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Studies for the Synthesis of Xenicane Diterpenes. A Stereocontrolled Total Synthesis of 4-Hydroxydictyolactone

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Abstract

The stereocontrolled total synthesis of 4-hydroxydictyolactone (**4**), a member of the xenicane diterpene family of natural products, is described. These studies feature the development of the B-alkyl Suzuki cross-coupling reaction for direct access to (*E*)-cyclononenes from acyclic precursors. The Ireland-Claisen rearrangement is effectively utilized to establish the backbone asymmetry of the contiguous C_2, C_3, C_{10} stereotriad of **4**. The synthesis strategy has devised an intramolecular Nozaki-Hiyama reductive allylation of a formate ester for the stereoselective formation of five-membered lactols **22**. In addition, an internally directed S_E' propargylation using allenylmagnesium bromide is described to establish the stereochemistry of the C_4 alcohol in **27**, and the terminal alkyne is subsequently functionalized via a regioselective *syn*-silylstannylation to yield **30**. Finally, the stereocontrolled phenylselenylation of the ester enolate derived from **43** leads to the desired *syn*-oxidative elimination to yield the natural product **4**.

Introduction

In 1979, Fenical and coworkers reported the isolation of dictyodiol (**1**), an unusual diterpene from the brown algae, *Dictyota crenulata*, which exhibited a rare nonconjugated (*E*),(*Z*)-cyclononadiene motif.[1] These efforts also identified dictyolactone (**2**) as a related metabolite from the sea hare *Aplysia depilans*. The investigation followed in the wake of the groundbreaking discovery of xenicin (**3**) from the soft coral *Xenia elongata*, which had been unambiguously elucidated by a single crystal X-ray diffraction study.[2] Subsequent reports have generally adopted a description of marine natural products displaying a cyclononene framework as examples of the xenicane family.[3] Faulkner offered an expansive viewpoint by proposing that five distinct diterpene skeletons could be traced to biosynthetic origins that incorporate xenicane precursors.[4] However, Kakisawa and coworkers have proven that the xenicanes from *Dictyotaceae* algae possess the antipodal configuration as compared to members of the family from soft coral in early studies establishing the tenets of the advanced Mosher ester analysis.[5] These findings have been taken into account for the illustration of the structures of Figure 1, and provide a cautionary note for the assignment of the absolute stereochemistry of related metabolites which may or may not be distributed through an aquatic environment of filtering organisms via a common food chain.

Guella and Pietra first described the isolation and structural elucidation of 4-hydroxydictyolactone (**4**) from *Dictyota ciliolata* in 1993 along with the identification of a related metabolite, 4-hydroxycrenulide (**5**).[6] The report also demonstrated that the ultraviolet irradiation of **4** produced a photoisomerization to yield **5**. While this transformation formally

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presents an intramolecular ene process, the concerted pathway would provide for an antarafacial homo[1,5]-hydrogen shift giving rise to the C_6 diastereomer of **5**. These efforts described the thermal isomerization of **4** leading to the corresponding (*Z*)-6,7-olefin which did not afford cyclopropane products upon irradiation. Based on their observations, Guella and Pietra speculated that a free radical mechanism may be operative in the formation of 4-hydroxycrenulide (**5**) and may characterize the increased reactivity of the strained (*Z*,*E*)-cyclononadiene ring system of 4-hydroxydictyolactone (**4**).

Numerous reports provide preliminary accounts of important biological activity among members of the xenicane family. Individual compounds have exhibited antibacterial and antifungal properties,[3a] ichthyotoxicity,[7] and the inhibition of HIV-1 reverse transcriptase.[8] Xenicanes, such as dictyotalide B[9] (**6**, Figure 1) display significant levels of cytotoxicity against B16 mouse melanoma cultures whereas florxenilide A,[10] a soft coral metabolite, exhibits potent cytotoxicity against human colon cancer cell lines even though these examples represent antipodal subgroups. Joalin (**7**) is an unusual member of the xenicane family bearing a nitrogen atom in addition to the distinctive bridgehead olefin.[11] A recent account has confirmed that several xenicane diterpenes target proliferating cells by the specific induction of apoptosis at micromolar concentrations.[12] Thus, this family of natural products may offer a new chemotype for the development of chemotherapeutic agents. A systematic structure-activity evaluation has not been undertaken, and many xenicanes have not been examined.

Our plans for the synthesis of 4-hydroxydictyolactone (**4**) were designed to explore the utility of the B-alkyl Suzuki reaction as a mild palladium-catalyzed cross-coupling event to incorporate the intact (*E*)-trisubstituted alkene in a direct ring closure of the nine-membered carbocycle (Scheme 1). Our rationale in support of this hypothesis and a preliminary account of our ongoing efforts have recently been described.[13] We postulated that the selective hydroboration of **9** would set the stage for the cross-coupling process followed by oxidation to the *trans*-fused lactone **8**. Further oxidation of **8** would introduce the α,β-unsaturation of the natural product **4**. Since the irreversible reductive elimination from a coordinated palladium intermediate would provide for the ring closure, we rationalized that the crucial formation of a palladium metallocycle would overcome the entropic features and steric constraints which often dominate processes involving direct closures in nine- and ten-membered carbocycles. The five-membered acetal of **9** was incorporated as an element of conformational bias to aid these efforts. However, our modeling suggested that the stereochemistry at C_1 of **9** would play an important role because the corresponding *cis*-disubstituted tetrahydrofuranyl system imposed significant steric interactions for transition states leading to metallocycle formation.

General methods for the direct closure of cyclononene systems are uncommon. While new opportunities have explored the synthesis of medium-ring carbocycles using ring-closing metathesis,[14] the formation of cyclononenes has presented problems for some RCM strategies.[15] On the other hand, two groups have independently described recent results for Nozaki-Hiyama-Kishi cyclizations directed toward pestalotiopsin, a caryophyllene sesquiterpenoid.[16] In classic studies by Professor E. J. Corey, the use of the Grob fragmentation was devised to address the synthesis of (±)-caryophyllene.[17] This stereocontrolled reaction established an important precedent for the preparation of (*E*)-cyclononenes via the fragmentation of fused bicyclic systems. Recently, Corey has reported the Grob fragmentation leading to a stable, chiral (*E*,*Z*)-cyclononadienone for the enantioselective synthesis of caryophylloids.[18] In a similar fashion, the Grob strategy has been successfully applied for total synthesis of the xeniolide, coraxeniolide A.[19]

The analysis of Scheme 1 readily identified the (*E*)-alkenyliodide **9** as the penultimate intermediate for a direct cyclization to afford the xenicane framework, and we envisioned the preparation of **9** via two sequential S_E' allylation processes. The latter of these events would

establish the chirality at C_4 and accommodate stereospecific incorporation of the (*E*)-alkenyl iodide from the aldehyde **10**. The initial S_E' allylation was projected as a stereocontrolled intramolecular reaction stemming from the reduction of bromide **11** to yield the tetrahydrofuranyl lactol of **10**.

Results and Discussion

The preparation of chiral, nonracemic **11** of Scheme 1 required a high degree of stereocontrol for the assembly of the contiguous stereotriad presented at C_2, C_3, and C_{10}. This objective can be problematic for synthesis because the consecutive tertiary centers of asymmetry are uniquely characterized by an arrangement of carbon alkyl substituents. The Claisen rearrangement appeared to be particularly well suited to meet this challenge.[20] As illustrated in Scheme 2, the synthesis of the nonracemic Ireland-Claisen precursor **15** began with the known oxidative cleavage of the diacetonide of D-mannitol, and a direct Wittig olefination in methanol yielded a 9:1 (*Z*:*E*) ratio of methyl esters leading to **12** (68% yield) after purification by flash chromatography.[21] Upon diisobutylaluminum hydride (DIBAL) reduction, the resulting *Z*-allylic alcohol was protected as its *para*-methoxybenzyl ether (PMB), and ketal hydrolysis led to O-silylation of the primary alcohol to yield **13**. Esterification of **13** with (*R*)-(+)-citronellic acid (**14**)[22] produced a single diastereomer **15** for subsequent kinetic deprotonation at −78 °C. However, the introduction of **15** into a THF solution containing lithium diisopropylamide (LDA) followed by trimethylsilyl chloride (TMSCl) and Et_3N led to substantial amounts of products derived from base-induced elimination which were identified as the TBS ether of (*E*,*E*)-5-*para*-methoxybenzyloxy-2,4-pentadien-1-ol and (*R*)-(+)-citronellic acid. The inverse addition of LDA into a cold reaction mixture containing **15**, TMSCl and Et_3N provided excellent conversion to the anticipated *E*(O)-trimethylsilyl ketene acetal, and heating at 70 °C resulted in the isolation of carboxylic acid **16** (dr 94:6) in high yield. The minimization of steric factors in the chair-like arrangement **17** accounts for the formation of the major diastereomer **16**, and the relative assignment of stereochemistry was confirmed by conversion to the *cis*-disubstituted butyrolactone **18** for NMR studies leading to the observed nuclear Overhauser enhancement correlations (NOESY) illustrated in Scheme 2.

