HETEROCYCLES, Vol. 104, No. 10, 2022, pp. 1709 - 1743. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 31st May, 2022, Accepted, 28th June, 2022, Published online, 12th July, 2022
DOI: 10.3987/REV-22-983

TOTAL SYNTHESIS OF (−)-EXIGUOLIDE, A POTENT ANTICANCER MARINE MACROLIDE

Haruhiko Fuwa*

Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan. Email: hfuwa.50m@g.chuo-u.ac.jp.

Abstract – (−)-Exiguolide is a marine macrolide natural product, isolated by Ohta and co-workers from a rare marine sponge, *Geodia exigua* Thiele, collected off Amami-Oshima, Japan. The structural complexity and potent anticancer activity of this natural product spurred the interest of the synthetic chemistry community. This review will focus on total and formal syntheses of exiguolide by Lee, Fuwa, Roulland, Scheidt, Reddy, Song, and Ishihara to illustrate advances in strategies for macrolide synthesis.

INTRODUCTION

(−)-Exiguolide ((−)-**1**, Figure 1) was isolated by Ohta, Ikegami, and co-workers from methanol extracts of a rare marine sponge, *Geodia exigua* Thiele, collected off Amami-Oshima, Kagoshima, Japan.[1] The gross structure of (−)-**1** was determined through extensive 2D-NMR analysis, and the relative configuration was assigned on the basis of NOE correlations and *J* values. The assigned relative configuration was supported by the *J*-based configurational analysis (JBCA) method.[2] However, the absolute configuration of (−)-**1** was left unassigned at that time. The absolute configuration was eventually established in an unambiguous manner through the total synthesis of the unnatural enantiomer, (+)-**1**, by Lee and co-workers.[3] Ohta et al. described that (−)-**1**, at a concentration of 21 μM or above, inhibited fertilization of sea urchin gametes, although (−)-**1** did not affect the development of fertilized eggs up to the gastrula stage, even at 100 μM.[1] Our group reported the total synthesis of (−)-**1** for the first time,[4] and also identified its potent anticancer activity against human non-small cell lung cancer (NSCLC) cell lines.[4b]

The structure of exiguolide is characterized by a 20-membered macrolactone skeleton, engrafted with two 2,6-*cis*-substituted tetrahydropyran rings and appended with a conjugated (*E*,*Z*,*E*)-triene side chain. The apparent structural resemblance of exiguolide with bryostatins[5] attracted the immense attention of synthetic chemists, as indicated by the fact that eight total syntheses and one formal synthesis have been described

over the past 15 years. This review summarizes total and formal syntheses of exiguolide as a model case to illustrate advances in improving the efficiency of macrolide synthesis.[6] As criteria, longest linear steps and 'ideality'[6d,f] will be given for each synthesis. 'Ideality' is expressed as percentage of the number of strategic steps in the total step count.[6d,f]

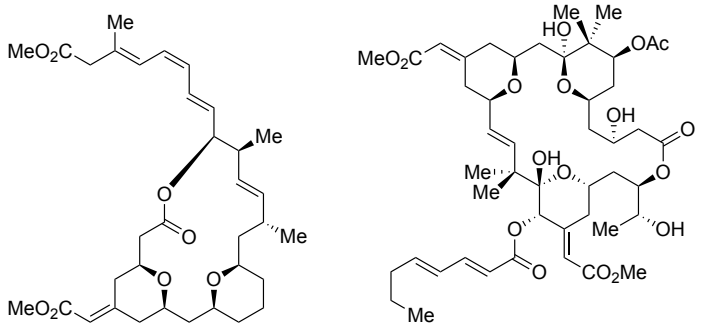
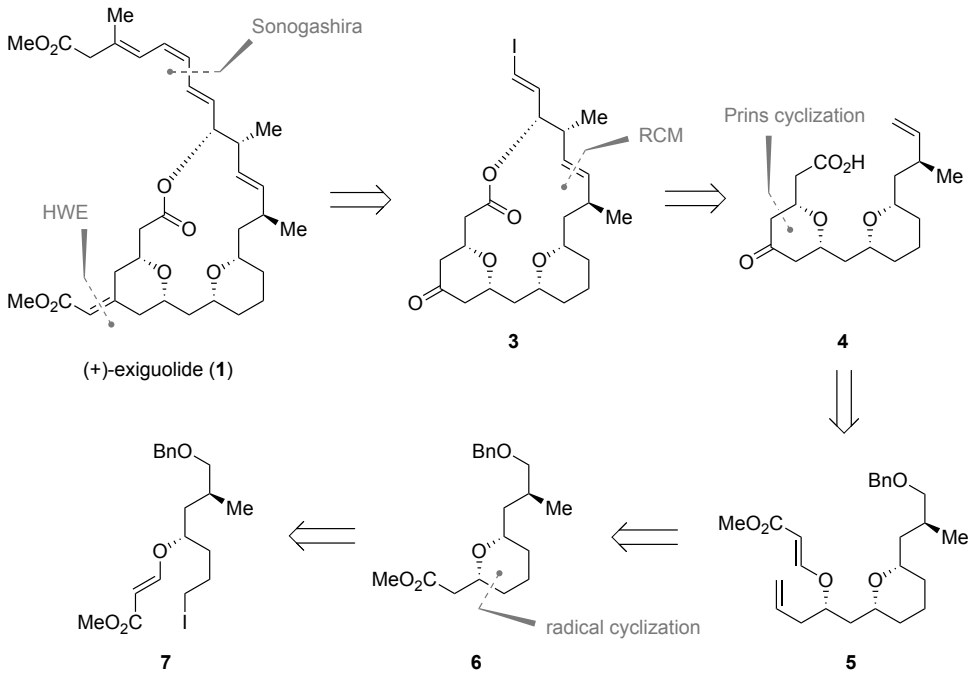


Figure 1. Structures of (−)-exiguolide ((−)-**1**) and (+)-bryostatin 1 ((+)-**2**)

TOTAL SYNTHESIS OF EXIGUOLIDE

1. Total synthesis of (+)-exiguolide by Lee and co-workers (2008)[3]

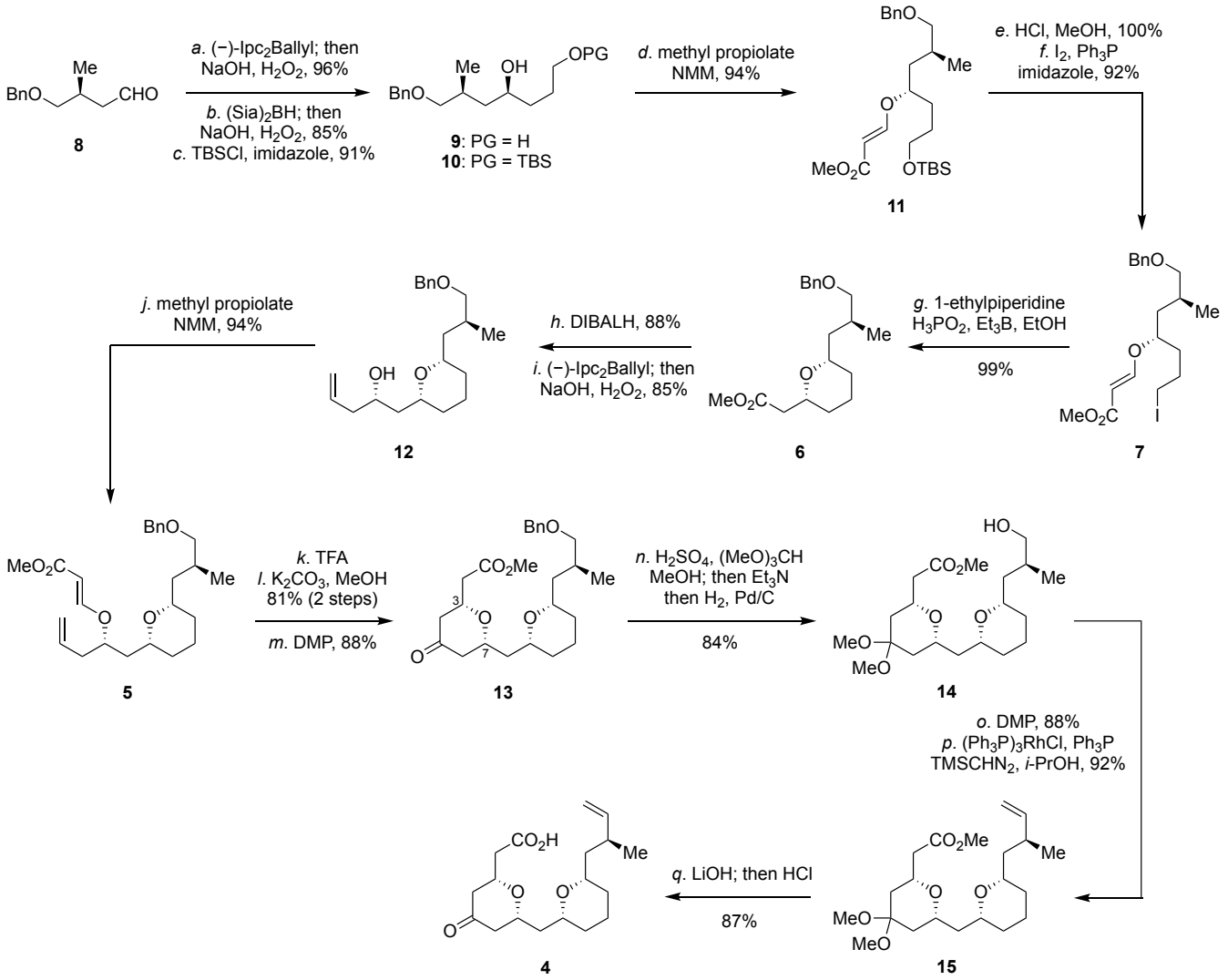
In 2008, Lee and co-workers disclosed the first total synthesis of (+)-exiguolide, the unnatural enantiomer. Lee's synthetic blueprint toward (+)-**1** is summarized in Scheme 1. The conjugated triene side chain and the α,β-unsaturated ester of (+)-**1** would be constructed at late stage of the total synthesis by means of a Sonogashira reaction[7] and a Horner–Wadsworth–Emmons (HWE) reaction,[8] respectively. The precursor macrocycle **3** would be available from carboxylic acid **4** via a ring-closing metathesis (RCM),[9] and the



Scheme 1. Synthesis plan toward (+)-exiguolide ((+)-**1**) by Lee

latter could be traced back to β-alkoxy acrylate **5** by considering an intramolecular Prins cyclization.[10] Compound **5** would be accessible from β-alkoxy acrylate **7** through an intramolecular radical cyclization[11] and subsequent derivatization of the radical cyclization product **6**.

The synthesis of carboxylic acid **4** started with known aldehyde **8**, which was available in five steps from (*S*)-Roche ester[12] (Scheme 2). Brown asymmetric allylation[13] of **8** using (−)-Ipc$_2$Ballyl, followed by

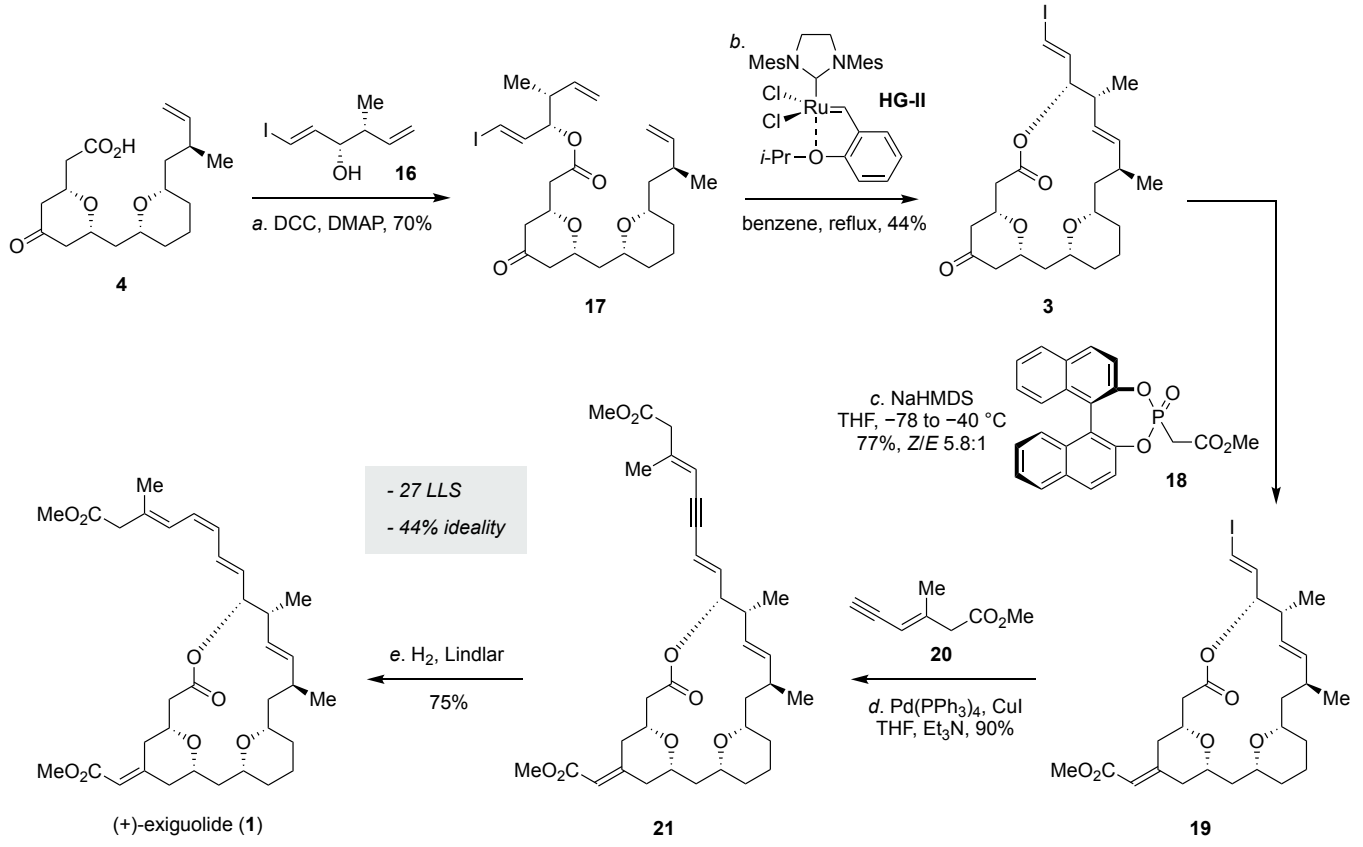


Scheme 2. Synthesis of carboxylic acid **4**

hydroboration of the resultant olefin with (Sia)$_2$BH, gave diol **9**. Selective silylation of the primary hydroxy group of **9** with TBSCl/imidazole delivered alcohol **10**. Treatment of **10** with methyl propiolate and NMM led to β-alkoxy acrylate **11**. Cleavage of the silyl ether and iodination of the derived alcohol afforded β-alkoxy acrylate **7**. Intramolecular radical cyclization[11] of **7** was efficiently achieved in the presence of 1-ethylpiperidinium hypophosphite and triethylborane in ethanol at room temperature[14] to provide tetrahydropyran **6** in 99% yield. Intramolecular radical cyclization of β-alkoxy acrylates have been extensively investigated by Lee and co-workers for stereoselective synthesis of tetrahydrofurans and

tetrahydropyrans.[11] DIBALH reduction of **6** gave the corresponding aldehyde, which was allylated with (−)-Ipc$_2$Ballyl[13] to deliver homoallylic alcohol **12**. Exposure of **12** to methyl propiolate and NMM provided β-alkoxy acrylate **5**. Intramolecular Prins cyclization[10] of **5**, followed by methanolysis of the trifluoroacetate moiety of the Prins product, and subsequent Dess–Martin oxidation[15] afforded ketone **13** in 71% overall yield from **5**. Partial racemization (ca. 7:1) was observed for the Prins cyclization,[16] and the minor diastereomer was deduced to be 3,7-bis-*epi*-**13**. Acetalization of **13** with a catalytic amount of H_2SO_4 in $(MeO)_3CH$/MeOH, neutralization with Et_3N, and hydrogenolysis of the benzyl group provided alcohol **14**. After Dess–Martin oxidation[15] of **14**, the derived aldehyde was methylenated[17] to give olefin **15**. Hydrolysis of the methyl ester and the dimethyl acetal afforded carboxylic acid **4**.

Now the stage was set for constructing the 20-membered macrolactone skeleton of (+)-**1** (Scheme 3). Esterification of **4** with alcohol **16**, available in two steps from (*E*)-β-iodoacrolein via a Brown asymmetric crotylation[18] and subsequent Sharpless kinetic resolution[19] to improve the optical purity, gave ester **17** (70%). Macrocyclic RCM[9] of **17** under the influence of the second-generation Hoveyda–Grubbs complex (**HG-II**)[20] delivered macrocyclic ketone **3** albeit in a moderate 44% yield. HWE reaction of **3** using phosphonate **18**[8] provided α,β-unsaturated ester **19** in 77% yield (*Z*/*E* 5.8:1). Sonogashira reaction[7] of **19** with alkyne **20**, prepared in four steps from 3-butyn-1-ol, led to conjugated enyne **21** (90%). Finally, semi-hydrogenation of **21** in the presence of Lindlar's catalyst furnished (+)-exiguolide ((+)-**1**).



Scheme 3. Total synthesis of (+)-exiguolide ((+)-**1**) by Lee

Lee's total synthesis of (+)-exiguolide ((+)-**1**) was accomplished in 27 longest linear steps (LLS) from (*S*)-Roche ester. Highlights of the present synthesis include: 1) an intramolecular β-alkoxy acrylate radical cyclization and 2) an intramolecular β-alkoxy acrylate Prins cyclization for stereoselective synthesis of the two tetrahydropyran rings; 3) a macrocyclic RCM for the closure of the 20-membered macrocyclic skeleton; and 4) a Sonogashira reaction/semi-hydrogenation sequence for stereoselective construction of the conjugated triene side chain.

In Lee's total synthesis of (+)-**1**, intramolecular radical[11] and Prins β-alkoxy acrylate cyclization[10] reactions were effectively applied to the synthesis of the two tetrahydropyran rings, while a number of non-constructive functional group interconversions were needed for preparing suitable cyclization precursors. The construction of the 20-membered macrolactone framework by means of a macrocyclic RCM[9] met with limited success presumably because of the low reactivity of the precursor diene, which has an allylic methyl group at each olefin.[21] Similar difficulties in forging the macrocyclic skeleton of (−)-**1** were described by Fuwa and co-workers, as will be summarized in the next section.

