and KHMDS), solvent (THF and toluene), and temperature, and it was proven that treatment of **12a** with KHMDS in THF at –78 °C gave the desired *cis*-disubstituted THF **13a** in 94% yield as a single diastereomer. On the other hand, when the TIPS ether **12b** was subjected to the same reaction conditions, *trans*-disubstituted THF **13b**, which is the C9 epimer of **13a**, was produced in 95% yield at a 71:1 diastereomeric ratio. The use of other silyl protecting groups such as *tert*-butyldimethylsilyl (TBS), triethylsilyl (TES), and trimethylsilyl (TMS) caused lowering the diastereoselectivity. The stereochemical outcomes in the formation of **13a** and **13b** are understandable by using transition states as described in Scheme 4. Thus, in the case of IAEA reaction of **12a**, the reaction would proceed through transition state **TS1**, wherein the *p*-methoxy benzyloxy group could participate in the chelation, to provide the *cis*-disubstituted THF **13a**. In contrast, the observed diastereoselectivity in the reaction of **12b** could be rationalized by nonchelate transition state **TS2**, which minimizes a steric repulsion between the bulky TIPS-protected hydroxy group and the amide enolate moiety. As described in Scheme 3, the left side chains were introduced by the reaction of the amides **13a** and **13b** with $CH_2{=}CH(CH_2)_7MgBr$ and subsequent diastereoselective reduction of the resulting ketones with L-Selectride to furnish alcohols **14a** and **14b**, respectively. Deprotection of the PMB ether **14a** and the TIPS ether **14b** produced the target compounds **10a** and **10b**.



Scheme 3. Stereodivergent synthesis of **10a** and **10b**.



Scheme 4. Plausible transition states in the IAEA reaction of **12a** and **12b**.

Porco's synthesis of sanggenons C and O[18]

Sanggenons C (**15a**, Figure 3) and O (**15b**) are flavonoid natural products isolated from the traditional Chinese herbal medicine "Sag-bai-pi" and the root bark of Chinese mulberry tree *Morus cathayana*.[19] These two natural products have the stereoisomeric relationship at the C2 and C3 positions. Their cyclohexene moieties are proposed to be biosynthetically produced by Diels–Alder reactions between a dehydroprenylated flavanone and a chalcone. Porco and co-workers tried the total synthesis of sanggenons C (**15a**) and O (**15b**) by employing stereodivergent reaction of a racemic mixture.[18,20]

First, double Claisen rearrangement of **16** with rare earth metal triflates was examined and $Yb(OTf)_3$ was found to give the desired double rearranged product **17** in 72% yield (Scheme 5). After protection of **17** with TBSOTf/Et_3N, cross-metathesis of the resulting diene with isobutene by using second generation Grubbs catalyst afforded prenylated product **18** in 92% yield in two steps. The obtained **18** was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide pentacyclic compound **19**. Porco and co-workers expected that the benzopyran **19** could undergo retro 6π electrocyclization to yield diene **20**, which could give the desired diene **21** via deprotonation/protonation. If this scenario would be realized, Diels–Alder products between the diene **21** and a dienophile could be formed. Furthermore, they considered that sanggenons C (**15a**) and O (**15b**) are both *endo*-adducts and possess the same absolute configuration in the cyclohexene moiety. Therefore, they envisioned that enantioselective Diels–Alder reaction between the racemic **21** and a dienophile could produce both of sanggenons C (**15a**) and O (**15b**) with the C2 and C3 stereoisomeric relationship in a stereodivergent manner. Thus, a screening of reaction conditions was conducted using a number of borates and 1,1'-bi-2-naphthol (BINOL) ligands. Finally, treatment of the racemic **19** with 2'-hydroxychalcone **22** in the presence of a catalytic amount of $B(OPh)_3$/(*R*)-3,3'-dibromo-BINOL **23** afforded two desired *endo*-cycloadducts. These two products were deprotected with aq. $NaHCO_3$ and $3HF{\cdot}Et_3N$ to produce sanggenons C (**15a**, 98% ee) and O (**15b**, 93% ee) in 54% combined yield in three steps with a 2:1 ratio.

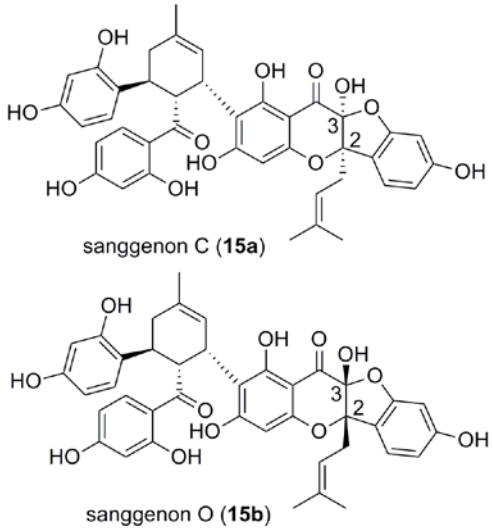
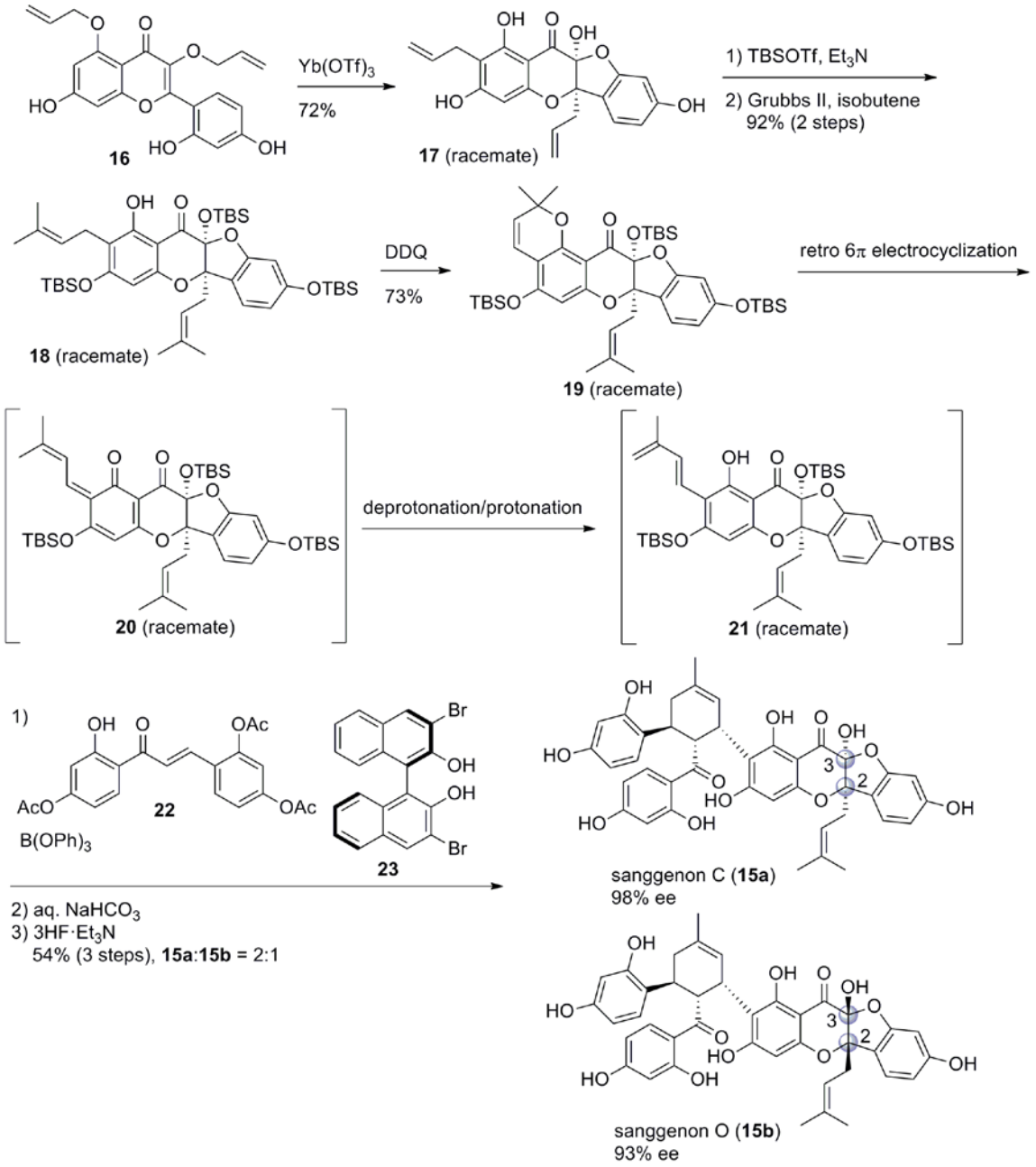