Carboxylic acid **16** was transformed into the pivaloate (Piv) **19** of Scheme 3 in four straightforward steps (70% overall from **16**), and esterification with formic acid led to **20** upon introduction of the allylic bromide. Adaptation of the Nozaki-Hiyama conditions[23] provided facile intramolecular cyclization to the lactol **22**. To the best of our knowledge, Nozaki-Hiyama cyclizations of formate esters have not been previously explored. Our results suggest that this strategy offers versatility and efficiency for the stereoselective synthesis of five and six-membered lactols and related derivatives.[24] Indeed, high stereocontrol at C_1 was observed for the S_E' allylation via internal coordination of the allylchromium species as suggested in **21** by the antiperiplanar disposition of H_A and H_B.

It is well known that crotyl halides undergo reduction to form (*E*)-allylic chromium(III) reagents regardless of the geometry of the starting butene, and the chromium species coordinate aldehydes for nucleophilic additions via closed six-membered transition states.[23] In Scheme 4, four possible arrangements are featured for a detailed analysis of the intramolecular S_E' reaction. The octahedral coordination complex of chromium is characterized by a combination of halogen (Cl, Br) and solvent (THF) ligands (L) in addition to the reactive partners of the allylation process. While our analysis does not consider boat-like transition states, two chair-like arrangements, **21a** and **21b**, may account for the formation of the observed diastereomer **(1*S*)-22**. The *trans*-fused bicyclic **21a** favorably illustrates complexation with the carbonyl, which is synclinal with respect to the formate hydrogen, and minimizes nonbonded interactions by pseudoequatorial placement of the highly branched C_2 substituent. Although the *cis*-fused transition state of **21b** displays the large pseudoaxial C_2 substituent on the convex face of the

bicycle, the axial ligand L_A may be destabilizing for electronic as well as steric reasons. Our considerations for the diastereofacial reactions leading to the *cis*-disubstituted lactol **(1*R*)-22** are illustrated in **21c** and **21d**. The less stable, pseudoaxial disposition of the branched C_2 substituent in **21c** also appears to present nonbonded interactions with axial L_B (THF), and these considerations become more severe in the *cis*-fused arrangement of **21d**. Our spectroscopic characterization of the lactols **22** (1:1 ratio) provided no evidence of the ring-opened hydroxyaldehyde tautomer, and the subsequent quantitative conversion of **22** to the corresponding methyl acetals (Scheme 3) gave an inseparable mixture of diastereoisomers **23a** and **23b** (dr 58:42). On the other hand, the triisopropylsilyl ether **24** was formed with excellent stereoselectivity (dr 91:9) and provided important advantages for the simplicity of reaction and product analysis in subsequent studies.

Upon preparation of aldehyde **25** (Scheme 5), we began studies of S_E' allylation reactions with Lewis acid activation. Our initial reactions with allylic silanes[25] and allenylic stannanes[26] were undertaken to probe aspects of inherent diastereofacial selectivity which were not readily apparent from Felkin-Anh modeling of **25**. Unfortunately a significant side reaction was encountered with the production of the diastereomeric acetals **26** resulting from a facile Lewis acid-catalyzed intramolecular Prins reaction and ketalization. Attempts to secure C_4 stereocontrol using nonracemic allenyl and allyl boron reagents[27] displayed poor reactivity toward this sterically congested aldehyde with slow conversion to many products. These observations led to the use of allenylmagnesium bromide[28] as a reactive nucleophile which proved to be operationally efficient for preparative scale reactions. Ethereal solutions of the Grignard reagent conveniently gave high yields of S_E' propargylation to afford the desired secondary alcohols (96%). Moreover, the carbonyl addition proceeded with good diastereofacial selectivity (dr 84:16), and subsequent flash chromatography led to useful quantities of pure **27**. This stereochemical outcome is rationalized by the internal γ-coordination of the divalent magnesium cation for S_E' delivery of the allenyl nucleophile via a cyclic six-membered arrangement depicted in **28**, and the C_4 stereochemistry of the secondary alcohol **27** was assigned by an advanced Mosher ester analysis.[5]

Our plans to utilize homopropargylic alcohol **27** for the stereocontrolled synthesis of the desired (*E*)-alkenyliodide **31** (Scheme 6) examined the Negishi zirconium-catalyzed carboalumination methodology[29] which led to low conversions and a number of side products. A major component of these attempts was isolated and identified as the bicyclic ketal **29** resulting from Lewis acid-catalyzed transketalization. Proton NMR studies demonstrated a distinctive NOESY correlation of H_A and H_B in **29** which offered additional confirmation of the C_4 stereochemical assignment in **27**. However, the participation of a proximate propargylic or homopropargylic alcohol is known greatly improve yields in carboalumination reactions.[29a, 30] Thus, it was not surprising that ketal **29** was found to be unreactive in further reactions to utilize this carboalumination to elaborate the terminal alkyne. In addition, we explored several protecting groups for the C_4 alcohol in **27**, and we observed very slow, low yielding conversions to the desired alkenyl iodide, as well as other byproducts, in these attempts to apply the Negishi protocol. To resolve these issues, the O-silylation of **27** and subsequent application of a regioselective *syn*-silylstannylation as described by RajanBabu and coworkers[31] was undertaken yielding **30**. A convenient three-step protocol from **30** cleanly allowed for the sequential replacement of stannyl and silyl substituents with complete retention of olefin geometry to give the (*E*)-trisubstituted alkene of **31**. Although this sequence has added three steps to our overall route, it is particularly noteworthy that these reactions can be efficiently applied as a general solution which is amenable to preparative scale processes.

Our studies of the B-alkyl Suzuki cross-coupling reaction[32] initially explored the reactivity of alkene **23** (Scheme 3) which was submitted for selective hydroboration at 22 °C. Coupling with the known iodide **32**[33] (Scheme 7) was observed to give **33** in 60–65% unoptimized yields

using $PdCl_2$(dppf), the most widely selected palladium catalyst and reaction conditions for B-alkyl Suzuki processes. The convenient preparation of the diol derivative **33** presented obvious opportunities to explore (*E*)-cyclononene formation. One approach was examined by the conversion of **33** into the aldehydic sulfone **34** as a precursor for an intramolecular Julia condensation. Our previous syntheses of dolabelladienones have described Julia condensations for direct ring closures leading to the formation of eleven-membered carbocycles.[34] In addition, two unrelated examples of the use of α-sulfonyl carbanions in cyclization reactions leading to (*E*)-cyclononenes have also been reported. A novel intramolecular transacylation strategy was devised for the synthesis of (±)-caryophyllene by Oishi and coworkers,[35] and Corey has described the successful capture of a π-allyl palladium intermediate via a β-ketosulfone for the recent total synthesis of antheliolide A.[36] Based on these encouraging reports, the allylic sulfone **34** was prepared from **33** (Scheme 7) by desilylation and subsequent displacement using sodium tolylsulfinate prior to deprotection and oxidation. Unfortunately our efforts to obtain the cyclic β-hydroxysulfones **35** upon treatment with various bases only resulted in the recovery of starting **34** in spite of evidence of α-sulfonyl carbanion formation via deuterium incorporation. As an alternative, we examined a reductive coupling strategy toward an effective closure by the straightforward conversion of **33** into the dialdehyde **36** (Scheme 7). Our previous studies for the total synthesis of (+)-4,5-deoxyneodolabelline demonstrated the use of $[V_2Cl_3(THF)_6]ZnCl_6$ for reductive coupling leading to nine-membered *syn*-diol formation.[37] However, the application of this vanadium-based pinacol reaction, in addition to experiments utilizing McMurry conditions,[38] with dialdehyde **36** led to the formation of many products. Reactions of samarium diiodide[39] with **36** produced the anticipated cycloheptanol **37** as an inseparable mixture of diastereomers.

Concomitant studies of the intramolecular B-alkyl Suzuki cross coupling[40] of **31** began to show promise (Scheme 8). Our initial reactions produced low yields (10–15%) of (*E*)-cyclononene product **38**, and small improvements were observed with the additions of thallium(I) ethoxide[41] and triphenylarsine. However, we noted a substantial difference in the rate of hydroboration of **31** compared to the corresponding methyl acetals **39** (Scheme 8).

These evaluations are summarized in Figure 2, and illustrate results for hydroboration with complete consumption of starting material followed by the usual basic oxidative quench. The triisopropylsiloxy acetal **31** (entry 1) reacted slowly and required excess reagent at elevated temperature for 72 hours. An analysis of the product distribution confirmed a competing hydroboration of the trisubstituted C_{13}–C_{14} alkene which led to substantial amounts of the C_8, C_{13} diol (product C). Our modeling of **31** suggested that the remote silyl ethers at C_4 and C_{19} imposed considerable steric hindrance blocking access to each face of the terminal olefin. Indeed, the removal of either of these silyl protecting groups led to more favorable reaction conditions and the chemoselective production of the expected primary alcohol (product A of Figure 2; see entries 2 and 3).

Based on these results, the B-alkyl Suzuki cyclization of **40** (Scheme 8) was examined with an improved outcome which generated approximately 65% mass recovery of the crude product **42** after flash silica gel chromatography. However, the starting alcohol **40** was susceptible to the internal ketalization as previously noted with the isolation of **29** of Scheme 6, and the cyclononene **42** demonstrated instability requiring repeated chromatography with diminishing yields. Thus, optimizations of the cyclization process focused on **39**, and modest incremental improvements, including the use of thallium carbonate, aqueous THF (10:1 by volume) and optimized dilution conditions, afforded reproducible and scalable reactions at room temperature leading consistently to 30% yields of pure **41**. Higher catalyst loading of $PdCl_2$(dppf) and reaction attempts that screened a selection of other related catalysts did not lead to improved yields. On the other hand, a significant breakthrough was achieved when we explored the use of $Pd(PPh_3)_4$ as a catalyst for the Suzuki cyclization event (Scheme 9).