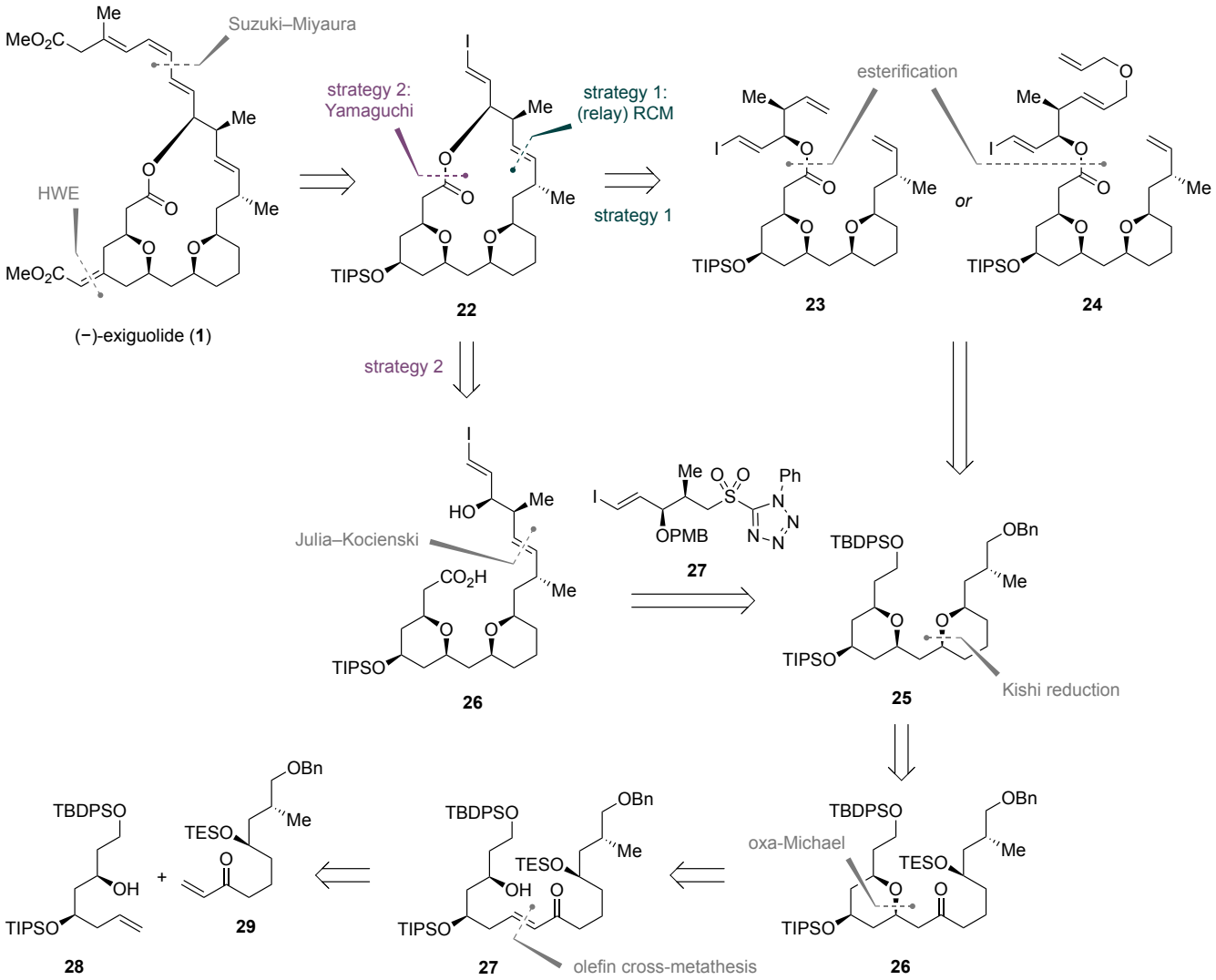
2. Total synthesis of (−)-exiguolide by Fuwa and co-workers. Part 1 (2010)[4]

Fuwa and co-workers reported the total synthesis of (−)-exiguolide ((−)-**1**) for the first time. Two approaches were devised for the construction of the 20-membered macrolactone skeleton **22**, as depicted in Scheme 4. Thus, they envisioned that the macrocycle **22** could be formed either via a (relay) ring-closing metathesis[9] of **23** (or **24**) (strategy 1) or via a Yamaguchi macrolactonization[22] of **26** (strategy 2). The common intermediate **25** was thought to be accessible from olefin **28** and vinyl ketone **29** by chartering a three-step olefin cross-metathesis/intramolecular oxa-Michael addition/Kishi reduction sequence.

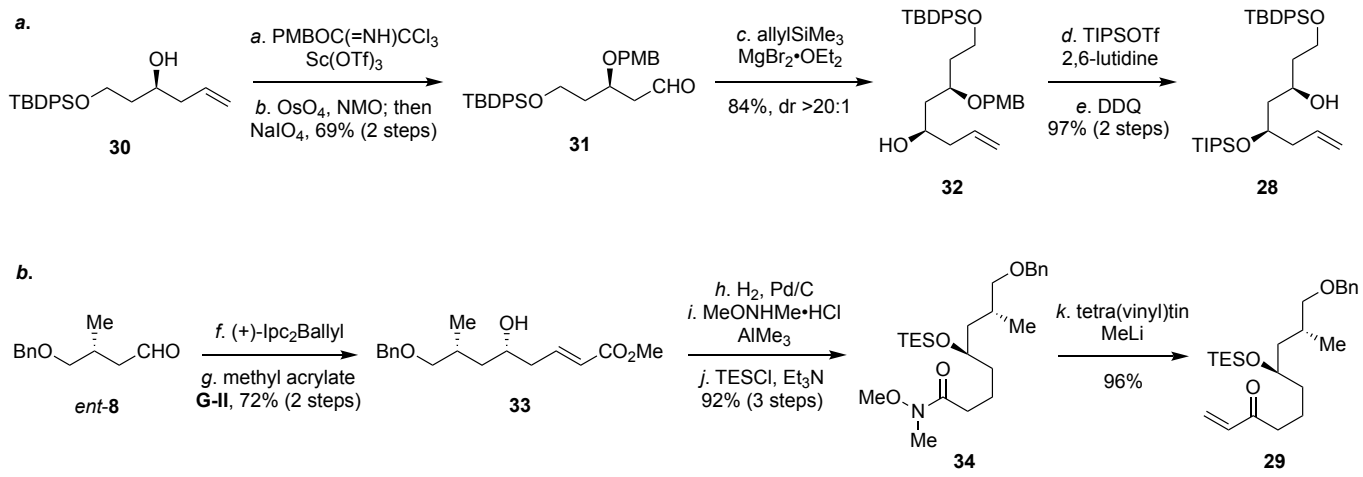
The synthesis of methylene bis-tetrahydropyran **25** commenced with protection of known homoallylic alcohol **30**[23] as its PMB ether, followed by cleavage of the double bond, to give aldehyde **31** (Scheme 5a). Chelate-controlled allylation of **31** delivered homoallylic alcohol **32** in 84% yield with greater than 20:1 diastereoselectivity. Silylation of **32** with TIPSOTf/2,6-lutidine and deprotection of the PMB group led to olefin **28**. Meanwhile, the coupling partner, vinyl ketone **29**, was synthesized from known aldehyde *ent*-**8**[12] (Scheme 5b). Asymmetric allylation of *ent*-**8** using (+)-Ipc_2Ballyl,[13] followed by olefin cross-metathesis[24] with methyl acrylate under **G-II**[25] catalysis, gave α,β-unsaturated ester **33**. Hydrogenation of the double bond, Weinreb amidation,[26] and silylation provided amide **34**, which was reacted with vinyllithium[27] to afford vinyl ketone **29**.

Olefin cross-metathesis[24] of olefin **28** and vinyl ketone **29** was achieved using **HG-II** complex[20] in CH_2Cl_2 at 35 °C to deliver α,β-unsaturated ketone **27** in 93% yield (Scheme 6). Treatment of **27** with a catalytic amount of KO*t*-Bu in THF at 0 °C triggered intramolecular oxa-Michael addition[28] to afford ketone **26** in

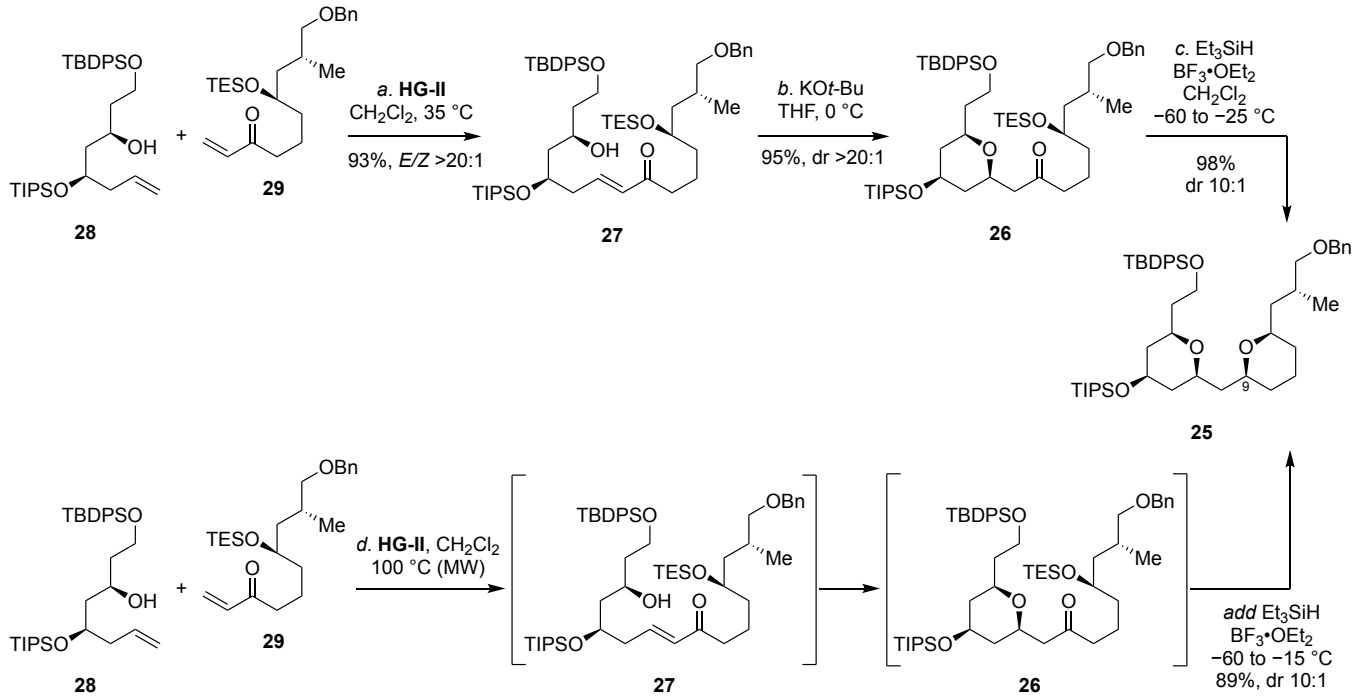
95% yield, forging the tetrahydropyran ring with >20:1 diastereoselection. Kishi reduction[29] of **26** (BF_3•OEt_2, Et_3SiH) effectively closed the second tetrahydropyran ring to provide methylene bis-



Scheme 4. Synthesis plan toward (−)-exiguolide (**1**) by Fuwa



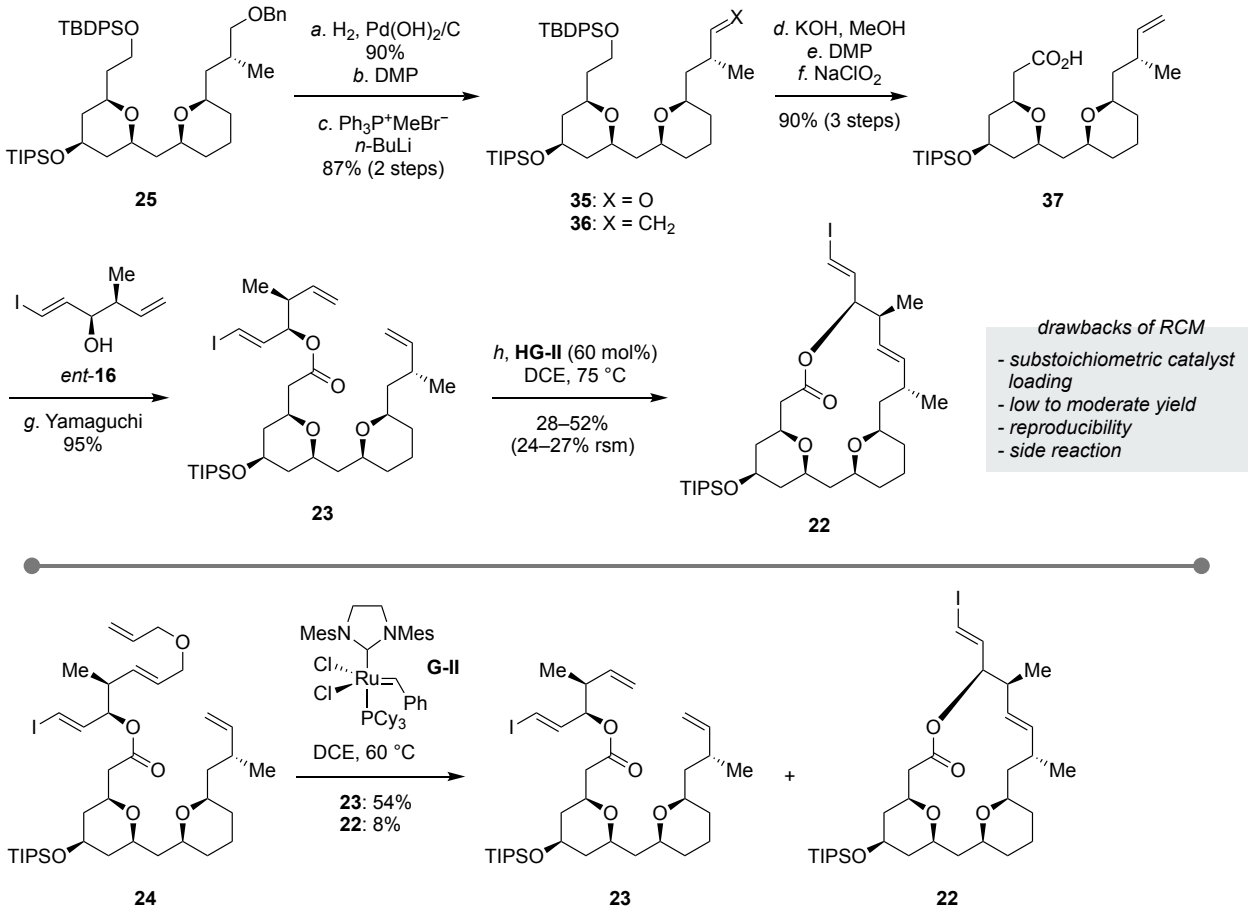
Scheme 5. Synthesis of homoallylic alcohol **28** and vinyl ketone **29**



Scheme 6. Synthesis of methylene bis-tetrahydropyran **25**

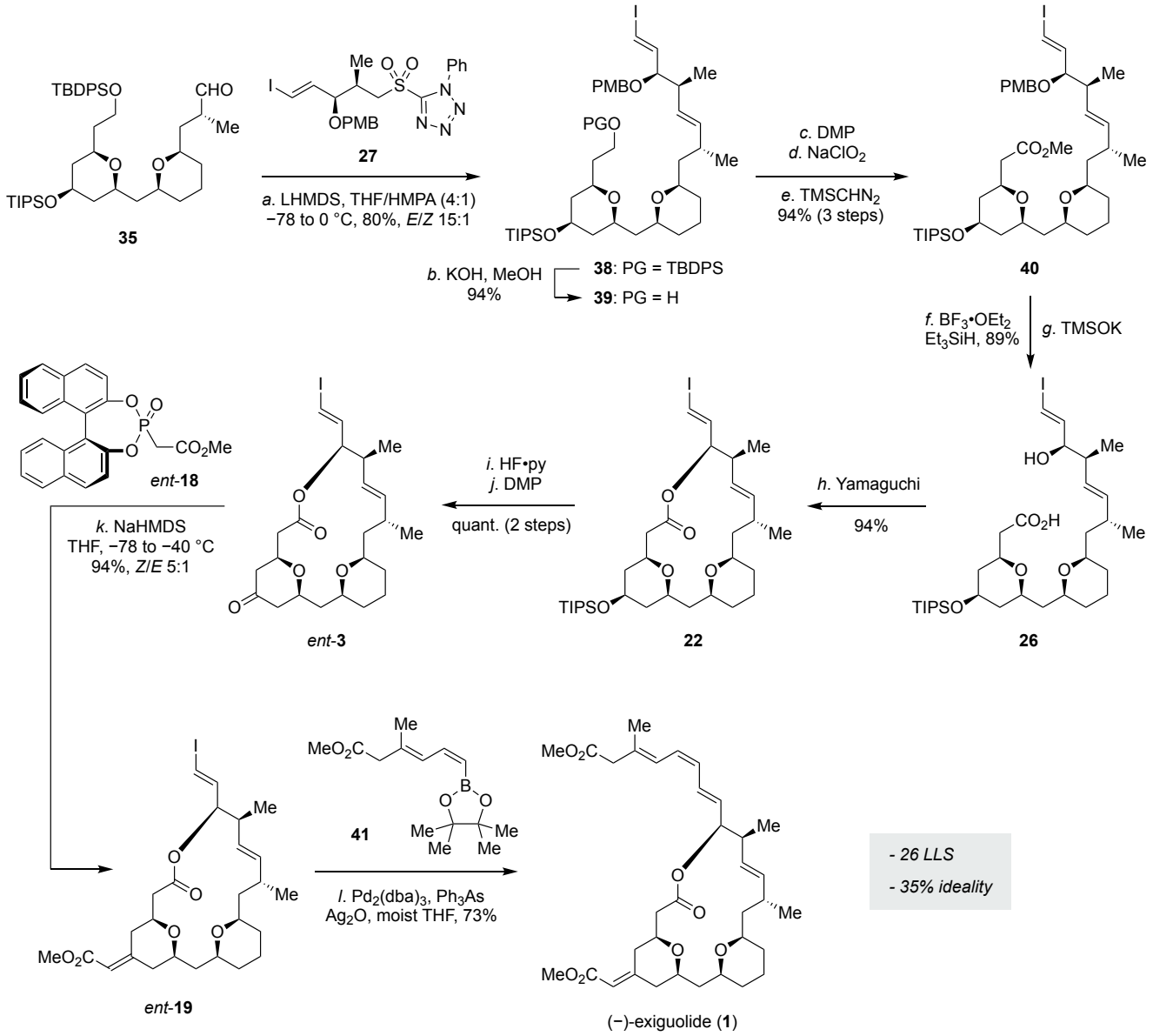
tetrahydropyran **25** in 98% yield with good diastereoselectivity at the C9 position. Importantly, running the olefin cross-metathesis[24] of **28** and **29** at elevated temperature conditions resulted in concomitant intramolecular oxa-Michael addition[28] to deliver ketone **26** directly, which without isolation underwent Kishi reduction[29] by adding $Et_3SiH/BF_3•OEt_2$ to the reaction mixture, affording methylene bis-tetrahydropyran **25** in 89% yield from **29**.