Figure 3. Structures of sanggenons C (**15a**) and O (**15b**).



Scheme 5. Stereodivergent synthesis of **15a** and **15b**.

Nishiyama's synthesis of hemifistularin 3 for the structural elucidation[21]

Hemifistularin 3 (**24**, Figure 4) is an antifouling natural product isolated from a sponge of the order *Verongida*.[22] Although the detailed NMR analysis revealed the relative configuration at the C12 oxygen atom and the C17 hydroxy group to be *trans*, the stereochemistry at the C7 position, which is a chiral center remote from the C12 and C17 positions, remained to be clarified. Nishiyama's group investigated the stereodivergent synthetic approach to hemifistularin 3 (**24**) aiming at its structural determination.[21]

Enantiomerically pure spiroisoxazolines **25a** and **25b** were prepared by the optical resolution. Thus, reaction of racemic **25** with (–)-camphanic chloride followed by recrystallization gave diastereomeric isomers **26a** and **26b**, which were treated with Cs_2CO_3 in MeOH to afford enantiomeric isomers **25a** and **25b**, respectively (Scheme 6). Condensation of the ester **25a** and amines **27a**,**27b**, and subsequent removal of the PMB groups with TFA provided the C7 diastereomeric isomers **24a** and **24b**, respectively. In the similar way, the ester **25b** was transformed to **24c** and **24d**. The synthetic products **24a** and **24b** exhibited the positive signs of specific rotation (**24a**: +125, **24b**: +130) in comparison with that of natural hemifistularin 3 (+110), which established that the natural product has the (12*S*,17*R*)-absolute configuration. However, small difference of the specific rotations and spectroscopic data between **24a** and **24b** could not lead to the structural elucidation of the natural product.

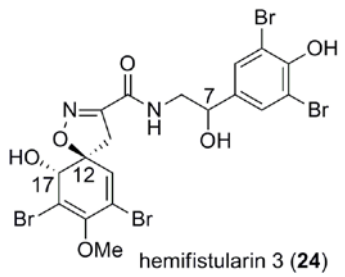
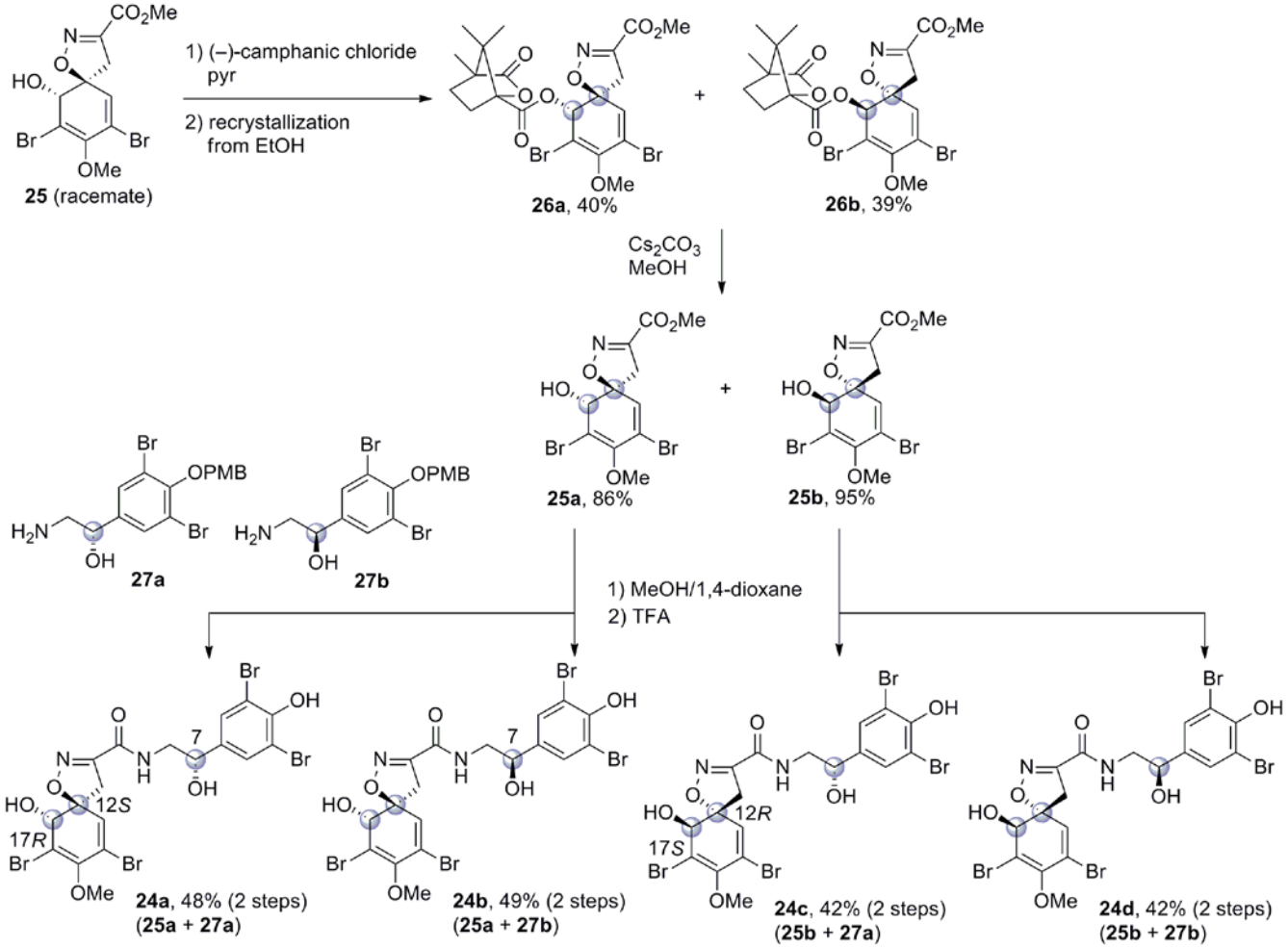
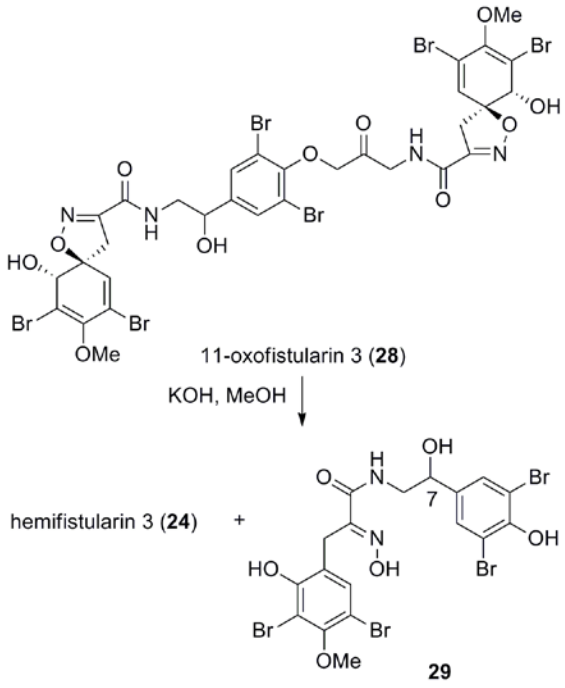


Figure 4. Relative configuration of hemifistularin 3 (**24**). The stereochemistry at the C7 position was unknown.