Adapting conditions as described by Nakada and coworkers,[42] the ring closure of **39** proceeded with surprising efficiency, and the crude product was treated with aqueous acetic acid to yield the diastereomeric lactols **38** (66% yield) after silica gel chromatographic purification. Subsequent oxidation of **38** under mild conditions produced the *trans*-fused cyclononene lactone **43**.

Our studies leading to the characterization of **43** suggested substantial conformational rigidity in this carbocyclic framework. Key NOESY correlations obtained from the 1H-NMR data are illustrated in Figure 3. Our conclusions parallel observations of the natural product itself which exists as two slowly equilibrating ring conformers **4a** (major) and **4b** (minor) at 23 °C (ratio 95:5).[6b]

The completion of the synthesis of 4-hydroxydictyolactone (**4**) required a final oxidation for introduction of the C_1/C_9 unsaturation from cyclononene **43**. As shown in Scheme 10, the *syn*-elimination of an intermediate selenoxide proved to be the most effective choice for this task. In fact, kinetic deprotonation of **43** led to a single phenylselenide (89% yield) and low temperature oxidation quantitatively produced the skipped cyclononadiene **44**. Unfortunately, rapid decomposition of **44** was observed under basic conditions of fluoride-induced desilylation whereas **44** was found to be remarkably robust under acidic conditions. Finally, the total synthesis of **4** was completed via the initial deprotection of the C_4 silyl ether **43** which was followed by formation of the α-phenylselenide **45** and oxidative elimination. Synthetic **4** proved to be identical in all respects, with the exception of optical rotation data, to naturally occurring 4-hydroxydictyolactone by comparisons with NMR spectra and HRMS data which were kindly provided by Professor Graziano Guella.[43]

In conclusion, we have reported an efficient, enantiocontrolled total synthesis of 4-hydroxydictyolactone (**4**), a prototypical example of the xenicane family of marine diterpenes. Key features of our investigation include the use of an intramolecular Nozaki-Hiyama reductive S_E' allylation of a formate ester for the facile stereoselective synthesis of five-membered lactols as well as an example of γ-chelation for an internally directed S_E' propargylation using allenylmagnesium bromide. Finally, our studies have documented the development of the B-alkyl Suzuki cross-coupling reaction as a useful strategy for cyclizations to directly afford complex (*E*)-cyclononene systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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43. We gratefully acknowledge Professor Graziano Guella of the University of Trento for his timely assistance in providing detailed authentic ^{1}H and ^{13}C NMR spectra and HRMS data for the natural product **4**. Although our synthetic material precisely matched the NMR spectra and the HRMS data for 4-hydroxydictyolactone, we report some disparity for the data recorded for optical rotations. Guella and Pietra (ref. [6b]) have described the optical rotation of naturally occurring **4** ($[\alpha]_D^{25}$ −247° (c 0.17, CCl_4)) whereas Tanaka and Higa (ref. [3a]) had previously obtained a sample of **4** ([α]D −153° (c 2.01, $CHCl_3$)) via the hydride reduction and Fetizon oxidation of 4-hydroxydictyodial. Although we have no reason to doubt the purity of our samples (> 95% purity), our optical rotation data for synthetic **4** ($[\alpha]_D^{22}$ −175° (c 0.13, CCl_4)) did not agree with the isolation reports.

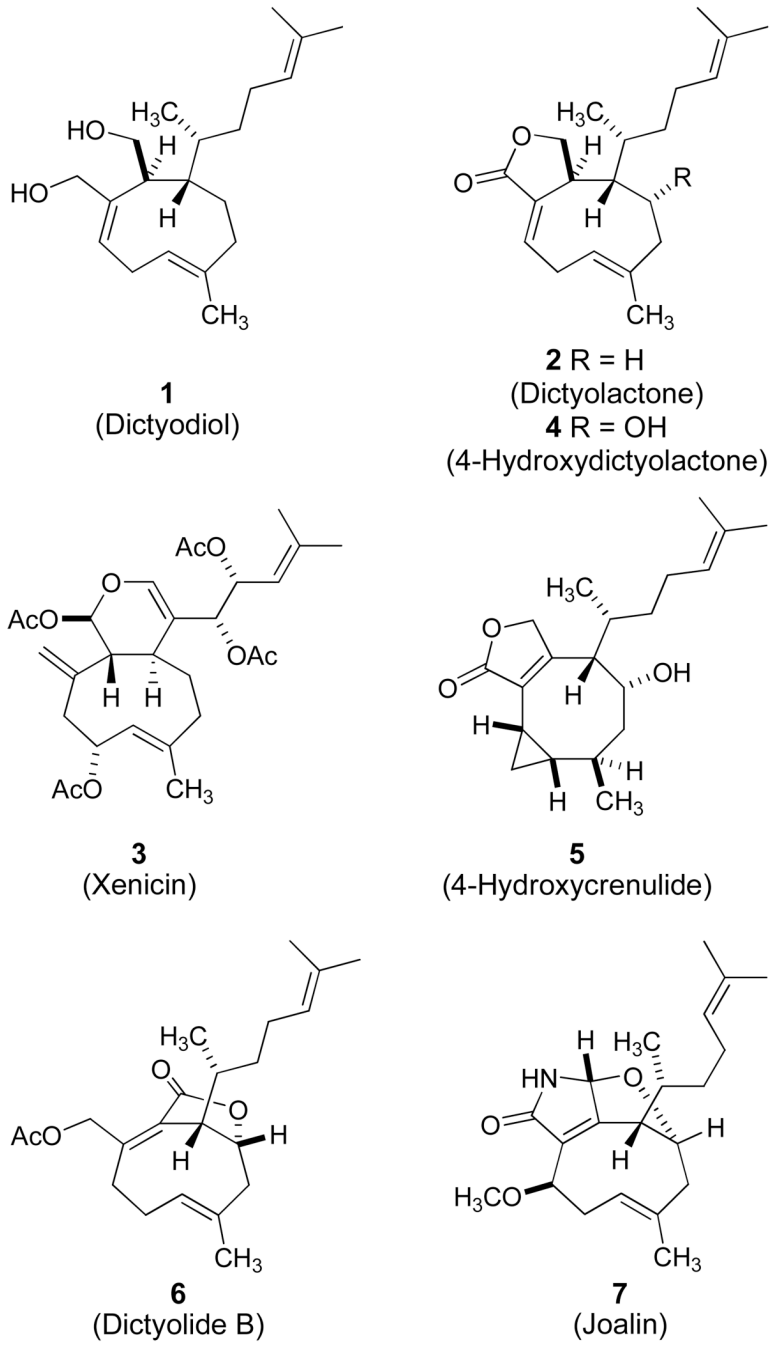
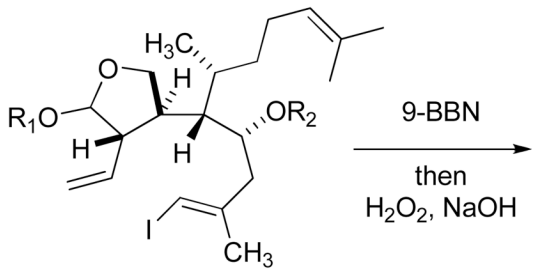
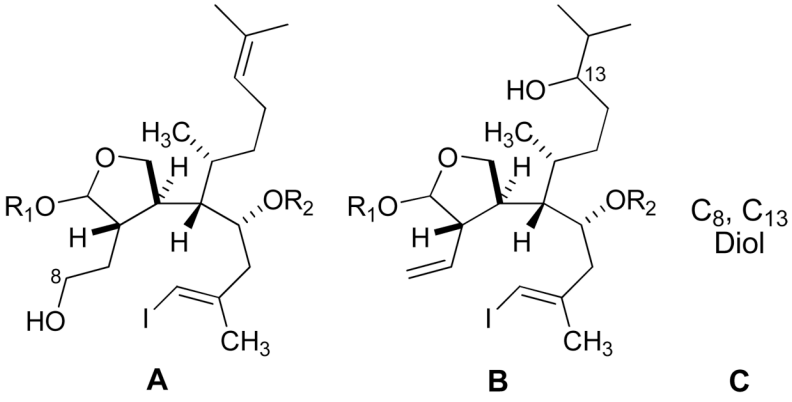


Figure 1.
Xenicane and Xenicane-Derived Marine Natural Products



31 R_1 = TIPS R_2 = TBS
39 R_1 = CH_3 R_2 = TBS
40 R_1 = CH_3 R_2 = H



Entry	R_1	R_2	Reaction Conditions[a]	Product Ratio[b] A : B : C
1	TIPS	TBS	9-BBN (5 eq.) THF, 80 °C, 72 h	1 : 1 : 4
2	CH_3	TBS	9-BBN (1.5 eq.) THF, rt, 12 h	>19 : 1 : 1
3	CH_3	H	9-BBN (1.2 eq.) THF, 0 °C, 1 h	>19 : 1 : 1

(a) All hydroborations were followed by basic oxidative work-up (NaOH, H_2O_2, EtOH, rt., 1h).
(b) Product ratios were estimated by the integration of ^{1}H-NMR data.