According to 'strategy 1', the synthesis of RCM precursor **23** was carried out in a straightforward manner from **25** (Scheme 7). Hydrogenolysis of the benzyl ether and Dess–Martin oxidation[15] gave aldehyde **35**, and subsequent Wittig methylenation delivered olefin **36**. Selective removal of the TBDPS group, followed by a two-stage oxidation, led to carboxylic acid **37**, which was esterified with alcohol *ent*-**16** to provide **23**. The reactivity of **23** toward Grubbs-type ruthenium olefin metathesis catalysts was surprisingly low, as only traces of the desired macrocycle **22** was detected in the reaction mixture when **G-II**[25] (30–60 mol%) was used in CH_2Cl_2 at reflux or toluene at 80 °C for two days. The RCM under forcing conditions (60 mol% of **HG-II**,[20] DCE, 75 °C, two days) provided macrocycle **22** in 28–52% yields with substantial amounts of **23** (24–27%) remained unreacted. The difficulties in the RCM were not only the low reactivity of the substrate but also a side reaction of the iodoolefin moiety of **22**/**23** with catalytically active ruthenium methylidene species, resulting in a formal loss of the iodine atom. The relay RCM[30] of **24** was unproductive and gave **23** in 54% yield as the major product,[31] along with **22** in only 8% yield.



Scheme 7. Synthesis and macrocyclic (relay) RCM of **23** and **24**

Accordingly, Fuwa and co-workers investigated the synthesis of macrocycle **22** on the basis of 'strategy 2', which relied on a Yamaguchi macrolactonization[22] for the closure of the macrolactone skeleton (Scheme 8). Julia–Kocienski olefination[32] of aldehyde **35** with sulfone **27** was achieved using LHMDS as a base in THF/HMPA (4:1, v/v) under carefully controlled conditions to afford olefin **38** in 80% yield with *E*/*Z* 15:1 selectivity. A series of routine protecting group and functional group interconversions led to seco-acid **26** via the intermediacy of methyl ester **40**. Macrolactonization of **26** under Yamaguchi conditions[22] afforded macrocycle **22** in an excellent 94% yield. The success of the macrolactonization was largely dependent on the final substrate concentration, which must be kept below 1 mM. Removal of the TIPS group from **22** followed by Dess–Martin oxidation[15] led to ketone *ent*-**3**. Stereoselective HWE reaction using phosphonate *ent*-**18**[8] provided α,β-unsaturated ester *ent*-**19** in 94% yield with *Z*/*E* 5:1 selectivity. After removing the undesired *E* isomer by flash column chromatography using silica gel, Suzuki–Miyaura reaction[33] of *ent*-**19** with pinacolboronate **41**, prepared via a Rh-catalyzed *trans*-selective hydroboration[34] of the corresponding alkyne, afforded (−)-exiguolide ((−)-**1**) in 73% yield.



Scheme 8. Total synthesis of (−)-exiguolide (**1**) by Fuwa (Part 1)

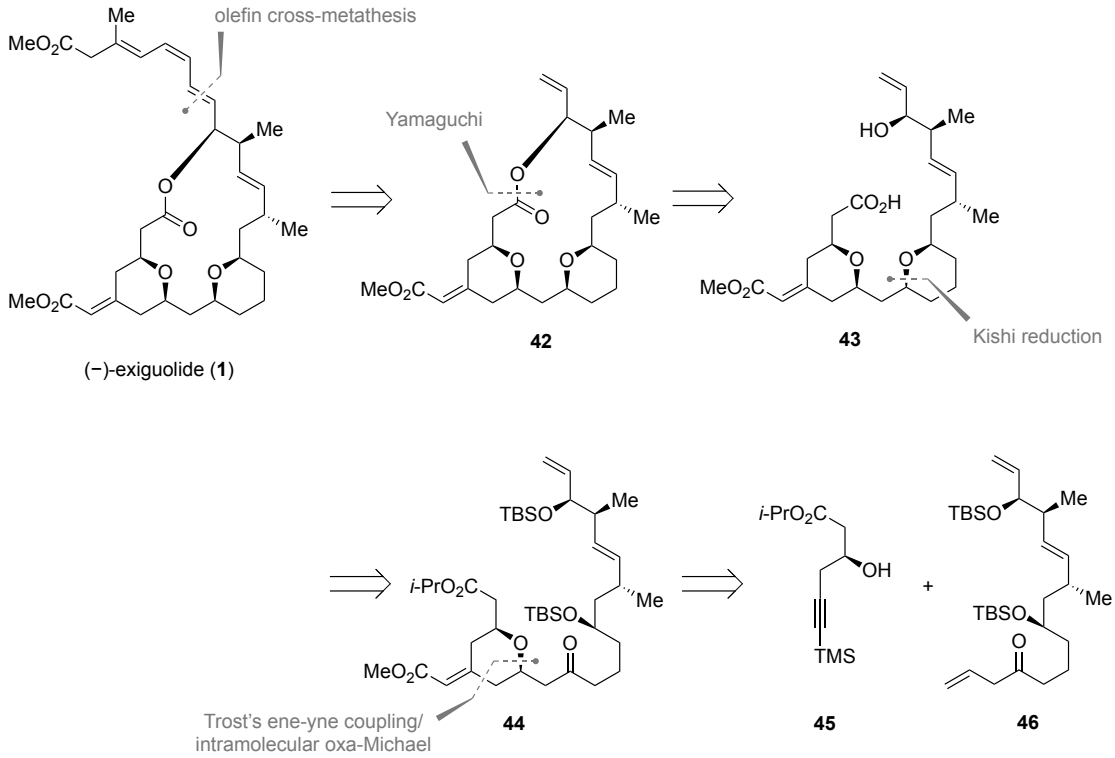
Fuwa's total synthesis of (−)-exiguolide ((−)-**1**) was completed in 26 longest linear steps from (*R*)-Roche ester. The present synthesis featured: 1) a tandem olefin cross-metathesis/intramolecular oxa-Michael addition/Kishi reduction for stereoselective synthesis of the methylene bis-tetrahydropyran substructure; 2) a Julia–Kocienski olefination[32] and 3) a Yamaguchi macrolactonization[22] for the construction of the 20-membered macrocyclic backbone; and 4) a Suzuki–Miyaura reaction[33] for stereoselective formation of the (*E*,*Z*,*E*)-triene side chain.

The tandem olefin cross-metathesis/intramolecular oxa-Michael addition[35] was found to be a versatile method for stereoselective synthesis of tetrahydropyran derivatives, as reviewed elsewhere,[36] and actually expedited the synthesis of the methylene bis-tetrahydropyran substructure **25**. However, preparation of the vinyl ketone precursor **29** required 11 steps from (*R*)-Roche ester and made the overall path to key

intermediate **25** lengthy. A six-step sequence of routine transformations required for advancing olefin **39** to seco-acid **26** is another shortcoming of the present synthesis. These issues were eventually addressed in Fuwa's second-generation synthesis of (−)-exiguolide, which will be discussed later.

3. Total synthesis of (−)-exiguolide by Roulland and co-workers (2010)[37]

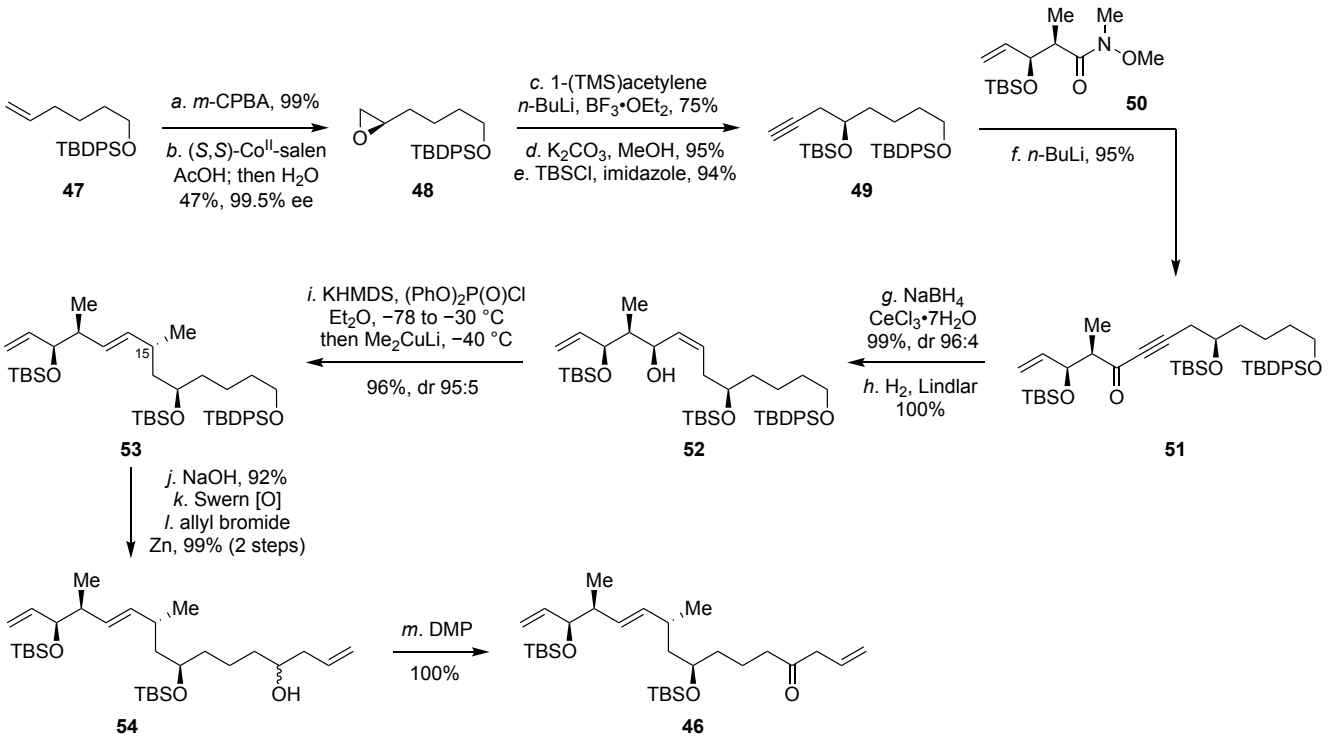
Almost simultaneously to the Fuwa group, Roulland and co-workers reported the total synthesis of (−)-exiguolide ((−)-**1**). Roulland et al. envisioned an olefin cross-metathesis[24] for the construction of the conjugated triene side chain of (−)-**1** (Scheme 9). The precursor **42** should be available from seco-acid **43** via a Yamaguchi macrolactonization.[22] Central to the Roulland's synthetic blueprint were a Ru-catalyzed ene-yne coupling/intramolecular oxa-Michael addition[38] (**45** + **46** → **44**) and a Kishi reduction[29] (**44** → **43**) for stereoselective synthesis of the two tetrahydropyran rings.



Scheme 9. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Roulland

The synthesis of olefin **46** commenced with epoxidation of 6-((*tert*-butyldiphenylsilyl)oxy)hex-1-ene (**47**) using *m*-CPBA followed by Jacobsen kinetic hydrolytic resolution[39] to give epoxide **48** in 47% yield with 99.5% ee (Scheme 10). Regioselective opening of **48** with 1-(trimethylsilyl)ethynyl difluoroborane,[40] removal of the TMS group, and silylation of the resultant alcohol delivered alkyne **49**. Deprotonation of **49** with *n*-BuLi and addition of the derived acetylide to known Weinreb amide **50**, available in three steps from a commercially available material,[41] afforded ynone **51**. After diastereoselective reduction of **51** under Luche conditions,[42] semi-hydrogenation of the derived propargylic alcohol gave *Z*-allylic alcohol **52**.

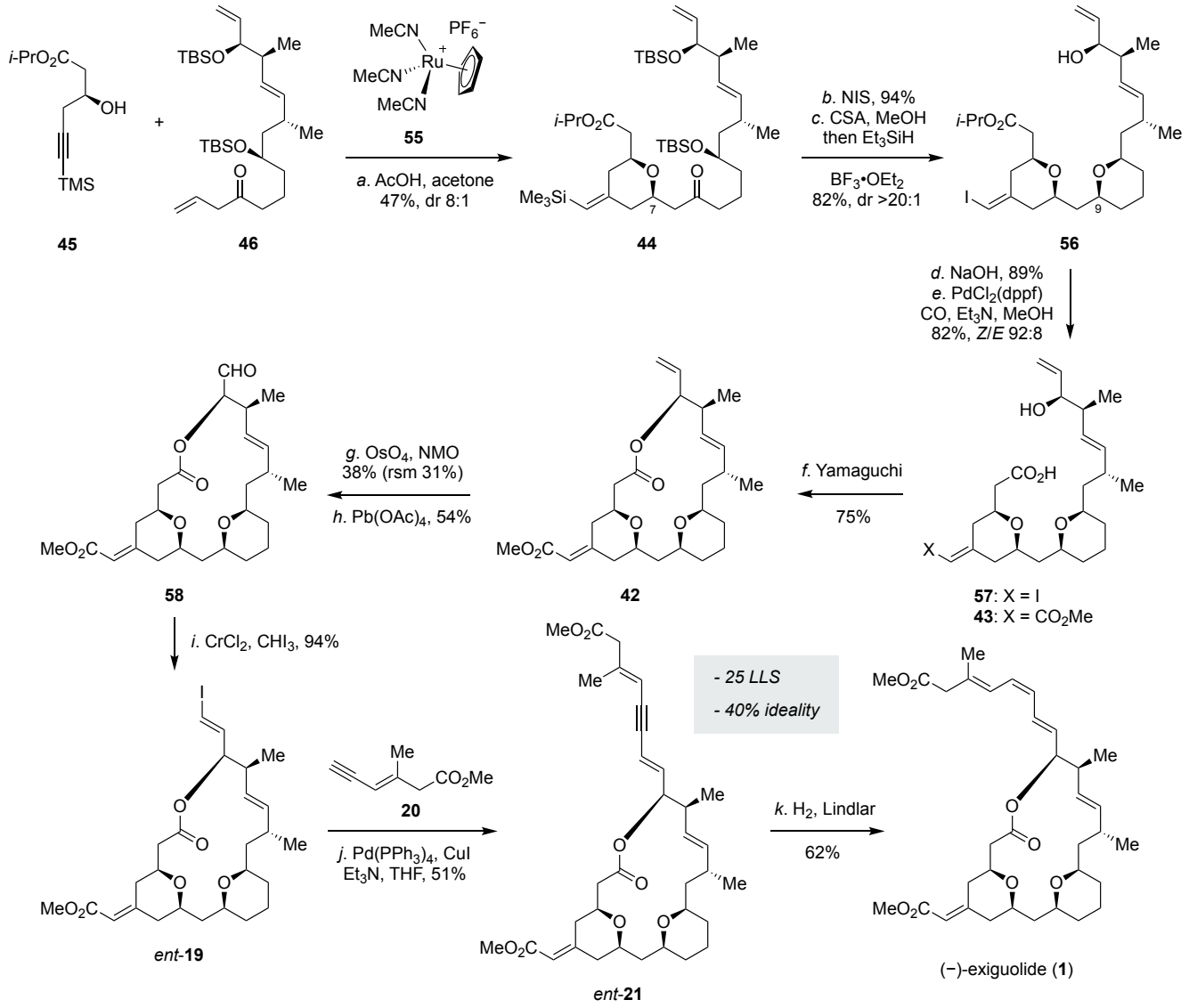
Treatment of **52** with KHMDS/$(PhO)_2P(O)Cl$ generated the corresponding phosphate, which was in situ reacted with Me_2CuLi to deliver olefin **53** in 96% yield with correct configuration at C15 (dr 95:5) via an S_N2' reaction. A four-step sequence of standard manipulations, i.e., desilylation, Swern oxidation, allylation, and Dess–Martin oxidation,[15] was required for advancing **53** to olefin **46**.



Scheme 10. Synthesis of olefin **46**

The crucial Ru-catalyzed yne–ene coupling/intramolecular oxa-Michael addition[38] of **46** with alkyne **45** was achieved in the presence of Ru complex **55** (7 mol%) and AcOH (3 mol%) in acetone at room temperature to provide tetrahydropyran **44** in 47% yield with 8:1 diastereoselectivity at C7. The minor diastereomer was separated by preparative HPLC. After iododesilylation of **44** with NIS[43] (94%), the TBS ethers were cleaved under acidic conditions with spontaneous formation of a methyl acetal at C9, and in situ Kishi reduction[29] afforded methylene bis-tetrahydropyran **56** in 82% yield with greater than 20:1 diastereoselection. Alkaline hydrolysis of **56** followed by Pd-catalyzed methoxycarbonylation gave α,β-unsaturated ester **43** with a slight stereochemical scrambling of the *Z* configuration (92:8). Macrolactonization of **43** under Yamaguchi conditions[22] furnished macrolactone **42** in 75% yield, after separation of the minor *E* isomer at the α,β-unsaturated ester moiety. The order of these three reactions (**56** → **57** → **43** → **42**) was crucial for the reproducibility of the Pd-catalyzed methoxycarbonylation. Unfortunately, at this stage, olefin cross-metathesis[24] of **42** turned out to be intractably difficult because **42** remained unchanged even under forcing conditions. Consequently, transformation of **42** to iodoolefin *ent*-**19** was examined to intercept Lee's total synthesis of (+)-exiguolide.[3] Site-selective dihydroxylation

followed by cleavage of the resultant diol gave aldehyde **58** albeit in a low yield. Takai iodoolefination[44] of **58** provided iodoolefin *ent*-**19**. Sonogashira reaction[7] of *ent*-**19** with **20** and semi-hydrogenation of the resultant enyne *ent*-**21** furnished (−)-exiguolide ((−)-**1**).



Scheme 11. Total synthesis of (−)-exiguolide ((−)-**1**) by Roulland

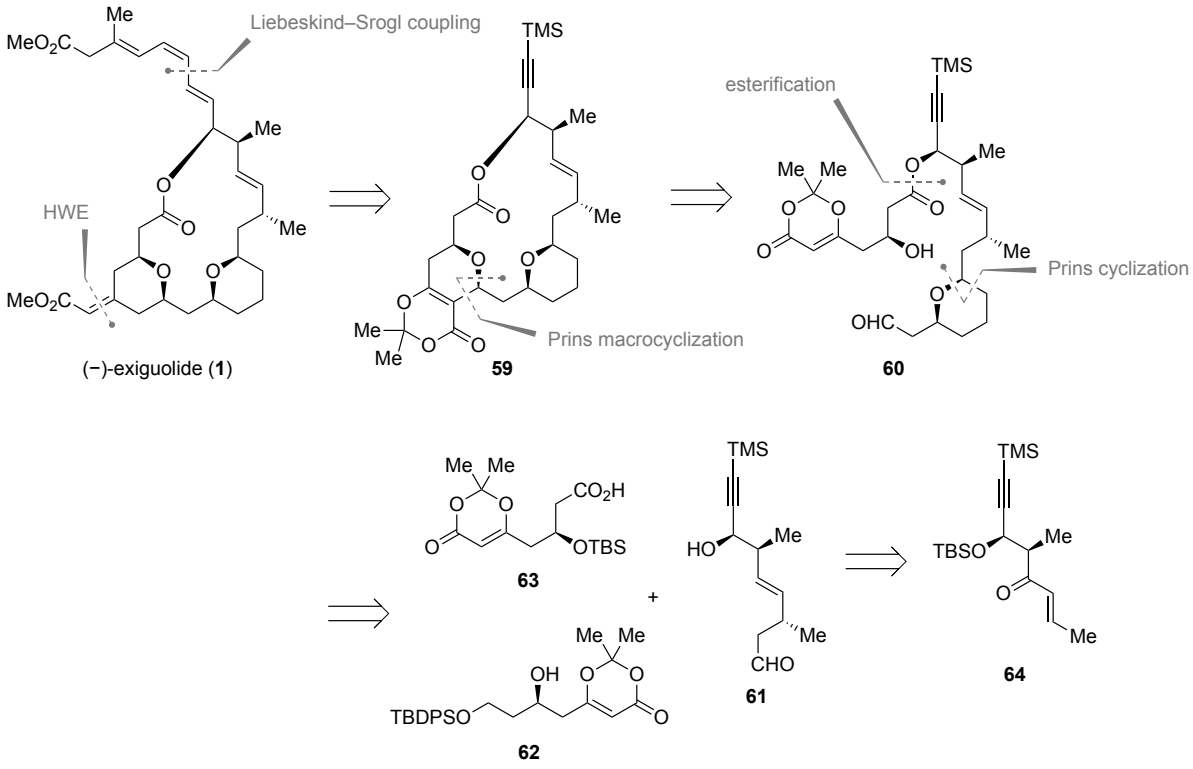
Roulland's total synthesis of (−)-exiguolide ((−)-**1**) proceeded in 25 longest linear steps from 5-hexen-1-ol. Key transformations are: 1) a tandem phosphorylation/organocuprate S_N2' reaction of a (*Z*)-allylic alcohol for introducing the C15 methyl group and the C16–C17 double bond with correct configuration; 2) a Ru-catalyzed yne–ene coupling/intramolecular oxa-Michael addition[38] and 3) a Kishi reduction[29] for stereoselective synthesis of the tetrahydropyran rings; and 4) a Yamaguchi macrolactonization[22] to forge the 20-membered macrocyclic backbone.

