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TOTAL SYNTHESIS OF TETRAHYDROPYRAN-CONTAINING NATURAL PRODUCTS EXPLOITING INTRAMOLECULAR OXA-CONJUGATE CYCLIZATION

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Abstract – A growing number of tetrahydropyran-containing biologically active substances are being discovered from nature. Intramolecular oxa-conjugate cyclization (IOCC) is known as one of the most powerful methodologies for the stereoselective synthesis of substituted tetrahydropyran derivatives, although there is clearly room for methodological improvement. In this review, we describe our successful total synthesis of tetrahydropyran-containing natural products by exploiting IOCC and the discoveries that we have made during the course of the synthetic campaigns.

CONTENTS

1. INTRODUCTION

A growing number of tetrahydropyran-containing biologically active substances are being discovered from nature. Tetrahydropyran-containing natural products, isolated as the secondary metabolites of marine organisms, have attracted intense interest from chemists and biologists because of their extraordinarily complex molecular architecture and highly potent and characteristic biological activities.[1,2] Two notable examples are macrolides and polycyclic ethers. These natural products are considered to be

promising leads for the development of innovative therapeutic agents and/or useful molecular probes for elucidating complex biological phenomena at the molecular level. For example, halichondrin B, isolated from the marine sponge *Halichondria okadaii* by the Uemura/Hirata group,[3] exhibits remarkably potent antitumor activity against human cancer cell lines as a cell cycle inhibitor that induces G2/M arrest and disrupts mitotic spindle organization[4] (Figure 1). This natural product has successfully served as a lead compound for the development of eribulin mesylate (Halaven®), an anticancer agent for the treatment of late-stage breast cancer, by Eisai Research Laboratories on the basis of the total synthesis by the Kishi group.[5,6] Due to their molecular complexity and biological significance, tetrahydropyran-containing natural products have been rewarding target molecules for the synthetic community. It is noteworthy that the tetrahydropyrans found in natural products are, in many cases, substituted at the C2 and C6 positions with *cis* configuration.

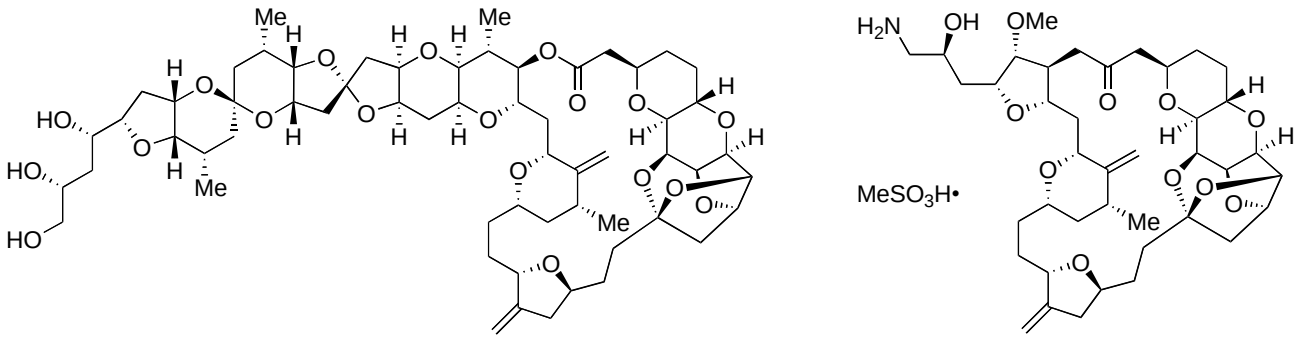
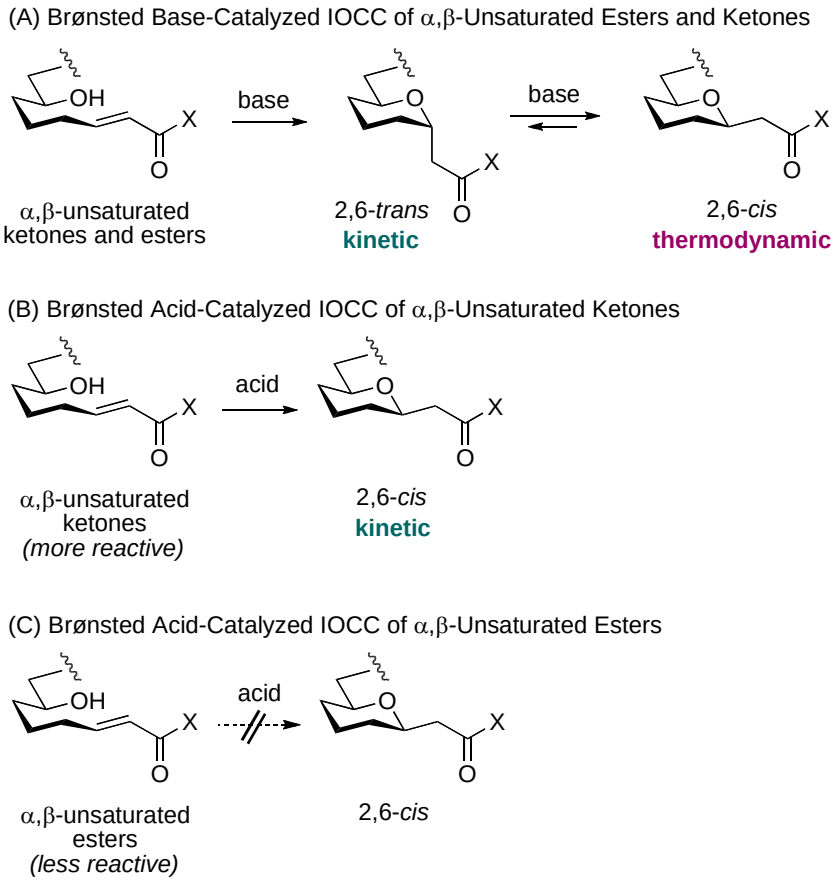


Figure 1. Structures of Halichondrin B and Eribulin Mesylate

Over the past three decades, organic chemists have made a concerted effort to develop versatile methodologies for the synthesis of 2,6-*cis*-substituted tetrahydropyran derivatives,[7] e.g., intramolecular oxa-conjugate cyclization (IOCC),[8-12] Prins-type cyclization,[13] modified Maitland—Japp reaction,[14] intramolecular Pd(II)-catalyzed alkoxycarbonylation,[15] and intramolecular Pd(II)-catalyzed S_N2' cyclization.[16,17] Among these methodologies, IOCC of α,β-unsaturated ketones and esters has frequently been exploited for the total synthesis of complex tetrahydropyran-containing natural products.[9-11] This is at least partly due to the synthetic versatility of the product tetrahydropyran that harbors carbonylmethyl functionality. Organocatalytic asymmetric IOCC reactions for the synthesis of tetrahydropyrans, flavones, and chromenes have also recently been reported.[12]

The mechanistic aspects of Brønsted base-catalyzed IOCC of α,β-unsaturated carbonyl compounds have been investigated independently by Martín, Banwell, and Schneider.[18] It has been established that, in general, IOCC of α,β-unsaturated ketones and esters proceeds by the action of an appropriate base, such as NaH or KO*t*-Bu, to give 2,6-*trans*-substituted tetrahydropyrans under kinetic conditions (Scheme 1A).[19] The corresponding 2,6-*cis* isomers would only be available via isomerization that involves a

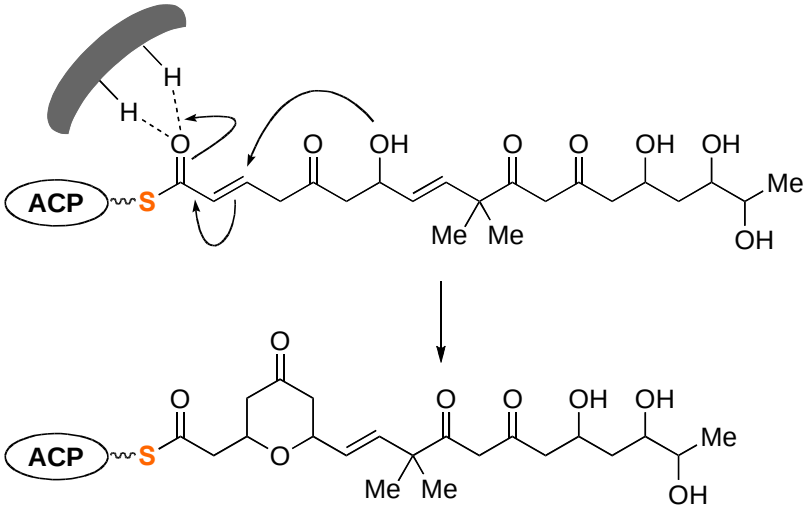
retro-IOCC/recyclization sequence under thermodynamic conditions. Accordingly, the stereoselectivity of IOCC of α,β-unsaturated ketones and esters may depend on their local structure and reaction conditions. Indeed, stereocontrolled synthesis of 2,6-*cis*-substituted tetrahydropyran derivatives has proved to be very difficult in some instances, even under thermodynamic conditions (*vide infra*).[20] It seems this is particularly true for IOCC of α,β-unsaturated esters, possibly because of the low acidity of the α-protons of the ester carbonyl group. Meanwhile, it has also been shown that α,β-unsaturated ketones, but not esters, participate in IOCC under the influence of a Brønsted acid to provide 2,6-*cis*-substituted tetrahydropyran derivatives (Schemes 1B and 1C).[21,22] Unfortunately, the mechanistic aspects of Brønsted acid-catalyzed IOCC of α,β-unsaturated carbonyl compounds have remained underexplored.



Scheme 1. IOCC of α,β-Unsaturated Esters and Ketones

It has recently been reported that the tetrahydropyran substructures embedded in several polyketide natural products, including pederin, ambruticin, bryostatins, jerangolid, and sorangicin, are formed through IOCC catalyzed by "pyran synthase" during their biosynthesis.[23] It is likely that biosynthetic IOCC involves carbonyl activation of α,β-unsaturated thioesters bound to acyl carrier proteins (ACPs) by H-bonding(s), thereby promoting intramolecular conjugate addition of the pendant hydroxy group to the conjugate acceptor (Scheme 2). The biosynthetic formation of tetrahydropyrans would be, at least in part, facilitated by enhanced electrophilicity of α,β-unsaturated thioesters when compared with the

corresponding oxoesters.[24] Thus, IOCC of α,β-unsaturated thioesters based on carbonyl activation would represent a "biomimetic" approach toward the synthesis of tetrahydropyran derivatives.

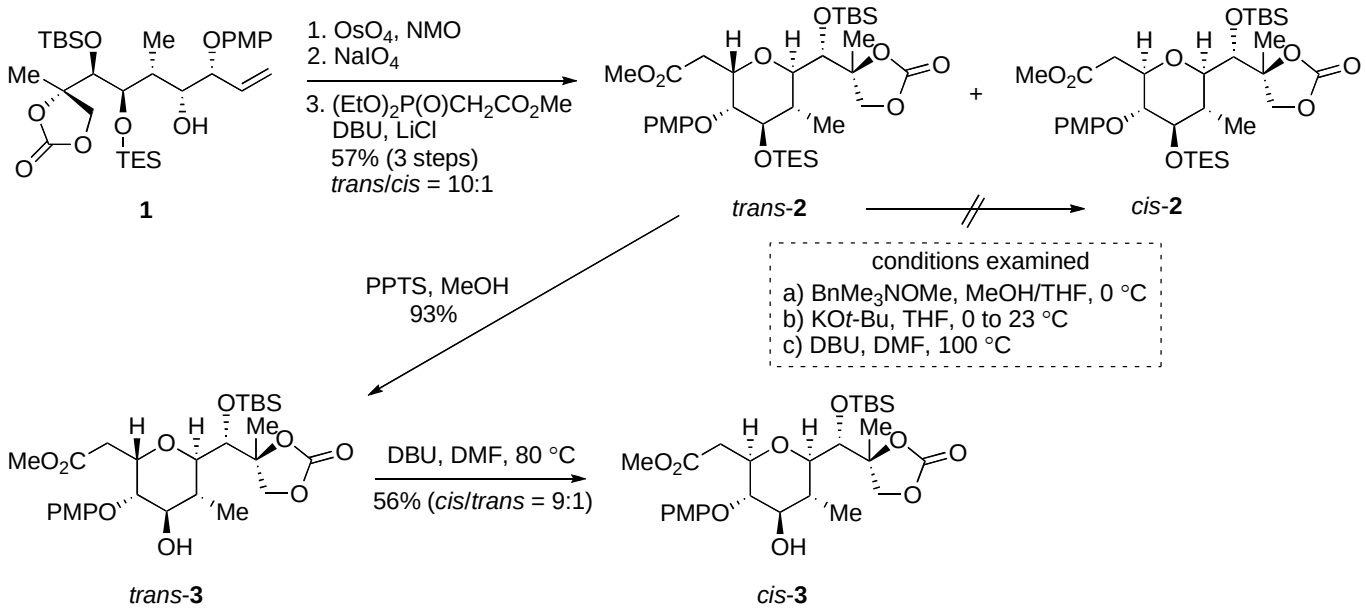


Scheme 2. Proposed Biosynthesis of the Tetrahydropyran Ring of Bryostatins

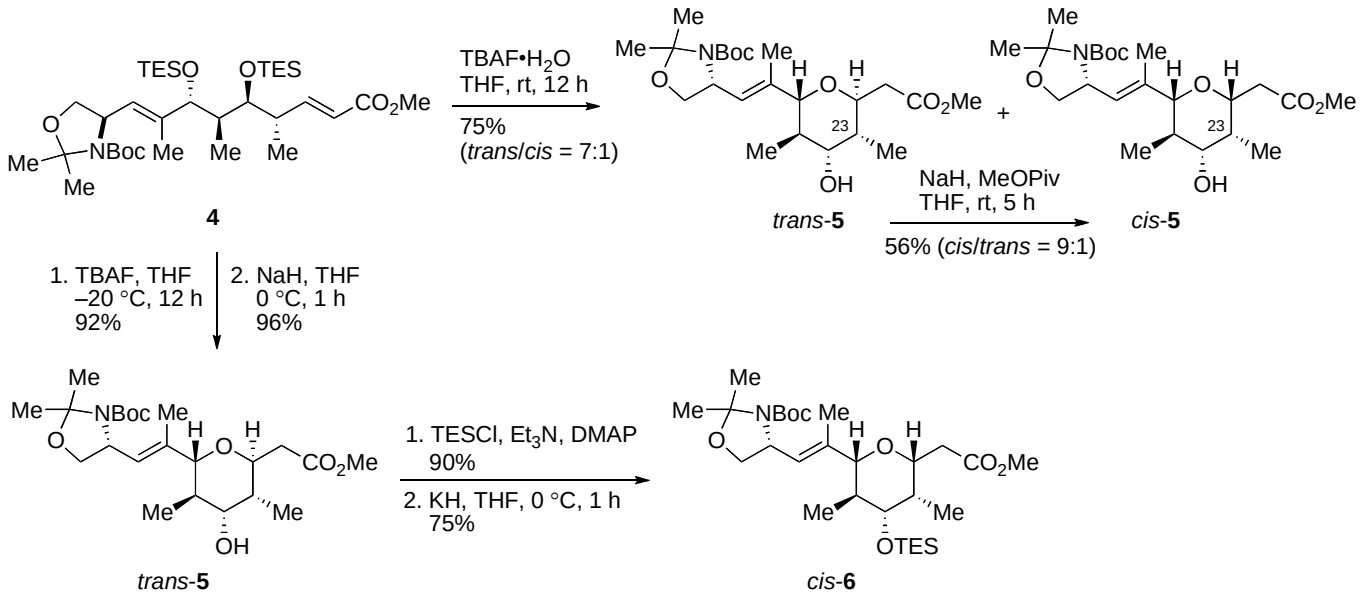
In recent years, there have been increasing interests in application of IOCC to stereoselective synthesis of complex tetrahydropyran derivatives. Roush and co-workers have described the synthesis of multi-substituted tetrahydropyran derivatives in their total synthesis of spongistatin 1 (Scheme 3).[20e] They initially found that oxidative cleavage of the double bond of **1** followed by Horner–Wadsworth–Emmons (HWE) olefination gave 2,6-*trans*-substituted tetrahydropyran *trans*-**2** with 10:1 diastereoselectivity. The latter process involved migration of the TES group and concomitant IOCC to forge the tetrahydropyran ring. Unfortunately, all attempts at isomerization of *trans*-**2** to thermodynamically more stable 2,6-*cis*-substituted tetrahydropyran *cis*-**2** were unsuccessful. However, they found that the isomerization could be achieved after removal of the TES group. Thus, treatment of *trans*-**3** with DBU in DMF at 80 °C led to *cis*-**3** in 56% yield with 9:1 diastereoselectivity.