Figure 2.
Hydroboration Studies.

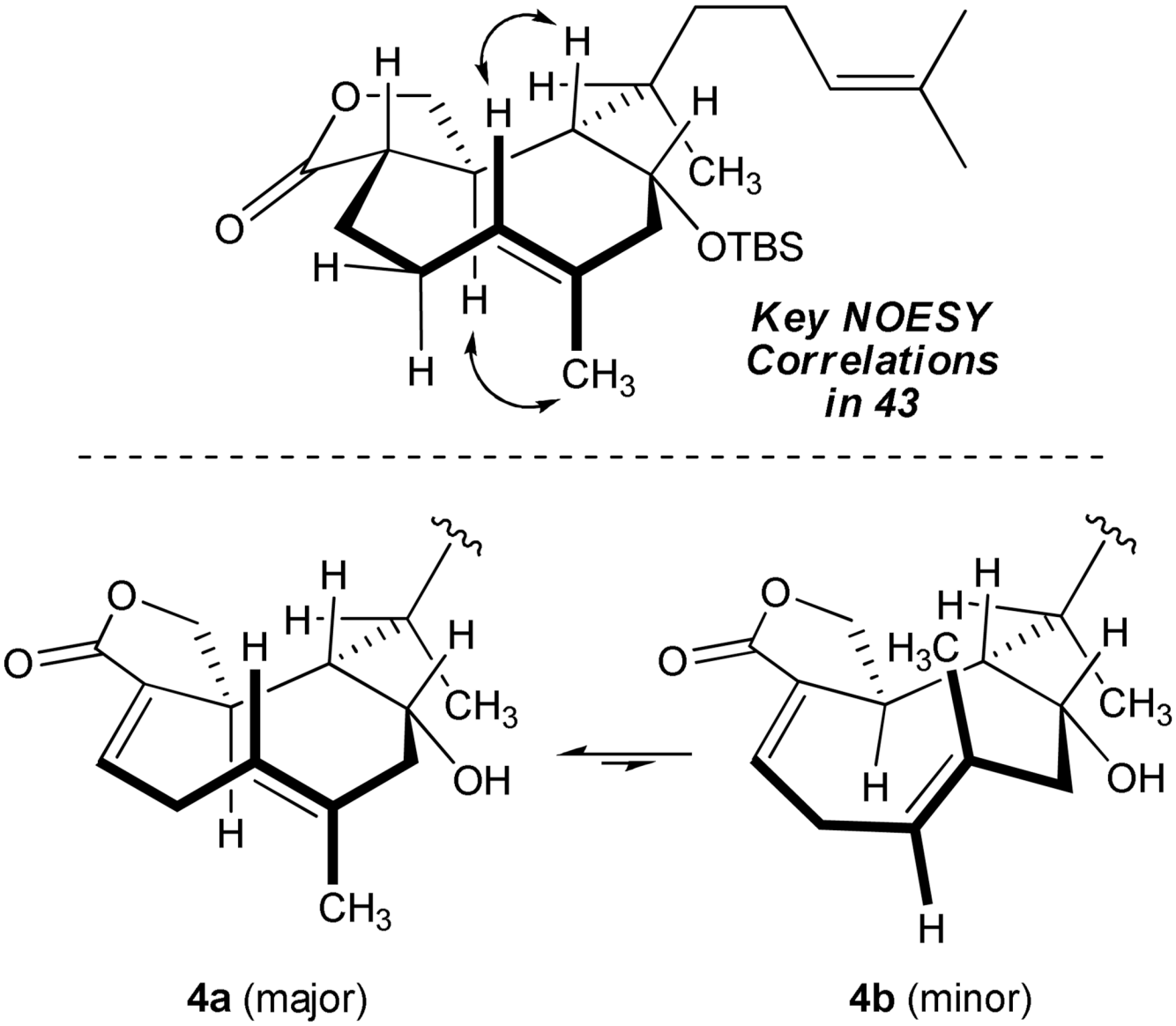
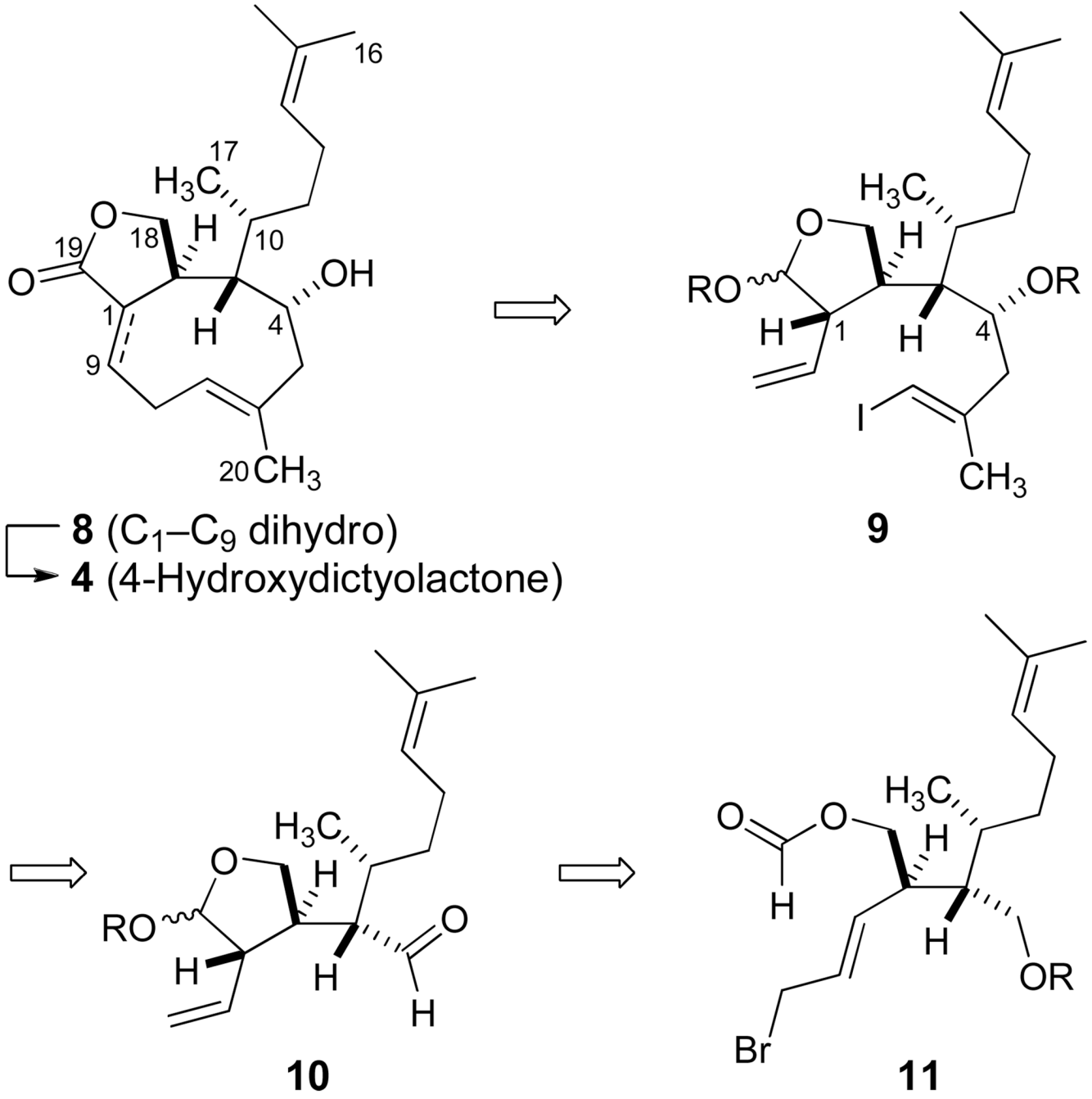
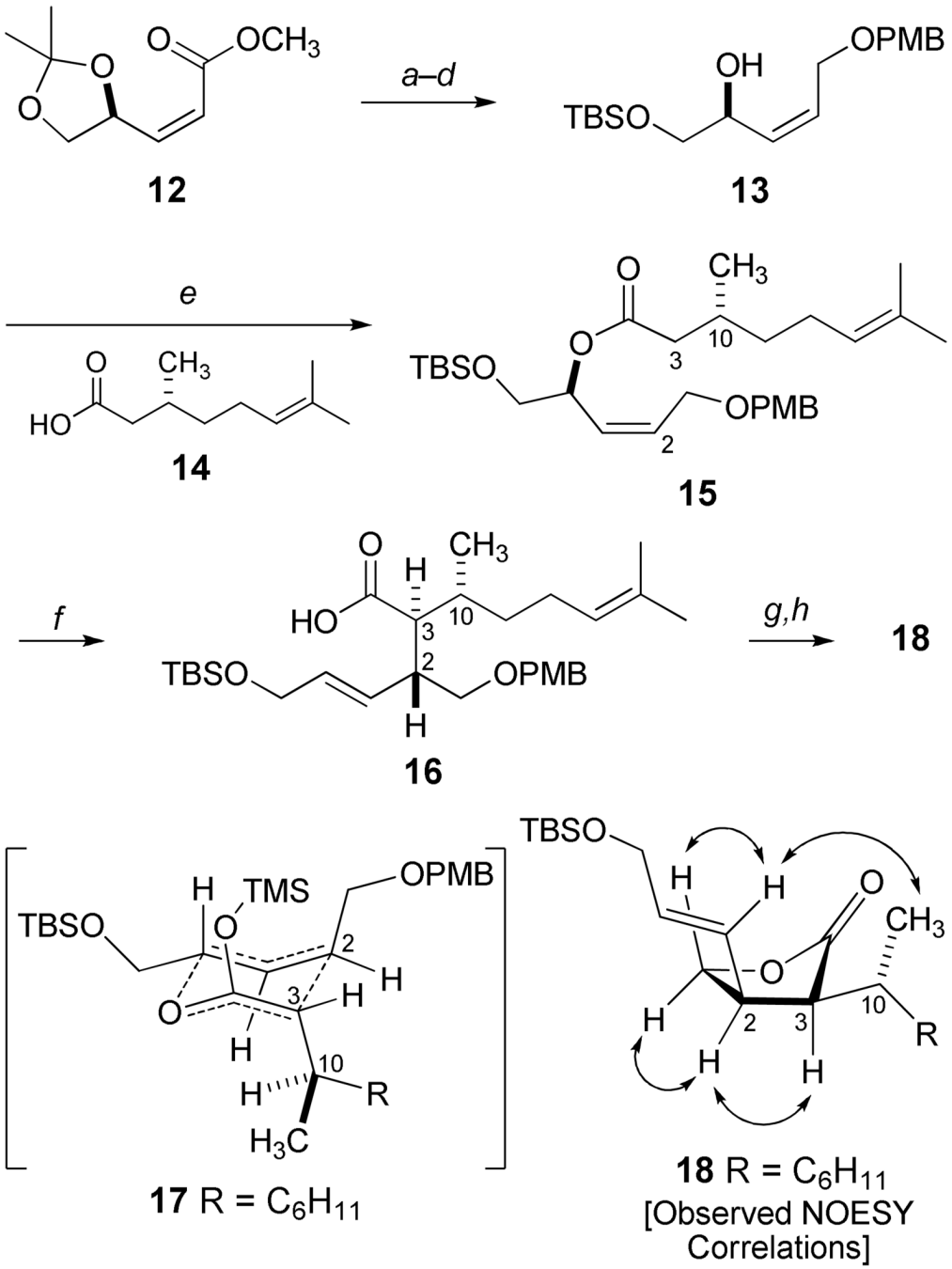