In Roulland's synthesis, the C15 methyl group and the C16–C17 double bond were elegantly installed by taking advantage of a substrate-controlled diastereoselective reduction and an S_N2' reaction. Nonetheless,

the first and second fragment assembly points (**49** + **50** → **51** and **45** + **46** → **44**) were in early to mid-stage of the total synthesis, thereby making the synthesis less convergent. The final route amendment also required some non-constructive functional group interconversions.

4. Total synthesis of (−)-exiguolide by Scheidt and co-workers (2011)[45]

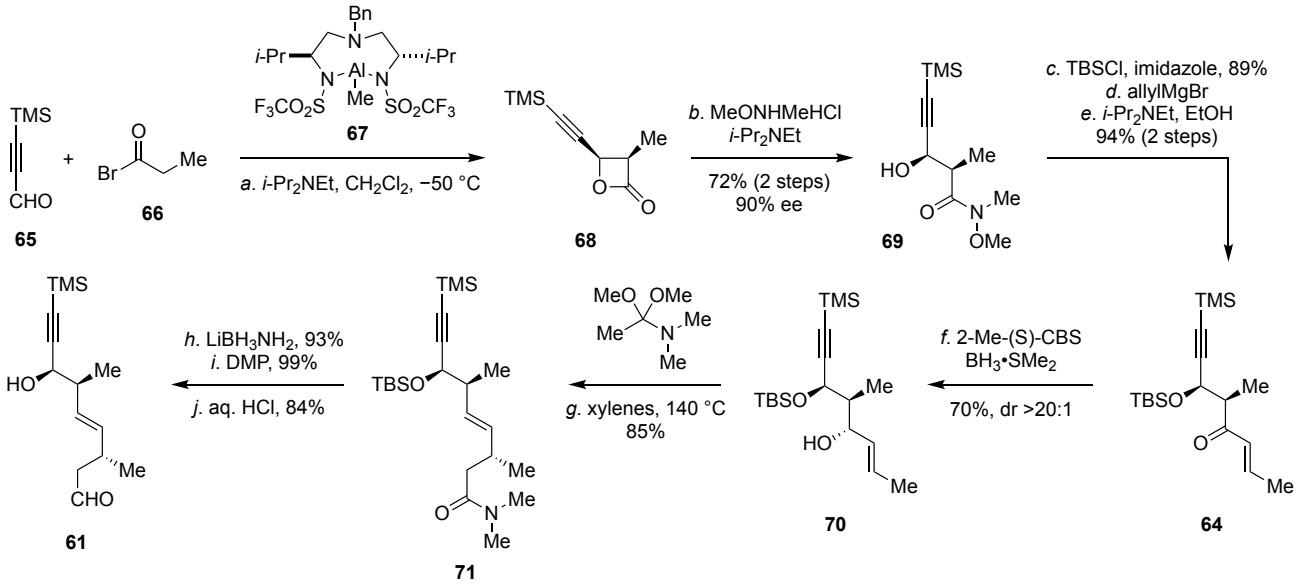
The Scheidt group achieved the total synthesis of (−)-exiguolide ((−)-**1**) by exploiting the Prins cyclization chemistry.[10] As summarized in Scheme 12, Scheidt et al. planned to construct the conjugated triene side chain of (−)-**1** through a Liebeskind–Srogl coupling[46] and the α,β-unsaturated ester via an asymmetric HWE reaction,[8] respectively. The precursor macrocycle **59** was envisioned to be accessible from aldehyde **60** by means of a Prins macrocyclization[47] that enables simultaneous construction of the 20-membered macrocyclic skeleton and one of the two tetrahydropyran rings. Aldehyde **60** would be synthesizable by a Prins cyclization[48] of aldehyde **61** and alcohol **62**, followed by esterification with carboxylic acid **63**. Aldehyde **61** was traced back to α,β-unsaturated ketone **64** by considering a Claisen-type rearrangement.



Scheme 12. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Scheidt

The synthesis of **61** started with catalytic asymmetric acyl halide/aldehyde cycloaddition of 3-(trimethylsilyl)-2-propynal (**65**), available in two steps from propargyl alcohol, and propionyl bromide (**66**) under the catalysis of **67**[49] to give β-lactone **68** that was transformed to Weinreb amide **69** upon exposure to MeONHMe•HCl/*i*-Pr_2NEt (72% for the two steps, 90% ee) (Scheme 13). Silylation of **69**, followed by

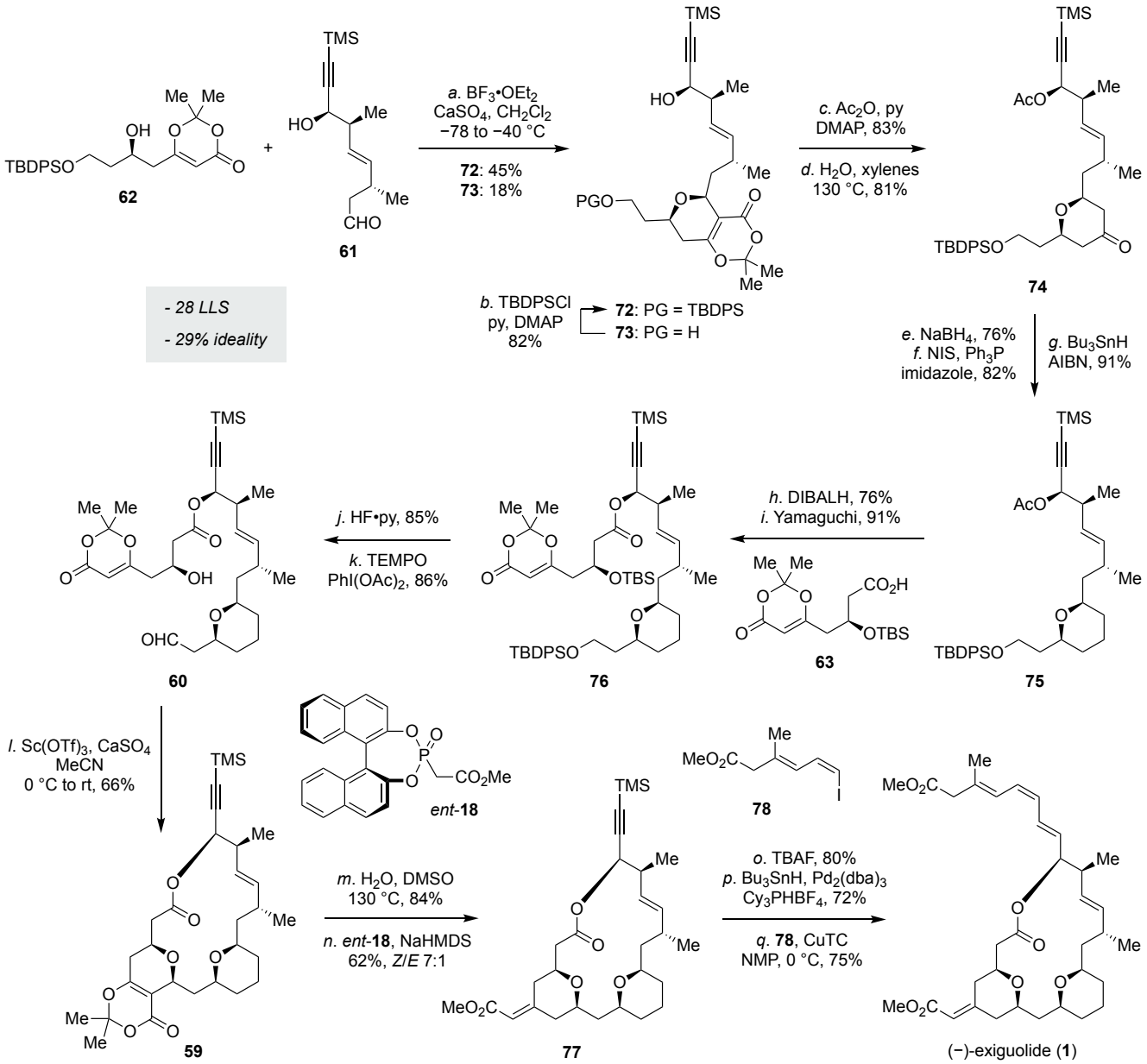
allylation with allylMgBr, and double bond isomerization catalyzed by *i*-Pr_2NEt delivered α,β-unsaturated ketone **64**. Asymmetric reduction of **64** with 2-Me-(*S*)-CBS oxazaborolidine/BH_3•SMe_2[50] provided allylic alcohol **70**. Eschenmoser–Claisen rearrangement of **70** upon treatment with *N*,*N*-dimethylacetamide dimethyl acetal afforded amide **71**. After reducing **71** with $LiBH_3NH_2$,[51] the resultant alcohol was oxidized[15] and then desilylated to deliver aldehyde **61**. Meanwhile, alcohol **62** and carboxylic acid **63** were available from 3-((*tert*-butyldiphenylsilyl)oxy)propanal in one step and 3-((*tert*-butyldimethylsilyl)oxy)propanal in four steps, respectively, via an asymmetric vinylogous Mukaiyama aldol reaction (not shown).[52]



Scheme 13. Synthesis of ketone **61**

Prins cyclization[48] of aldehyde **61** and alcohol **62** was best achieved, after extensive survey of reaction conditions, in the presence of BF_3•OEt_2 and $CaSO_4$ (CH_2Cl_2, −78 to −40 °C). Under these conditions, Prins product **72** was obtained in 45% yield, along with its TBDPS-deprotected counterpart **73** in 18% yield.[53] The primary alcohol of **73** could be re-silylated selectively with TBDPSCl, pyridine, and DMAP to give **72** (82%). After acetylation of **72**, the dioxinone moiety was collapsed thermally to deliver ketone **74**. The superfluous carbonyl group of **74** was removed by a three-step sequence of reduction, iodination, and tin hydride reduction to afford 2,6-*cis*-configured tetrahydropyran **75**. Removal of the acetate, followed by esterification with carboxylic acid **63** under Yamaguchi conditions,[22] provided ester **76**. After desilylation with HF•py, the liberated primary alcohol was selectively oxidized with TEMPO/$PhI(OAc)_2$[54] to afford aldehyde **60**. Treatment of **60** with $Sc(OTf)_3$ in the presence of $CaSO_4$ (MeCN, 0 °C to room temperature) resulted in Prins macrocyclization[47] to furnish macrocycle **59** in 66% yield. Decarboxylation of **59** and HWE reaction of the derived ketone using chiral phosphonate *ent*-**18**[8] gave α,β-unsaturated ester **77**. After desilylation, hydrostannation of the resultant terminal alkyne[55] delivered the corresponding (*E*)-

vinylstannane. CuTC-mediated Liebeskind–Srogl coupling[46] with iodoolefin **78** completed the total synthesis of (−)-exiguolide ((−)-**1**). The minor *E* enoate was removed at this stage by preparative reverse-phase HPLC purification.

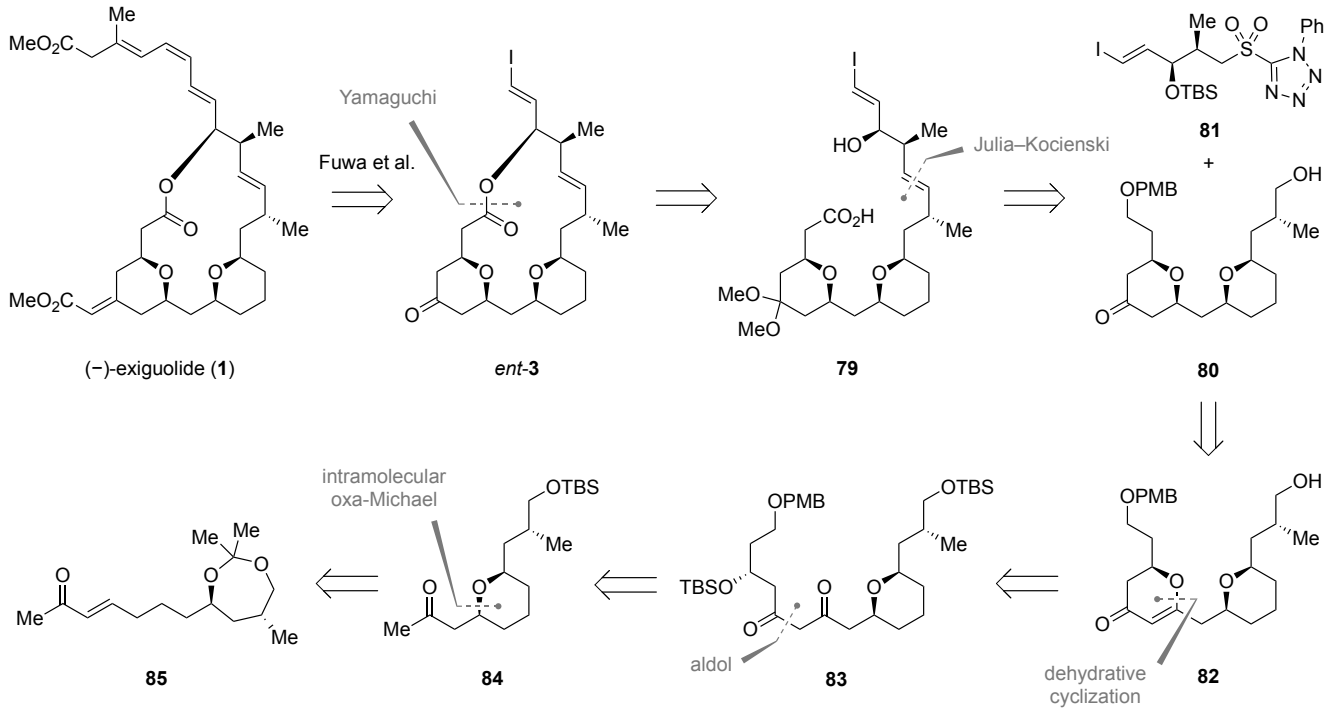


Scheme 14. Total synthesis of (−)-exiguolide ((−)-**1**) by Scheidt

The Scheidt total synthesis of (−)-exiguolide ((−)-**1**) proceeded in 28 longest linear steps from propargyl alcohol (26 longest linear steps from 3-(trimethylsilyl)-2-propynal (**65**)). The present synthesis was an exhibition of the Prins cyclization chemistry;[10] the two tetrahydropyran rings and the macrocyclic skeleton of (−)-**1** were constructed by Prins (macro)cyclizations.[47,48] At the same time, however, non-constructive functional group interconversions required for removing the unnecessary dioxinone moiety from the Prins cyclization products would be a shortcoming of the present synthesis.

5. Formal synthesis of (−)-exiguolide by Reddy and Rao (2012)[56]

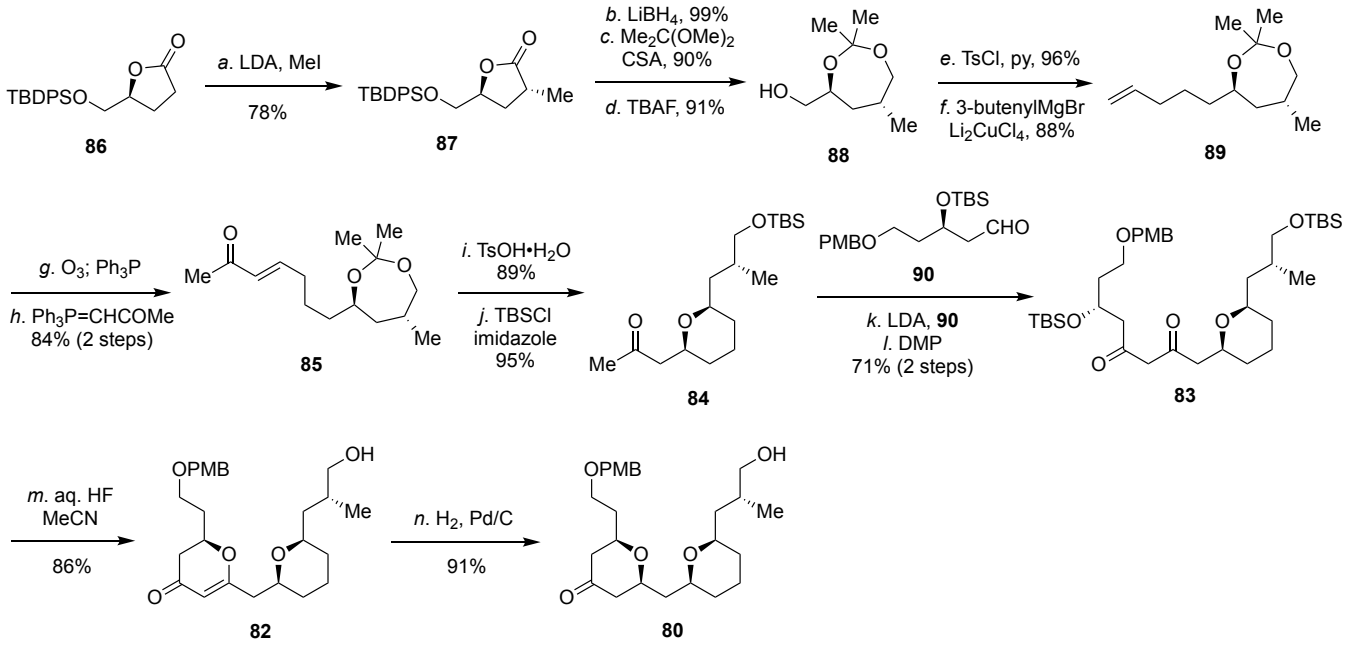
Reddy and Rao reported a formal synthesis of (−)-exiguolide ((−)-**1**), which was based on a chiral-pool approach. Their synthesis plan entailed a Yamaguchi macrolactonization[22] of seco-acid **79** for the construction of the 20-membered macrocyclic skeleton *ent*-**3** (Scheme 15). Seco-acid **79**, in turn, would be accessible from tetrahydropyranone **80** via a Julia–Kocienski olefination[32] with sufone **81**. Reddy and Rao envisaged to synthesize **80** through a dehydrative cyclization of diketone **83** to give dihydropyrone **82** and an intramolecular oxa-Michael addition[28] of α,β-unsaturated ketone **85** to give tetrahydropyran **84**.