Forsyth et al. have synthesized the 2,6-*cis*-substituted tetrahydropyran subunit of phorboxazole A via IOCC under basic conditions (Scheme 4).[20a] Treatment of α,β-unsaturated ester **4** with TBAF•H_2O in THF at room temperature for 12 h delivered two cyclization products *trans*-**5** and *cis*-**5**, the former being favored under these conditions (75% combined yield, *trans*/*cis* = 7:1). Although they found that *cis*-**5** could be obtained as the major diastereomer by extending the reaction time, the product yield declined to 29% as saponification of the ester and epimerization of the C23 stereogenic center occurred as side reactions. Exposure of *trans*-**5** to NaH in the presence of methyl pivaolate (THF, room temperature, 5 h) resulted in epimerization to give *cis*-**5** in 56% yield with 9:1 diastereoselectivity. However, epimerization at the C23 stereogenic center was still observed as a side reaction. They eventually developed a four-step sequence for the synthesis of *cis*-**6** from **4**. Thus, removal of the silyl groups with TBAF under low temperature conditions followed by treatment with NaH gave 2,6-*trans*-substituted tetrahydropyran

trans-**6**. After silylation of the free hydroxy group, the resultant product was exposed to KH (THF, 0 °C, 1 h) to achieve isomerization to thermodynamically more stable 2,6-*cis*-substituted tetrahydropyran *cis*-**6** (60% overall yield from **4**).



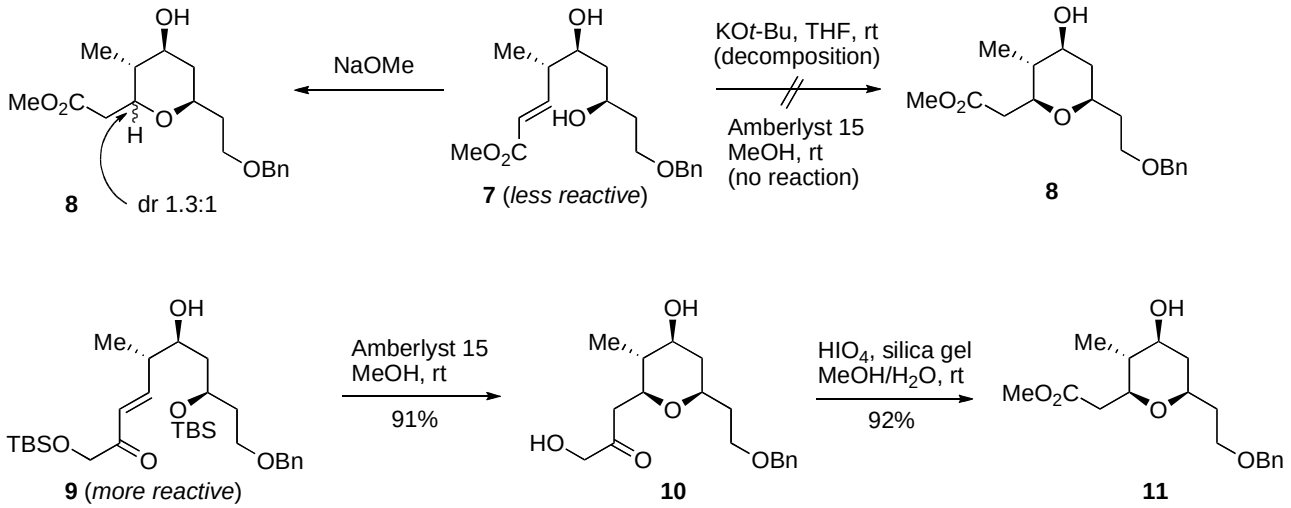
Scheme 3. Synthesis of Substituted Tetrahydropyran Derivatives by Roush *et al*.



Scheme 4. Synthesis of Substituted Tetrahydropyran Derivatives by Forsyth et al.

Bates and Song have reported a stereoselective synthesis of the tetrahydropyran subunit of clavosolide A (Scheme 5).[20b] They initially investigated IOCC of α,β-unsaturated ester **7** in the presence of a base. However, upon treatment of **7** with NaOMe, the cyclization product **8** was obtained with a rather disappointing diastereoselectivity (yield not given). Changing the base to KO*t*-Bu resulted in material decomposition. Treatment of **7** with acidic methanol did not induce IOCC at all, presumably due to the

low reactivity of the α,β-unsaturated ester. Accordingly, they resorted to *more reactive* α,β-unsaturated ketone **9**, which upon exposure to Amberlyst 15 resin in methanol underwent clean desilylation and concomitant IOCC to deliver 2,6-*cis*-substituted tetrahydropyran **10** in 91% yield. This was successfully converted to ester **11** by periodic acid treatment in aqueous methanol.



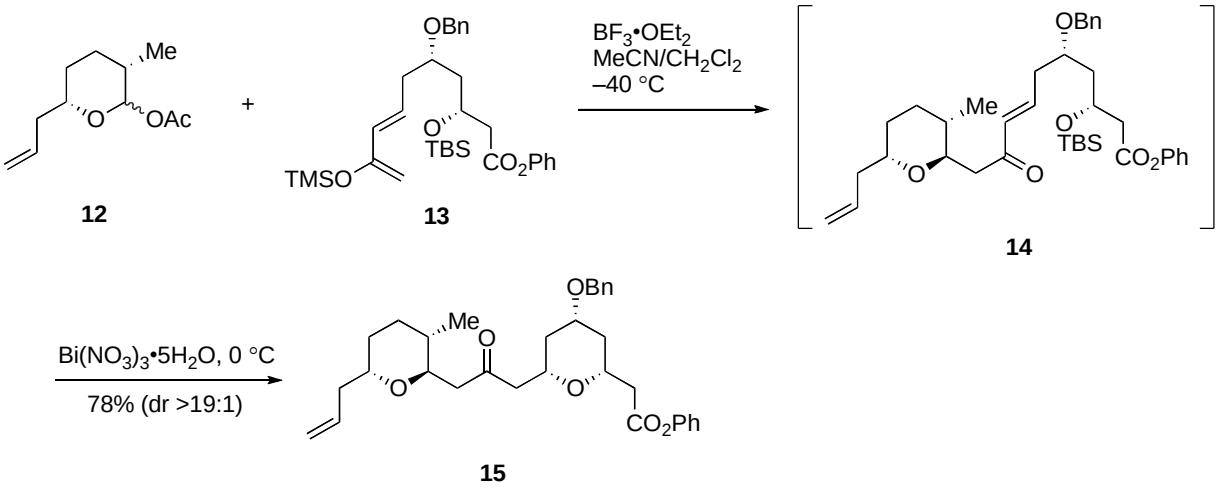
Scheme 5. Synthesis of Substituted Tetrahydropyran Derivatives by Bates and Song

The above examples highlight the feasibility of IOCC for the synthesis of complex tetrahydropyran derivatives. However, at the same time, it appears that the stereoselectivity of IOCC of α,β-unsaturated esters depends heavily on their structure and the reaction conditions employed. In addition, isomerization of 2,6-*trans*-substituted tetrahydropyrans to the corresponding 2,6-*cis* isomers may require the use of a strong base and/or harsh reaction conditions in some cases (e.g., *trans*-**3** to *cis*-**3**, *trans*-**6** to *cis*-**6**).

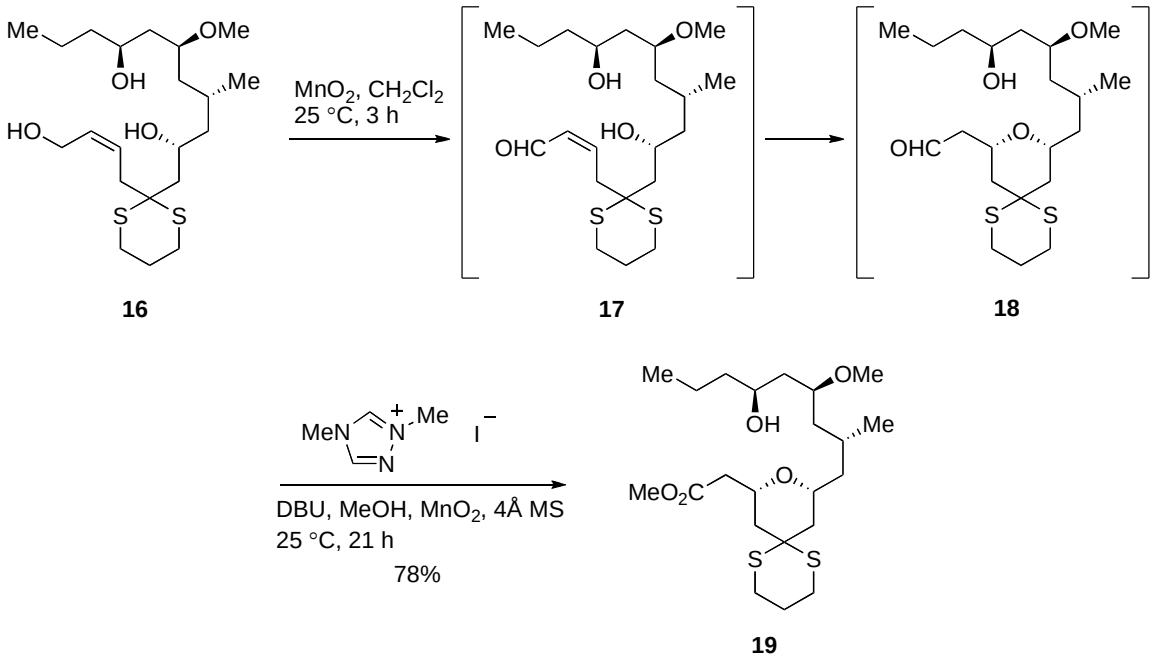
Tandem reactions involving IOCC provide an efficient means to synthesize complex tetrahydropyran derivatives. Evans and Andrews devised a tandem Mukaiyama aldol/$Bi(NO_3)_3$•$5H_2O$-catalyzed IOCC reaction during the course of their total synthesis of (+)-leucascandrolide A (Scheme 6).[21c] Thus, treatment of acetate **12** with enol silane **13** in the presence of BF_3•OEt_2 followed by addition of a catalytic amount of $Bi(NO_3)_3$•$5H_2O$ provided ketone **15** in 78% yield with >19:1 diastereoselectivity. It can be envisaged that the initial Mukaiyama aldol reaction generated α,β-unsaturated ketone **14**, and subsequent addition of $Bi(NO_3)_3$•$5H_2O$ effected IOCC with spontaneous loss of the silyl group. Notably, isomerization of 2,6-*trans*-substituted tetrahydropyran to thermodynamically more stable 2,6-*cis* isomer did not occur under the reaction conditions.

Hong et al. have synthesized the 2,6-*cis*-substituted tetrahydropyran embedded in (+)-neopeltolide based on their tandem allylic oxidation/IOCC reaction (Scheme 7).[21b] Exposure of allylic alcohol **16** to MnO_2 gave α,β-unsaturated aldehyde **17**, which underwent concomitant IOCC to deliver 2,6-*cis*-substituted tetrahydropyran **18**. This was *in situ* oxidized to the corresponding ester **19**. This methodology cleverly

leverages the *gem*-disubstituent effect to realize exclusive formation of 2,6-*cis*-substituted tetrahydropyran **19**.



Scheme 6. Tandem Mukaiyama Aldol/$Bi(NO_3)_3$•$5H_2O$-Catalyzed IOCC Reaction by Evans and Andrews



Scheme 7. Tandem Allylic Oxidation/IOCC Reaction by Hong *et al*.

In the following sections, we wish to describe our total synthesis of tetrahydropyran-containing natural products exploiting IOCC and illustrate what we discovered during these synthetic campaigns.

2. TOTAL SYNTHESIS OF (+)-NEOPELTOLIDE

(+)-Neopeltolide (**20**, Figure 2) was isolated from a deep-water sponge that belongs to the family Neopeltidae by Wright and co-workers.[25] Its gross structure and relative configuration were proposed on the basis of extensive 2D NMR analysis. However, Panek and Scheidt later independently revised the assignment of the relative configuration at the C11 and C13 stereogenic centers and ultimately

determined the complete stereostructure of this natural product through total synthesis.[26] Wright *et al*. have shown that **20** exhibits highly potent antiproliferative activity against several cancer cell lines, including the P388 mouse leukemia, the A549 human lung adenocarcinoma, and the NCI-ADR-RES human ovarian carcinoma cell lines, with single-digit nanomolar concentrations. A flow cytometric analysis on the cell cycle progress of A549 cell lines revealed that 100 nM of **20** arrests the cell cycle at the G1 phase. In addition, **20** shows antifungal activity against the fungal pathogen *Candida albicans*. Kozmin and co-workers reported the cytochrome bc_1 complex as the molecular target of **20** and inhibition of mitochondria ATP synthesis as the molecular basis of the potent biological activity.[27] These structural and biological aspects of **20** make it an intriguing target molecule for the synthetic community. So far, nine total syntheses and five formal syntheses of **20** have been reported.[28]

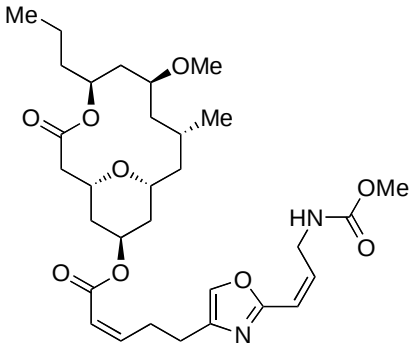
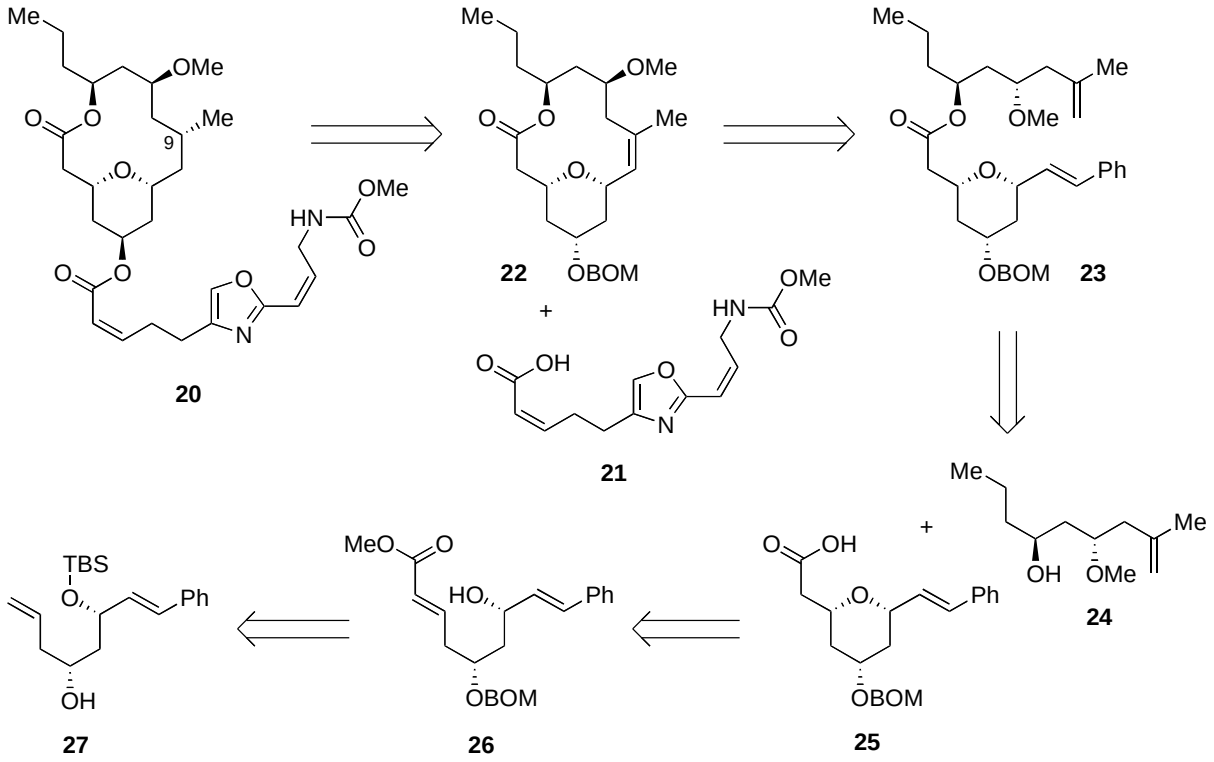


Figure 2. Structure of (+)-Neopeltolide (**20**)