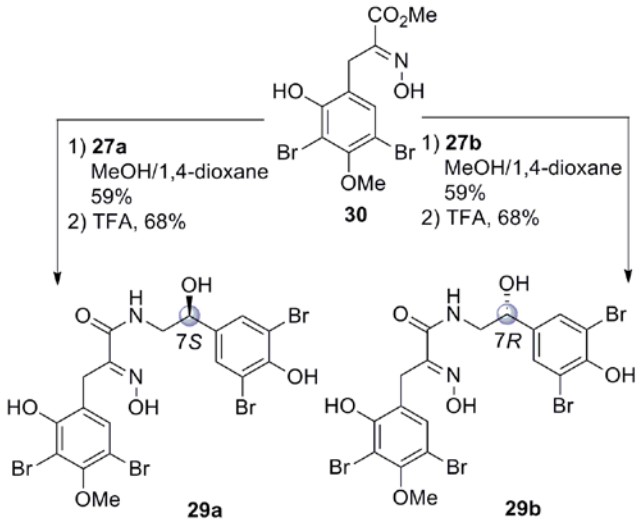


Scheme 6. Stereodivergent synthesis of **24a**–**24d**.

The isolation paper[22a] reported that alkaline degradation of 11-oxofistularin 3 (**28**) produced oxime **29** along with hemifistularin 3 (**24**), as described in Scheme 7. The formation of **29** is understandable by ring-opening of spiroisoxazole moieties of **28** or **24**. This observation indicates that the C7 stereochemistry of **29** is same as that of **24**. Therefore, Nishiyama and co-workers next examined the synthesis of possible stereoisomers of **29**. Reaction of ester **30** with the amines **27a** and **27b** followed by deprotection of PMB ethers furnished **29a** and **29b**, respectively (Scheme 8). Comparison of the specific rotations between the synthetic products (**29a**: +6.7, **29b**: –6.3) and the degraded product **29** (+20) elucidated the absolute stereochemistry of hemifistularin 3 (**24**) to be (7*S*,12*S*,17*R*) as depicted in **24a**.



Scheme 7. Alkaline degradation of 11-oxofistularin 3 (**28**).



Scheme 8. Stereodivergent synthesis of **29a** and **29b**.

Pietruszka's synthesis of solandelactone I for the structural elucidation[23]

Solandelactone I (**31**, Figure 5), which possesses the cyclopropyl and lactone moieties as a structural feature, was isolated from the hydroid *Solanderia secunda* in 1996.[24] The relative configuration at the C7, C8, and C10 positions of the cyclopropyl and lactone portions was determined by the nuclear Overhauser effect (NOE) observations. However, the stereochemistry of the vicinal diol group at the C13 and C14 positions was not elucidated. Therefore, Pietruszka and co-workers tried to synthesize all four possible diastereomers of solandelactone I (**31**).[23]

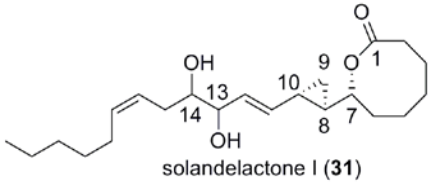
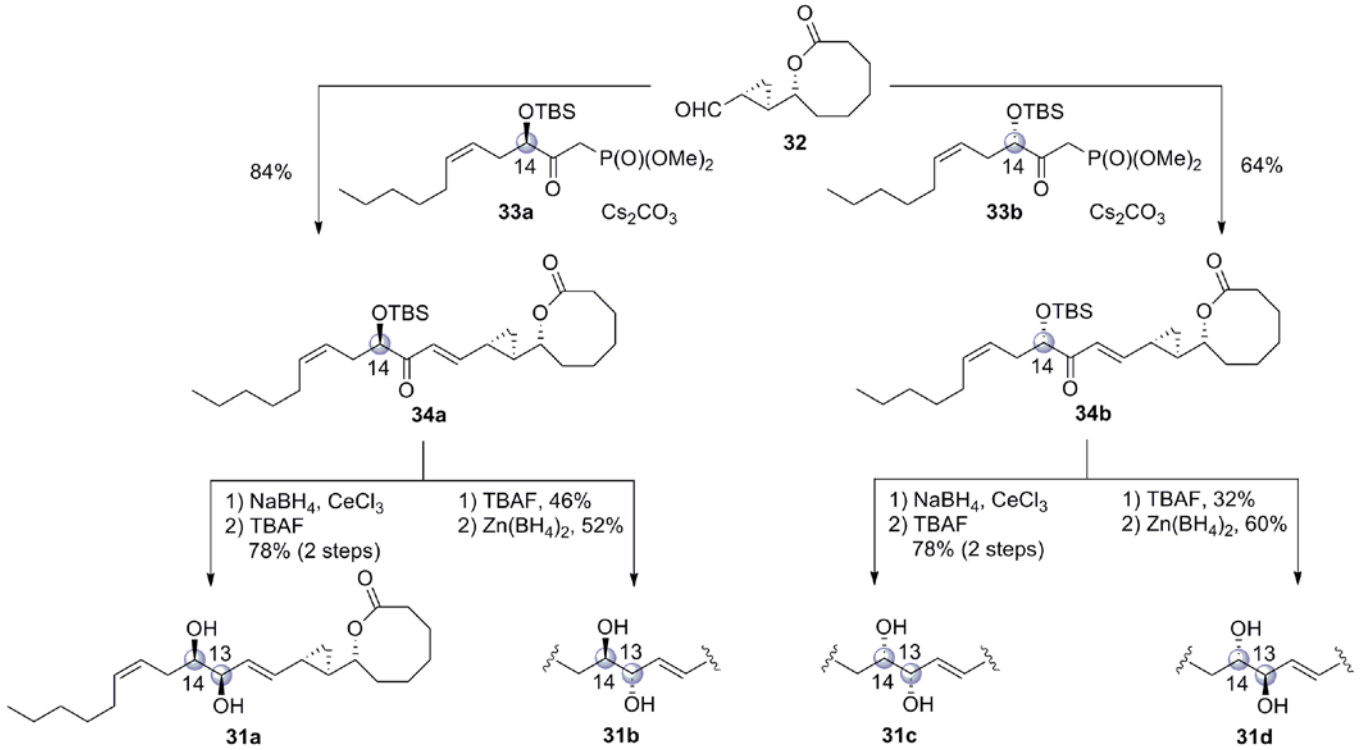


Figure 5. Relative configuration of solandelactone I (**31**). The stereochemistries at the C13 and C14 positions were unknown.