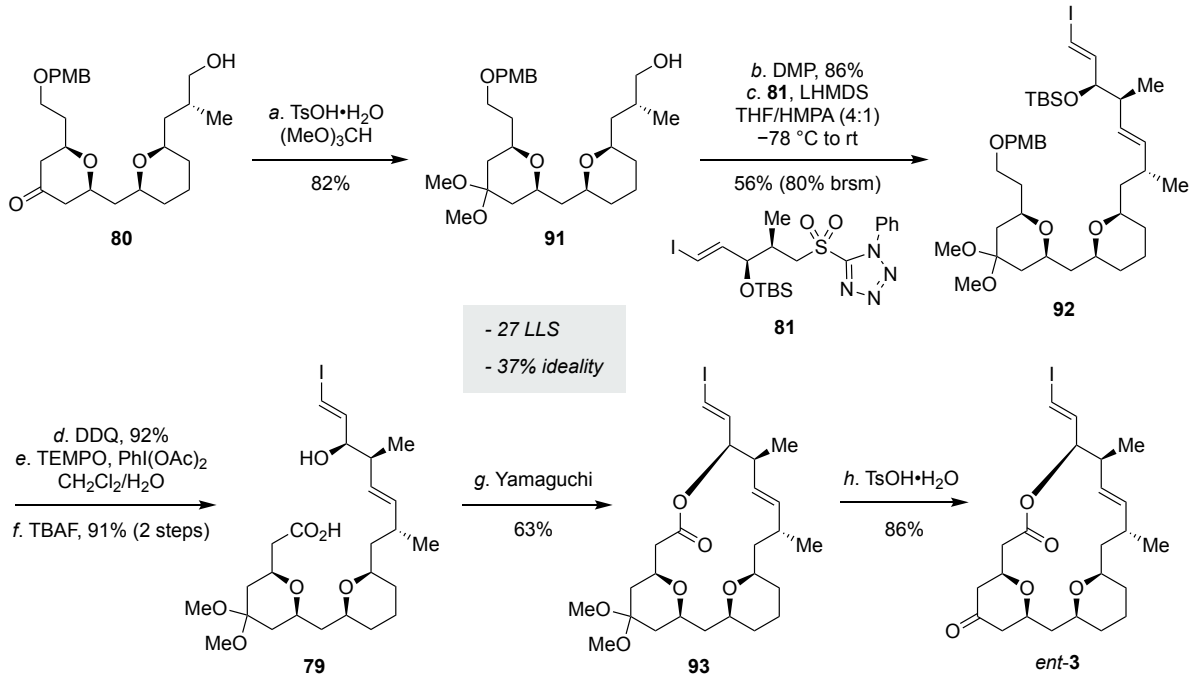
Scheme 15. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Reddy and Rao

The synthesis of tetrahydropyranone **80** started with stereoselecive methylation of known γ-lactone **86**, available in three steps from L-glutamic acid,[57] to give methylated product **87** (Scheme 16). Reduction of the lactone with $LiBH_4$, followed by protection of the resultant 1,4-diol as its acetonide, and desilylation delivered alcohol **88**. Tosylation and copper-catalyzed Grignard reaction led to olefin **89**, which was homologated via ozonolysis and Wittig reaction to afford α,β-unsaturated ketone **85**. Upon exposure of **85** to $TsOH•H_2O$, loss of the acetonide and spontaneous intramolecular oxa-Michael addition[28] took place to provide 2,6-*cis*-substituted tetrahydropyran **84**, after silylation. Aldol reaction of **84** with aldehyde **90**, prepared in six steps from L-aspartic acid,[58] followed by oxidation of the resultant aldol product, delivered diketone **83**. Treatment of **83** with aq. HF in MeCN triggered desilylation and concomitant dehydrative cyclizaion to afford dihydropyrone **82**. Hydrogenation of **82** provided 2,6-*cis*-substituted tetrahydropyranone **80** exclusively.

Completion of the formal synthesis of (−)-exiguolide ((−)-**1**) is summarized in Scheme 17. Acetalization of tetrahydropyranone **80** with TsOH•H_2O/$(MeO)_3CH$ gave methyl acetal **91**. Dess–Martin oxidation[15] of **91**, followed by Julia–Kocienski olefination[32] with sulfone **81**, provided olefin **92** in 56% yield (80% yield based on recovery of starting material) with *E*/*Z* >20:1. Removal of the PMB group and oxidation of the resultant alcohol gave, after desilylation, seco-acid **79**. Macrolactonization of **79** under Yamaguchi conditions[22] delivered macrolactone **93** in 63% yield. Finally, unmasking the methyl acetal under acidic conditions afforded ketone *ent*-**3**, thereby intercepting Fuwa's synthesis.[4]



Scheme 16. Synthesis of tetrahydropyranone **80**

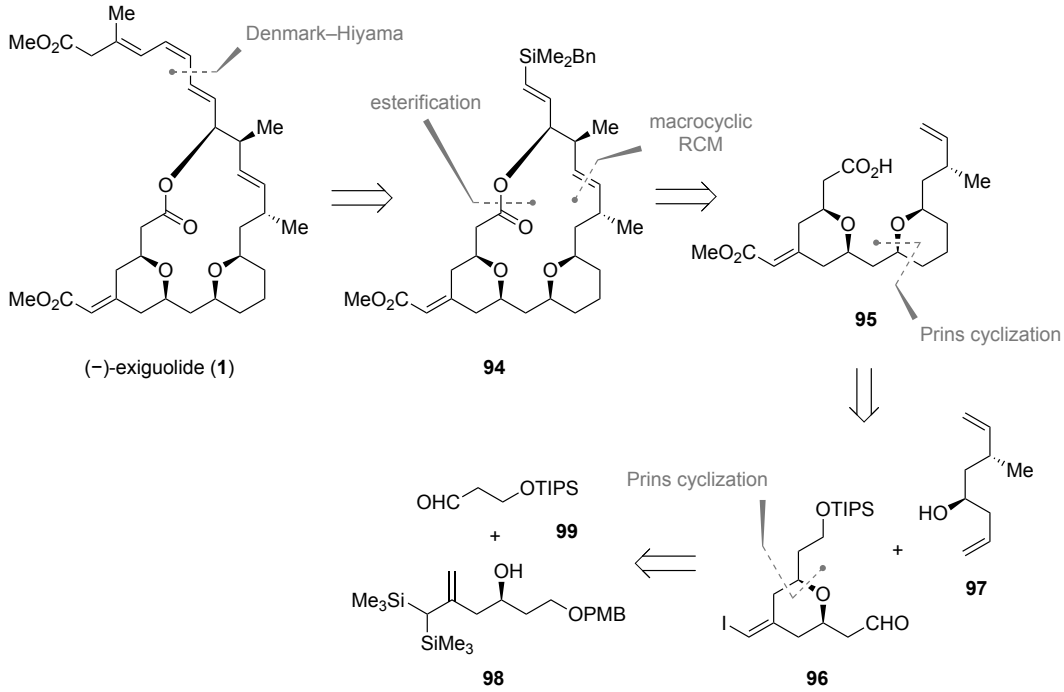


Scheme 17. Formal synthesis of (−)-exiguolide ((−)-**1**) by Reddy and Rao

The formal synthesis of (−)-exiguolide ((−)-**1**) by Reddy and Rao required 25 longest linear steps from L-glutamic acid for intercepting Fuwa's intermediate *ent*-**3** (27 longest linear steps to (−)-**1**). An intramolecular oxa-Michael addition[28] and a dehydrative diketone cyclization/hydrogenation were exploited for stereoselective construction of the two tetrahydropyran rings.

6. Total synthesis of (−)-exiguolide by Song and co-workers. Part 1 (2015)[59]

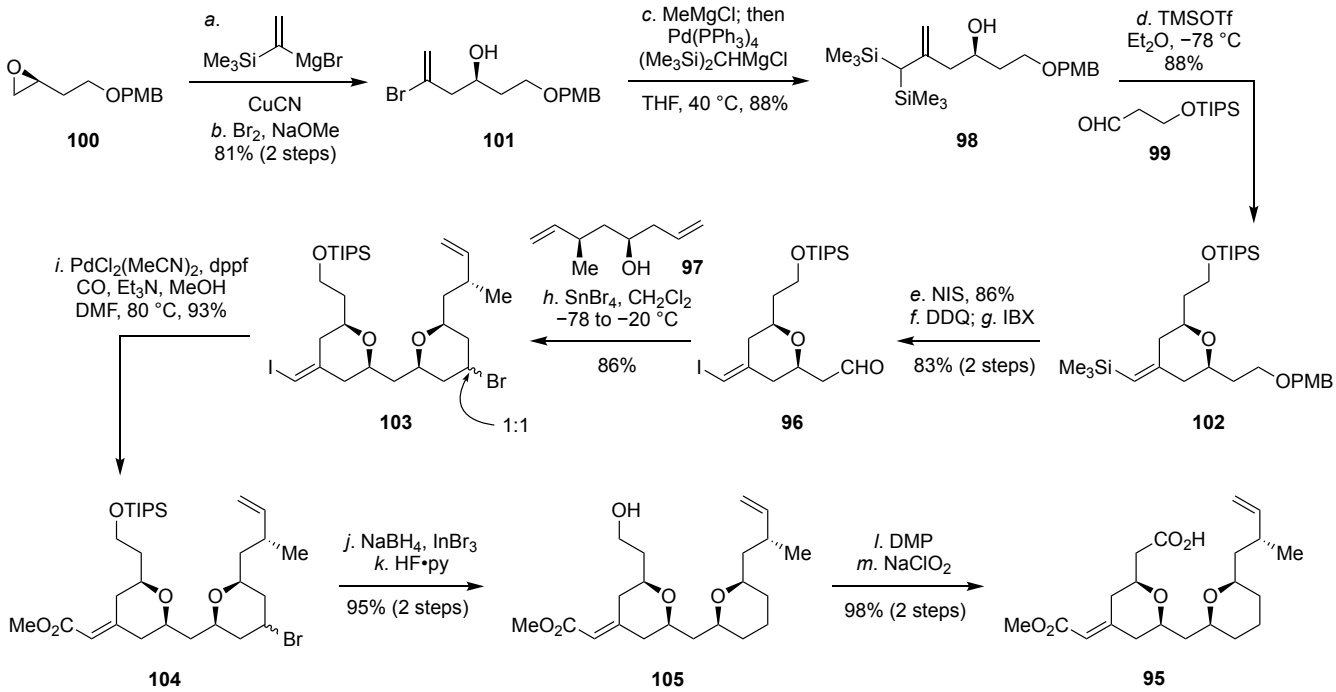
Song and co-workers reported the total synthesis of (−)-exiguolide ((−)-**1**) by exploiting the Prins cyclization chemistry.[10] Song et al. envisioned the synthesis plan toward (−)-**1** as depicted in Scheme 18. The conjugated triene side chain of (−)-**1** would be constructed via a Denmark–Hiyama cross-coupling[60] of vinylsilane **94**, which in turn could be synthesized from carboxylic acid **95** through an esterification followed by a macrocyclic RCM.[9] Carboxylic acid **95** was retrosynthetically broken down to aldehyde **96** and homoallylic alcohol **97** and then to homoallylic alcohol **98** and aldehyde **99** by considering a two-fold Prins cyclization.



Scheme 18. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Song

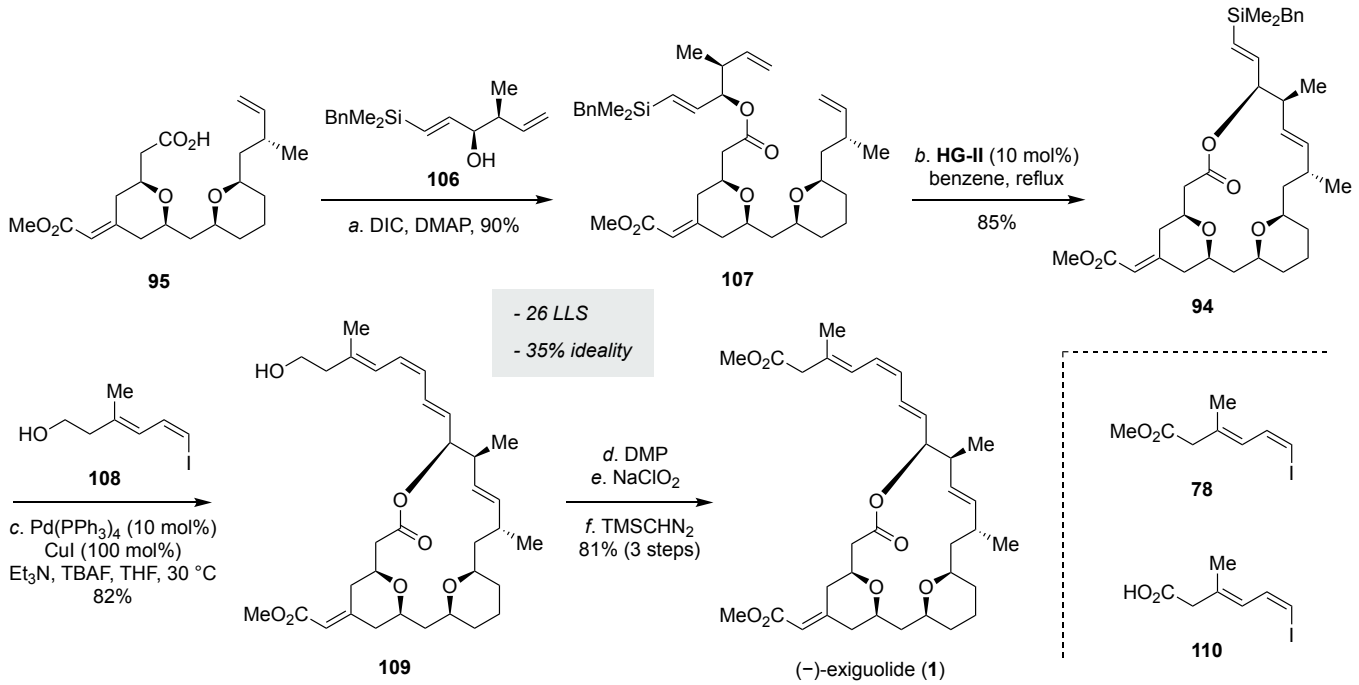
The synthesis of carboxylic acid **95** commenced with regioselective opening of epoxide **100**,[61] which was available in seven steps from (*S*)-malic acid, with CH_2=C($SiMe_3$)MgBr/CuCN to give, after bromodesilylation, homoallylic alcohol **101** (Scheme 19). Kumada cross-coupling[62] of **101** with bis(trimethylsilyl)methylmagnesium chloride provided γ-bis(trimethylsilyl)methyl-substituted homoallylic alcohol **98**. Prins cyclization of **98** with 3-((triisopropylsilyl)oxy)propanal (**99**) in the presence of TMSOTf afforded 2,6-*cis*-substituted tetrahydropyran **102** in 88% yield, with exclusive *Z*-selectivity at the exocyclic

vinylsilane, which served as a functional handle for elaborating the (*Z*)-α,β-unsaturated ester moiety of (−)-**1**.[63] Iododesilylation of **102** with NIS,[43] removal of the PMB group, and oxidation of the liberated hydroxy group led to aldehyde **96**, ready for the second Prins cyclization with homoallylic alcohol **97** that was prepared in five steps from a commercially available material through an asymmetric conjugate addition and an asymmetric allylation (*vide infra*). Thus, treatment of a mixture of **96** and **97** with $SnBr_4$[64] afforded 2,6-*cis*-substituted tetrahydropyran **103** in 86% yield. Pd-Catalyzed methoxycarbonylation of **103** delivered α,β-unsaturated ester **104**. The order of this reaction sequence was important, as a Prins cyclization of the methoxycarbonyl counterpart of **96** resulted in the desired Prins product in only 45% yield. Reduction of the bromide of **104** with $NaBH_4/InBr_3$,[65] followed by desilylation, and a two-stage oxidation of the derived alcohol **105** afforded carboxylic acid **95**.



Scheme 19. Synthesis of carboxylic acid **95**

Total synthesis of (−)-exiguolide ((−)-**1**) was achieved in six steps from **95** (Scheme 20). Esterification of **95** with alcohol **106**, prepared in six steps from 3-benzyldimethylsilyl propargyl alcohol,[66] gave ester **107**. Macrocyclic RCM[9] of **107** was efficiently achieved under the influence of 10 mol% **HG-II**[20] in refluxing benzene to deliver macrocycle **94** in 85% yield as a single *E* isomer. This result was in a marked contrast to those of relevant RCM reported by Lee[3] and Fuwa.[4] Denmark–Hiyama cross-coupling[60] of **94** with iodoolefin **108** in the presence of 10 mol% $Pd(PPh_3)_4$ and 100 mol% CuI (Et_3N, TBAF, THF, 30 °C) afforded conjugated triene **109** in 82% yield. Notably, the same reaction using iodoolefin **78** or **110** as a coupling partner was unproductive. Finally, a two-stage oxidation of **109** followed by esterification with $TMSCHN_2$ furnished (−)-exiguolide ((−)-**1**).