Figure 3.
Ring Conformers of **43** and **4**.



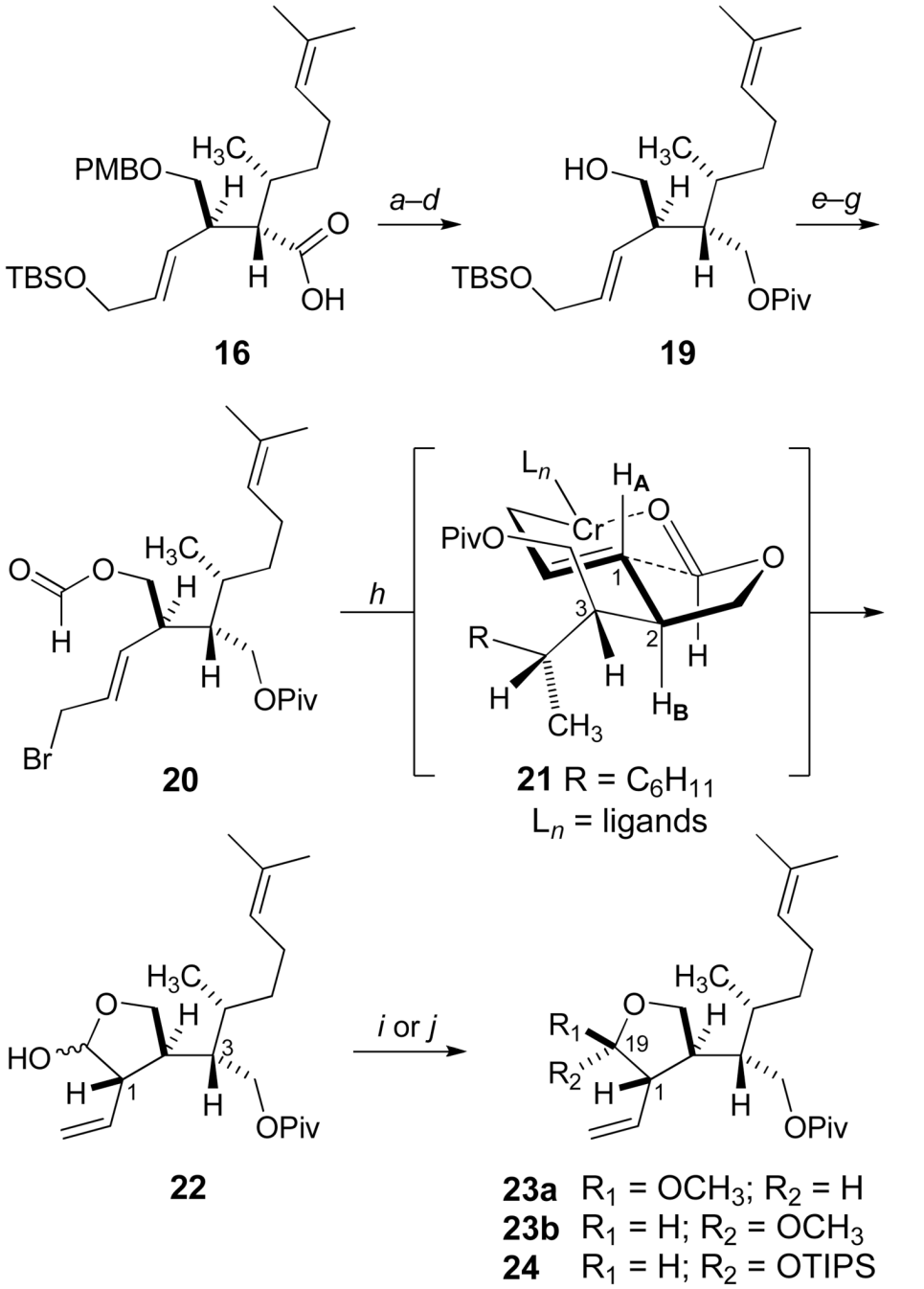
Scheme 1.
Retrosynthetic Analysis of **4**.



Scheme 2.

Development of the C_2, C_3, C_{10} Stereotriad of **16**.a

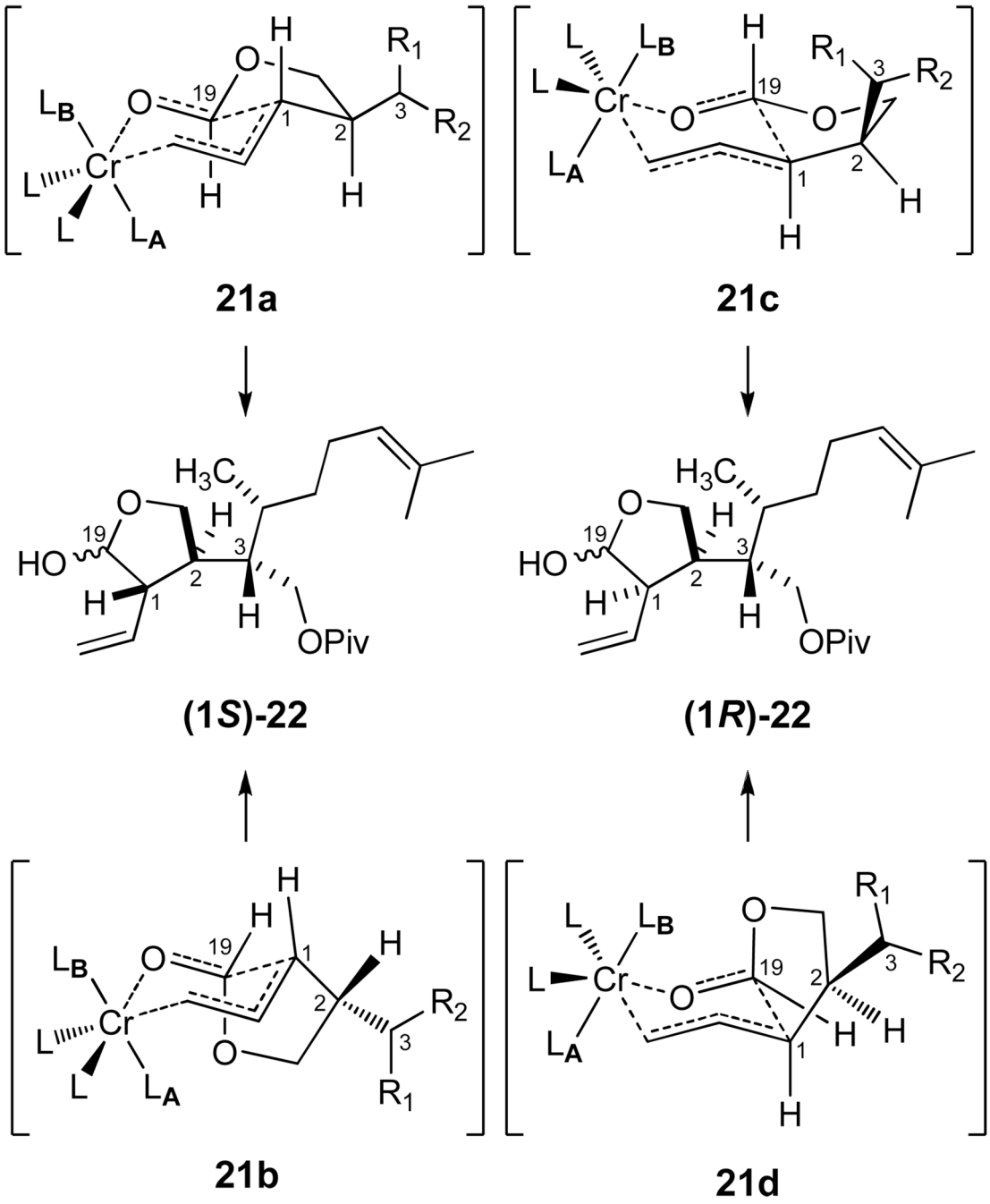
[a]Reagents and Conditions: a) DIBAL, CH_2Cl_2, −78 °C, 98%; b) PMBCl, NaH, DMF, 0 °C to rt, 97%; c) 1M HCl, MeOH, 100%; d) TBSCl, imidazole, CH_2Cl_2, 92%; e) **14**, EDCI, DMAP, CH_2Cl_2, 97%; f) TMSCl, Et_3N, −78 °C, then LDA, −78 °C then reflux, 85%, *dr = 94:6*; g) DDQ, CH_2Cl_2, H_2O, 0 °C; f) EDCI, DMAP, CH_2Cl_2