Horner–Wadsworth–Emmons reaction between aldehyde **32**[25] and phosphonates **33a** and **33b**, which were respectively prepared from L- and D-serines in optically pure forms, afforded α,β-unsaturated ketones **34a** and **34b** (Scheme 9). This is the first branching point to deliver the C14 stereoisomers. Next task is to supply the C13 stereoisomers by the second branching. Thus, the Felkin–Anh type 1,2-reduction utilizing the C14 chiral center of **34a** with $NaBH_4/CeCl_3$ followed by removal of the TBS protecting group gave *syn*-diol **31a**. In addition, after the deprotection of the TBS ether **34a**, the chelation-controlled diastereoselective reduction of the resulting α-hydroxy ketone with $Zn(BH_4)_2$ produced *anti*-diol **31b**. In parallel, the α-siloxy ketone **34b** was converted to *syn*-diol **31c** and *anti*-diol **31d** by the diastereoselective reduction, respectively. The detailed NMR comparison between the synthesized products **31a**–**31d** and natural solandelactone I revealed that **31c** exhibits a better match with the natural product data. The specific rotation of **31c** was –48.6 (c = 0.50, MeOH), which was agreement with that for the natural product, –37.0 (c = 0.50, MeOH). Therefore, the absolute configuration of natural solandelactone I was elucidated to be that described in **31c**. This structural assignment is supported by the proposed biosynthesis of solandelactones.[24]



Scheme 9. Stereodivergent synthesis of **31a**–**31d**.

Takamura's synthesis of the C79–C104 fragment of symbiodinolide for the structural elucidation[26]

Symbiodinolide (**35**, Figure 6), a polyol marine natural product, was isolated from the cultured dinoflagellate *Symbiodinium* sp. in 2007.[27] The planar structure of **35** was elucidated by the detailed 2D NMR analysis. However, the complete stereochemical determination of **35** remains an unsolved issue due to its huge and complicated molecular structure characterized by a molecular weight of 2,860 and 61 stereogenic centers. The stereochemistries in the C91–C99 carbon chain portion of **35** were assigned by the $^{3}J_{H,H}$ coupling constants and NOE observations of the natural product.[27] Takamura's research group investigated stereoselective synthesis of the C79–C104 fragment **36a** bearing the proposed relative configuration.

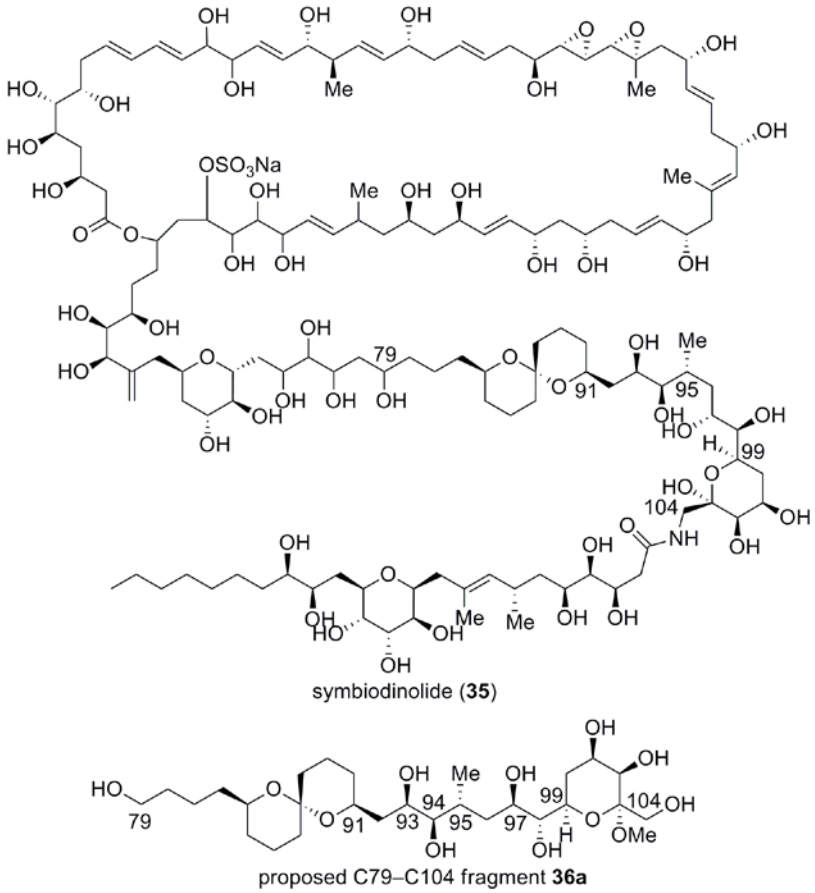
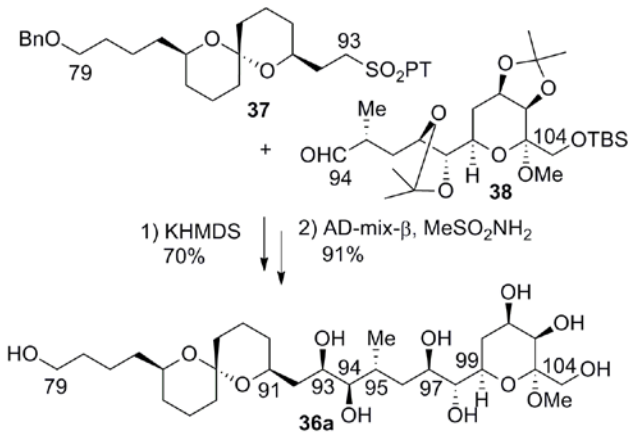


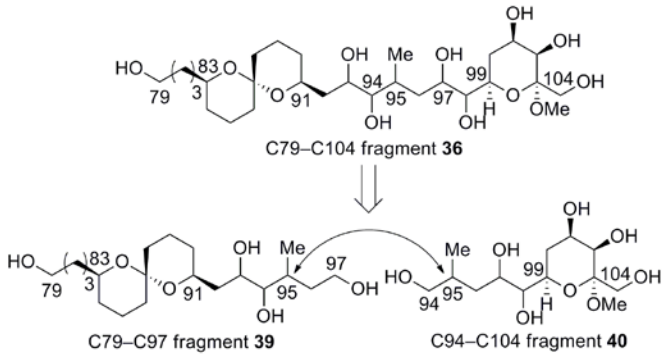
Figure 6. Structures of symbiodinolide (**35**) and its proposed C79–C104 fragment **36a**.

The stereoselective and streamlined synthesis of the C79–C104 fragment **36a** possessing the proposed stereostructure was achieved by using Julia–Kocienski olefination between PT-sulfone **37** and aldehyde **38** and subsequent Sharpless asymmetric dihydroxylation (Scheme 10). Comparison of the ^{13}C NMR data between the synthetic product **36a** and the natural product revealed that the stereochemistry of the C91–C99 carbon chain moiety of **35** should be reinvestigated.[26a]



Scheme 10. Stereoselective synthesis of **36a**.

Since there are seven chiral centers in the C91–C99 carbon chain portion, the number of possible diastereomers of this moiety is $2^6 = 64$. If all these possible 64 diastereomers could be synthesized, the stereostructure of this part might be elucidated by comparing the NMR data between the synthetic products and the natural product. However, the supply of 64 diastereomers by chemical synthesis would require a substantial amount of work. Therefore, toward the structural determination of the C79–C104 fragment, Takamura and co-workers divided the C79–C104 fragment **36** into the C79–C97 fragment **39** and the C94–C104 fragment **40** (Scheme 11). Thus, in this plan, after the configurational determination of each of the C79–C97 fragment **39** and the C94–C104 fragment **40**, the relative configuration of the C79–C104 fragment **36** would be assigned by connecting each stereostructure of the C79–C97 fragment **39** and the C94–C104 fragment **40** by the C95 stereochemistry contained in both fragments.