Scheme 20. Total synthesis of (−)-exiguolide ((−)-**1**) by Song (Part 1)

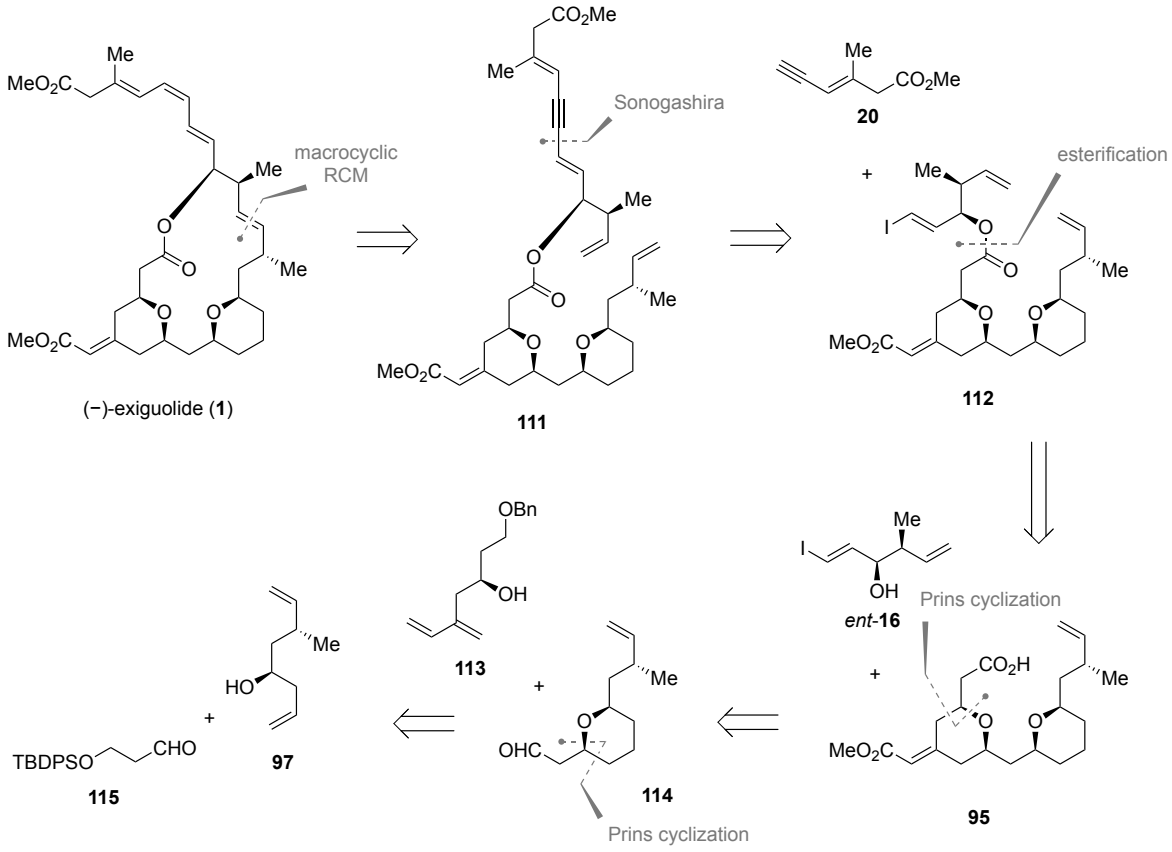
The key transformations of the present total synthesis include: 1) a TMSOTf-promoted Prins cyclization[63] of γ-bis(trimethylsilyl)methyl-substituted homoallylic alcohol **98** and aldehyde **99** for stereoselective synthesis of a 2,6-*cis*-substituted tetrahydropyran ring having an exocyclic vinylsilane moiety; 2) a $SnBr_4$-mediated Prins cyclization[64] of aldehyde **96** and homoallylic alcohol **97** for expedient, stereoselective synthesis of the second 2,6-*cis*-substituted tetrahydropyran ring; 3) a macrocyclic RCM[9] for the closure of the 20-membered macrolactone skeleton; and 4) a Denmark–Hiyama cross-coupling[60] for stereoselective construction of the conjugated triene side chain.

The present total synthesis (−)-exiguolide ((−)-**1**) was completed in 26 longest linear steps from (*S*)-malic acid. Taking into consideration the fact that the starting material, epoxide **100**, is also available in three steps from D-aspartic acid,[67] the longest linear steps can be shortened to 22. The efficiency of the present synthesis should come from the step-economical characteristic of the Prins cyclization chemistry.[10] The remarkable chemoselectivity and efficiency of the macrocyclic RCM of **107** bearing a vinylsilane and an α,β-unsaturated ester should also be noted.

7. Total synthesis of (−)-exiguolide by Song and co-workers. Part 2 (2015)[68]

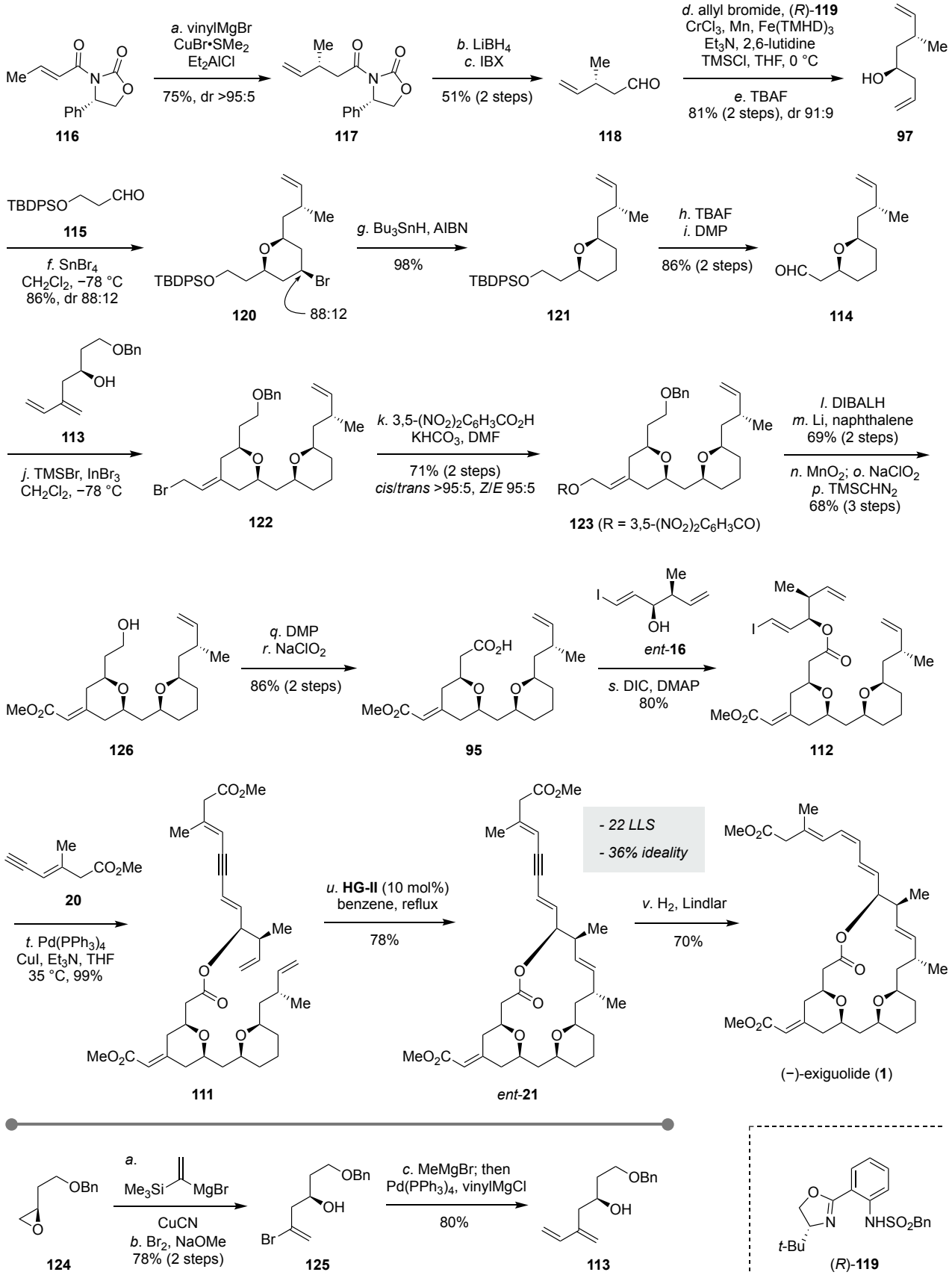
Song et al. disclosed another total synthesis of (−)-exiguolide ((−)-**1**), which was based on modification of the 'first-generation' synthesis discussed above. In the 'second-generation' synthesis, they planned to forge the macrocyclic backbone of (−)-**1** after introducing the conjugated side chain. This retrosynthetic consideration should be risk-taking with respect to the chemoselectivity of the prospecting RCM but worthwhile pursuing to minimize unnecessary oxidation state adjustments at the final stage of the total

synthesis. The RCM precursor **111** should be available from iodoolefin **112** by considering a Sonogashira cross-coupling,[7] and the latter in turn would be traced back to carboxylic acid **95**. Song et al. envisioned that compound **95** could be accessed from homoallylic alcohol **97** via aldehyde **114** through a two-fold Prins cyclization.[10] In the second-generation synthesis, the order of constructing the two tetrahydropyran rings of (−)-**1** was reversed from that of the first-generation synthesis, and γ-vinyl-substituted homoallylic alcohol **113** was used instead of γ-bis(trimethylsilyl)methyl-substituted homoallylic alcohol **98** for the Prins cyclization to construct the tetrahydropyran ring having an exocyclic α,β-unsaturated ester.



Scheme 21. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Song (Part 2)

Song's second-generation synthesis of (−)-exiguolide ((−)-**1**) commenced with asymmetric conjugate addition[69] of vinylmagnesium bromide to *N*-enoyl 4(*S*)-phenyl-2-oxazolidinone **116** to give olefin **117** in 75% yield with greater than 95:5 diastereoselectivity (Scheme 22). Removal of the chiral auxiliary of **117** by $LiBH_4$ reduction, followed by oxidation of the resultant alcohol, delivered aldehyde **118**. Kishi Fe/Cr-mediated asymmetric allylation[70] of **118** and subsequent TBAF treatment led to homoallylic alcohol **97** in 81% yield with 91:1 diastetreoselection. Prins cyclization of homoallylic alcohol **97** and 3-((*tert*-butyldiphenylsilyl)oxy)propanal (**115**) in the presence of $SnBr_4$ in CH_2Cl_2 at −78 °C[64] gave, after tin-mediated radical debromination of **120**, 2,6-*cis*-substituted tetrahydropyran **121** in 84% overall yield.



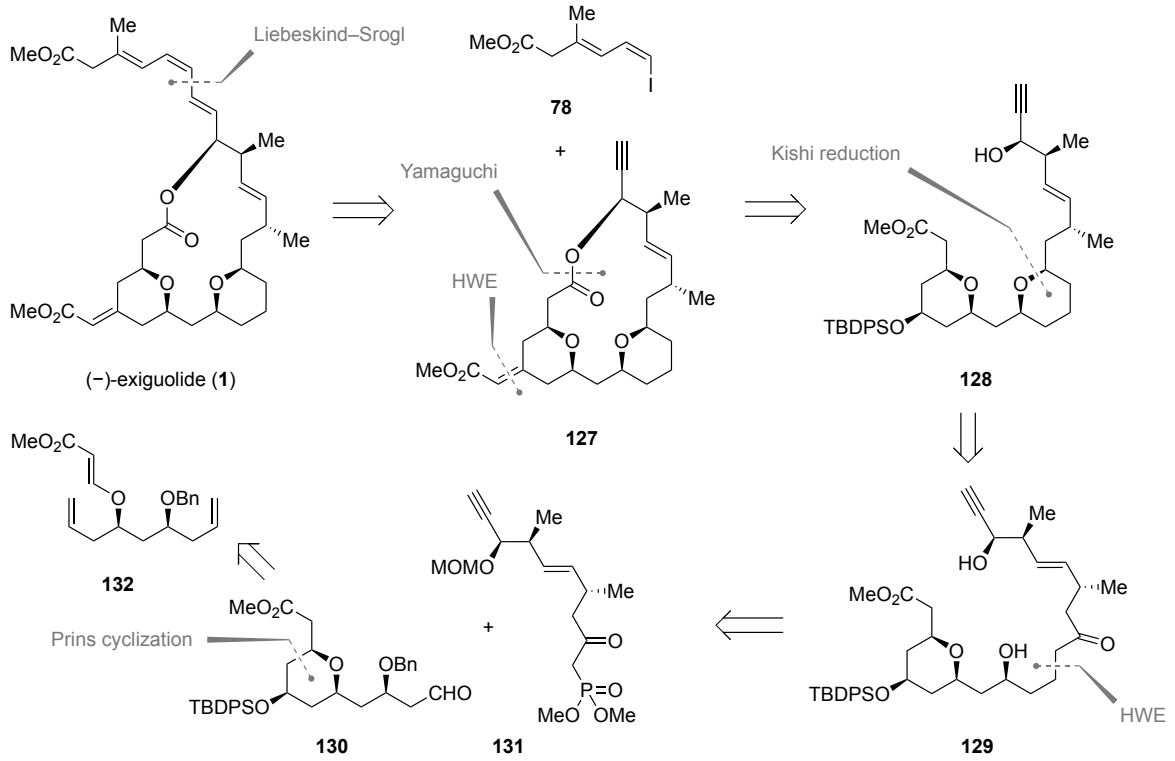
Scheme 22. Total synthesis of (−)-exiguolide ((−)-**1**) by Song (Part 2)

Desilylation of **121** and oxidation of the liberated alcohol delivered aldehyde **114**. Prins cyclization of **114** with γ-vinyl-substituted homoallylic alcohol **113** under the influence of TMSBr/$InBr_3$ in CH_2Cl_2 at −78 °C,[71] followed by immediate displacement of the derived allylic bromide **122** with 3,5-dinitrobenzoic acid/$KHCO_3$, afforded 2,6-*cis*-substituted tetrahydropyran **123** in 71% yield for the two steps, with *cis*/*trans* >95:5 and *Z*/*E* 95:5 selectivities. Compound **113** was prepared from known epoxide **124**[72] in three steps through regioselective opening with CH_2=C($SiMe_3$)MgBr/CuCN, bromodesilylation, and Kumada cross-coupling[62] with vinylmagnesium chloride. Compound **123** was then transformed to carboxylic acid **95** via a seven-step sequence of standard functional group interconversions. Esterification of **95** with alcohol *ent*-**16** gave ester **112**. Sonogashira cross-coupling[7] of **112** with alkyne **20** afforded enyne **111** in 99% yield. In line with previous work by Lee[3] and Fuwa,[4] attempted macrocyclic RCM[9] of **112** by the action of Grubbs, Hoveyda–Grubbs or Zhan catalyst only delivered the corresponding macrocycle in ~30% yield with poor reproducibility. In contrast, macrocyclic RCM of **111** under the influence of 10 mol% **HG-II**[20] in refluxing benzene proceeded in a chemoselective fashion to afford macrocycle *ent*-**21** in 78% yield. Semi-hydrogenation of *ent*-**21** under Lindlar catalyst furnished (−)-exiguolide ((−)-**1**).

Song's second-generation synthesis of (−)-exiguolide ((−)-**1**) was completed in 22 longest linear steps from commercially available 4(*S*)-3-[2(*E*)-but-2-enoyl]-4-phenyl-1,3-oxazolidin-2-one (**116**). The present synthesis was highlighted by a two-fold Prins cyclization[10] for stereoselective closure of the two tetrahydropyran rings and a remarkably chemoselective macrocyclic RCM[9] for the construction of the 20-membered macrolactone framework. However, an array of functional group interconversions required for the transformation of ester **123** to carboxylic acid **95** should be a shortcoming of the present synthesis.

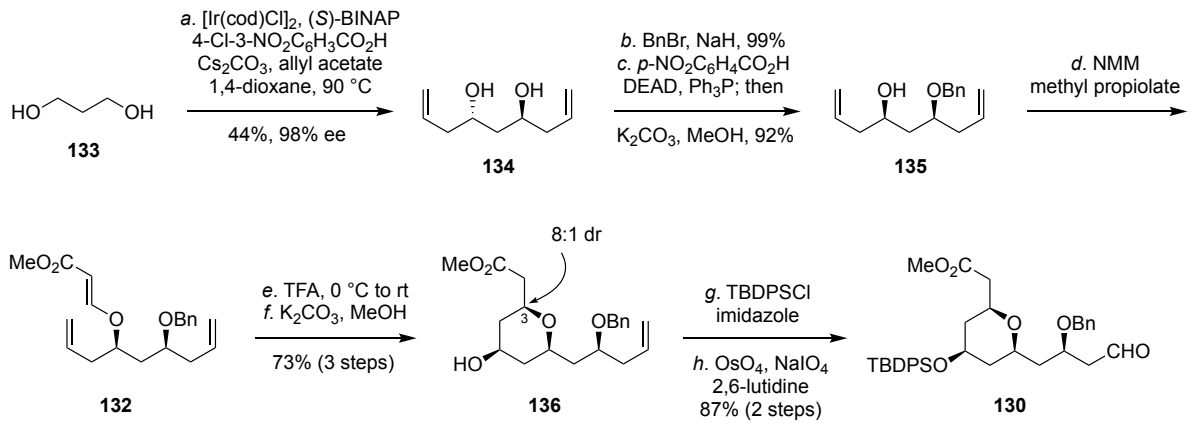
8. Total synthesis of (−)-exiguolide by Ishihara and co-workers (2020)[73]

Ishihara and co-workers accomplished the total synthesis of (−)-exiguolide ((−)-**1**) according to a retrosynthetic analysis summarized in Scheme 23. The conjugated triene side chain of (−)-**1** would be constructed from alkyne **127** through a hydrostannation and a subsequent Liebeskind–Srogl cross-coupling[46] with iodoolefin **78**, as previously described by Scheidt et al.[45] Alkyne **127** would be accessible from hydroxy ester **128** via a Yamaguchi macrolactonization[22] and an asymmetric HWE reaction.[8] Hydroxy ester **128** was traced back to hydroxy ketone **129** by considering a Kishi reduction,[29] and the latter was retrosynthetically disconnected to aldehyde **130** and phosphonate **131**. The tetrahydropyran ring of **130** was envisioned to be forged via a Prins cyclization[10] of β-alkoxy acrylate **132**.



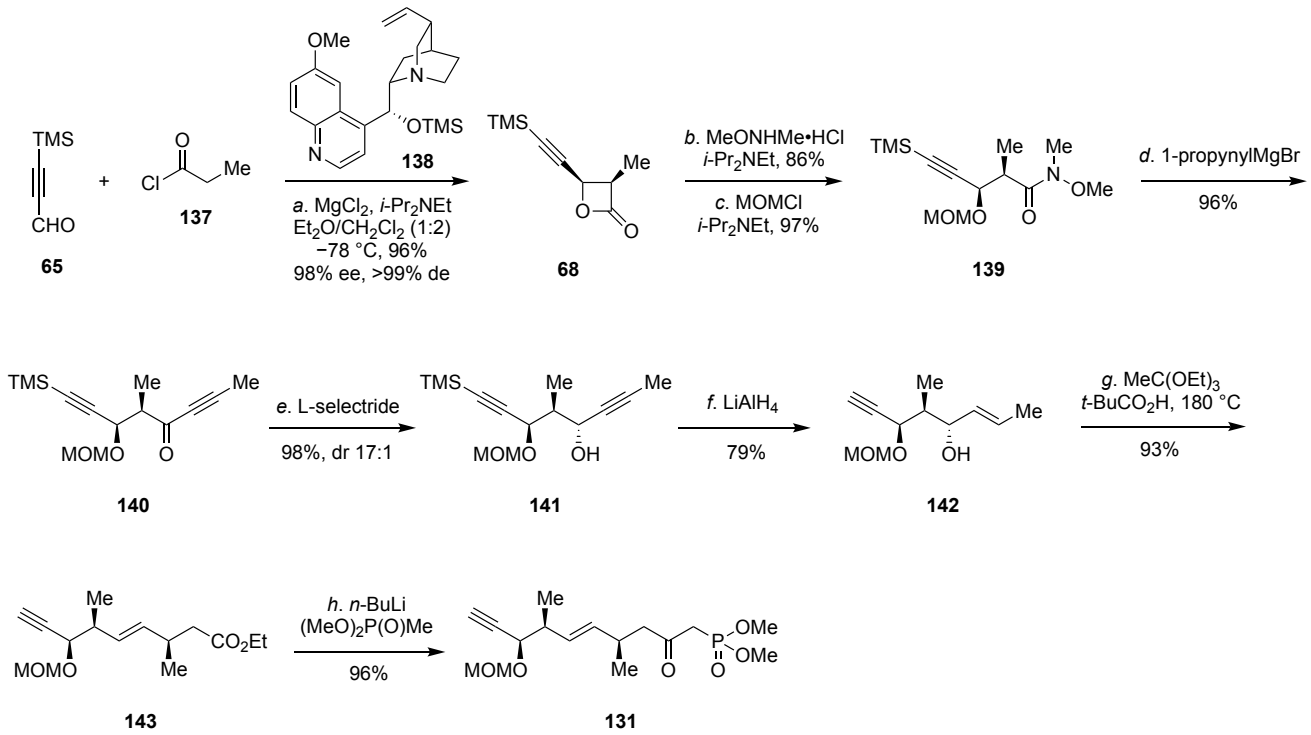
Scheme 23. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Ishihara

The synthesis of aldehyde **130** started with Krische asymmetric allylation[74] of 1,3-propanediol (**133**) to give C_2-symmetric diol **134** in 44% yield with 98% ee (Scheme 24). Mono-benzylation of **134** followed by Mitsunobu inversion[75]/methanolysis provided alcohol **135**. Exposure of **135** to methyl propiolate and NMM delivered β-alkoxy acrylate **132**. Prins cyclization[10] of **132** in TFA at room temperature afforded, after treatment with K_2CO_3/MeOH, 2,6-*cis*-substituted tetrahydropyran **136** in 73% yield from **135**, with 8:1 diastereoselectivity at the C3 position. Silylation of **136** with TBDPSCl/imidazole, followed by oxidative cleavage of the double bond, provided aldehyde **130**.