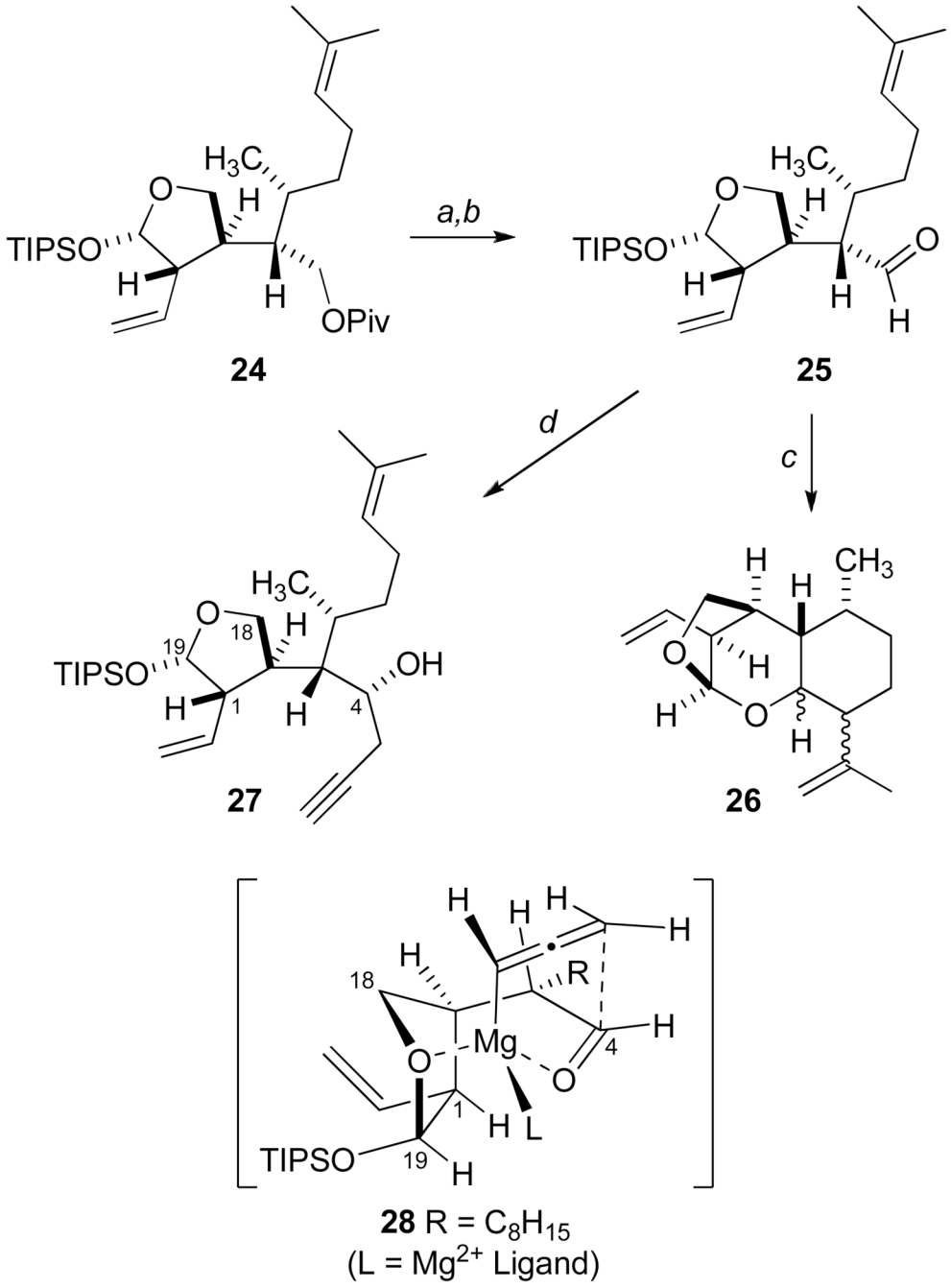
Scheme 3.

Intramolecular Nozaki-Hiyama Coupling of Formate Ester **20**.a

[a]Reagents and Conditions: a) MeI, K_2CO_3, DMF, 97%; b) DIBAL, CH_2Cl_2, −78 °C, 100%; c) PivCl, pyr, CH_2Cl_2, 95%; d) DDQ, pH 7.0 buffer, CH_2Cl_2, 0 °C, 76%; e) Formic Acid, EDCI, DMAP, CH_2Cl_2, 96%; f) Bu_4N^+ $Ph_3SiF_2^-$, AcOH, THF, 99%; g) CBr_4, PPh_3, CH_2Cl_2; h) $CrCl_2$, THF, 92% (2 steps), *dr* > 95:5 *at* C_1; i) PPTs, MeOH, 100%; j) TIPSOTf , 2,6-lutidine, CH_2Cl_2, 0 °C, 90%, *dr = 91:9 at* C_{19}.



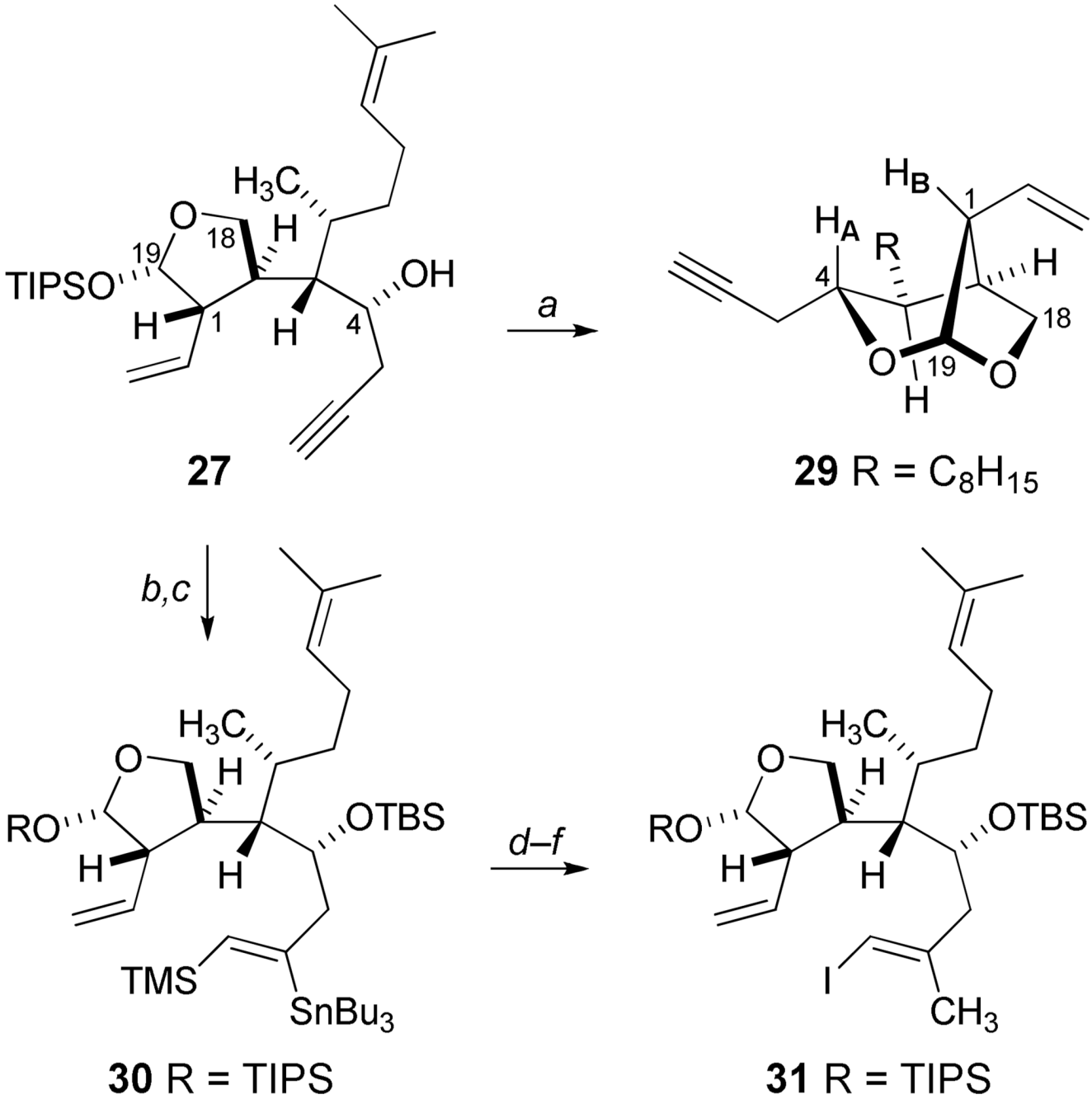
Scheme 4.
Transition State Analysis Toward the Formation of **22**.