Scheme 11. Strategy for the stereostructural elucidation of the C94–C104 fragment **36**.

The C79–C97 fragment **39** possesses three chiral centers in the carbon chain portion (C93, C94, and C95), therefore, there are eight possible diastereomers of this fragment (Figure 7). Stereodivergent synthesis of all these eight diastereomers **39a**–**39h** was examined. Thus, reaction of aldehyde **41** and dithiane **42** gave C93 stereoisomers **43a** and **43b** in a 1:1 diastereomeric ratio (Scheme 12). The dithiane moiety of **43a** was hydrolyzed to afford ketone **44**, which is a common synthetic intermediate for the synthesis of **39a** and **39b**. After the TBS protection of **44**, the Felkin–Anh type reduction of the resulting α-siloxy ketone by utilizing the C93 stereochemistry was performed with

diisobutylaluminum hydride (DIBAL-H) to provide alcohol **45a** as a sole product. Finally, deprotection of **45a** produced the tetraol **39a**. Next, the chelation-controlled reduction of the α-hydroxy ketone **44** was successfully carried out with L-Selectride in the presence of $ZnCl_2$ as a chelating reagent[28] to furnish *anti*-diol **45b** in 86% yield. The protecting groups of **45b** was removed to give the tetraol **39b**, which is the C94 epimer of **39a**. In parallel, both of **39c** and **39d** were synthesized from the alcohol **43b**, stereodivergently. In addition, other diastereomers **39e**–**39h** were also supplied by using the enantiomer of **42** in a similar way. Comparison of the ^{13}C NMR data between the synthetic products **39a**–**39h** and natural product **35** turned out the relative configuration of the C79–C97 fragment of the natural product to be that depicted in either **39a** or **39f**.

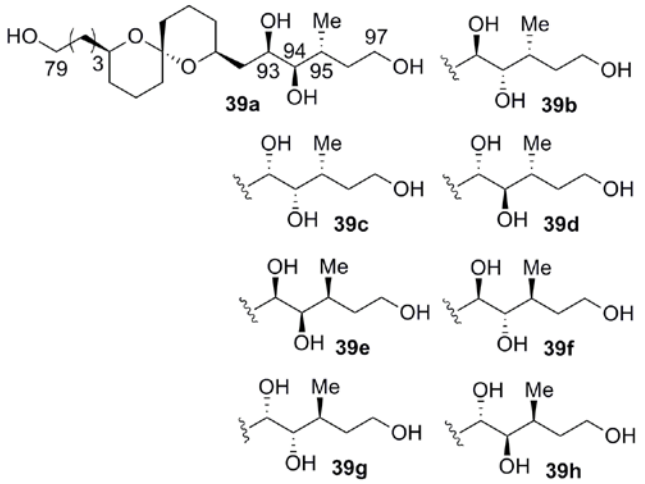
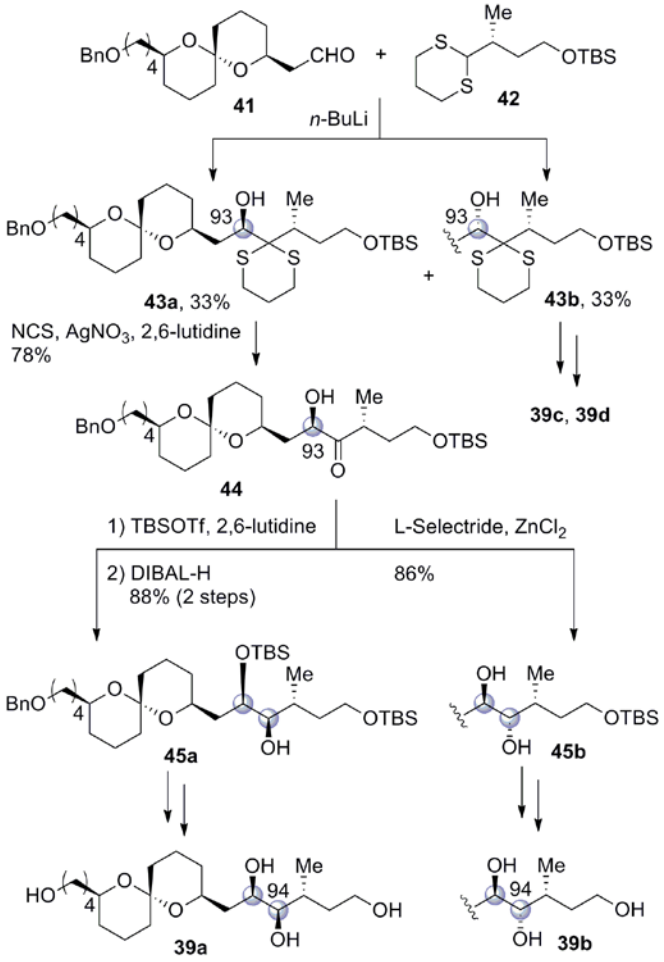


Figure 7. Eight possible diastereomers of the C79–C97 fragment.



Scheme 12. Stereodivergent synthesis of **39a**–**39d**.

As in the case of the C79–C97 fragment **39**, there are eight possible diastereomers of the C94–C104 fragment **40** because of the presence of three stereogenic centers in the carbon chain moiety (C95, C97, and C98, Figure 8). Therefore, sereodivergent synthesis of all these diastereomers **40a**–**40h** was pursued. Hydrolysis of the dithiane moiety of **46** provided α-hydroxy ketone **47** (Scheme 13). The chelation-controlled diastereoselective reduction of **47** with $Zn(BH_4)_2$ followed by deprotection of the resulting **48a** afforded the hexaol **40a**. On the other hand, the hexaol **40b**, which is the C97 epimer of **40a**, was delivered by the Felkin–Anh controlled diastereoselective reduction of α-siloxy ketone prepared from **47** with DIBAL-H and subsequent deprotection of **48b**. Other six hexaols **40c**–**40h** were also synthesized in a stereodivergent way. Comparison of the ^{13}C NMR data of the synthetic **40a**–**40h** with those of the natural product revealed the relative stereochemistry of the C94–C104 fragment of natural product **35** to be that shown in either **40a** or **40e**.