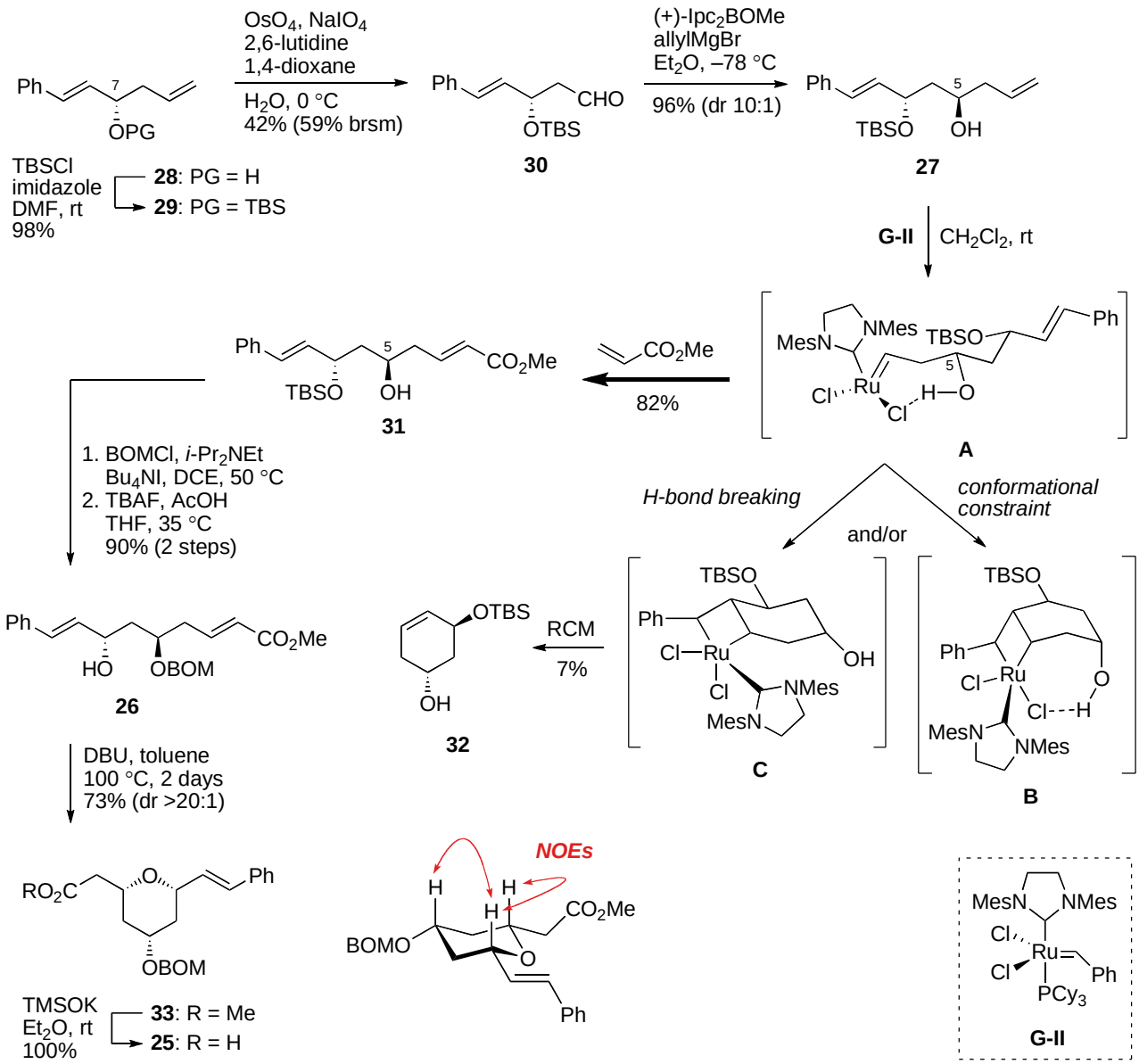
We reported our first-generation total synthesis of **20** in 2008, which hinges on Suzuki–Miyaura coupling of an acetate-derived enol phosphate[29,30] and subsequent ring-closing metathesis (RCM)[31,32] to forge the 2,4,6-trisubstituted tetrahydropyran substructure.[33] Unfortunately, our first-generation synthetic route was rather lengthy and not amenable to the development of a focused library of synthetic analogues to fully explore the structure–activity relationships of **20**. Accordingly, we planned a second-generation synthetic approach toward **20** as shown in Scheme 8.[11d] As previously reported, we envisioned the oxazole-containing side chain **21** to be appended to the macrolactone core **22** at the final stage of the total synthesis via Mitsunobu esterfication.[34] The most important feature of our second-generation synthetic plan was the formation of the 14-membered macrocycle by means of RCM of diene **23**. Molecular modeling suggested that the *Re* face of the RCM product **22** would be more sterically encumbered than the *Si* face, implying that stereoselective hydrogenation of **22** would give **20** with the correct configuration at the C9 stereogenic center. The diene **23** would be available from alcohol **24** and carboxylic acid **25**. We naturally thought that the latter fragment could be synthesized via IOCC of α,β-unsaturated ester **26** under thermodynamic control. We planned to obtain **26** from homoallylic alcohol **27** by means of chemoselective olefin cross-metathesis (CM),[35] although we were fully aware that competitive RCM could occur as a side reaction.



Scheme 8. Synthesis Plan toward (+)-Neopeltolide

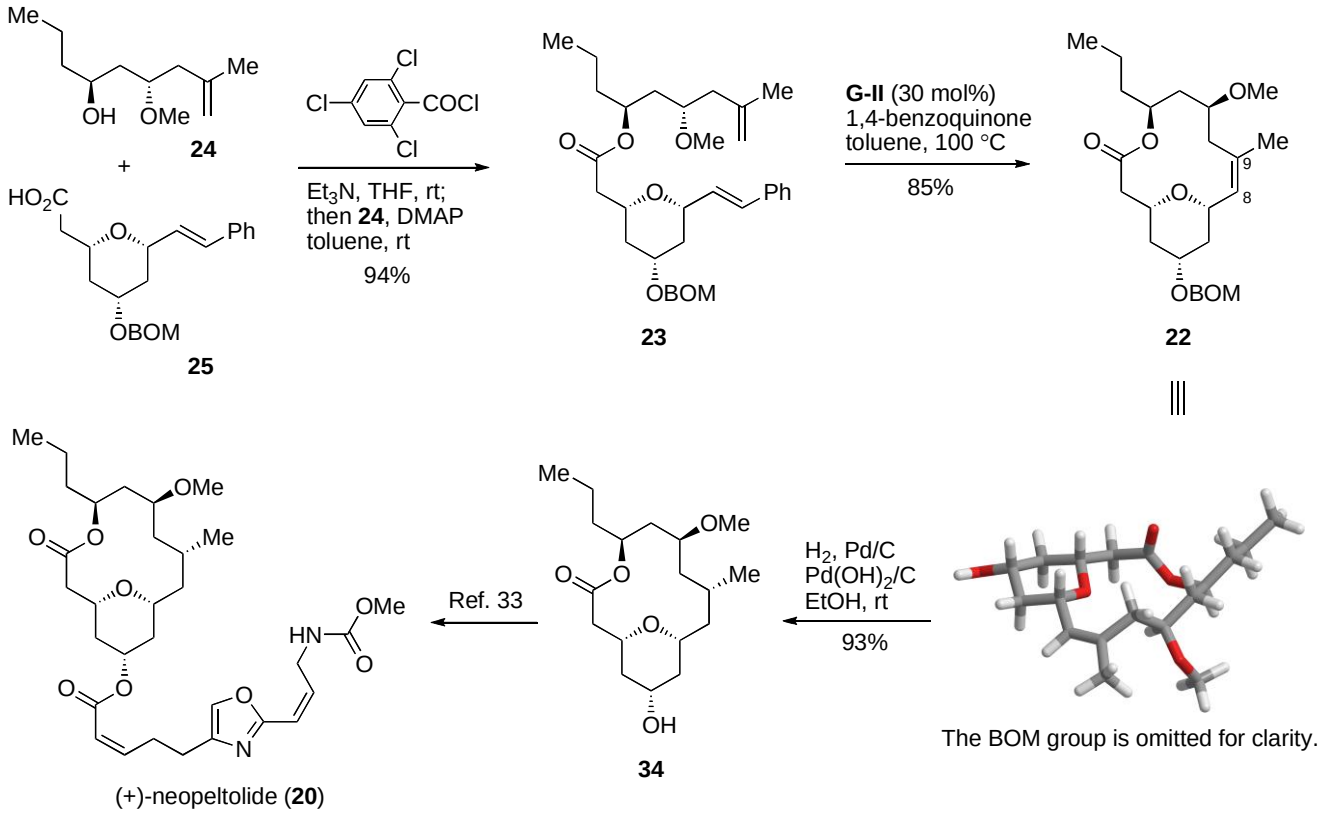
The synthesis of carboxylic acid **25**, summarized in Scheme 9, started with silylation of the known homoallylic alcohol **28**[36] to give silyl ether **29**. We planned to exploit a bulky silyl group for the protection of the C7 hydroxy group, as it would be helpful for preventing competitive RCM during the projected CM of **27** with methyl acrylate.[37] Selective one-pot dihydroxylation/periodate cleavage[38] delivered aldehyde **30**. Brown allylation of **30** using *B*-allyl-(+)-diisopinocampheylborane[39] provided homoallylic alcohol **27** as an inseparable 10:1 mixture of diastereomers. Installation of the requisite α,β-unsaturated ester unit was best accomplished by CM of **27** with excess methyl acrylate under the influence of the Grubbs' second-generation catalyst (**G-II**)[40] (CH_2Cl_2, room temperature), which led to α,β-unsaturated ester **31** in 82% yield, along with cyclohexene derivative **32** in 7% yield. It was critically important to leave the C5 hydroxy group free, since this functionality would form an H-bonding with one of the two chlorine atoms of the catalyst and direct the intermediary ruthenium alkylidene complex **A**[41] to undergo the desired CM pathway, leading to α,β-unsaturated ester **31**. In contrast, the RCM product **32** would be formed via the ruthenacyclobutane **B** that suffers from unfavorable steric repulsions, or via the ruthenacyclobutane **C** by breaking the H-bonding. Accordingly, the H-bonding formed between the C5 hydroxy group and the chlorine atom of the catalyst would act as a conformational constraint and make the RCM energetically less favored than the CM.[42] Protection of the C5 hydroxy group as its benzyloxymethyl (BOM) ether (BOMCl, *i*-Pr_2NEt, *n*-Bu_4NI) followed by cleavage of the silyl group (tetra-*n*-butylammonium fluoride (TBAF), AcOH) gave α,β-unsaturated ester **26** as the IOCC precursor.

We have examined a variety of conditions and eventually found that exposure of **26** to excess DBU in toluene at 100 °C for two days resulted in stereoselective formation of the desired 2,6-*cis*-substituted tetrahydropyran **33** in 73% yield with more than 20:1 diastereoselectivity. Careful monitoring of the cyclization revealed that a mixture of the 2,6-*cis* isomer and the corresponding 2,6-*trans* isomer was initially formed with low stereoselectivity, and the proportion of the desired 2,6-*cis* isomer increased slowly as the reaction time progressed. This observation suggests that the isomerization of the kinetically formed 2,6-*trans* isomer to the thermodynamically more stable 2,6-*cis* isomer required unexpectedly harsh reaction conditions and prolonged reaction time. Finally, saponification of the ester group using potassium trimethylsilanoate (TMSOK)[43] provided carboxylic acid **25**.



Scheme 9. Synthesis of Carboxylic Acid **25**

The second-generation total synthesis of (+)-neopeltolide (**20**) was completed as illustrated in Scheme 10. Esterification of **25** with alcohol **24** under Yamaguchi conditions[44] delivered diene **23**. Although RCM of **23** turned out to be a nontrivial matter, we eventually found that the RCM could be efficiently performed using **G-II** catalyst in the presence of 1,4-benzoquinone[45] in toluene at 100 °C, leading to (*Z*)-olefin **22** in 85% yield. Syringe pump addition of a toluene solution of the catalyst over a period of 6 hours was imperative for achieving a satisfactory conversion. As expected, hydrogenation of the C8–C9 double bond occurred from the less hindered *Si* face of the molecule with concomitant loss of the BOM group to afford the neopeltolide macrolactone **34**. Finally, as previously reported,[33] coupling of **34** with the known carboxylic acid **21** under Mitsunobu conditions (diisopropyl azodicarboxylate (DIAD), Ph_3P) furnished (+)-neopeltolide (**20**). The spectroscopic properties and specific rotation value of our synthetic material were in complete agreement with those of the natural product. Furthermore, the synthetic **20** exhibited potent antiproliferative activity against mouse P388 leukemia cells, in accordance with the natural product. Our second-generation synthesis proceeded in 13 linear steps from commercially available *trans*-cinnamaldehyde and represents the shortest asymmetric synthesis of **20** reported so far.



Scheme 10. Total Synthesis of (+)-Neopeltolide

3. TOTAL SYNTHESIS OF (−)-ASPERGILLIDES A AND B

In 2008, Kusumi and co-workers reported the isolation and structure determination of aspergillides A–C (**35**–**37**, Figure 3), tetrahydropyran-containing 14-membered macrolides.[46] These naturally occurring

substances were isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313, cultured in a bromine-modified medium, as the moderately cytotoxic constituents. Kusumi *et al*. initially assigned the stereostructure of **35**–**37** on the basis of extensive 2D NMR experiments coupled with modified Mosher analysis. A year later, Hande and Uenishi reported the first total synthesis of the proposed structure of (−)-aspergillide A.[47] However, they found that the spectroscopic properties of their synthetic material were not in accordance with those of the authentic natural product but instead identical with those of natural (−)-aspergillide B. Thus, the original structural assignment of (−)-aspergillide A by the Kusumi group has to be reconsidered. Finally, Kusumi *et al*. have successfully determined the complete stereostructure of (−)-aspergillides A and B based on X-ray crystallographic analysis of the respective *m*-bromobenzoate.[48] The unique stereostructure of aspergillides immediately spurred the interest of the synthetic community. Nagasawa and Kuwahara reported the first total synthesis of (−)-aspergillide A[49] and (+)-aspergillide C,[50] and since then a number of total and formal syntheses of aspergillides and their synthetic analogues have appeared.[51] The recent total synthesis of aspergillides A–C by Shishido and co-workers,[10a,g,h] who exploited transannular IOCC for the construction of the 14-membered macrolactone framework, is of particular interest (Scheme 11).

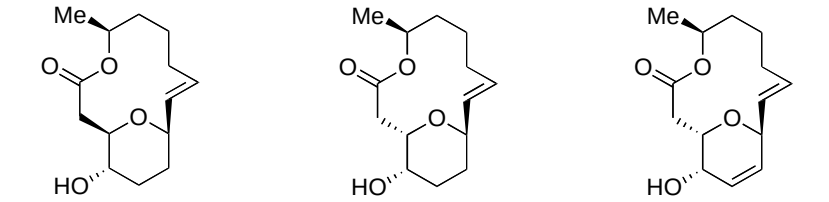
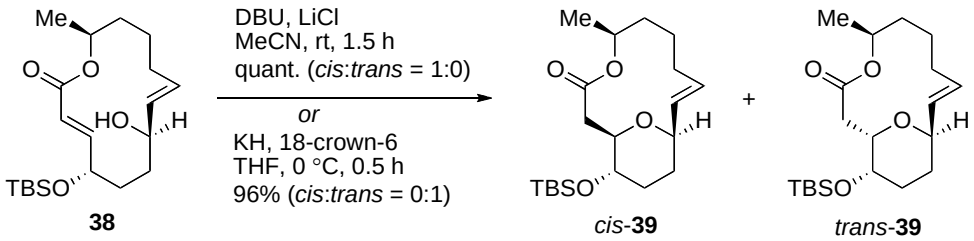
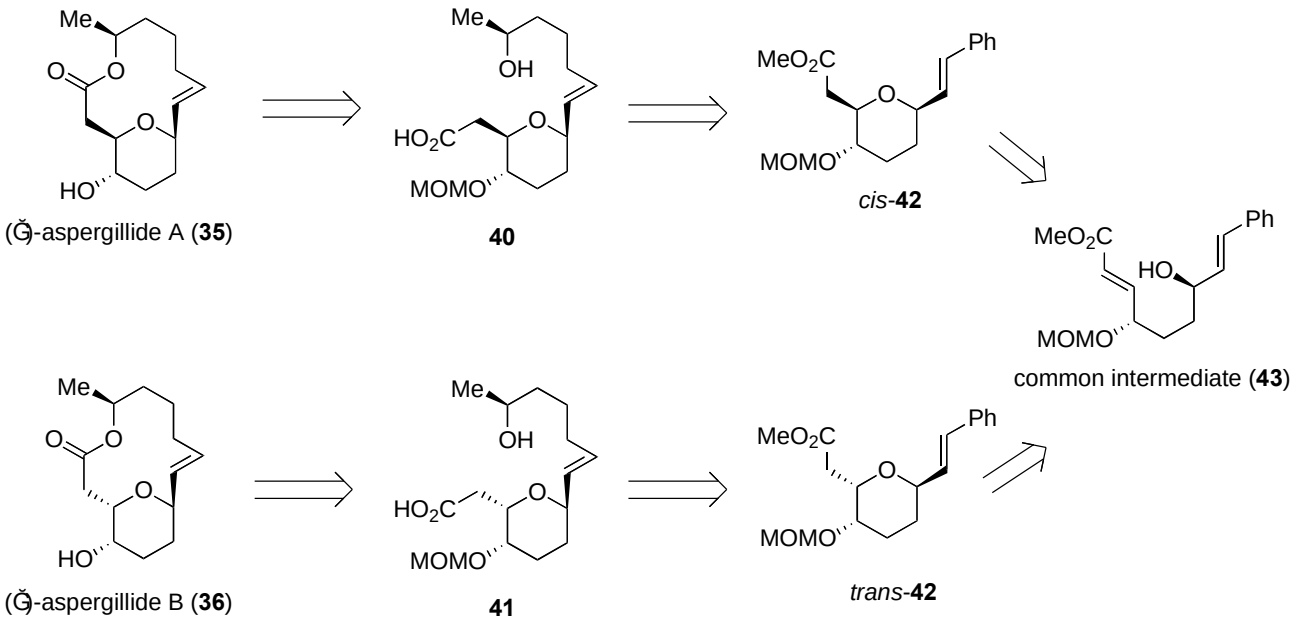


Figure 3. Structures of Aspergillides A–C



Scheme 11. Transannular IOCC en route to Aspergillides A and B by Shishido *et al*.