Scheme 5.

Diastereoselective Propargylation of Aldehyde **25**.a

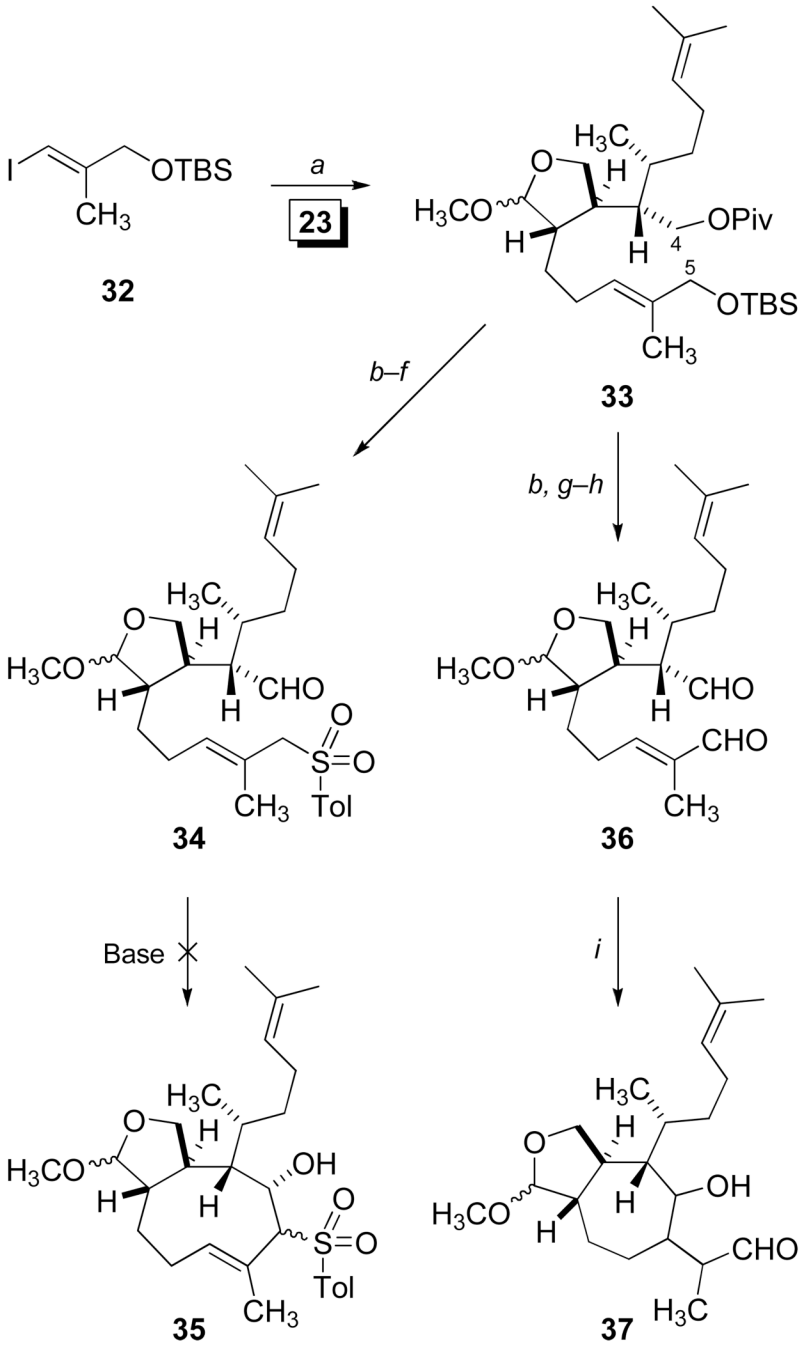
[a]Reagents and Conditions: a) DIBAL, CH_2Cl_2, −78 °C, 96%; b) TPAP, NMO, 4Å MS, CH_2Cl_2, 99%; c) $SnCl_4$, CH_2Cl_2, −78 °C d) Propargyl bromide, Mg^0, $HgCl_2$, Et_2O, −20 °C, 96%, *dr = 84:16*.



Scheme 6.

Functionalization of Alkyne **27**.a

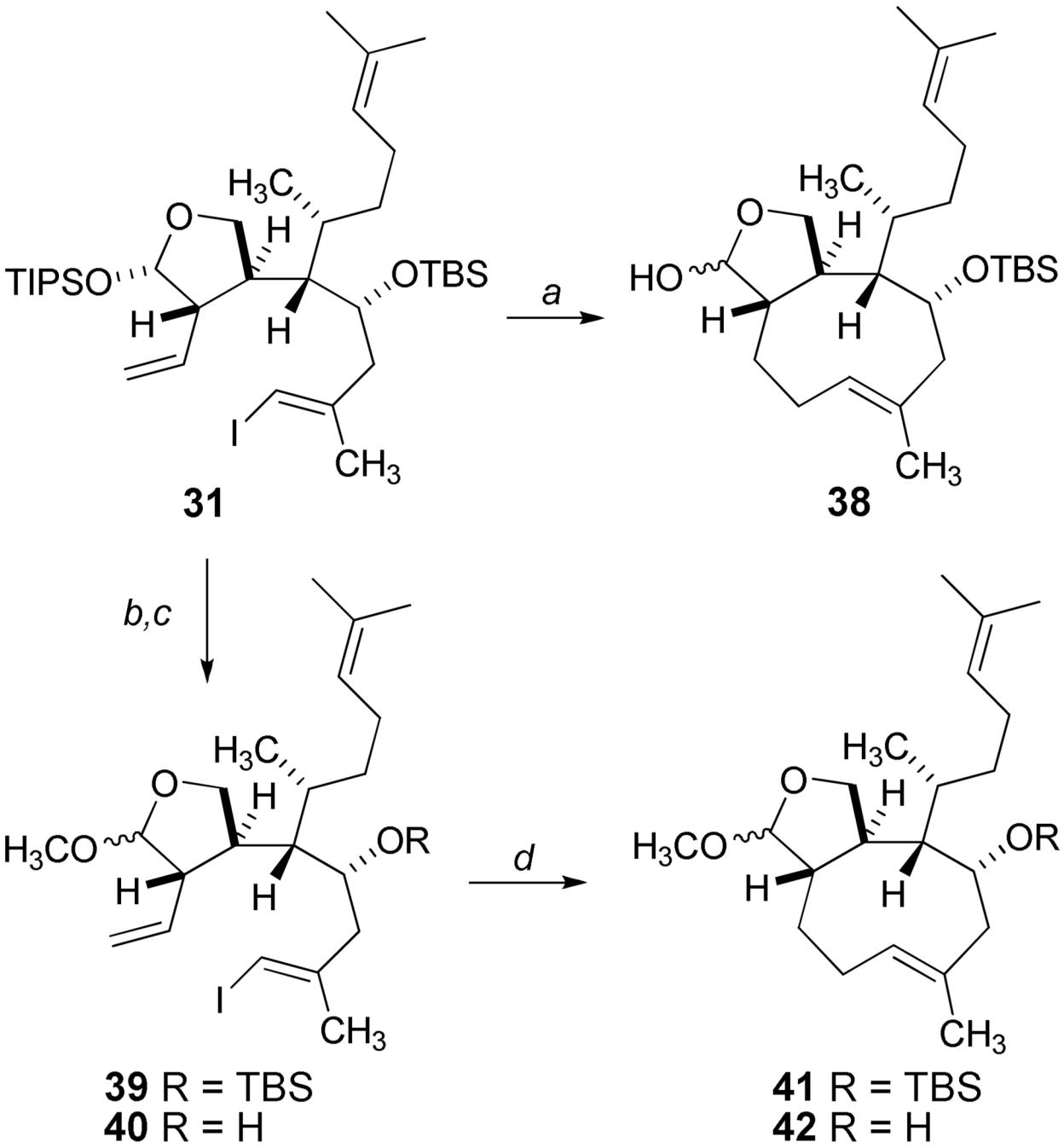
[a]Reagents and Conditions: a) A1Me_3, Cp_2ZrCl_2, CH_2Cl_2, 0 °C, 62%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 94%; c) $Me_3SiSnBu_3$, $Pd(PPh_3)_4$, THF, reflux, 85%; d) I_2,2,6-di-*t*-butyl-4-methylpridine, CH_2Cl_2, −40 °C, 93%; e) MeLi, CuI, THF, −20 °C, 98%; f) NIS, CH_3CN, rt, 82%.