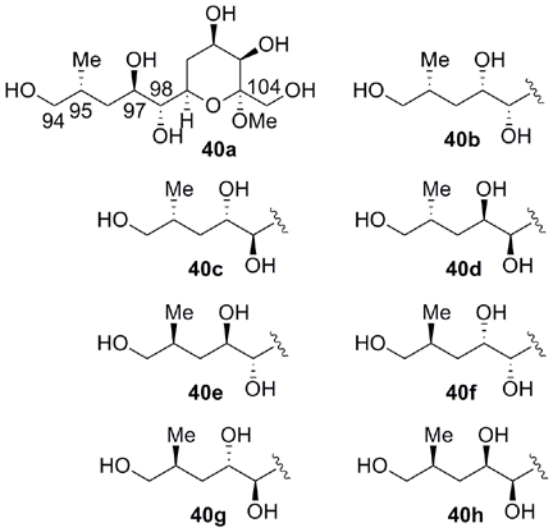
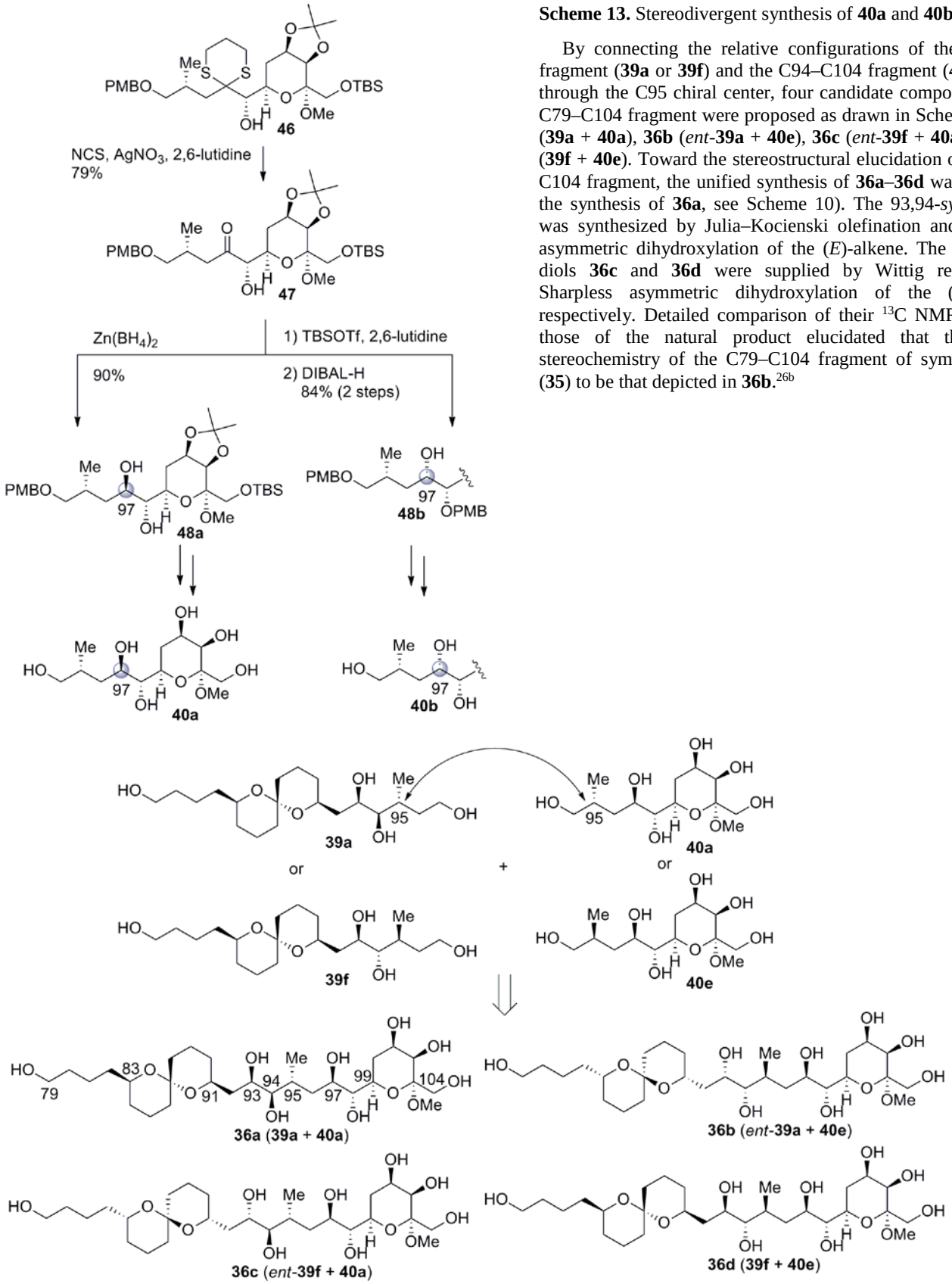


Figure 8. Eight possible diastereomers of the C94–C104 fragment.



Scheme 14. Four candidate compounds of the C79–C104 fragment.

Scheme 13. Stereodivergent synthesis of **40a** and **40b**.

By connecting the relative configurations of the C79–C97 fragment (**39a** or **39f**) and the C94–C104 fragment (**40a** or **40e**) through the C95 chiral center, four candidate compounds of the C79–C104 fragment were proposed as drawn in Scheme 14; **36a** (**39a** + **40a**), **36b** (*ent*-**39a** + **40e**), **36c** (*ent*-**39f** + **40a**), and **36d** (**39f** + **40e**). Toward the stereostructural elucidation of the C79–C104 fragment, the unified synthesis of **36a**–**36d** was tried (For the synthesis of **36a**, see Scheme 10). The 93,94-*syn*-diol **36b** was synthesized by Julia–Kocienski olefination and Sharpless asymmetric dihydroxylation of the (*E*)-alkene. The 93,94-*anti*-diols **36c** and **36d** were supplied by Wittig reaction and Sharpless asymmetric dihydroxylation of the (*Z*)-alkenes, respectively. Detailed comparison of their ^{13}C NMR data with those of the natural product elucidated that the relative stereochemistry of the C79–C104 fragment of symbiodinolide (**35**) to be that depicted in **36b**.[26b]

Takamura and Kadota's synthesis of gummiferol for the structural elucidation and the structure–activity relationship study[29]

Gummiferol (**49**, Figure 9) was isolated from the leaves of *Adenia gummifera*.[30] This natural product exhibits a cytotoxicity against 13 mammalian cancer cell lines including strong activity against P388 murine leukemia cells and U373 human glioma cells. The planar structure of gummiferol, which has featured the conjugated triacetylene moiety and its neighboring diepoxide portion, was elucidated by the analyses of HRMS, IR, UV, and 2D NMR spectra. The *trans*-configurations at the C8/C9 and C10/C11 epoxide moieties were determined by the coupling constants of $^3J_{H,H}$, respectively. However, the absolute stereostructure of the diepoxide portion at the C8 to C11 positions was not clarified. Therefore, Takamura and Kadota's research group examined the synthesis of all four possible stereoisomers of gummiferol (**49**) toward its stereochemical elucidation.[29]