Scheme 24. Synthesis of aldehyde **130**

Meanwhile, the synthesis of the coupling partner, phosphonate **131**, commenced with Nelson's catalytic asymmetric acyl halide/aldehyde cycloaddition of 3-(trimethylsilyl)-2-propynal (**65**) and propionyl chloride (**137**) under the catalysis of *Cinchona* alkaloid **138**[76] to give β-lactone **68** in 96% yield with 98% ee and >99% de (Scheme 25). Treatment of **68** with MeONHMe•HCl/*i*-Pr_2NEt, followed by protection of the liberated alcohol with MOMCl/*i*-Pr_2NEt, delivered MOM ether **139**. Alkynylation of **139** with 1-propynylmagnesium bromide led to ynone **140**, which was reduced with L-selectride to provide propargylic alcohol **141**. After reducing **141** with $LiAlH_4$, Johnson–Claisen rearrangement of the resultant allylic alcohol **142** afforded ester **143**, which was reacted with an anion generated from dimethyl methylphosphonate and *n*-BuLi to deliver phosphonate **131**.

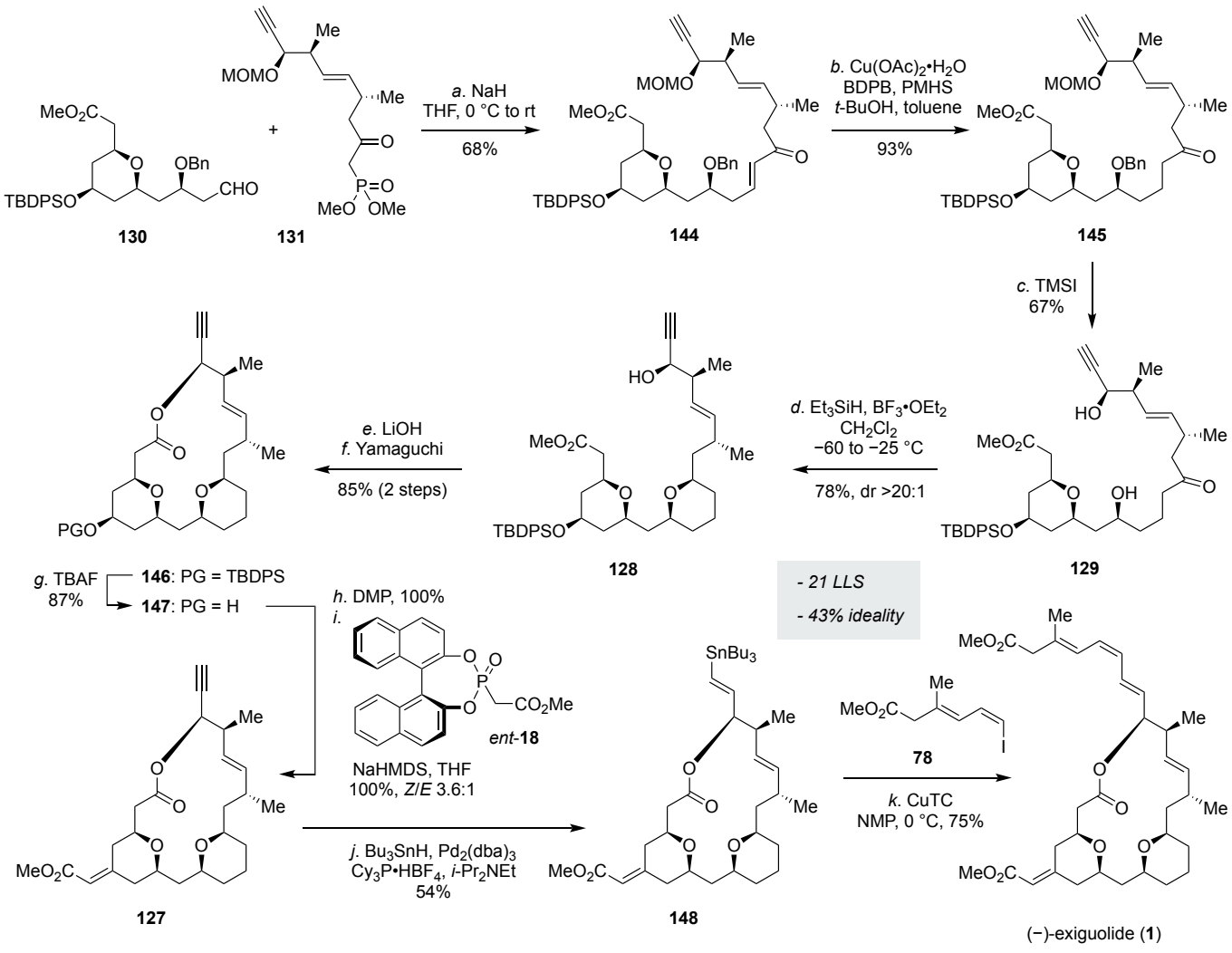


Scheme 25. Synthesis of phosphonate **131**

With the requisite fragments **130** and **131** in hand, Ishihara et al. proceeded to complete the total synthesis of (−)-**1**, as summarized in Scheme 26. HWE reaction of **130** and **131** provided α,β-unsaturated ketone **144** in 68% yield. Conjugate reduction of **144** under Lipshutz conditions[77] gave ketone **145**, which was treated with TMSI to remove the MOM and benzyl groups to deliver dihydroxy ketone **129**. Kishi reduction[29] of **129** with Et_3SiH/BF_3•OEt_2 afforded 2,6-*cis*-substituted tetrahydropyran **128** in 78% yield with greater than 20:1 diastereoselectivity. Hydrolysis of the methyl ester of **128**, followed by Yamaguchi macrolactonization[22] of the derived seco-acid, afforded macrolactone **146** in 85% yield for the two steps. Removal of the TBDPS group from **146** gave alcohol **147**, which was oxidized and then subjected to asymmetric HWE reaction using *ent*-**18**[8] to provide α,β-unsaturated ester **127** quantitatively with *Z*/*E* 3.6:1

selectivity. Without separation of the *Z*/*E* isomers, hydrostannation of **127** with Bu_3SnH in the presence of $Pd_2(dba)_3/Cy_3P•HBF_4$ and *i*-Pr_2NEt[55] delivered (*E*)-vinylstannane **148**. Liebeskind–Srogl coupling[46] of **148** with iodoolefin **78** completed the synthesis of (−)-exiguolide ((−)-**1**). The minor *E* isomer at the exocyclic α,β-unsaturated ester moiety was removed during the course of HPLC purification of (−)-**1**.

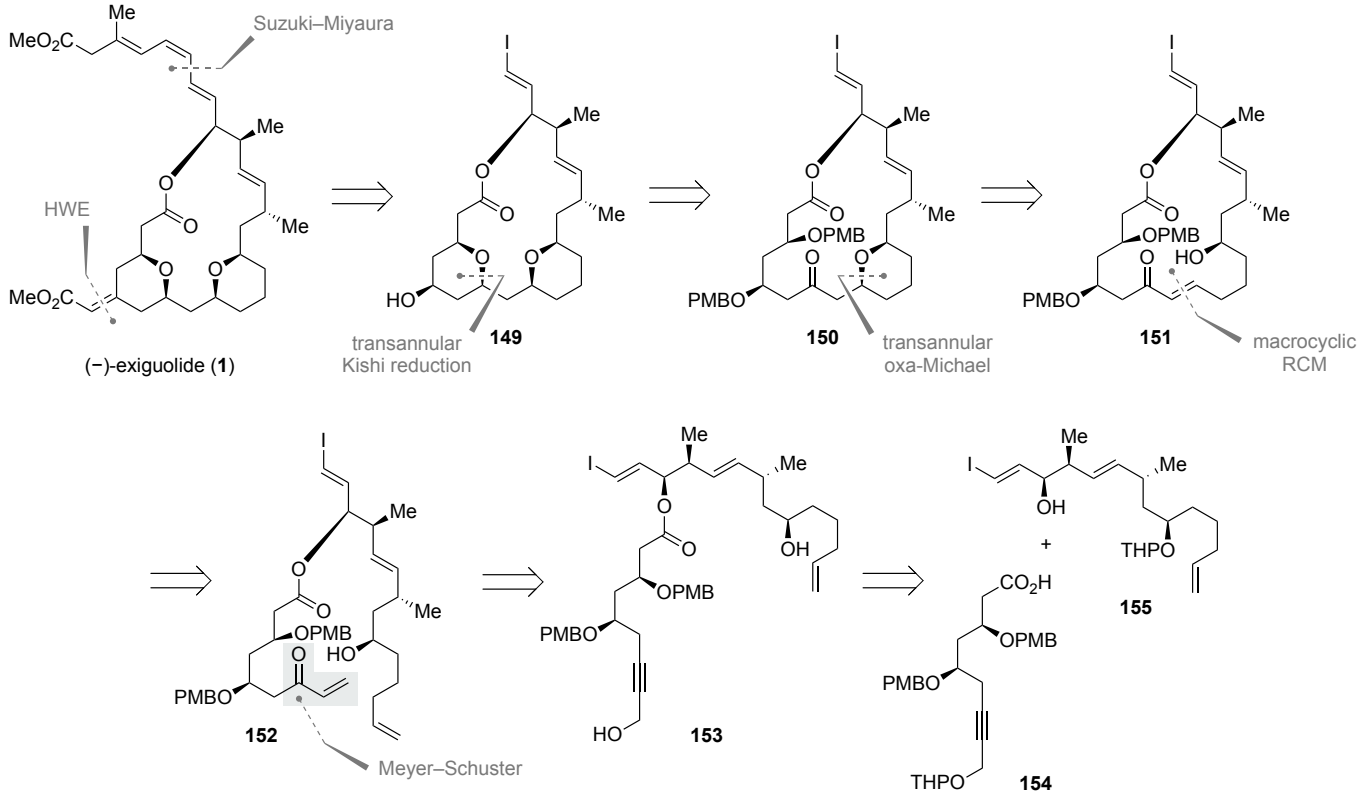
The Ishihara synthesis of (−)-exiguolide ((−)-**1**) proceeded in 21 longest linear steps from propargyl alcohol (19 longest linear steps from 3-(trimethylsilyl)-2-propynal (**65**)). The salient features of the present synthesis include: 1) a Prins cyclization of β-alkoxy acrylate **132** and 2) a Kishi reduction of dihydroxy ketone **129** for the stereoselective formation of the two tetrahydropyran rings; 3) a Yamaguchi macrolactonization for the closure of the 20-membered macrocyclic backbone; and 4) a Liebeskind–Srogl cross-coupling for the construction of the conjugated triene side chain. The Ishihara synthesis compares favorably with previous syntheses by Lee, Fuwa, Roulland, Scheidt, and Song, not only in terms of longest linear steps but also with respect to 'ideality'.[6d,f]



Scheme 26. Total synthesis of (−)-exiguolide ((−)-**1**) by Ishihara

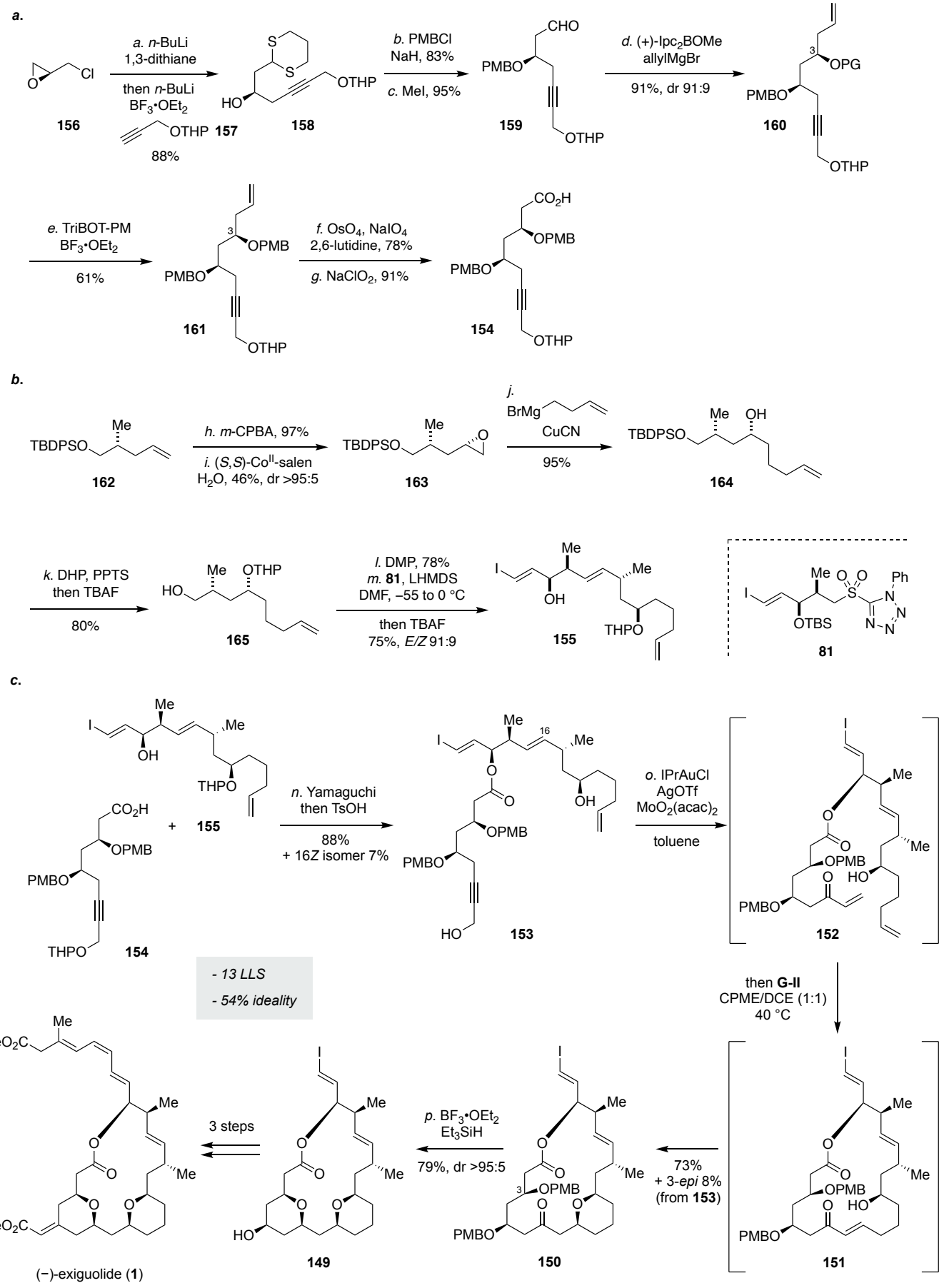
9. Total synthesis of (−)-exiguolide by Fuwa and co-workers. Part 2 (2022)[78]

The Fuwa group recently disclosed a concise synthesis of (−)-exiguolide ((−)-**1**), by exploiting their macrocyclization/transannular pyran cyclization strategy. Specifically, the synthetic blueprint proposed by Fuwa et al., as illustrated in Scheme 27, was based on a consideration that integrating a macrocyclic RCM[9] to forge the 20-membered macrolactone skeleton and an oxa-Michael addition[28] to close one of the two tetrahydropyran rings should reduce the number of non-constructive functional group manipulations and enable an expedient synthetic access to the complex structure of (−)-**1**. Thus, Fuwa et al. envisioned that macrocycle **149** could be retrosynthetically traced back to alkoxy ketone **150** by means of a transannular Kishi reduction,[29,79] and the latter should be accessible from propargylic alcohol **153** via the intermediary of vinyl ketone **152** and macrocyclic α,β-unsaturated ketone **151** by considering a sequence of Meyer–Schuster rearrangement,[80] macrocyclic RCM,[9] and transannular oxa-Michael addition.[28,79] Propargylic alcohol **153** would be available from carboxylic acid **154** and alcohol **155**.



Scheme 27. Synthesis plan toward (−)-exiguolide ((−)-**1**) by Fuwa (Part 2)

The synthesis of carboxylic acid **154**, summarized in Scheme 28a, started with addition of 2-lithio-1,3-dithiane to (*S*)-epichlorohydrin (**156**), followed by addition of an alkynyldifluoroborane generated from 2-(2-propynyloxy)tetrahydropyran (**157**),[40] to give alcohol **158**. Protection of **158** as its PMB ether and removal of the dithioacetal delivered aldehyde **159**. Brown asymmetric allylation of **159** using (+)-$Ipc_2Ballyl$[13] provided homoallylic alcohol **160** in 91% yield with 91:9 dr. After protecting **160** with



Scheme 28. Total synthesis of (−)-exiguolide ((−)-**1**) by Fuwa (Part 2)

TriBOT-PM/BF_3•OEt_2,[81] the double bond was cleaved and the resultant aldehyde oxidized to give carboxylic acid **154**.

The synthesis of alcohol **155** is depicted in Scheme 28b. Epoxidation of olefin **162**, available in one step from (*R*)-2-methylpent-4-en-1-ol, with *m*-CPBA and subsequent Jacobsen hydrolytic kinetic resolution[39] provided epoxide **163** in a diastereometically pure form. Copper-catalyzed regioselective epoxide opening using 3-butenylmagnesium bromide gave alcohol **164**. Protection of **164** as its THP ether and in situ desilylation delivered alcohol **165**. Dess–Martin oxidation[15] of **165**, followed by Julia–Kocienski olefination[32] of the derived aldehyde with sulfone **81**, and in situ desilylation afforded alcohol **155** (75%, *E*/*Z* 91:9). Sulfone **81** was prepared in five steps from (*E*)-β-(trimethylsilyl)acrolein (or six steps from (*E*)-3-(trimethylsilyl)prop-2-en-1-ol).