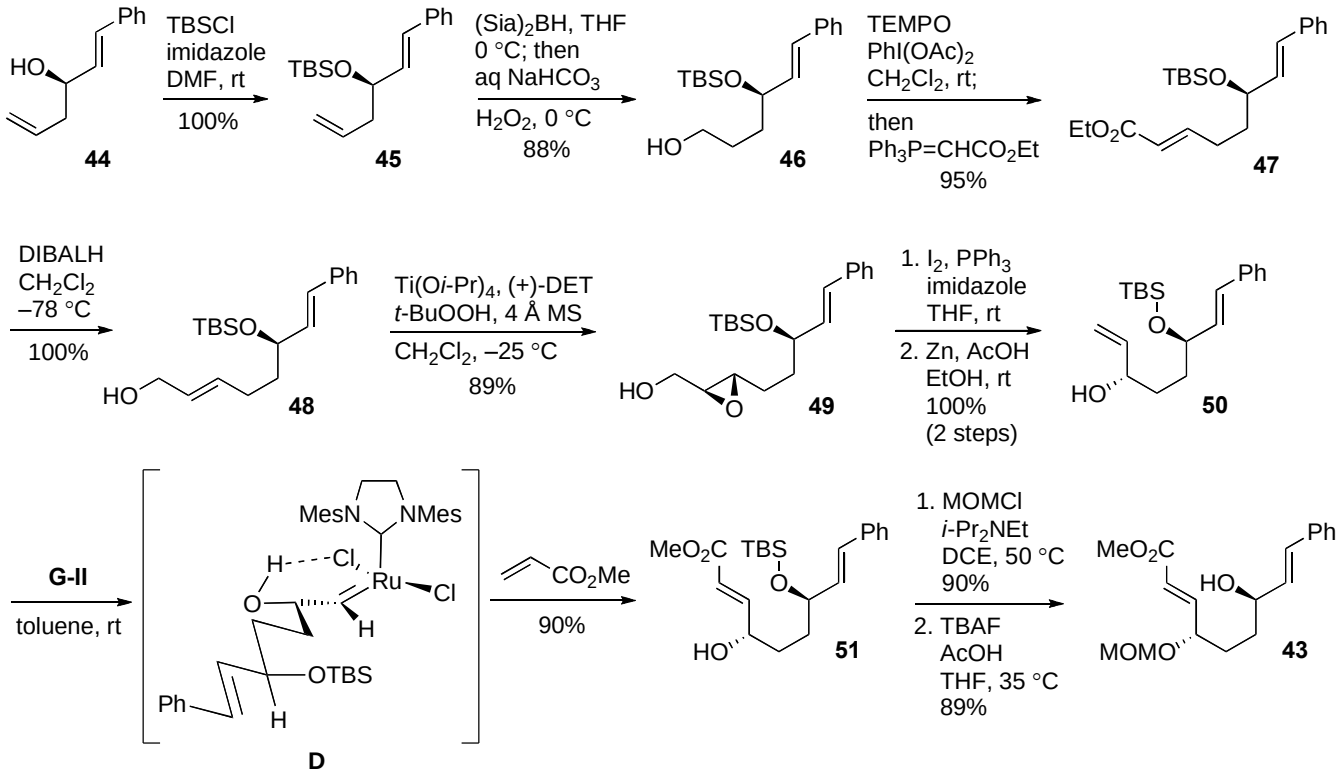
Intrigued by the structural and biological aspects, we embarked on the total synthesis of (−)-aspergillides A and B.[11e,f] Since the sole structural difference between these two natural products is the configuration at the C3 stereogenic center,[52] we envisioned a unified synthetic strategy that relies on (i) the construction of the 14-membered macrocyclic framework via Yamaguchi macrolactonization and (ii) stereodivergent synthesis of the 2,6-*cis* and 2,6-*trans*-substituted tetrahydropyrans (*cis*-**42** and *trans*-**42**, respectively), from a common precursor, i.e., α,β-unsaturated ester **43**, by means of IOCC (Scheme 12).



Scheme 12. Synthesis Plan toward Aspergillides A and B

The synthesis of α,β-unsaturated ester **43** started with the known homoallylic alcohol **44** (Scheme 13).[36] This material could be prepared from *trans*-cinnamaldehyde by using Maruoka asymmetric allylation[36] or by enzymatic resolution of the corresponding racemic alcohol (Amano lipase AK, vinyl acetate, *i*-Pr_2O, 40 °C, 47% (>99% ee by chiral HPLC analysis); then K_2CO_3, MeOH, 93%). Protection of **44** with TBSCl/imidazole gave silyl ether **45** quantitatively. Hydroboration of the terminal olefin followed by oxidative workup gave alcohol **46**. Oxidation with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and $PhI(OAc)_2$[53] and *in situ* Wittig homologation of the derived aldehyde provided α,β-unsaturated ester **47**, which was reduced with DIBALH to afford allylic alcohol **48**. Sharpless asymmetric epoxidation using diethyl (+)-tartrate ((+)-DET) gave epoxy alcohol **49** as a single stereoisomer. Iodination followed by zinc reduction delivered allylic alcohol **50**. Upon treatment of **50** with **G-II** catalyst in the presence of methyl acrylate, CM proceeded cleanly to afford α,β-unsaturated ester **51** in 90% yield, with no trace amount of the corresponding RCM product. The preference for the CM pathway could be ascribed to the "H-bonding effect," similar to that observed for homoallylic alcohol **27** (Scheme 9). Thus, an H-bonding formed between the allylic hydroxy group and the catalyst would lock the conformation of the ruthenium alkylidene intermediate so that it could not undergo RCM. Protection of the hydroxy group of **51** (MOMCl, *i*-Pr_2NEt) followed by desilylation (TBAF, AcOH) afforded α,β-unsaturated ester **43**.

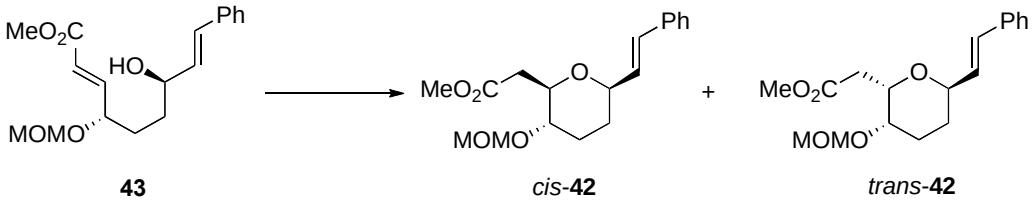
With the requisite α,β-unsaturated ester **43** available, we investigated the stereodivergent synthesis of 2,6-*cis* and 2,6-*trans*-substituted tetrahydropyrans *cis*-**42** and *trans*-**42**, respectively, by means of IOCC (Table 1). At first, IOCC of **43** under kinetic conditions was examined. As expected, treatment of **43** with KO*t*-Bu in THF at −78 °C for 30 min led to *trans*-**42** in 96% yield with 17:1 diastereoselectivity (entry 1). However, what we soon recognized was that the stereoselective formation of *cis*-**42** was not trivial.



Scheme 13. Synthesis of α,β-Unsaturated Ester **43**

Exposure of **43** to KO*t*-Bu (THF, 0 °C, 2 h) resulted in a 2.5:1 mixture of *trans*-**42** and *cis*-**42** (entry 2). Extending the reaction time and/or elevating the reaction temperature induced degradation of the material. Changing the base to NaH (THF, room temperature, 2 h) was ineffective for improvement of the stereochemical outcome (entry 3), and forcing the reaction conditions caused material decomposition. Treatment of **43** with a catalytic amount of DBU (CH_2Cl_2, room temperature, 99 h) also resulted in an unsatisfactory diastereoselectivity (entry 4). Unlike KO*t*-Bu or NaH, DBU was found to isomerize *trans*-**42** to *cis*-**42** under forcing conditions without material degradation. Thus, heating a toluene solution of **43** in the presence of excess DBU at 100 °C for 54 h led to a 7:1 mixture of *cis*-**42** and *trans*-**42** in 85% yield (entry 5). Finally, by elevating the reaction temperature to 135 °C, we could isolate an 11:1 mixture of *cis*-**42** and *trans*-**42** in 81% yield (entry 6). These diastereomers were separable by flash chromatography on silica gel. The relative stereochemistry of *cis*-**42** and *trans*-**42** was established by NOE experiments and $^3J_{H,H}$ analysis (Figure 4). Thus, we were able to synthesize *cis*-**42** and *trans*-**42** in a stereodivergent manner simply by switching the reaction conditions. However, at the same time, we learned that stereoselective synthesis of 2,6-*cis*-substituted tetrahydropyrans by means of IOCC might at least in some cases be quite difficult even under thermodynamic conditions, probably because the propensity of 2,6-*trans*-substituted tetrahydropyrans to isomerize to the corresponding 2,6-*cis* isomers depends on their local structure.

Table 1. Screening of Reaction Conditions



43 *cis*-**42** *trans*-**42**

Entry	Reagents and conditions	Yield/%[a]	*cis*/*trans*[b]
1	KO*t*-Bu (0.05 equiv), THF, −78 °C, 30 min	96	1:17
2	KO*t*-Bu (0.2 equiv), THF, 0 °C, 2 h	89	1:2.5
3	NaH (1.5 equiv), THF, room temperature, 2 h	98	1:1.4
4	DBU (0.3 equiv), CH_2Cl_2, room temperature, 99 h	93	1:1.4
5[c]	DBU (10 equiv), toluene, 100 °C, 54 h	85	7:1
6[c]	DBU (10 equiv), toluene, 135 °C, 36 h	81	11:1

[a]Isolated yield of a purified mixture of *cis*-**42** and *trans*-**42**. [b]Diastereomer ratio was determined by ^{1}H NMR analysis of crude mixture. [c]Reaction performed in a sealed tube.

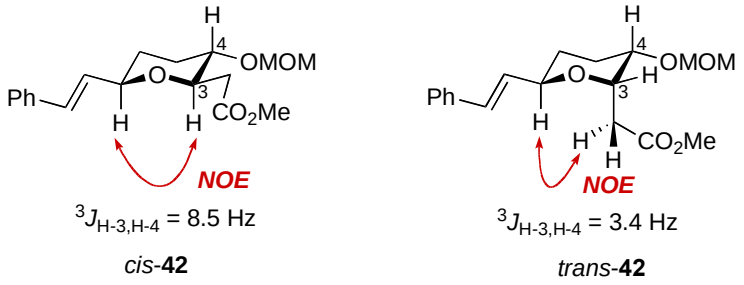
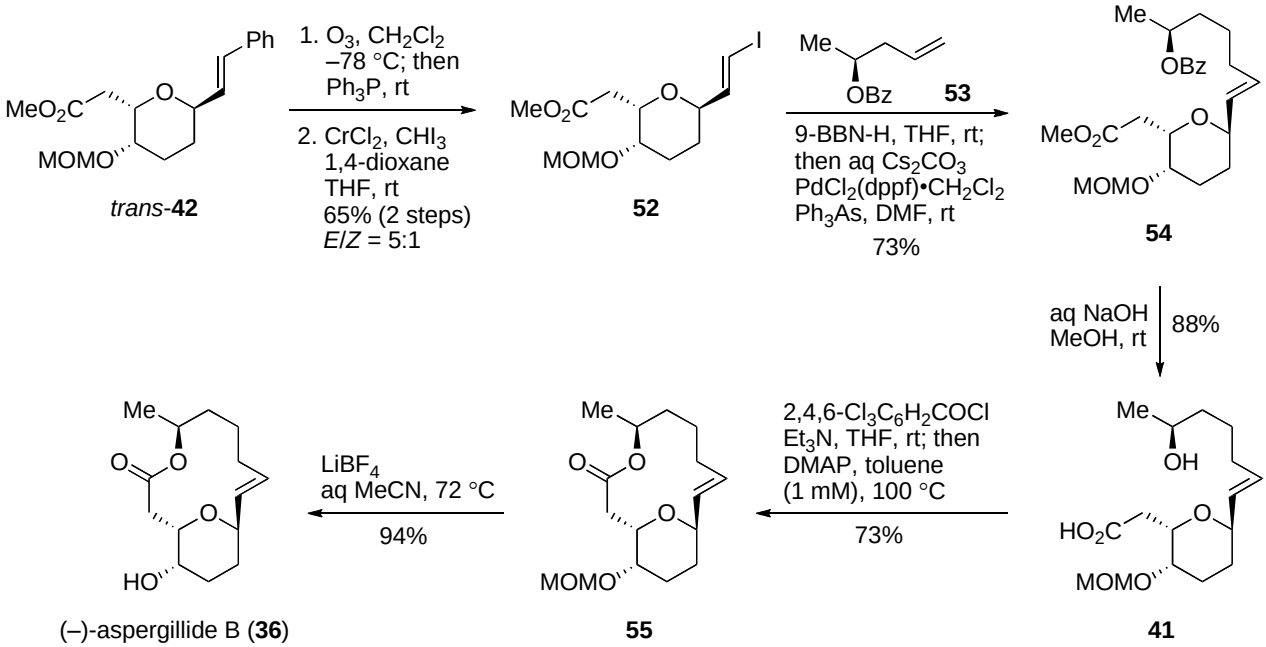


Figure 4. Stereochemical Assignment of *cis*-**42** and *trans*-**42**

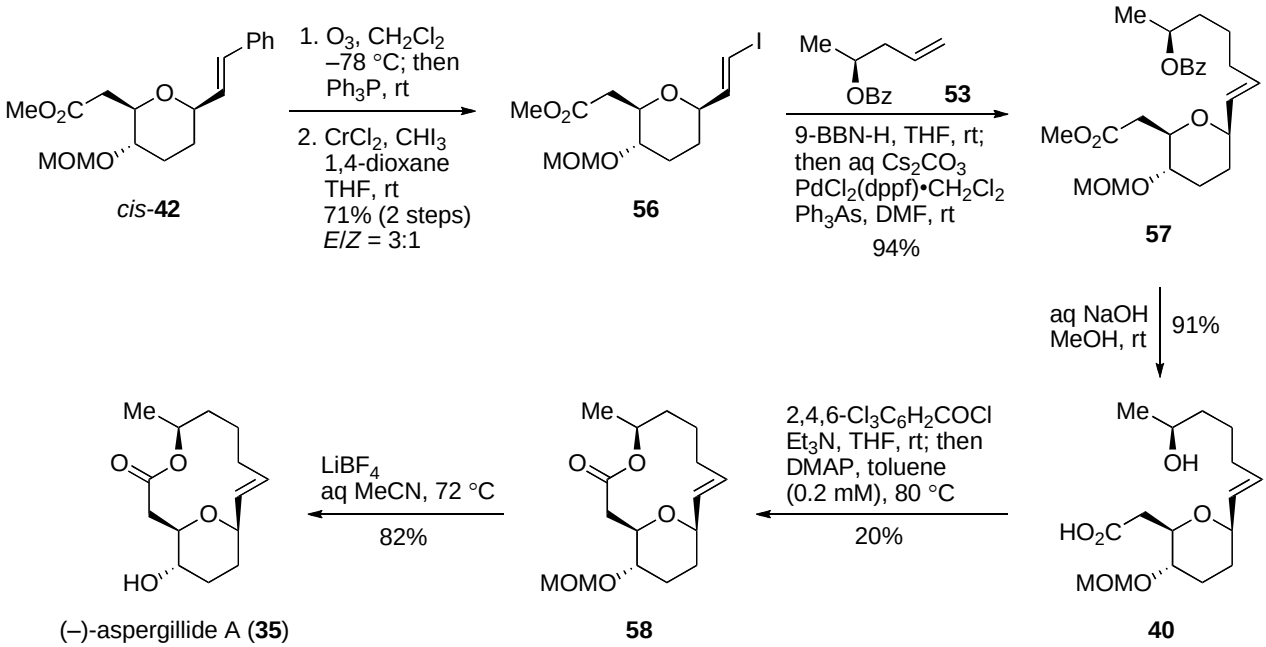
The total synthesis of (−)-aspergillide B (**36**) is depicted in Scheme 14. Ozonolysis of the styryl group of *trans*-**42** followed by Takai olefination ($CrCl_2$, CHI_3, 1,4-dioxane/THF, room temperature)[54] delivered (*E*)-vinyl iodide **52**. Suzuki—Miyaura coupling of **52** with an alkylborane derived from olefin **53**[55] (aqueous Cs_2CO_3, $PdCl_2$(dppf)•CH_2Cl_2, Ph_3As, THF/DMF, room temperature)[56] gave (*E*)-olefin **54**. Hydrolysis of the methyl ester and benzoyl group afforded hydroxy acid **41**. Yamaguchi macrolactonization under high-dilution conditions proceeded without incident to provide macrolactone **55** in 73% yield. Finally, cleavage of the MOM group ($LiBF_4$, aqueous CH_3CN, 72 °C) furnished (−)-aspergillide B (**36**). The spectroscopic data, including the ^{1}H, ^{13}C NMR, HRMS and specific rotation value, of the synthetic material were in full accordance with those of the authentic sample.

The total synthesis of (−)-aspergillide A (**35**) was performed in the same way as that described for (−)-aspergillide B (**36**) (Scheme 15). In this case, however, Yamaguchi macrolactonization to forge the 14-membered macrocyclic skeleton proved to be quite challenging, since the conformation of the

tetrahydropyran ring must change from an energetically favored "all-equatorial" chair to an energetically disfavored "all-axial" chair during the formation of the ester linkage. We were able to isolate the 14-membered macrolactone **58** only in low yield. The MOM group was then removed to complete the total synthesis of (−)-aspergillide A (**35**). The synthetic material was identical to the natural product in all respects ($[\alpha]_D$, ^{1}H, ^{13}C NMR, HRMS).