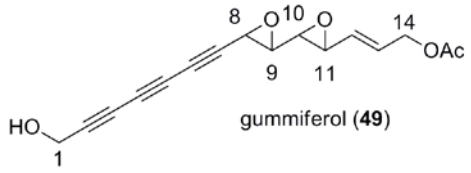
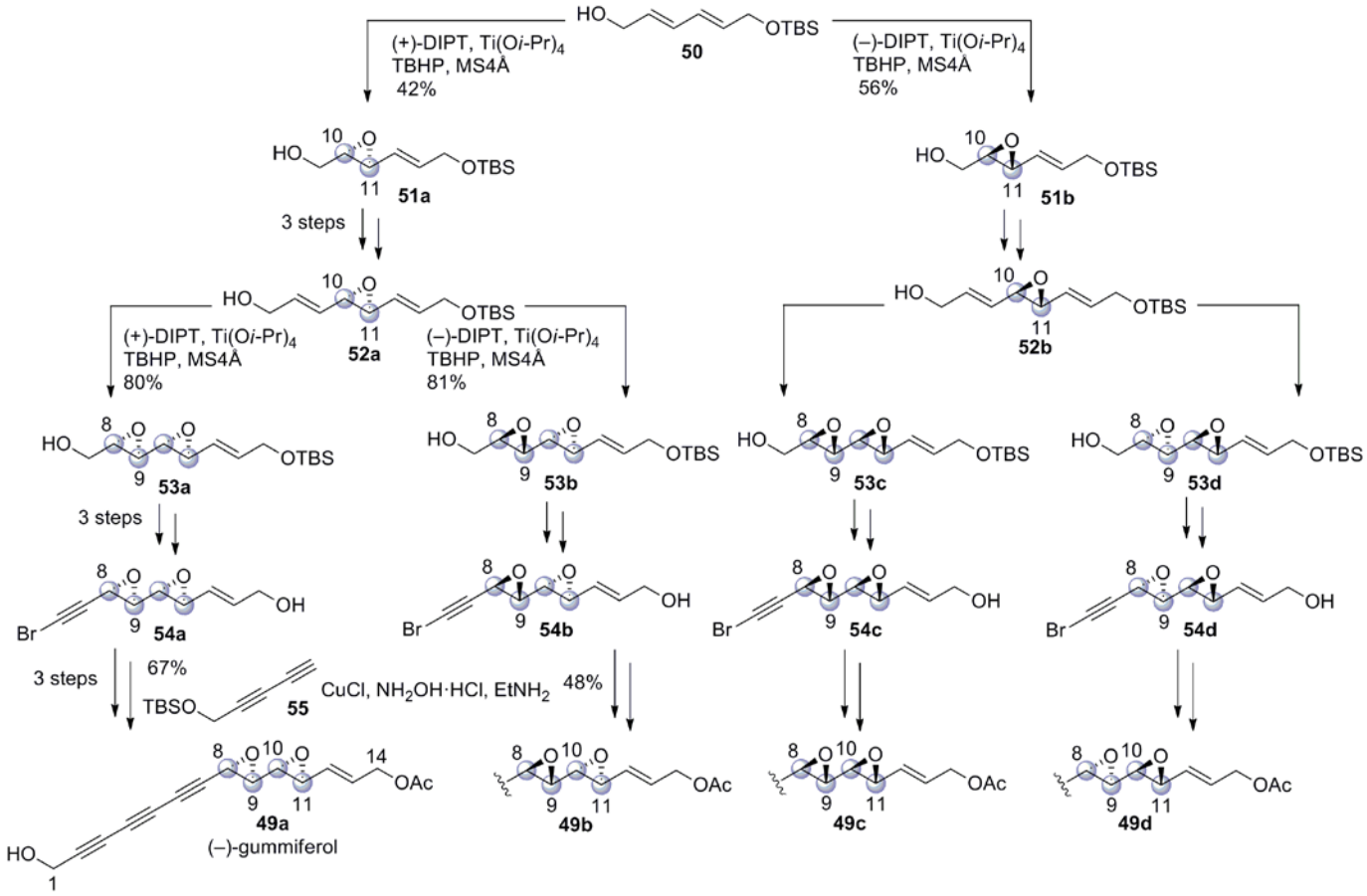


Figure 9. Planar structure of gummiferol (**49**).

This research group introduced the stereochemistries at the C8 to C11 positions by utilizing the stepwise Sharpless asymmetric epoxidation,[31] stereoselectively and respectively. Thus, as shown in Scheme 15, treatment of dienol **50** with (+)-diisopropyl tartrate (DIPT) and (–)-DIPT in the presence of Ti(O*i*-Pr)$_4$/*tert*-butyl hydroperoxide (TBHP)/molecular sieves (MS) 4Å afforded epoxy alcohols **51a** and **51b** as a single stereoisomer, respectively. The absolute stereochemistry of the synthetic **51a** was confirmed by epoxide ring-opening at the allylic C11 position of **51a** with Red-Al[32] and subsequent modified Mosher method.[33] After two-carbon elongation of the alcohols **51a**,**51b** was carried out in three steps to provide allylic alcohols **52a**,**52b**, *syn*- and *anti*-diepoxides **53a**,**53c** and **53b**,**53d** were synthesized as a single diastereomer, respectively, by applying Sharpless asymmetric epoxidation[31] to **52a**,**52b**. The diepoxy alcohols **53a**–**53d** were transformed to bromoacetylenes **54a**–**54d** in a parallel synthesis. Finally, construction of the triacetylene moieties by using Cadiot–Chodkiewicz coupling[34] between **54a**–**54d** and diacetylene **55** was performed to produce all four possible stereoisomers of gummiferol, **49a**–**49d**. Detailed comparison of the NMR data and specific rotations between the synthetic **49a**–**49d** and the natural product revealed the absolute configuration of natural (–)-gummiferol to be that described in **49a**.



Scheme 15. Stereodivergent synthesis of **49a**–**49d**.

Next, the growth-inhibitory activity of the synthetic products against HL60 human leukemia cells and HeLa S_3 human cervical cancer cells was evaluated. Interestingly, (–)-gummiferol (**49a**) and its stereoisomers **49b**–**49d** exhibited the similar activity without regard to the stereochemistry of the diepoxide portion (Figure 10). The truncated diepoxide analogue **56** was inactive against both HL60 and HeLa S_3 cells. On the other hand, the structurally simplified triacetylene analogues **57**–**62** retained the cytotoxic activity against both HL60 and HeLa S_3 cells. These results elucidated the following two points about

the structure–activity relationship: (1) The stereostructure of the diepoxide unit has little influence on the cytotoxicity. (2) The triacetylene moiety is essential for exerting the cytotoxicity.

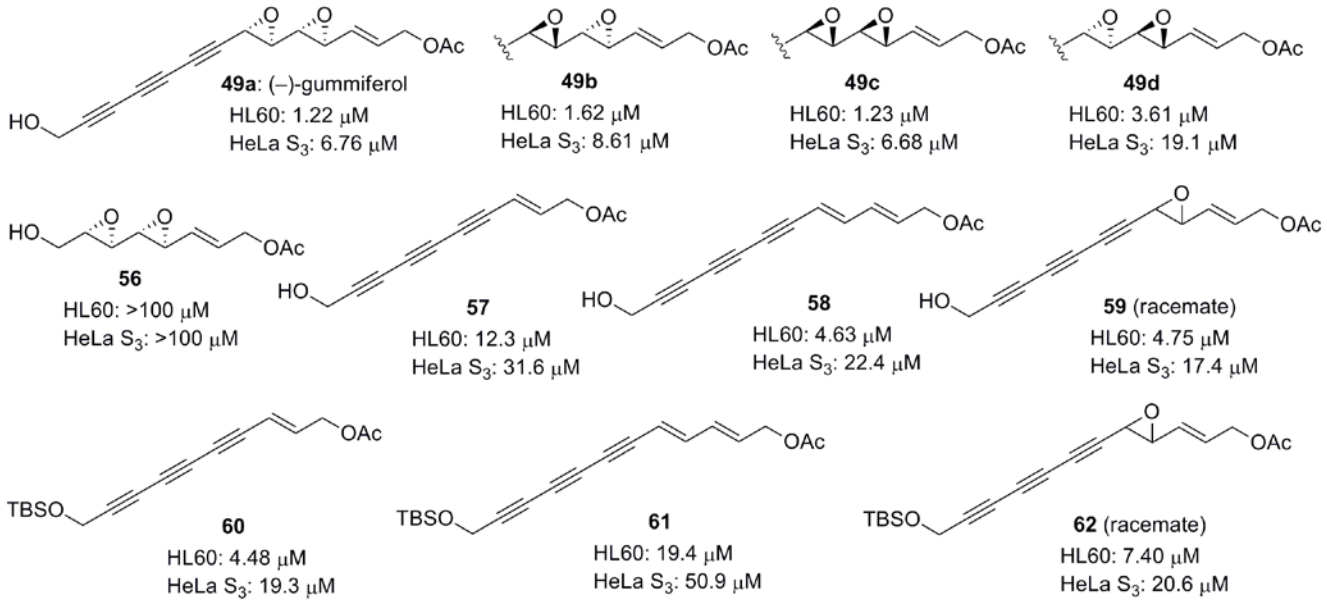


Figure 10. IC_{50} Values of the synthetic gummiferol and its analogues against human cancer cells.