Assembly of the key intermediates and completion of the total synthesis are illustrated in Scheme 28c. Esterification of carboxylic acid **154** and alcohol **155** under Yamaguchi conditions,[22] and in situ acidic treatment resulted in a clean delivery of propargylic alcohol **153**. The minor 16*Z* isomer was removed at this stage. Meyer–Schuster rearrangement of **153** under modified Akai conditions[82] produced transient vinyl ketone **152**, which without isolation was reacted with **G-II** in CPME/DCE (1:1, v/v) at 40 °C to promote macrocyclic RCM[9] and spontaneous transannular oxa-Michael addition[28,79] under Ru and Au catalysis, giving rise to alkoxy ketone **150** in 73% yield from **153** as a single stereoisomer, after separation of the minor C3 diastereomer resulting from the Brown asymmetric allylation of **159**. The transannular oxa-Michael addition proceeded with greater than 95:5 diastereoselectivity. Treatment of **150** with BF_3•OEt_2/Et_3SiH resulted in cleavage of the PMB ethers and concomitant transannular Kishi reduction[29,79] to afford macrocycle **149** in 79% yield with >95:5 dr. A three-step sequence as described earlier[4] completed the total synthesis of (−)-**1**.

The 13-step total synthesis of (−)-exiguolide ((−)-**1**) by Fuwa et al. was highlighted by 1) a tandem Meyer–Schuster rearrangement/macrocyclic RCM/transannular oxa-Michael addition and 2) a transannular Kishi reduction to construct the complex skeleton of the target natural product in only two steps. With respect to its longest linear steps and ideality, the present synthesis is significantly more efficient than other previous syntheses, indicating that the reaction integration[83] of ring construction steps may potentially help increasing the synthetic efficiency of polyketide macrolide natural products.

CONCLUSION

This review summarized eight total syntheses and one formal synthesis of exiguolide, covering from 2008 to early 2022.[84,85] During the past 15 years, the synthetic efficiency of polyketide macrolide natural products has remarkably improved with the advent of new synthetic methods. In particular, Prins cyclization[10] has found its use in expedient synthesis of 2,6-*cis*-configured tetrahydropyran derivatives from readily available

materials. Moreover, Prins macrocyclization[47] has emerged as a means to construct a macrocyclic backbone and an embedded 2,6-*cis*-configured tetrahydropyran ring in a single step. It is clear that the Prins cyclization chemistry has made a significant impact on the way of synthesis planning toward polyketide macrolide natural products, as can be seen in total syntheses of exiguolide by Lee,[3] Scheidt,[45] Song,[59,68] and Ishihara.[73] Another important way to improve the synthetic efficiency would be the concept of reaction integration.[83g] Integrating multiple transformations into a single step by bypassing the isolation and purification of transient intermediates will help shorten the synthetic path toward complex molecules. In fact, the latest total synthesis of (−)-exiguolide by Fuwa et al.[78] took full advantage of reaction integration to reach the target in a succinct manner.

Nevertheless, greater than 20 linear steps were required for most of previous syntheses of exiguolide. From a holistic point of view, it should be recalled that the longest linear sequence of a given synthesis can be considered as a function of multiple variables including the number of steps required to prepare each fragment and the number of steps necessitated after the point of convergence.[86] While all previous syntheses of exiguolide were based on convergent synthesis planning, most of them involved assembly of two fragments of largely different complexity for the construction of the macrocyclic skeleton and hence required a relatively longer linear sequence to access the fragment of greater complexity. Further advances in synthetic method development for short synthesis and straightforward assembly of polyketide fragments are of great importance in the field of macrolide synthesis.

ACKNOWLEDGEMENTS

This work was supported in part by KAKENHI (Grant Nos. 21H02637 and 22K05336) and by a Chuo University Grant for Special Research.

REFERENCES AND NOTES

1. S. Ohta, M. M. Uy, M. Yanai, E. Ohta, T. Hirata, and S. Ikegami, *Tetrahedron Lett.*, 2006, **47**, 1957.
2. N. Matsumori, D. Kaneno, M. Murata, H. Nakamura, and K. Tachibana, *J. Org. Chem.*, 1999, **64**, 866.
3. M. S. Kwon, S. K. Woo, S. W. Na, and E. Lee, *Angew. Chem. Int. Ed.*, 2008, **47**, 1733.
4. (a) H. Fuwa and M. Sasaki, *Org. Lett.*, 2010, **12**, 584; (b) H. Fuwa, T. Suzuki, H. Kubo, T. Yamori, and M. Sasaki, *Chem. Eur. J.*, 2011, **17**, 2678.
5. J. Cossy, *C. R. Chim.*, 2008, **11**, 1477.
6. (a) B. M. Trost, *Science*, 1991, **254**, 1471; (b) P. A. Wender, V. A. Verma, T. J. Paxton, and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40; (c) T. Newhouse, P. S. Baran, and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (d) T. Gaich and P. S. Baran, *J. Org. Chem.*, 2010, **75**, 4657; (e) Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866; (f) D. S. Peters, C. R. Pitts, K. S. McClymont, T. P. Stratton, C. Bi, and P. S. Baran, *Acc. Chem. Res.*, 2021, **54**, 605.

7. For reviews on Sonogashira reaction, see: (a) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084; (b) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874.
8. (a) K. Tanaka, Y. Ohta, K. Fuji, and T. Taga, *Tetrahedron Lett.*, 1993, **34**, 4071; (b) D. A. Evans, P. H. Csarter, E. M. Carreira, A. B. Charette, J. A. Prunet, and M. Lautens, *J. Am. Chem. Soc.*, 1999, **121**, 7540; (c) K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S. Nishiyama, and S. Yamamura, *Angew. Chem. Int. Ed.*, 2000, **39**, 2290.
9. For reviews on ring-closing olefin metathesis, see: (a) C. Lecourt, S. Dhambri, L. Allievi, Y. Sanogo, N. Zeghbib, R. B. Othman, M.-I. Lannou, G. Sorin, and J. Ardisson, *Nat. Prod. Rep.*, 2018, **35**, 105; (b) I. Cheng-Sánchez and F. Sarabia, *Synthesis*, 2018, **50**, 3749; (c) A. Fürstner, *Chem. Commun.*, 2011, **47**, 6505; (d) J. Prunet, *Eur. J. Org. Chem.*, 2011, 3634.
10. For selected reviews on Prins reaction, see: (a) P. Padmaja, P. N. Reddy, and B. V. S. Reddy, *Org. Biomol. Chem.*, 2020, **18**, 7514; (b) B. V. S. Reddy, P. N. Nair, A. Antony, and N. Srivastava, *Eur. J. Org. Chem.*, 2017, 5484; (c) C. Díez-Poza and A. Barbero, *Eur. J. Org. Chem.*, 2017, 4651; (d) X. Han, G. R. Peh, and P. E. Floreancig, *Eur. J. Org. Chem.*, 2013, 1193.
11. (a) E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim, and W. S. Jang, *Angew. Chem. Int. Ed.*, 2002, **41**, 176; (b) E. Lee and S. J. Choi, *Org. Lett.*, 1999, **1**, 1127; (c) E. Lee, S.-K. Yoo, H. Choo, and H. Y. Song, *Tetrahedron Lett.*, 1998, **39**, 317; (d) E. Lee, S.-K. Yoo, Y.-S. Cho, H.-S. Cheon, and Y. H. Chong, *Tetrahedron Lett.*, 1997, **38**, 7757.
12. A. K. Ghosh, Y. Wang, and J. T. Kim, *J. Org. Chem.*, 2001, **66**, 8973.
13. H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, 1983, **105**, 2092.
14. E. Lee and H. O. Han, *Tetrahedron Lett.*, 2002, **43**, 7295.
15. D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277.
16. R. Jasti and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2006, **128**, 13640.
17. H. Lebel and V. Paquet, *J. Am. Chem. Soc.*, 2004, **126**, 320.
18. H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.*, 1986, **108**, 5919.
19. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
20. S. B. Garber, J. S. Kingsbury, B. L. Gray, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.
21. (a) F. C. Courchay, T. W. Baughman, and K. B. Wagener, *J. Organomet. Chem.*, 2006, **691**, 585; (b) M. Ulman and R. H. Grubbs, *Organometallics*, 1998, **17**, 2484.
22. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.
23. L. V. Heumann and G. E. Keck, *Org. Lett.*, 2007, **9**, 4275.
24. For a review on olefin cross-metathesis, see: S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.*, 2003, **42**, 1900.

25. M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.
26. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171.
27. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.
28. For reviews on oxa-Michael addition, see: (a) T. Ahmad and N. Ullah, *Org. Chem. Front.*, 2021, **8**, 1329; (b) J. Hu, M. Bian, and H. Ding, *Tetrahedron Lett.*, 2016, **57**, 5519; (c) C. F. Nising and S. Bräse, *Chem. Soc. Rev.*, 2012, **41**, 988; (d) H. Fuwa, *Heterocycles*, 2012, **85**, 1255.
29. M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976.
30. T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, and H. Zhao, *J. Am. Chem. Soc.*, 2004, **126**, 10210.
31. For related examples, see: (a) T. R. Hoye, M. E. Danielson, A. E. May, and H. Zhao, *J. Org. Chem.*, 2010, **75**, 7052; (b) S. Y. Yun, E. C. Hansen, I. Volchkov, E. J. Cho, W. Y. Lo, and D. Lee, *Angew. Chem. Int. Ed.*, 2010, **49**, 4261.
32. P. R. Blakemore, W. J. Cole, P. J. Kocieński, and A. Morley, *Synlett*, 1998, 26.
33. For selected reviews on Suzuki–Miyaura reaction, see: (a) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (b) A. Suzuki, *Angew. Chem. Int. Ed.*, 2011, **50**, 6723.
34. T. Ohmura, Y. Yamamoto, and N. Miyaura, *J. Am. Chem. Soc.*, 2000, **122**, 4990.
35. H. Fuwa, K. Noto, and M. Sasaki, *Org. Lett.*, 2010, **12**, 1636.
36. For reviews on tandem olefin cross-metathesis/intramolecular (hetero-)Michael addition, see: (a) M. Sánchez-Roselló, J. Miró, and C. del Pozo, *Synthesis*, 2017, **49**, 2787; (b) H. Fuwa and M. Sasaki, *Bull. Chem. Soc. Jpn.*, 2016, **89**, 1403.
37. (a) C. Cook, X. Guinchard, F. Liron, and E. Roulland, *Org. Lett.*, 2010, **12**, 744; (b) C. Cook, F. Liron, X. Guinchard, and E. Roulland, *J. Org. Chem.*, 2012, **77**, 6728.
38. B. M. Trost, M. U. Frederiksen, and M. T. Rudd, *Angew. Chem. Int. Ed.*, 2005, **44**, 6630.
39. (a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, and E. N. Jacobsen, *Science*, 1997, **277**, 936; (b) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
40. M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.
41. J.-A. Funel and J. Prunet, *J. Org. Chem.*, 2004, **69**, 4555.
42. A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
43. D. P. Stamos, A. G. Taylor, and Y. Kishi, *Tetrahedron Lett.*, 1996, **37**, 8647.
44. K. Takai, K. Nitta, and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.
45. E. A. Crane, T. P. Zabawa, R. L. Farmer, and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2011, **50**, 9112.
46. G. D. Allred and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1996, **118**, 2748.
47. For a review on Prins macrocyclization, see: E. A. Crane and K. A. Scheidt, *Angew. Chem. Int. Ed.*,

2010, **49**, 8316.
48. W. J. Morris, D. W. Custar, and K. A. Scheidt, *Org. Lett.*, 2005, **7**, 1113.
49. (a) S. G. Nelson, T. J. Peelen, and Z. Wan, *J. Am. Chem. Soc.*, 1999, **121**, 9742; (b) S. G. Nelson and Z. H. Wan, *Org. Lett.*, 2000, **2**, 1883.
50. E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
51. A. G. Myers, B. H. Yang, and D. J. Kopecky, *Tetrahedron Lett.*, 1996, **37**, 3623.
52. D. W. Custar, T. P. Zabawa, J. Hines, C. M. Crews, and K. A. Scheidt, *J. Am. Chem. Soc.*, 2009, **131**, 12406.
53. In the Supporting Information of ref. 45, the yield of **72** and **73** was reported to be 26% and 29%, respectively.
54. A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, and G. Piancatelli, *J. Org. Chem.*, 1997, **62**, 6974.
55. A. Darwish, A. Lang, T. Kim, and J. M. Chong, *Org. Lett.*, 2008, **10**, 861.
56. (a) C. R. Reddy and N. N. Rao, *RSC Adv.*, 2012, **2**, 7724; (b) C. R. Reddy and N. N. Rao, *Tetrahedron Lett.*, 2010, **51**, 5840.
57. Y. Shito, K. Kato, M. Fujii, Y. Ida, and H. Akita, *Tetrahedron*, 2006, **62**, 8687.
58. J. A. Frick, J. B. Klassen, A. Bathe, J. M. Abramson, and H. Rapoport, *Synthesis*, 1992, 621.
59. H. Li, H. Xie, Z. Zhang, Y. Xu, J. Lu, L. Gao, and Z. Song, *Chem. Commun.*, 2015, **51**, 8484.
60. For selected reviews on Hiyama reaction, see: (a) Y. Nakao and T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893; (b) S. E. Denmark and J. H.-C. Liu, *Angew. Chem. Int. Ed.*, 2010, **49**, 2978.
61. M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, and S. V. Ley, *Org. Lett.*, 2003, **5**, 4819.
62. (a) K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 4374; (b) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1958; (c) C. E. I. Knappke and A. J. von Wangelin, *Chem. Soc. Rev.*, 2011, **40**, 4948.
63. (a) J. Lu, Z. Song, Y. Zhang, Z. Gan, and H. Li, *Angew. Chem. Int. Ed.*, 2012, **51**, 5367; (b) Y. Zhang, J. Lu, H. Li, X. Sun, L. Gao, and Z. Song, *Synlett*, 2019, **30**, 753.
64. S. Marumoto, J. J. Jaber, J. P. Vitale, and S. D. Rychnovsky, *Org. Lett.*, 2002, **4**, 3919.
65. H. Zhou and T. P. Loh, *Tetrahedron Lett.*, 2009, **50**, 4368.
66. S. E. Denmark and S. Fujimori, *J. Am. Chem. Soc.*, 2005, **127**, 8971.
67. F. Glaus and K.-H. Altmann, *Angew. Chem. Int. Ed.*, 2012, **51**, 3405.
68. Z. Zhang, H. Xie, H. Li, L. Gao, and Z. Song, *Org. Lett.*, 2015, **17**, 4706.
69. D. R. Williams, W. S. Kissel, and J. J. Li, *Tetrahedron Lett.*, 1998, **39**, 8593.
70. M. Kurosu, M. H. Lin, and Y. Kishi, *J. Am. Chem. Soc.*, 2004, **126**, 12248.

71. K. P. Chan and T. P. Loh, *Org. Lett.*, 2005, **7**, 4491.
72. Q. R. Liang, Y. Q. Sun, B. X. Yu, X. G. She, and X. F. Pan, *J. Org. Chem.*, 2007, **72**, 9846.
73. K. Oka, S. Fuchi, K. Komine, H. Fukuda, S. Hatakeyama, and J. Ishihara, *Chem. Eur. J.*, 2020, **26**, 12862.
74. (a) I. S. Kim, M.-Y. Ngai, and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 14891; (b) Y. Lu, I. S. Kim, A. Hassan, D. J. Del Valle, and M. J. Krische, *Angew. Chem. Int. Ed.*, 2009, **48**, 5018.
75. For reviews on Mitsunobu reaction, see: (a) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, and K. V. P. P. Kumar, *Chem. Rev.*, 2009, **109**, 2551; (b) O. Mitsunobu, *Synthesis*, 1981, 1.
76. C. Zhu, X. Shen, and S. G. Nelson, *J. Am. Chem. Soc.*, 2004, **126**, 5352.
77. B. A. Baker, Ž. V. Bošković, and B. H. Lipshutz, *Org. Lett.*, 2008, **10**, 289.
78. D. Mizukami, K. Iio, M. Oda, Y. Onodera, and H. Fuwa, *Angew. Chem. Int. Ed.*, 2022, **61**, e202202549.
79. For reviews on transannular reactions, see: (a) E. Reyes, U. Uria, L. Carrillo, and J. L. Vicario, *Tetrahedron*, 2014, **70**, 9461; (b) P. A. Clarke, A. T. Reeder, and J. Winn, *Synthesis*, 2009, 691.
80. For reviews on Meyer–Schuster rearrangement, see: (a) F. Justaud, A. Hachem, and R. Grée, *Eur. J. Org. Chem.*, 2021, 514; (b) V. Cadierno, P. Crochet, S. E. García-Garrido, and J. Gimeno, *Dalton Trans.*, 2010, **39**, 4015; (c) D. A. Engel and G. B. Dudley, *Org. Biomol. Chem.*, 2009, **7**, 4149.
81. K. Yamada, H. Fujita, M. Kitamura, and M. Kunishima, *Synthesis*, 2013, **45**, 2989.
82. M. Egi, Y. Yamaguchi, N. Fujiwara, and S. Akai, *Org. Lett.*, 2008, **10**, 1867.
83. For selected reviews, see: (a) M. M. Lorion, K. Maindan, A. R. Kapdi, and L. Ackermann, *Chem. Soc. Rev.*, 2017, **46**, 7399; (b) G. K. Zieliński and K. Grela, *Chem. Eur. J.*, 2016, **22**, 9440; (c) J. E. Camp, *Eur. J. Org. Chem.*, 2017, 425; (d) T. L. Lohr and T. J. Marks, *Nat. Chem.*, 2015, **7**, 477; (e) C. M. R. Volla, I. Atodiresei, and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (f) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442; (g) J. Yoshida, K. Saito, T. Nokami, and A. Nagaki, *Synlett*, 2011, 1189.
84. For synthetic studies on exiguolide, see: A. Riefert and M. E. Maier, *Synthesis*, 2018, **50**, 3131.
85. For synthesis-driven structure–activity relationship investigations, see: H. Fuwa, K. Mizunuma, M. Sasaki, T. Suzuki, and H. Kubo, *Org. Biomol. Chem.*, 2013, **11**, 3442.
86. I. T. Hsu, M. Tomanik, and S. B. Herzon, *Acc. Chem. Res.*, 2021, **54**, 903.

Haruhiko Fuwa received his B.Sc., M.Sc. and D.Sc. degrees from the Department of Chemistry, School of Science, The University of Tokyo under the guidance of the late Professor Kazuo Tachibana. After spending two and a half years with Professor Hideaki Natsugari at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, he moved to the Graduate School of Life Sciences, Tohoku University, where he worked with Professor Makoto Sasaki as Assistant and then Associate Professor. Finally, he went back to Tokyo and started his independent career at the Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University as a Full Professor. He was awarded The Chemical Society of Japan Award for Young Chemists (2010) and The Young Scientists' Prize, The Commendation for Science and Technology by the Minister of Education, Sports, Culture, Science and Technology (2011). His research interests include synthetic methods development and its application to total synthesis and chemical biology of natural products.