Scheme 14. Total Synthesis of (−)-Aspergillide B



Scheme 15. Total Synthesis of (−)-Aspergillide A

4. TOTAL SYNTHESIS OF (−)-EXIGUOLIDE

The novel 20-membered macrolide (−)-exiguolide (**59**, Figure 5) was isolated from the methanol extract of the sponge *Geodia exigua* Thiele collected off Amami-Oshima by Ohta, Ikegami, and co-workers.[57] The gross structure of **59** was determined by extensive 2D NMR analysis, and the relative configuration was established through conformational analysis mainly based on NOE correlations and $^{3}J_{H,H}$ values. The *J*-based configuration analysis (JBCA) method developed by Murata *et al*.[58] was used to confirm the relative stereochemistry. The absolute configuration of **59** was finally determined by the total synthesis of (+)-exiguolide, the unnatural enantiomer, by Lee and co-workers.[59] Ohta *et al*. have reported that (−)-exiguolide (**59**) specifically inhibits the fertilization of sea urchin (*Hemicentrotus pulcherrimus*) gametes at a concentration of 21 μM but not embryogenesis of the fertilized egg even at 100 μM. However, further detailed studies on the biological activity of **59** have been precluded due to its extremely limited availability in nature. The characteristic molecular structure reminiscent of potent antitumor agents bryostatins[60,61] coupled with the natural scarcity heightened the interest of the synthetic community.[10b,h,62]

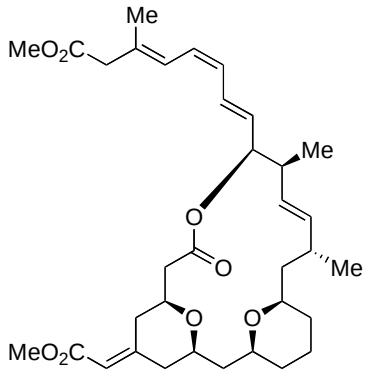
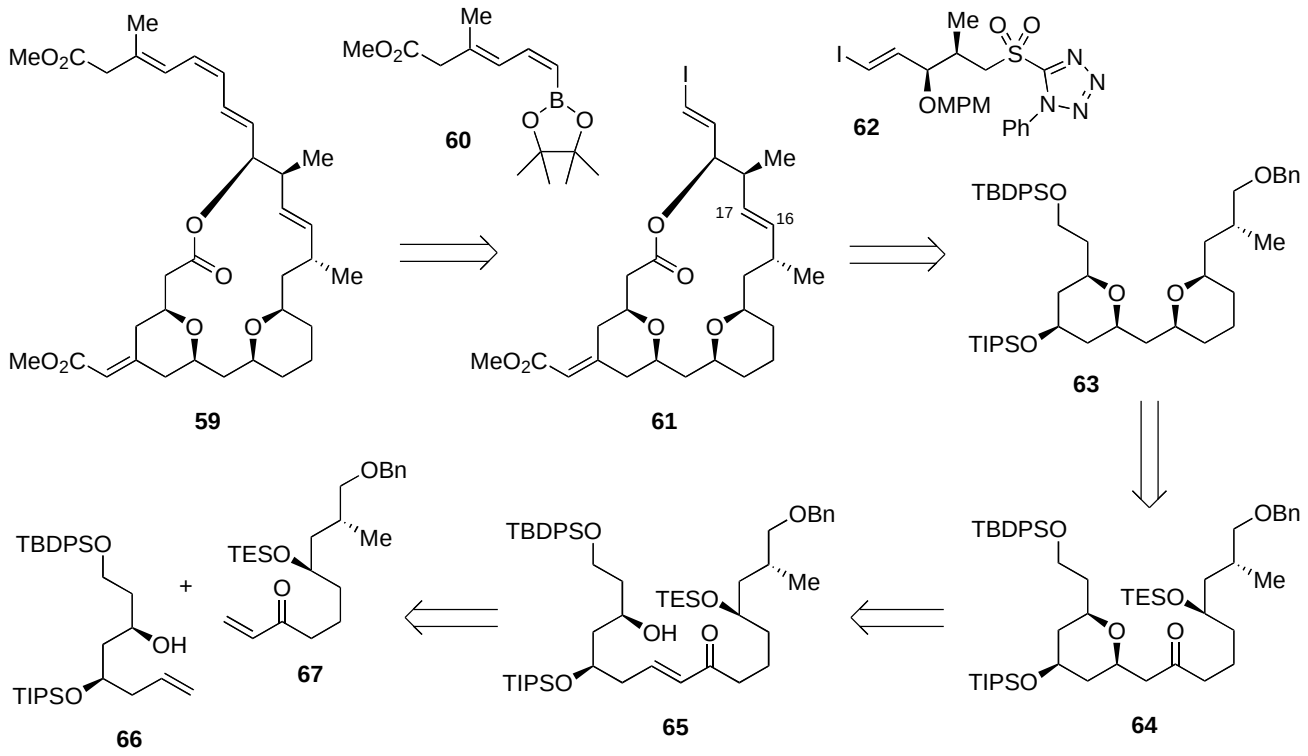


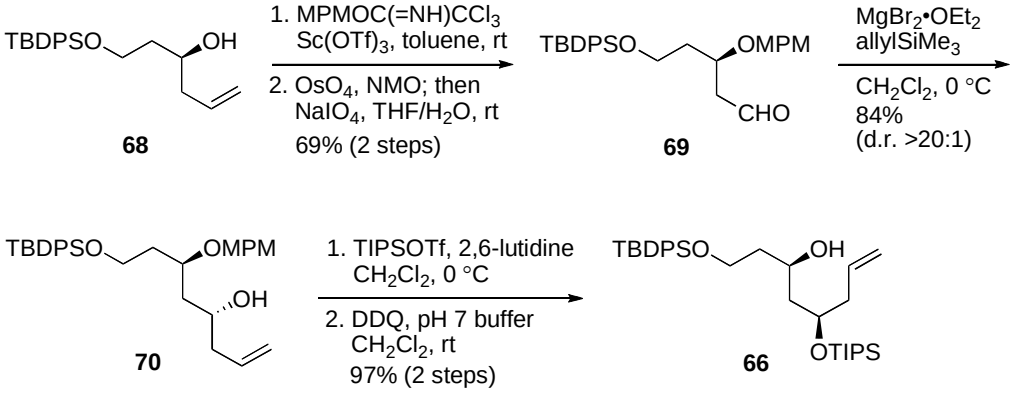
Figure 5. Structure of (−)-Exiguolide (**59**)

Our synthesis plan toward **59** is illustrated in Scheme 16. The triene side chain would be elaborated at the final stage of the total synthesis by means of Suzuki–Miyaura coupling of (*Z*)-vinyl boronate **60** and (*E*)-vinyl iodide **61**.[11b,h] It was envisioned that the 20-membered macrolactone framework of **61** would be accessible from **63** through Julia–Kocienski olefination[63] to forge the C16–C17 double bond followed by Yamaguchi macrolactonization. We planned to synthesize methylene bis(tetrahydropyran) **63** via reductive etherification[64] of silyloxy ketone **64**, which in turn would be available from α,β-unsaturated ketone **65** by means of IOCC under thermodynamic conditions. Finally, **65** should be obtainable from hydroxy olefin **66** and α,β-unsaturated ketone **67** through CM. It is noteworthy that our synthetic plan would enable a three-step access to the key synthetic intermediate methylene bis(tetrahydropyran) **63** from readily available acyclic fragments **66** and **67** by leveraging the high functional group tolerability and bond-forming ability of ruthenium-catalyzed olefin metathesis.



Scheme 16. Synthesis Plan toward (−)-Exiguolide

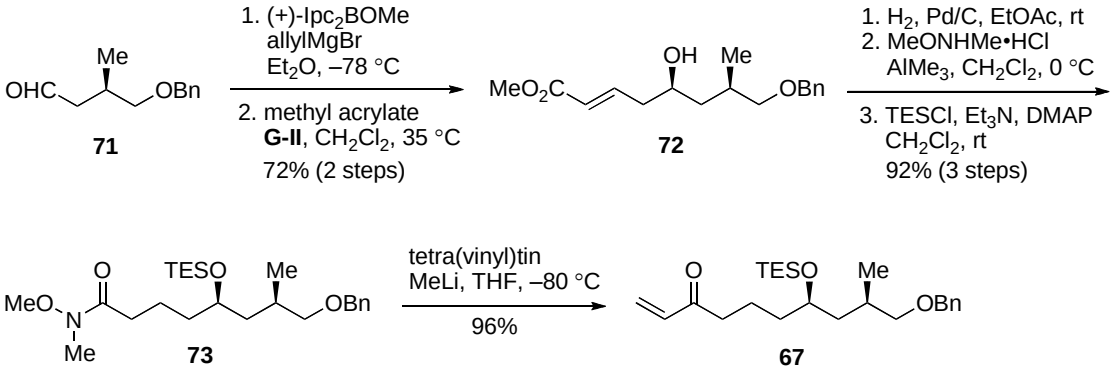
The synthesis of hydroxy olefin **66** commenced with protection of the known homoallylic alcohol **68**[65] as its MPM ether (MPMOC(=NH)CCl_3, $Sc(OTf)_3$)[66] followed by oxidative cleavage of the double bond to deliver aldehyde **69** (Scheme 17). Diastereoselective allylation of **69** under chelate control ($MgBr_2$•OEt_2, $allylSiMe_3$, CH_2Cl_2, 0 °C) provided homoallylic alcohol **70** as a single stereoisomer. Silylation (TIPSOTf, 2,6-lutidine) and deprotection of the MPM group using DDQ afforded hydroxy olefin **66**.



Scheme 17. Synthesis of Hydroxy Olefin **66**

The synthesis of α,β-unsaturated ketone **67** started with the known aldehyde **71**[67] (Scheme 18). Brown allylation of **71** using (+)-$Ipc_2Ballyl$ followed by CM with methyl acrylate in the presence of **G-II** gave α,β-unsaturated ester **72**. Hydrogenation of the double bond, Weinreb amidation[68] (MeONHMe•HCl, $AlMe_3$), and silylation of the secondary hydroxy group (TESCl, Et_3N, DMAP) provided amide **73**. Finally,

addition of vinyl lithium generated *in situ* from tetra(vinyl)stannane and methyl lithium afforded α,β-unsaturated ketone **67**.[69]



Scheme 18. Synthesis of α,β-Unsaturated Ketone **67**

Prior to coupling of **66** and **67**, we examined CM of **66** with methyl vinyl ketone as a model reaction and encountered unexpected outcomes (Table 2). Upon treatment of a mixture of **66** and methyl vinyl ketone with 10 mol% of the Hoveyda–Grubbs second-generation catalyst (**HG-II**)[70] in CH_2Cl_2 at 35 °C, α,β-unsaturated ketone **74** was isolated in 88% yield, as expected (entry 1). By contrast, when the reaction was carried out in 1,2-dichloroethane (DCE) at 80 °C, we were surprised to find that the only isolable product was 2,6-substituted tetrahydropyran **75** (80% yield, *cis*/*trans* 9:1, entry 2). We found that **G-II** catalyst is less effective for promoting the present reaction (entry 3). The best result was obtained by running the reaction in CH_2Cl_2 at 100 °C under microwave (MW) irradiation (94% yield, *cis*/*trans* 7:1, entry 4). These results indicated that domino CM/IOCC occurred under elevated temperature conditions, although the actual species responsible for the IOCC step remained unclear.

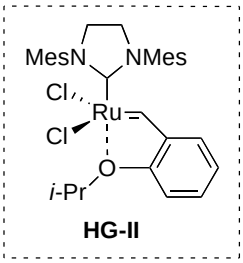
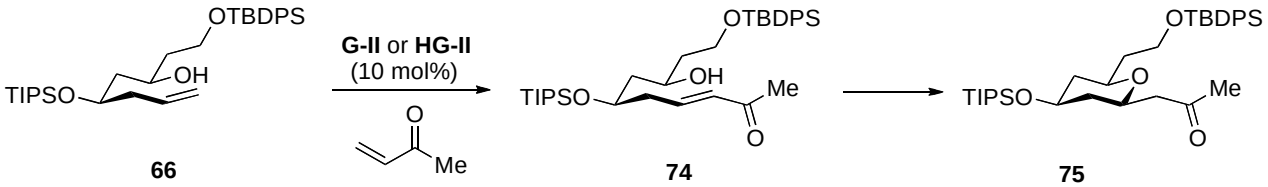


Table 2. Model Experiments on CM



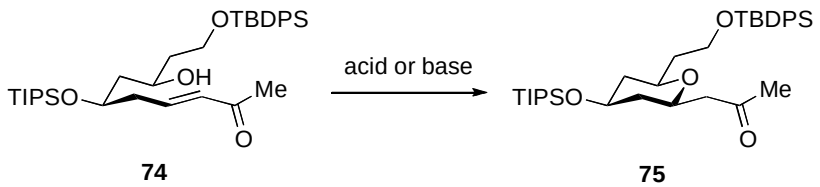
Entry	Reagents and conditions[a]	Yield/% **74**	**75** (*cis*/*trans*)[a]
1	**HG-II**, CH_2Cl_2, 35 °C, 12 h	88	
2	**HG-II**, DCE, 80 °C, 15 h		80 (9:1)
3	**G-II**, DCE, 80 °C, 15 h	19	31 (2:3)[b]
4	**HG-II**, CH_2Cl_2, 100 °C (MW), 30 min		94 (7:1)

[a]Diastereomer ratio was determined by ^{1}H NMR analysis. [b]**66** was recovered in 43% yield.

We have also studied IOCC of α,β-unsaturated ketone **74** under a variety of conditions (Table 3). Treatment of **74** with NaH (1.5 equiv) in THF at room temperature for 1 h gave 2,6-*trans*-substituted tetrahydropyran **75** as the major diastereomer with moderate diastereoselectivity (*cis*/*trans* 1:2, 89% combined yield, entry 1). Changing the base to KO*t*-Bu (0.2 equiv) and running the reaction in THF at 0 °C for 15 min resulted in isolation of 2,6-*cis*-substituted tetrahydropyran **75** in 72% yield with good diastereoselectivity (*cis*/*trans* 6:1, entry 2). The stereochemical outcome could be further improved simply by extending the reaction time so as to allow the reaction to reach thermodynamic equilibrium (*cis*/*trans* >20:1, 88% yield, entry 3). Since it is known that α,β-unsaturated ketones participate in Brønsted acid-catalyzed IOCC, we have also examined IOCC of **74** under acidic conditions: Exposure of **74** to *p*-TsOH•H_2O (0.1 equiv) in CH_2Cl_2 at room temperature for 2 h delivered 2,6-*cis*-substituted tetrahydropyran **75** in 89% yield with greater than 20:1 diastereoselectivity (entry 4). This result and the previous studies demonstrate that Brønsted acid-catalyzed IOCC of α,β-unsaturated ketones generally provides 2,6-*cis*-substituted tetrahydropyrans with excellent diastereoselectivity. However, it remains elusive whether the stereoselectivity is kinetically or thermodynamically controlled.

Having gathered preliminary information on CM and IOCC, we proceeded to the synthesis of methylene bis(tetrahydropyran) **63** as summarized in Scheme 19. Treatment of a mixture of **66** and **67** with **HG-II** (10 mol%) in CH_2Cl_2 at 35 °C for 21 h led to α,β-unsaturated ketone **65** in 93% yield with excellent *E*/*Z* selectivity. Exposure of **65** to KO*t*-Bu (20 mol%) in THF at 0 °C for 1 h afforded thermodynamically favored silyloxy ketone **64** in 95% yield as a single stereoisomer. Finally, direct reductive etherification of **64** (BF_3•OEt_2, 1:5 Et_3SiH/CH_2Cl_2, −60 to −25 °C, 45 min) furnished **63** in near quantitative yield with good stereoselectivity (d.r. 10:1). More importantly, **63** could be synthesized from **66** and **67** in one-pot by exploiting domino CM/IOCC that was discovered during the model experiments described above.