Conclusion

This digest summarizes recent topics of stereodivergent synthesis of natural products. In the divergent synthesis, it is necessary to synthesize more than one target compound. In other words, stereodivergent synthesis cannot be realized if even one of target compounds is lacking. This significant issue needs to be deeply considered in planning the stereodivergent synthetic route. In addition, common synthetic intermediates and stereodiversification steps from common intermediates should be taken into account. Thus, setting stereodiversification steps at the late-stage of synthesis leads to proposal of the efficient synthetic scheme due to decreasing the number of total steps required for delivery of all target compounds. To supply all stereoisomers of natural products in a divergent manner accelerates structural elucidation and stereostructure–activity relationship study of natural products, and also provides the opportunity to develop the novel synthetic strategy and reaction.[35] It is expected that the stereodivergent strategy will be more and more utilized in the synthesis of not only natural products but also agrochemicals, pharmaceuticals, and organic materials.

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References and notes

1. (a) Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161; (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629.
2. Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III*, Willey-VCH: Weinheim, 2011.
3. (a) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038; (b) Danishefsky, S. *Nat. Prod. Rep.* **2010**, *27*, 1114.
4. (a) Schreiber, S. L. *Science* **2000**, *287*, 1964; (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
5. In this digest, the carbons with different stereochemistry in the compounds are circled in a pale blue color.
6. Boger has pointed out that divergent synthesis requires an identical intermediate to be converted, separately, to at least two members of the class of compounds. See: Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.
7. Haydl, A. M.; Berthold, D.; Spreider, P. A.; Breit, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 5765.
8. For a review, see: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.
9. For selected examples, see: (a) Gorminsky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584; (b) Arbour, J. L.; Rzepa, H. S.; Contreras-García, J.; Adrio, L. A.; Barreiro, E. M.; Hii, K. K. *Chem. Eur. J.* **2012**, *18*, 11317; (c) Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721; (d) Shu, X.-Z.; Nguyen, S. C.; He, Y.; Oba, F.; Zhang, Q.; Canlas, C.; Somorjai, G. A.; Alivisatos, A. P.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 7083.
10. For selected examples, see: (a) Oderinde, M. S.; Hunter, H. N.; Bremner, S. W.; Organ, M. G. *Eur. J. Org. Chem.* **2012**, 175; (b) Niu, W.; Yeung, Y.-Y. *Org. Lett.* **2015**, *17*, 1660.
11. For a selected example, see: Mohapatra, D. K.; Umamaheshwar, G.; Rao, M. M.; Umadevi, D.; Yadav, J. S. *RSC Adv.* **2014**, *4*, 8335.
12. Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746.
13. (a) Poch, G. K.; Gloer, J. B. *J. Nat. Prod.* **1989**, *52*, 257; (b) Tarman, K.; Palm, G. J.; Porzel, A.; Merzweiler, K.; Arnold, N.; Wessjohann, L. A.; Unterseher, M.; Lindequist, U. *Phytochem. Lett.* **2012**, *5*, 83.
14. Miller, D. G.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 2924.
15. Jang, H.; Shin, I.; Lee, D.; Kim, H.; Kim, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 6497.
16. (a) Warren, R. G.; Wells, R. J.; Blount. J. F. *Aust. J. Chem.* **1980**, *33*, 891; (b) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227.
17. For a review, see: Kim, D. *Synlett* **2014**, *25*, 33.
18. Qi, C.; Xiong, Y.; Eschenbrenner-Lux, V.; Cong, H.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2016**, *138*, 798.
19. (a) Nomura, T.; Fukai, T.; Hano, Y.; Uzawa, J. *Heterocycles* **1981**, *16*, 2141; (b) Shi, Y.-Q.; Fukai, T.; Nomura, T. *Heterocycles* **2001**, *54*, 639; (c) Shi, Y.-Q.; Fukai, T.; Ochiai, M.; Nomura, T. *Heterocycles* **2001**, *55*, 13.
20. For a review of stereodivergent reaction of a racemic mixture, see: Miller, L. C.; Sarpong, R. *Chem. Soc. Rev.* **2011**, *40*, 4550.
21. Kubo, H.; Matsui, K.; Saito, T.; Nishiyama, S. *Tetrahedron* **2014**, *70*, 6392.
22. (a) Mancini, I.; Guella, G.; Laboute, P.; Debitus, C.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3121; (b) Diers, J. A.; Pennaka, H. K.; Peng, J.; Bowling, J. J.; Duke, S. O.; Hamann, M. T. *J. Nat. Prod.* **2004**, *67*, 2117.

23. Eichenauer, N. C.; Tschersich, R.; Pietruszka, J. *J. Nat. Prod.* **2015**, *78*, 2782.
24. Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J. Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron* **1996**, *52*, 10583.
25. Eichenauer, N. C.; Nordschild, A. C. M.; Bischop, M.; Schumacher, D.; Mackwitz, M. K. W.; Tschersich, R.; Wilhelm, T.; Pietruszka, J. *Eur. J. Org. Chem.* **2015**, 5620.
26. (a) Takamura, H.; Fujiwara, T.; Kawakubo, Y.; Kadota, I.; Uemura, D. *Chem. Eur. J.* **2016**, *22*, 1979; (b) Takamura, H.; Fujiwara, T.; Kawakubo, Y.; Kadota, I.; Uemura, D. *Chem. Eur. J.* **2016**, *22*, 1984.
27. Kita, M.; Ohishi, N.; Konishi, K.; Kondo, M.; Koyama, T.; Kitamura, M.; Yamada, K.; Uemura, D. *Tetrahedron* **2007**, *63*, 6241.
28. Robertson, J.; Unsworth, W. P.; Lamont, S. G. *Tetrahedron* **2010**, *66*, 2363.
29. (a) Takamura, H.; Wada, H.; Lu, N.; Kadota, I. *Org. Lett.* **2011**, *13*, 3644; (b) Takamura, H.; Wada, H.; Lu, N.; Ohno, O.; Suenaga, K.; Kadota, I. *J. Org. Chem.* **2013**, *78*, 2443.
30. Fullas, F.; Brown, D. M.; Wani, M. C.; Wall, M. E.; Chagwedera, T. E.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1995**, *58*, 1625.
31. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
32. Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.
33. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
34. (a) Chodkiewicz, W.; Cadiot, P. C. R. *Hebd. Seances Acad. Sci.* **1955**, *241*, 1055; (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd Ed., Elsevier: Amsterdam, 1988; (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
35. As noted in the introduction part, this digest deals with selected publications reported during the past five years. Curran and co-workers developed fluorous mixture synthesis as a powerful tool to make stereoisomer libraries of natural products, which resulted in the structural elucidation of several natural products. See: (a) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766; (b) Curran, D. P.; Sui, B. *J. Am. Chem. Soc.* **2009**, *131*, 5411; (c) Sui, B.; Yeh, E. A.-H.; Curran, D. P. *J. Org. Chem.* **2010**, *75*, 2942; (d) Zhang, K.; Gudipati, V.; Curran, D. P. *Synlett* **2010**, 667; (e) Bajpai, R.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 20435; (f) Moretti, J. D.; Wang, X.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 7963; (g) Curran, D. P.; Sinha, M. K.; Zhang, K.; Sabatini, J. J.; Cho, D.-H. *Nat. Chem.* **2012**, *4*, 124.