Table 3. Model Experiments on IOCC

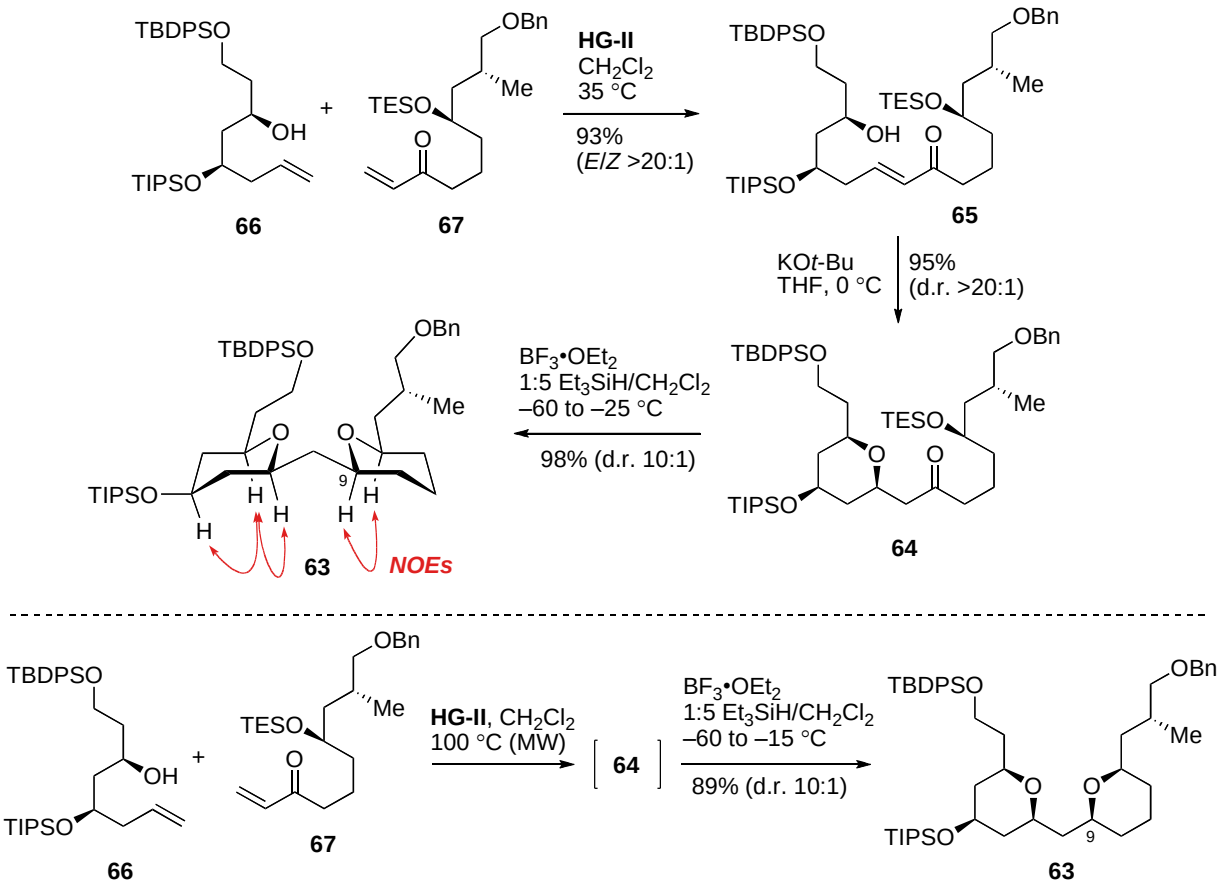


74 **75**

Entry	Reagents and conditions	Yield/%	*cis*/*trans*[a]
1	NaH (1.5 equiv), THF, room temperature, 1 h	89	1:2
2	KO*t*-Bu (0.2 equiv), THF, 0 °C, 15 min	72	6:1
3	KO*t*-Bu (0.2 equiv), THF, 0 °C, 1 h	88	>20:1
4	*p*-TsOH•H_2O (0.1 equiv), CH_2Cl_2, room temperature, 2 h	89	>20:1

[a]Diastereomer ratio was estimated by ^{1}H NMR analysis on a purified mixture of *cis*- and *trans*-isomers.

Thus, microwave irradiation of a mixture of **66**, **67**, and **HG-II** (10 mol%) in CH_2Cl_2 at 100 °C for 30 min cleanly generated silyloxy ketone **64**, which without isolation was treated with BF_3•OEt_2/Et_3SiH (CH_2Cl_2, −60 to −15 °C, 50 min) to afford **63** in 89% yield with approximately 10:1 diastereoselectivity at the C9 stereogenic center.

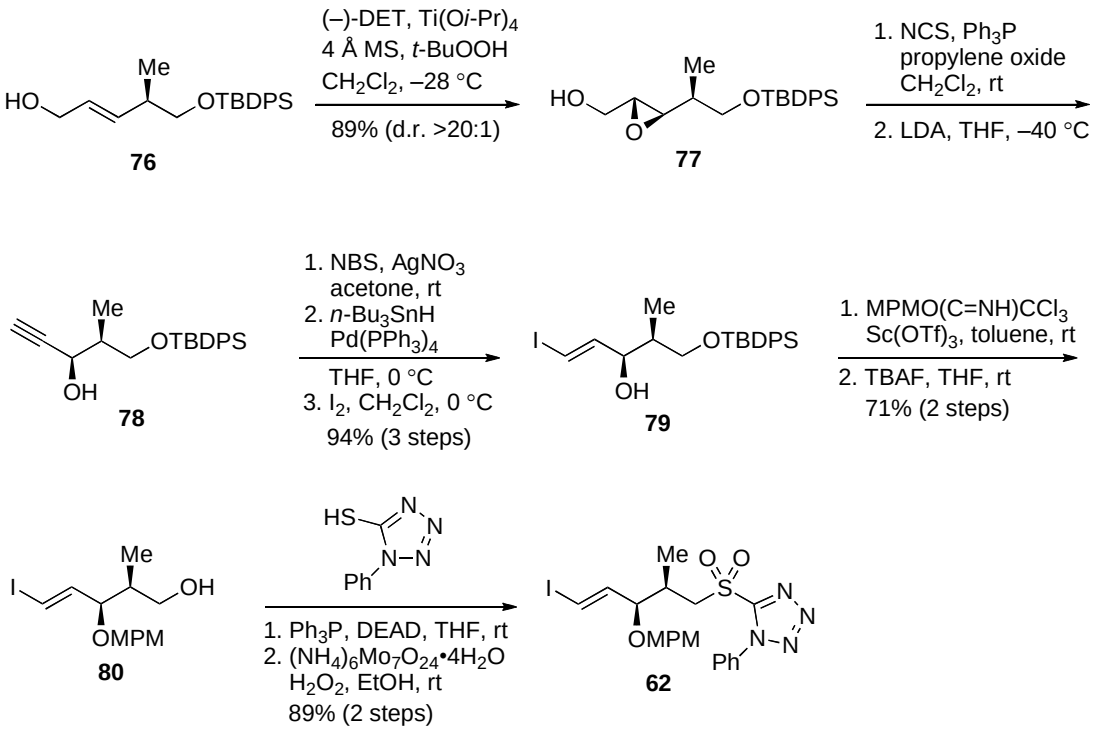


Scheme 19. Synthesis of Methylene Bis(tetrahydropyran) **63**

The synthesis of sulfone **62**, delineated in Scheme 20, started with Sharpless asymmetric epoxidation of the known allylic alcohol **76**[71] to give epoxy alcohol **77** as a single stereoisomer. Chlorination[72] followed by treatment with excess LDA according to the Takano procedure[73] led to propargylic alcohol **78**. Bromination of the terminal alkyne (NBS, $AgNO_3$), palladium-catalyzed hydrostannylation (*n*-Bu_3SnH, $Pd(PPh_3)_4$),[74] and iododestannylation provided (*E*)-vinyl iodide **79**. Protection of the secondary hydroxy group as its MPM ether and ensuing desilylation delivered alcohol **80**, which was coupled with 1-phenyl-1*H*-tetrazole-5-thiol and oxidized with peroxide[75] to afford the requisite sulfone **62**.

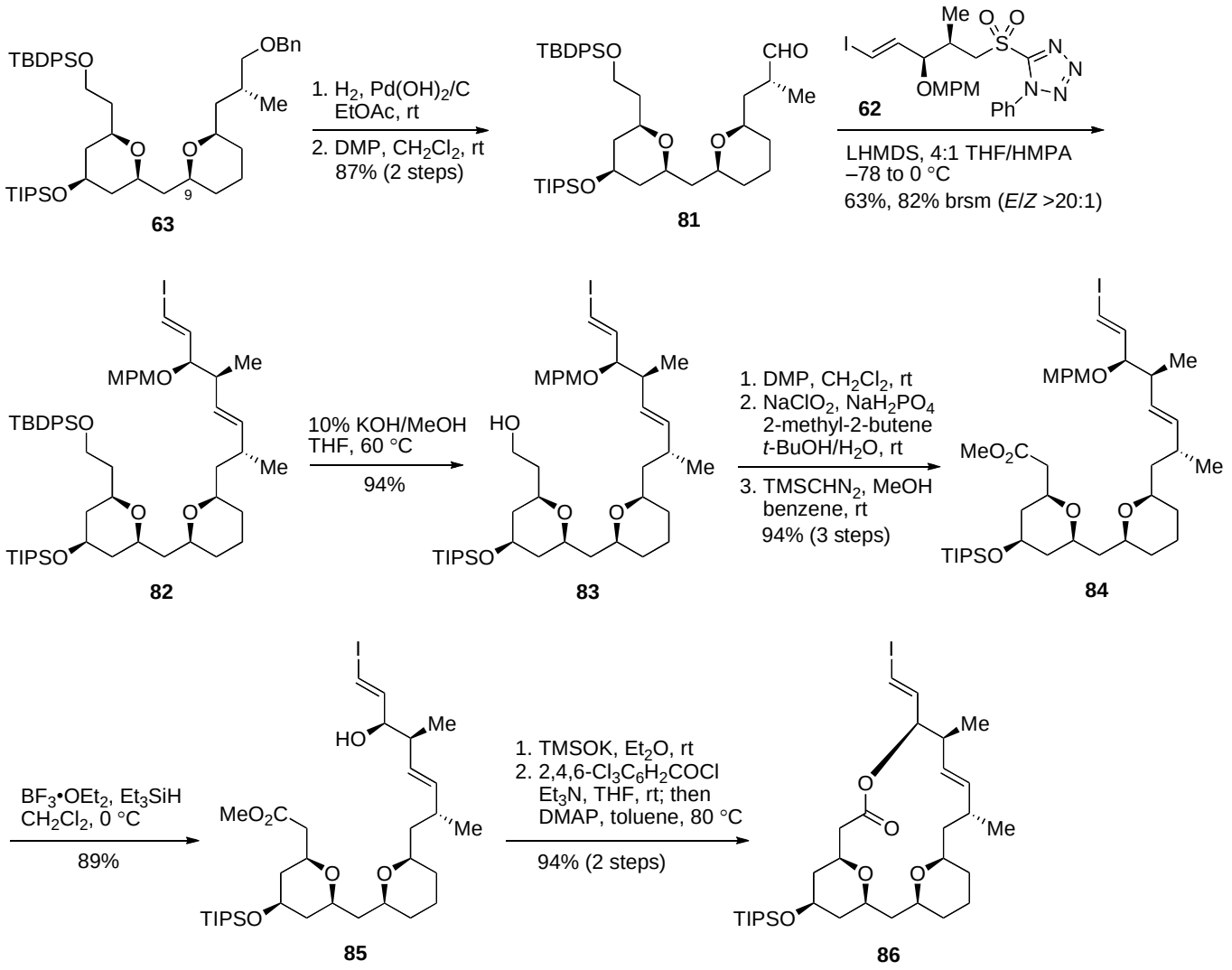
As illustrated in Scheme 21, Julia–Kocienski olefination of aldehyde **81**, derived from **63** in two steps, with an anion generated from sulfone **62** and LHMDS (4:1 THF/HMPA, −78 to 0 °C) to deliver (*E*)-olefin **82** in 63% yield (*E*/*Z* >20:1) along with recovered **81** (23%). Selective deprotection of the TBDPS group under basic conditions gave alcohol **83**. Dess–Martin oxidation,[76] Pinnick oxidation,[77] and esterification led to ester **84**. Cleavage of the MPM ether was best performed by treatment with

BF_3•OEt_2/Et_3SiH to provide alcohol **85**. Saponification of the methyl ester followed by Yamaguchi macrolactonization of the derived seco-acid afforded 20-membered macrolactone **86** in 94% yield for the two steps. Although the macrolactonization necessitates the use of high-dilution conditions (final substrate concentration: 1 mM) to avoid dimerization, we could successfully synthesize more than 200 milligrams of **86**.



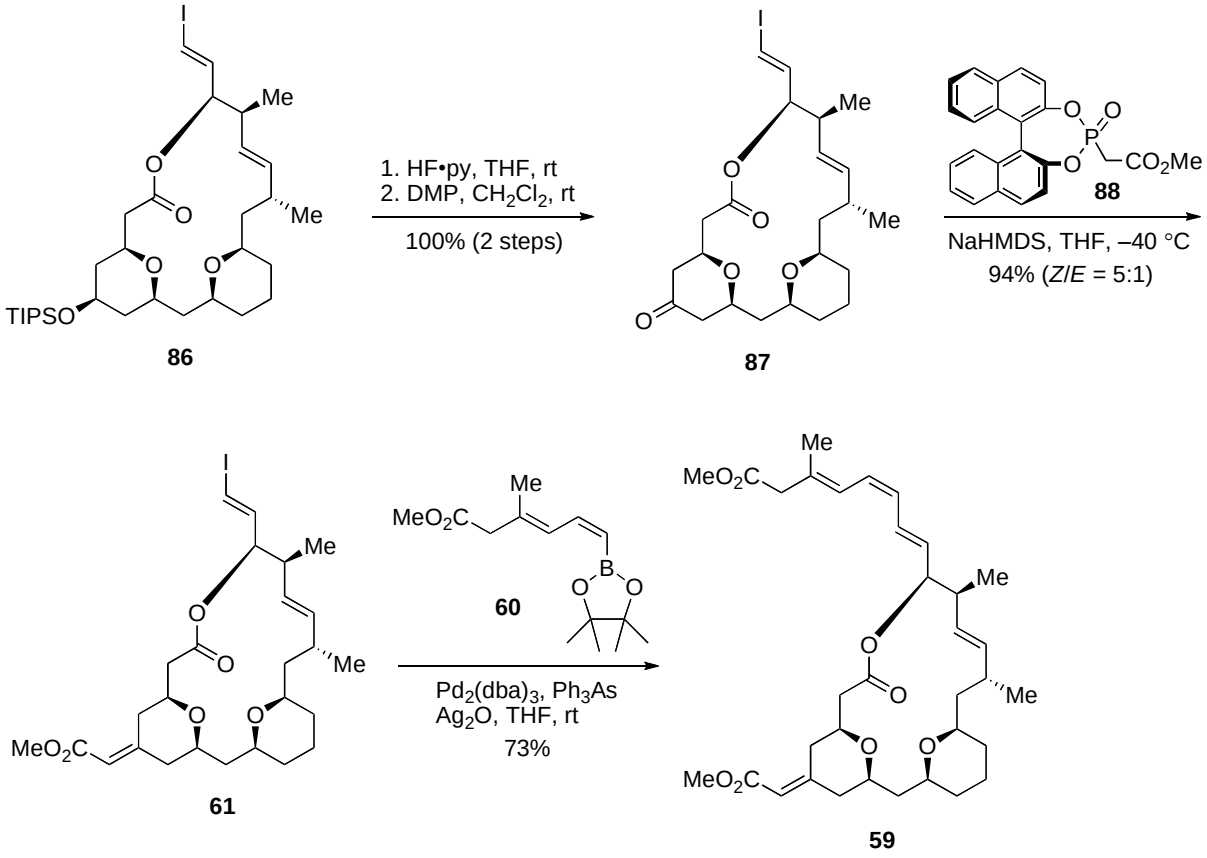
Scheme 20. Synthesis of Sulfone **62**

The final stage of the total synthesis of (−)-exiguolide (**59**) is summarized in Scheme 22. Desilylation of **86** followed by oxidation provided ketone **87**. HWE olefination using chiral phosphonate **88** developed by Fuji and co-workers[78] afforded α,β-unsaturated ester **61** (*Z*/*E* = 5:1, 94% combined yield). The undesired (*E*)-isomer could be removed by flash chromatography on silica gel. Finally, Suzuki–Miyaura coupling of **61** with (*Z*)-vinylboronate **60**[79] ($Pd_2(dba)_3$, Ph_3As, Ag_2O, THF, room temperature)[80] furnished (−)-exiguolide (**59**) in 73% yield. It was important to use moist THF as the solvent, since the coupling reaction did not proceed to an appreciable extent under strictly anhydrous conditions.[81] The ^1H, ^{13}C NMR and HRMS spectra were in full accordance with those of the authentic sample. The specific rotation value of the synthetic material ($[\alpha]_D^{24}$ −121.5 (*c* 0.22, $CHCl_3$)) differed slightly from that of the natural product ($[\alpha]_D^{25}$ −92.5 (*c* 0.069, $CHCl_3$)) but matched well with that of the synthetic (+)-exiguolide ($[\alpha]_D^{25}$ +119 (*c* 0.11, $CHCl_3$)) except for the sign of the rotation. Thus, we have successfully completed the total synthesis of (−)-exiguolide, the natural enantiomer, for the first time. Notably, through our total synthesis, more than 40 milligrams of synthetic (−)-exiguolide was made available for detailed biological assessment.



Scheme 21. Synthesis of 20-Membered Macrolactone via Julia—Kocienski olefination/Yamaguchi Macrolactonization Strategy

We initially assessed the antiproliferative activity of **59** against a panel of 39 human cancer cell lines[82,83] and found that this natural product inhibits the proliferation of NCI-H460 human lung large cell carcinoma, A549 human lung adenocarcinoma, SK-OV-3 human ovarian carcinoma, and MKN74 human gastric carcinoma cells, with GI_{50} values of 0.01, 0.65, 0.70, and 0.69 μM, respectively. Importantly, **59** may be cytostatic to these sensitive cell lines, since it did not completely abolish the cell viability even at higher concentrations (LC_{50} >100 μM). Furthermore, the biological mode-of-action of **59** was suggested to be unique and does not share similarity with that of more than 100 anticancer agents on the basis of the COMPARE analysis. These results strongly suggest that **59** is a novel anticancer agent with a unique mechanism that warrants further biological investigations.

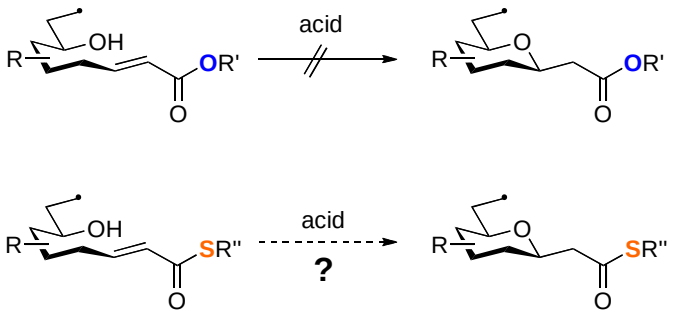


Scheme 22. Total Synthesis of (−)-Exiguolide

5. BRØNSTED ACID-CATALYZED INTRAMOLECULAR OXA-CONJUGATE CYCLIZATION OF α,β-UNSATURATED ESTER SURROGATES

From our synthetic studies on (+)-neopeltolide, (−)-aspergillides A and B, and (−)-exiguolide, we have learned that Brønsted base-catalyzed IOCC of α,β-unsaturated ketones gives easy access to 2,6-*cis*-substituted tetrahydropyrans under thermodynamic conditions, while that of α,β-unsaturated esters requires, at least in some cases, harsh reaction conditions and extended reaction times for selective formation of 2,6-*cis*-substituted tetrahydropyrans. The observed reactivity difference can be ascribed to the fact that the α-hydrogen atoms of esters are less acidic than those of ketones. In addition, Brønsted acid-catalyzed IOCC of α,β-unsaturated ketones provides 2,6-*cis*-substituted tetrahydropyrans in a highly stereoselective manner, while that of less electrophilic α,β-unsaturated esters does not take place in general. In gathering all the available inforation, it occurred to us that it might be possible to synthesize 2,6-*cis*-substituted tetrahydropyrans by means of Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates with enhanced reactivity. Our idea was supported by recent biosynthetic studies which suggested that the tetrahydropyran subunits of several polyketide natural products are formed via IOCC of α,β-unsaturated thioesters promoted by carbonyl activation through H-bonding(s).[23] Accordingly, we decided to investigate IOCC of α,β-unsaturated thioesters under acid catalysis (Scheme 23),[11a,c] although

there have been only a handful of reports that describe the use of α,β-unsaturated thioesters as conjugate acceptors.[84]



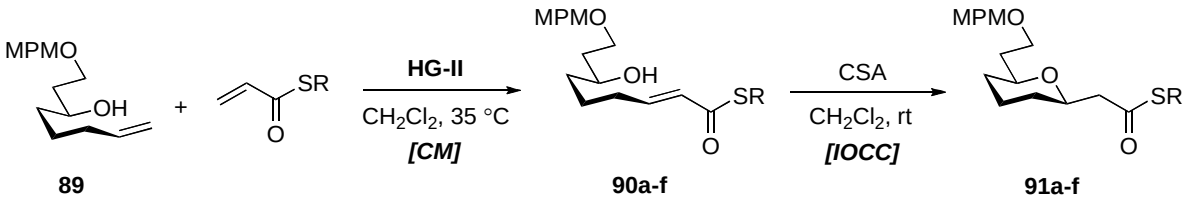
Scheme 23. Our Initial Assumption

We began our investigation by treating a series of α,β-unsaturated thioesters with various acids. Preliminary experiments showed that Brønsted acids such as CSA, *p*-TsOH, CH_3SO_3H, or TFA are able to promote the cyclization, whereas Lewis acids including $MgBr_2$, $InCl_3$, $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$ and $Yb(OTf)_3$ are uniformly ineffective. Our observation is in accordance with that of Spencer et al., who reported that protons are the actual species responsible for Lewis acid-mediated hetero-Michael additions to α,β-unsaturated carbonyl compounds.[85] Among the Brønsted acids examined, CSA was found to be the acid of choice. Thus, IOCC of a series of α,β-unsaturated thioesters, prepared by CM,[86] was examined by using CSA as the catalyst (Table 4).[87] In all cases, the reaction was performed in the presence of CSA (20 mol%) in CH_2Cl_2 at room temperature and stopped before full conversion, because partial loss of the MPM group was observed even under these mild conditions. From these experiments, we found that *S*-aryl thioesters **90b-d**,**f** (entries 2—4, and 6) are more reactive than *S*-ethyl thioester **90a** (entry 1), and *S*-(*p*-tolyl)thioester **90c** turned out to be the most reactive of the thioesters examined (entry 3).

The scope of Brønsted acid-catalyzed IOCC of α,β-unsaturated thioesters was investigated as summarized in Table 5.[87] A variety of substrates underwent smooth cyclization upon treatment with 20 mol% of CSA in DCE at 70 °C, giving the respective 2,6-*cis*-substituted tetrahydropyrans in excellent yields with high diastereoselectivity (d.r. from 14:1 to >20:1). The cyclization of δ-substituted α,β-unsaturated thioesters was found to be more facile than that of the non-substituted ones. One drawback of the present IOCC is the elevated temperature conditions required to complete the reaction within a reasonable reaction time. Unfortunately, it appears that acid-sensitive substrates are not compatible with these reaction conditions.

To overcome the shortcomings of Brønsted acid-catalyzed IOCC of α,β-unsaturated thioesters, we strove to discover more reactive α,β-unsaturated ester surrogates.[11a] We were particularly interested in α,β-unsaturated amides and imides because of their easy accessibility and convertibility.[88] Thus, various substrates were efficiently prepared by means of CM (**HG-II** (5—10 mol%), CH_2Cl_2, 35 °C)[89] and treated

Table 4. Preparation and Brønsted Acid-Catalyzed IOCC of α,β-Unsaturated Thioesters



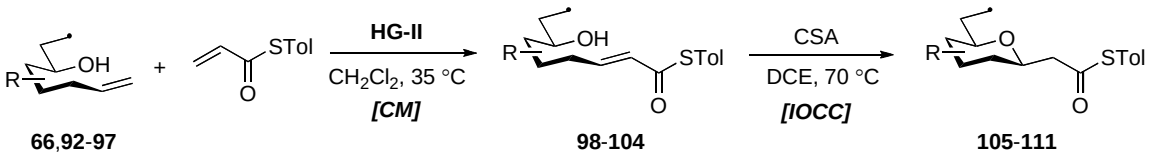
89 **90a-f** **91a-f**

		CM[a]		IOCC[b]	
Entry	R	Yield/%	Time/h	Yield/% (rsm[c])	*cis*/*trans*[d]
1[e]	Et	**90a**: 93	21	**91a**: 43 (26)	15:1
2	Ph	**90b**: 94	40	**91b**: 56 (41)	>20:1
3	*p*-MeC_6H_4	**90c**: 92	40	**91c**: 72 (12)	>20:1
4	*p*-$MeOC_6H_4$	**90d**: 82	44	**91d**: 69 (16)	>20:1
5	*p*-$NO_2C_6H_4$	**90e**: 94	45	**91e**: 29 (65)	>20:1
6	1-naphthyl	**90f**: 87	73	**91f**: 56 (35)	>20:1

[a]CM: All reactions were performed using **HG-II** (10 mol%) and thioacrylate (3 equiv) in CH_2Cl_2 at 35 °C. [b]IOCC: All reactions were performed using CSA (20 mol%) in CH_2Cl_2 at room temperature unless otherwise noted and stopped when cleavage of the MPM ether was observed by TLC analysis. [c]rsm = recovered starting material. [d]Determined by 600 MHz ^{1}H NMR analysis. [e]Reaction performed using 70 mol% of CSA.

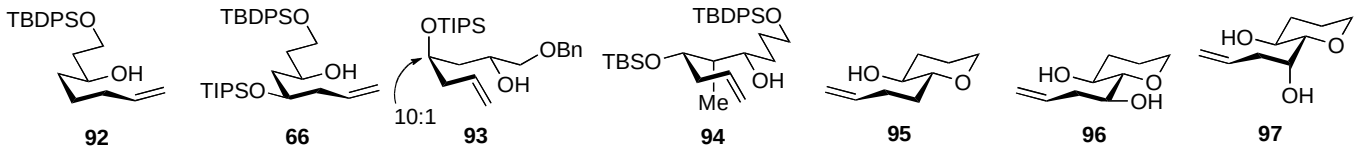
with CSA (20 mol%) in CH_2Cl_2 at room temperature (Table 6). Not unexpectedly, pyrrolidyl amide **112a** did not participate in IOCC because of its low reactivity toward conjugate additions (entry 1). On the other hand, imide **112b** displayed high reactivity and gave 2,6-*cis*-substituted tetrahydropyran **113b** in 94% yield with good diastereoselectivity (entry 2). This result demonstrated the importance of the carbonyl group of the pyrrolidine ring. A slight improvement of the diastereoselectivity was observed for IOCC of 2-oxazolidinone imide **112c** (entry 3). The reaction of **112c** proceeded more slowly than that of **112b** but gave the corresponding 2,6-*cis*-substituted tetrahydropyran **113c** in 94% yield with 13:1 diastereoselectivity. The above results suggested that the reactivity of α,β-unsaturated amides/imides toward IOCC might be inversely correlated with the electron-donating ability of the nitrogen atom, while maintaining sufficient Lewis basicity of the carbonyl oxygen and robustness of the C–N bond.[90] Accordingly, we chose to examine α,β-unsaturated amides/imides of aromatic amines. IOCC of 2-benzoxazolidinone imide **112d** gave 2,6-*cis*-substituted tetrahydropyran **113d** as a single stereoisomer but unfortunately did not complete even after 40 h (entry 4). Indole amide **112e** cyclized smoothly to provide 2,6-*cis*-substituted tetrahydropyran **113e** in 90% yield with excellent diastereoselectivity (entry 5, d.r. 15:1), whereas indoline amide **112f** was much less reactive than **112e** and gave **113f** in moderate yield (49%) after 25 h (entry 6). Finally, IOCC of 2,5-dimethylpyrrole amide **112g**[91] completed within 24 h and provided 2,6-*cis*-substituted tetrahydropyran **113g** as a single stereoisomer in 90% yield (entry 7).

Table 5. Scope of Brønsted Acid-Catalyzed IOCC of α,β-Unsaturated Thioesters

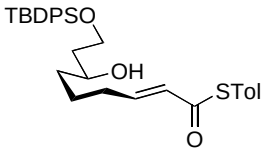
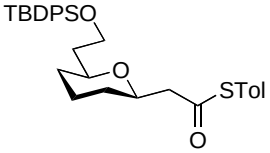
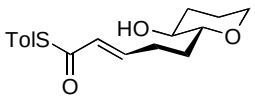
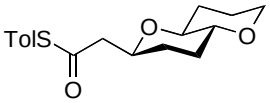
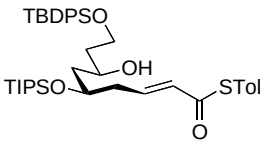
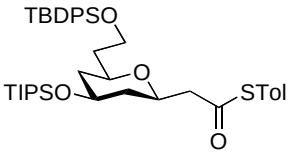
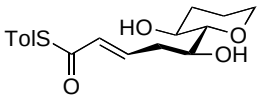
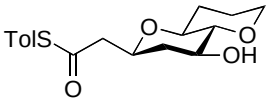
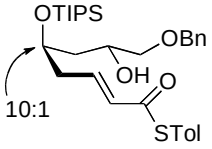
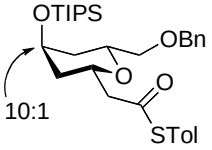
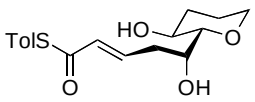
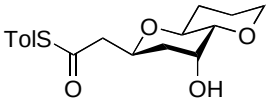
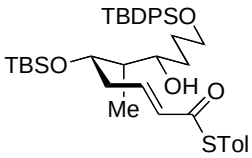
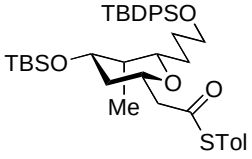


66,**92**-**97** **98**-**104** **105**-**111**

Olefins:



92 **66** **93** **94** **95** **96** **97**

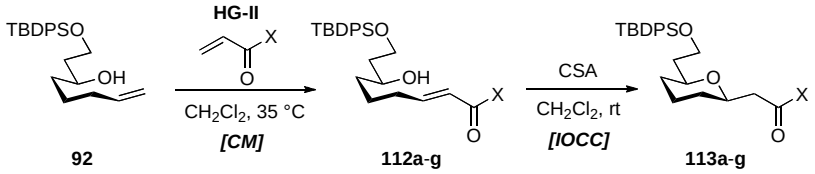
Olefin	CM[a] Product	IOCC[b] Product (*cis*/*trans*[c])	Olefin	CM[a] Product	IOCC[b] Product (*cis*/*trans*[c])
92	 **98**: 90%	 **105**: 88% (>20:1)	**95**	 **102**: 93%	 **109**: 92% (>20:1)
66	 **99**: 84%	 **106**: 90% (>20:1)	**96**	 **103**: 94%	 **110**: 91% (>20:1)
93	 **100**: 82%	 **107**: 96% (>20:1)	**97**	 **104**: 82%	 **111**: 97% (>20:1)
94	 **101**: 79%	 **108**: 92% (14:1)			

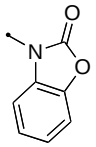
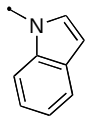
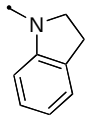
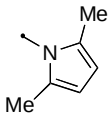
[a]CM: All reactions were performed using **HG-II** (10 mol %) and thioacrylate (3 equiv) in CH_2Cl_2 at 35 °C. [b]IOCC: All reactions were performed using CSA (20 mol %) in DCE at 70 °C. [c]Determined by 600 MHz ^{1}H NMR analysis.

Taking the reactivity, stereoselectivity, and convertibility into consideration, the subsequent substrate scope experiments were carried out for α,β-unsaturated 2-oxazolidinone imides and 2,5-dimethylpyrrole amides.[92]

As summarized in Table 7, a series of α,β-unsaturated 2-oxazolidinone imides and 2,5-dimethylpyrrole amides were prepared from the corresponding olefins by means of CM (**HG-II** (10 mol%), CH_2Cl_2, 35 °C). Upon treatment of α,β-unsaturated 2-oxazolidinone imides with CSA (20 mol%) in CH_2Cl_2 at room temperature, the respective 2,6-*cis*-substituted tetrahydropyrans were obtained in high yields with a

Table 6. IOCC of α,β-Unsaturated Amides/Imides

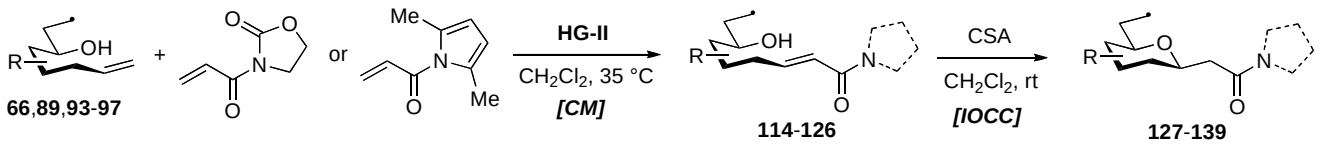


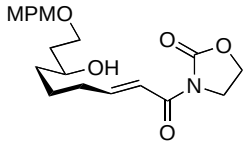
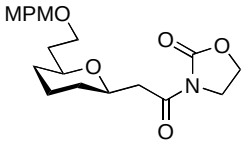
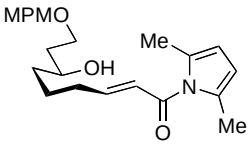
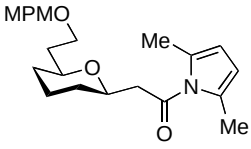
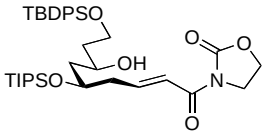
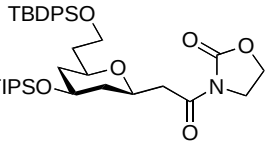
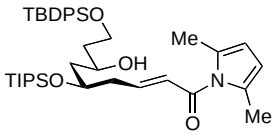
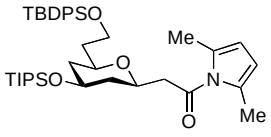
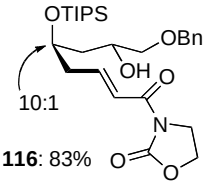
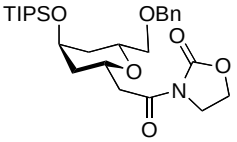
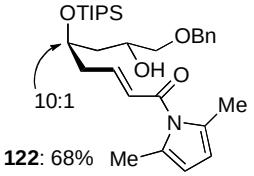
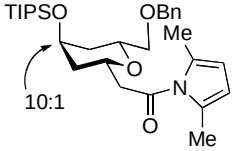
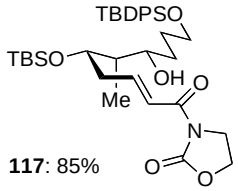
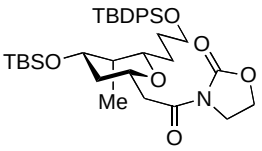
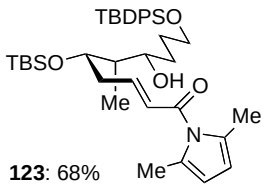
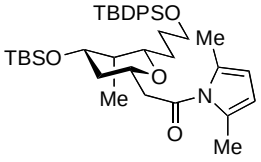
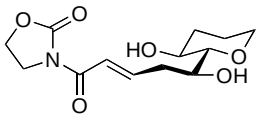
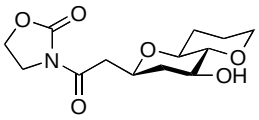
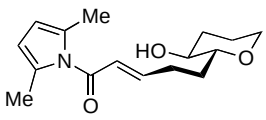
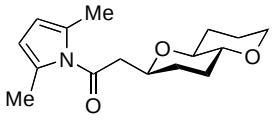
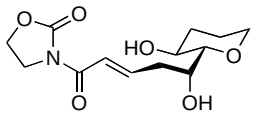
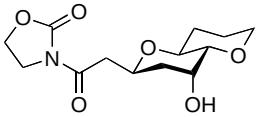
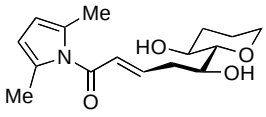
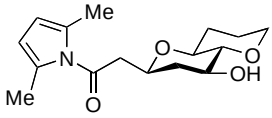
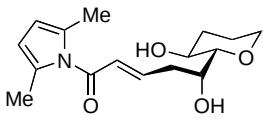
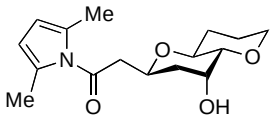
		CM[a]		IOCC[b]	
Entry	X	Product	Time/h	Product	cis/trans[c]
1		**112a**: 96%	25	**113a**: 0%[d]	N/A[e]
2		**112b**: 72%	6.5	**113b**: 94%	8:1
3		**112c**: 86%	26	**113c**: 94%	13:1
4		**112d**: 91%	40	**113d**: 66%[f]	>20:1
5		**112e**: 85%	25	**113e**: 90%[g]	15:1
6		**112f**: 76%	25	**113f**: 49%[h]	10:1
7		**112g**: 76%	24	**113g**: 90%	>20:1

[a]CM: All reactions were performed using **HG-II** (5—10 mol %) in CH_2Cl_2 at 35 °C. [b]IOCC: All reactions were performed using CSA (20 mol %) in CH_2Cl_2 at room temperature. [c]Determined by 600 MHz ^{1}H NMR analysis. [d]**112a** was recovered in 92% yield. [e]Not applicable. [f]**112d** was recovered in 17% yield. [g]**112e** was recovered in 7% yield. [h]**112f** was recovered in 38% yield.

synthetically useful level of diastereoselectivity (from 9:1 to >20:1). Moreover, Brønsted acid-catalyzed IOCC of α,β-unsaturated 2,5-dimethylpyrrole amides proceeded smoothly under the same reaction conditions to afford 2,6-*cis*-substituted tetrahydropyrans with excellent stereoselectivity (d.r. >20:1 in all

Table 7. Scope of IOCC of α,β-Unsaturated Amides/Imides

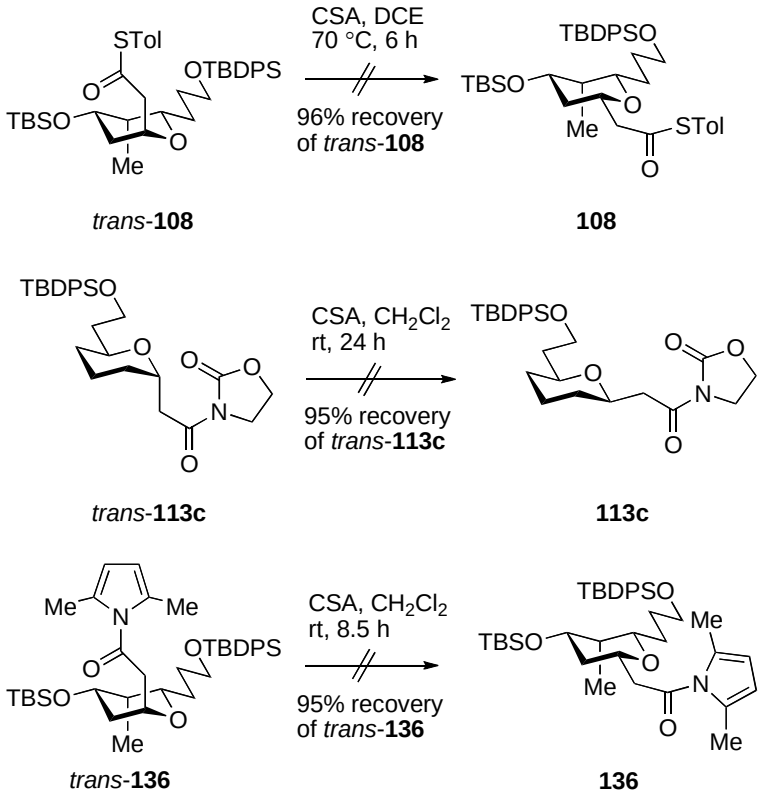


Olefin	CM[a] Product	IOCC[b] Product (*cis*/*trans*[c])	Olefin	CM[a] Product	IOCC[b] Product (*cis*/*trans*[c])
89	 **114**: 84%	 **127**: 86% (14:1)	**89**	 **120**: 66%	 **133**: 88% (>20:1)
66	 **115**: 81%	 **128**: 96% (9:1)	**66**	 **121**: 70%	 **134**: 91% (>20:1)
93	 **116**: 83%	 **129**: 90% (>20:1)	**93**	 **122**: 68%	 **135**: 92% (>20:1)
94	 **117**: 85%	 **130**: 88% (10:1)	**94**	 **123**: 68%	 **136**: 86% (7:1)
96	 **118**: 85%	 **131**: 83% (11:1)	**95**	 **124**: 68%[d]	 **137**: 93% (>20:1)
97	 **119**: 81%	 **132**: 86% (>20:1)	**96**	 **125**: 71%[e]	 **138**: 91% (>20:1)
			97	 **126**: 64%	 **139**: 93% (>20:1)

[a]CM: All reactions were performed using **HG-II** (10 mol %) in CH_2Cl_2 at 35 °C. [b]IOCC: All reactions were performed using CSA (20 mol %) in CH_2Cl_2 at room temperature. [c]Determined by 600 MHz ^1H NMR analysis. [d]Isolated as a 6:1 mixture of *E*/*Z* isomers. [e]Isolated as a 9:1 mixture of *E*/*Z* isomers.

but one case). Thus, we have successfully demonstrated that the reactivity of α,β-unsaturated 2-oxazolidinone imides and 2,5-dimethylpyrrole amides toward Brønsted acid-catalyzed IOCC is much higher than that of the thioester counterparts and provides an efficient access to 2,6-*cis*-substitued tetrahydropyrans in a highly stereoselective manner.

We were intrigued with the mechanistic basis for the stereoselectivity of Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates. We first examined whether the stereoselectivity is kinetically or thermodynamically controlled (Scheme 24). Treatment of 2,6-*trans*-substituted tetrahydropyrans with CSA under the cyclization conditions did not induce isomerization at all, and only resulted in recovery of starting materials. These experiments have clearly shown that the stereochemical outcome of the Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates is *kinetically* controlled rather than as a consequence of thermodynamic equilibration.



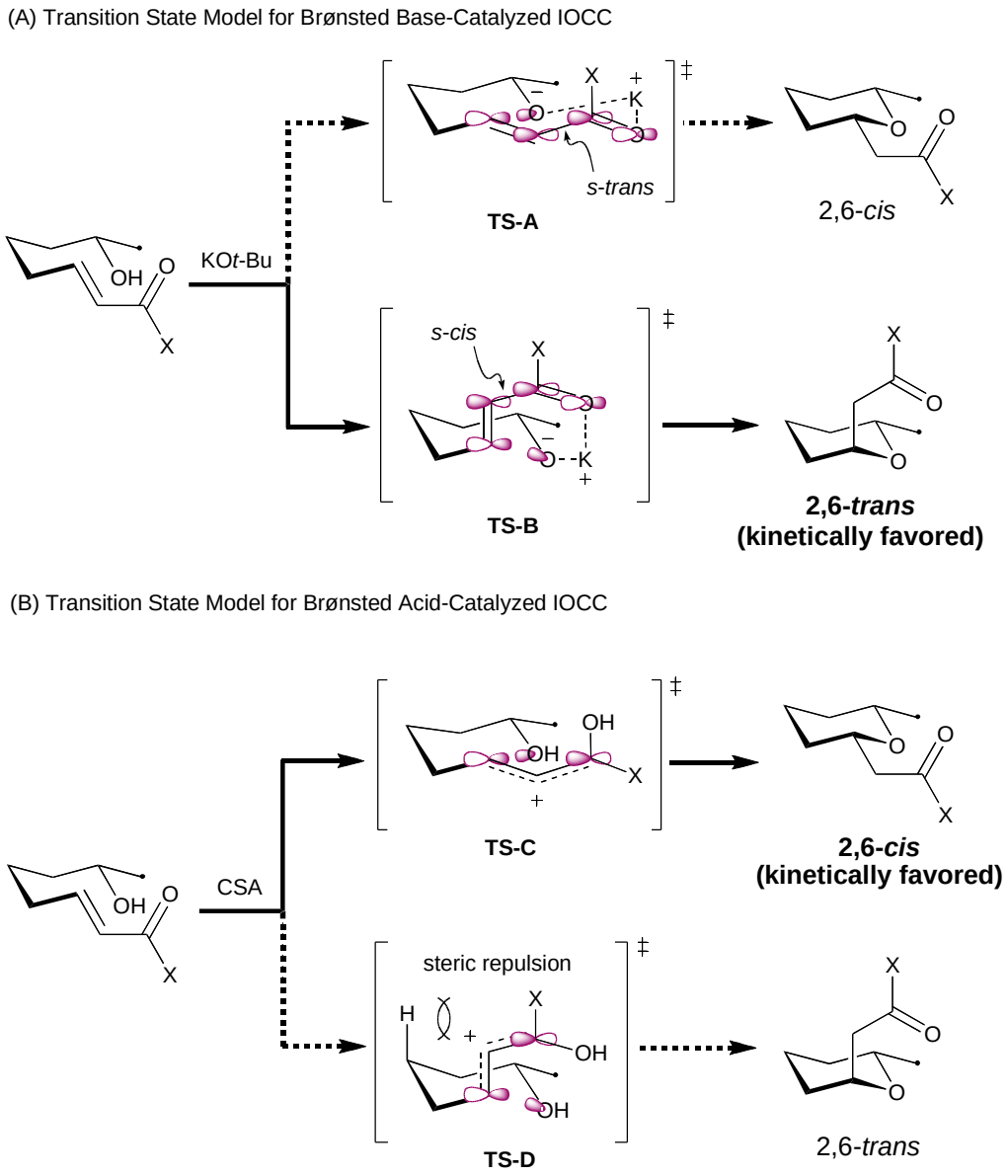
Scheme 24. Isomerization Experiments

Several arguments have been put forward in regard to the stereoselectivity of Brønsted base-catalyzed IOCC of α,β-unsaturated esters. Since Banwell et al. have shown that the olefin geometry of α,β-unsaturated esters has a profound influence on the stereochemical outcome of the cyclization,[18a,d] the following discussion will focus on commonly used (*E*)-α,β-unsaturated esters. Previous studies have shown that IOCC of α,β-unsaturated esters under basic conditions provides 2,6-*trans*-substituted tetrahydropyrans as the kinetic product.[18a-e] Martín and co-workers proposed, on the basis of theoretical

and experimental studies, a chelate-controlled transition state model, where an alkali metal cation (e.g., Na^+, K^+) coordinates with the carbonyl oxygen atom and incoming alkoxide (Scheme 25A).[18b,c] In the transition state A (**TS-A**), the pro-equatorial α,β-unsaturated carbonyl moiety needs to be in energetically disfavored *s-trans* conformation[93] to form the chelate complex, while in **TS-B** the pro-axial conjugate acceptor in *s-cis* conformation well accommodates the chelation. However, Yonemitsu et al. have shown that IOCC of α,β-unsaturated esters catalyzed by a quaternary ammonium base also leads to 2,6-*trans*-substituted tetrahydropyrans under kinetic control,[18g] indicating that the Martín's chelate-controlled model does not fully account for the origin of the stereoselectivity. Schneider and Schuffenhauer have explained the stereochemical outcome of Brønsted base-catalyzed IOCC of α,β-unsaturated esters by a stereoelectronic effect.[18e] Semi-empirical calculations suggested that in **TS-B** the LUMO of the pro-axial conjugate acceptor would effectively overlap with the lone pair orbital of the incoming alkoxide with a nearly tetrahedral attack angle (the Bürgi–Dunitz trajectory),[94] while the HOMO/LUMO interaction would be weaker in **TS-A** because the attack angle in **TS-A** is estimated to be smaller than that in **TS-B**.[18b,c,e] Thus, it appears that the stereoelectronic effect would primarily govern the stereoselectivity of Brønsted base-catalyzed IOCC of α,β-unsaturated esters.

We provided a model that accounts for the excellent diastereoselectivity observed for Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates on the basis of the frontier molecular orbital theory (Scheme 25B). Houk and Strozier have shown that protonation of acrolein renders the energy levels and coefficients of the frontier molecular orbitals "more like those of an allylic cation mixed with a lone-pair orbital of oxygen."[95] Jensen and co-workers have postulated that acid-catalyzed hydration of aliphatic α,β-unsaturated ketones proceeds via protonation of the carbonyl oxygen followed by addition of H_2O to the resultant allylic cationic species.[96] Inspired by these previous studies, we propose that Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates would also involve an allylic cationic transition structure and proceed via an S_N1-like mechanism.[97] Thus, we considered two chair-like transition structures, **TS-C** and **TS-D**, and assumed that the conformations of **TS-C** and **TS-D** would be basically similar to those of **TS-A** and **TS-B**, respectively. Taking the coefficients of the frontier molecular orbitals of allylic cations into account, the stabilizing HOMO/LUMO interaction in **TS-C** would be greater than that in **TS-D**. In addition, **TS-D** would suffer from unfavorable 1,3-diaxial steric repulsions. Accordingly, we concluded that **TS-C** would be energetically favored over **TS-D** by both stereoelectronic and steric effects. Our transition state model well explains the observed stereoselectivity of Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates.

On the basis of our NMR experiments, the reactivity order of α,β-unsaturated ester surrogates toward Brønsted acid-catalyzed IOCC was established to be: 2,5-dimethylpyrrole amides > 2-oxazolidinone imides > *S*-(*p*-tolyl)thioesters (data not shown). In contrast to α,β-unsaturated esters, these surrogates are



Scheme 25. Transition State Models for IOCC

reactive enough to undergo Brønsted acid-catalyzed IOCC. The high reactivity of these surrogates could be explained by their propensity to form the corresponding allylic cationic species upon protonation of the carbonyl group. It is known that keto–enol tautomerization of aliphatic esters is not facile because the lone pair of the ester oxygen delocalizes to the carbonyl group and reduces the acidity of the α-hydrogens.[98] When compared to aliphatic oxoesters, the corresponding thioesters, 2-oxazolidinone imides, and 2,5-dimethylpyrrole amides would be more prone to keto–enol tautomerization because of the low electron-donating ability of the sulfur or nitrogen atom as well as sufficient Lewis basicity of the carbonyl oxygen.[98] On the basis of these arguments, it is conceivable that protonation of α,β-unsaturated ester surrogates would easily generate the corresponding allylic cationic species that react intramolecularly with the proximal hydroxy group, while it would be difficult to form such an allylic cationic species from less reactive α,β-unsaturated esters.

Lastly, we have confirmed that the cyclization products (e.g., **105**, **113c**, and **113g**) could be converted to the corresponding aldehydes, amides, carboxylic acids, esters, and ketones by exploiting well-established methods.[99-108]

6. SUMMARY

We have completed total syntheses of oxacyclic natural products, (+)-neopeltolide,[11d] (−)-aspergillides A and B,[11e,f] (−)-exiguolide,[11b,h] and (±)-centrolobine,[11i] by exploiting IOCC for the stereoselective synthesis of their tetrahydropyran substructures. During these synthetic campaigns, we have learned that Brønsted base-catalyzed IOCC of α,β-unsaturated esters requires, at least in some cases, harsh reaction conditions and extended reaction times for stereoselective synthesis of 2,6-*cis*-substituted tetrahydropyrans. It appears that this shortcoming limits the utility of IOCC in the context of complex molecule synthesis. Accordingly, we strove for the development of new methodologies that enable the synthesis of 2,6-*cis*-substituted tetrahydropyrans in a highly stereoselective manner and eventually discovered two new processes: (1) a domino CM/IOCC reaction catalyzed by the **HG-II** complex[11g] and (2) Brønsted acid-catalyzed IOCC of α,β-unsaturated ester surrogates.[11a,c] The ready availability of precursors, high functional group compatibility, high diastereoselectivity, and operational simplicity are the hallmarks of our methodologies. Further studies on the application of our newly developed methodologies to the total synthesis of natural products are currently underway.

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spectra of natural (−)-exiguolide and for fruitful discussions on the spectroscopic data. This work was supported in part by a Grant-in-Aid for Young Scientists (A) from the Japan Society for Promotion of Science (JSPS).

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