Scheme 7.

Attempted Cyclization via C_4–C_5 Bond Formation.a

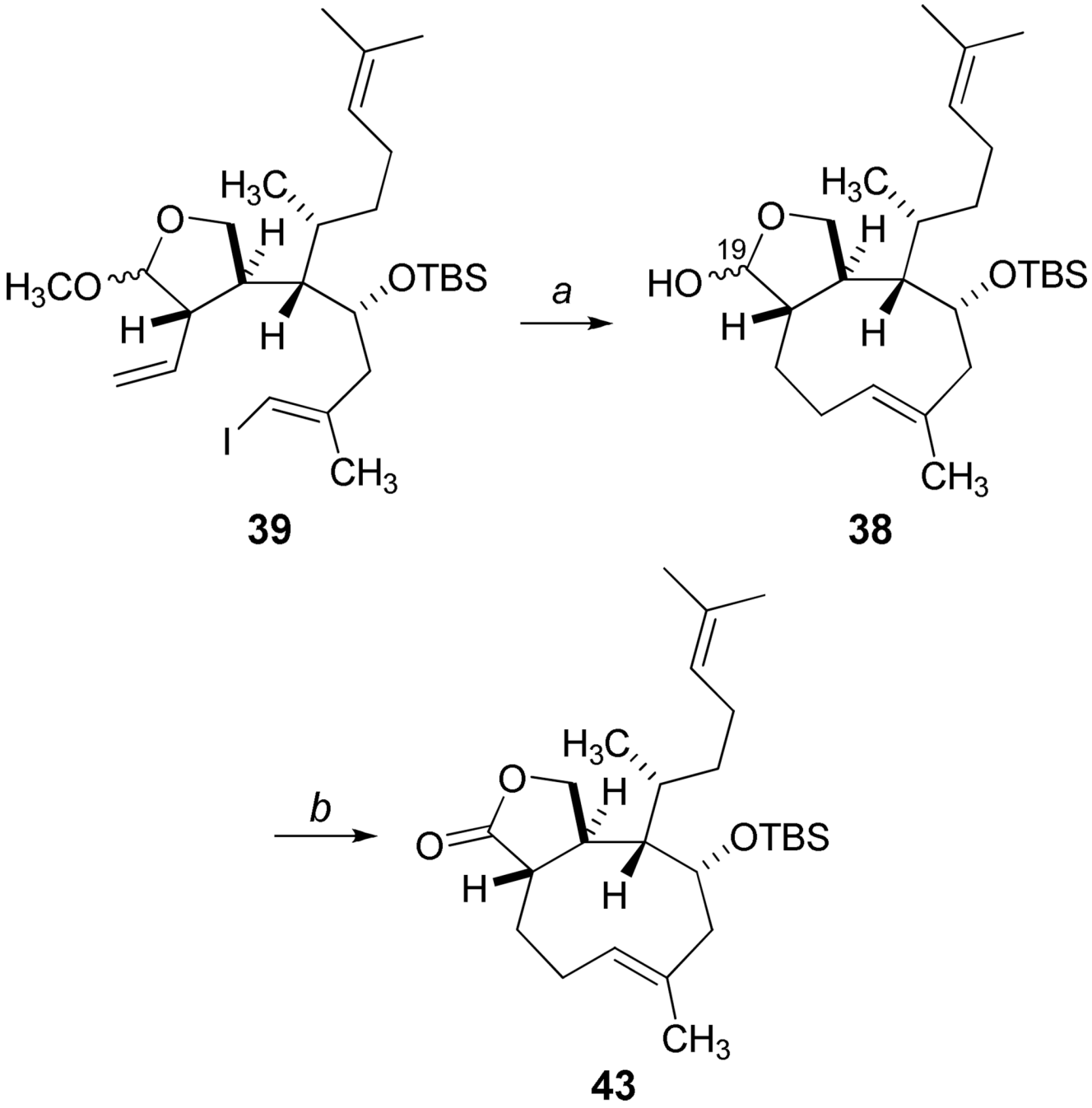
[a]Reagents and Conditions: a) **23**, 9-BBN, THF, rt, then **32**, $PdCl_2$(dppf), Cs_2CO_3, $AsPh_3$, H_2O, DMF, 60% (unopt.); b) Bu_4N^+ $Ph_3SiF_2^-$, AcOH, THF, 93%; c) I_2, PPh_3, imidazole, CH_2Cl_2; d) Sodium tolylsulf inate, DMF, rt, 86% (2 steps); e) DIBAL, CH_2Cl_2, −78 °C; f) Dess-Martin Periodinane, Pyr., CH_2Cl_2, 94% (2 steps); g) DIBAL, CH_2Cl_2, −78 °C, 97%;h) Dess-Martin Periodinane, Pyr., CH_2Cl_2, 93%; i) SmI_2, THF, −78 °C.



Scheme 8.

Initial Studies of B-Alkyl Suzuki Macrocyclization.a

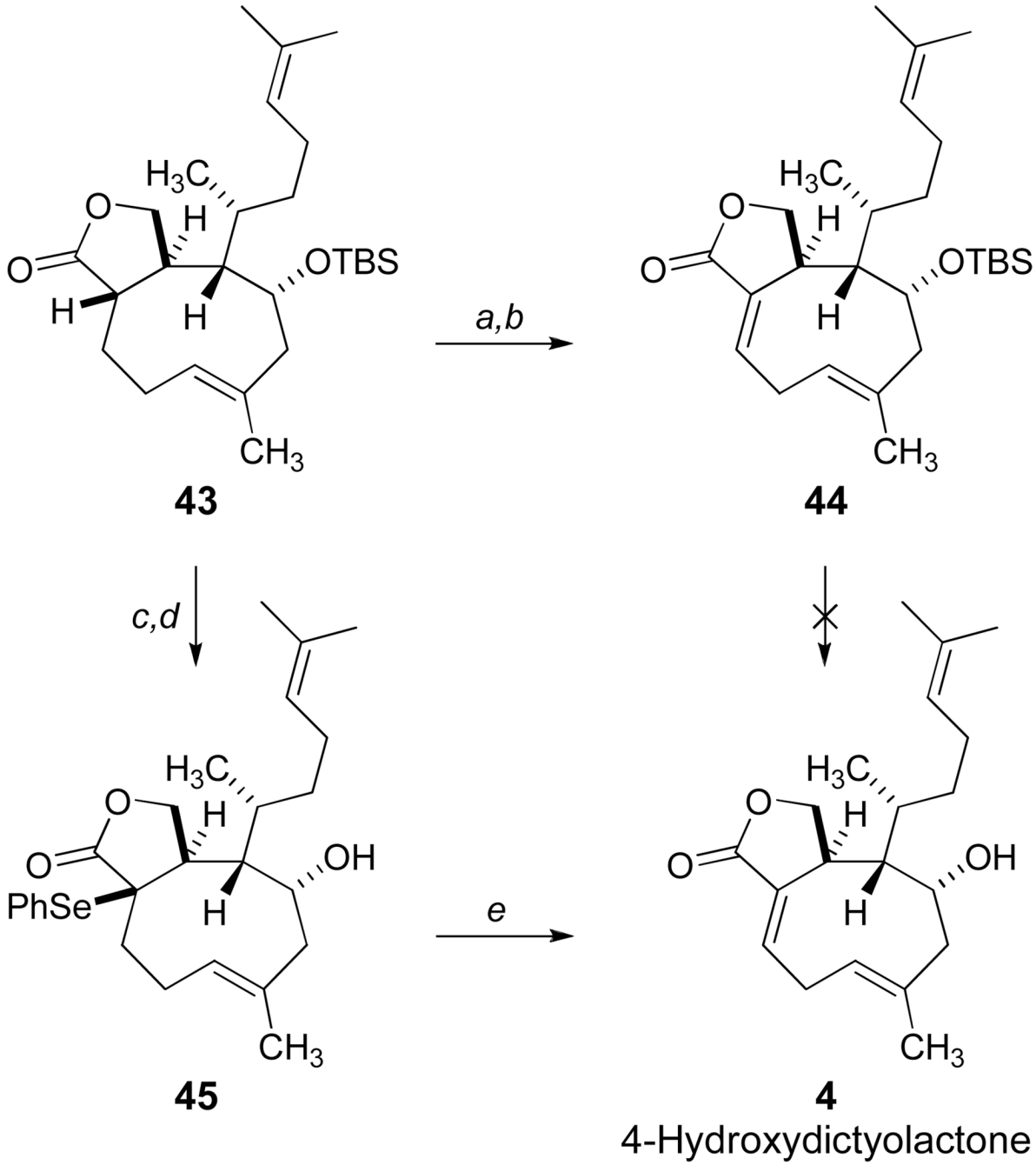
[a]Reagents and Conditions: a) 9-BBN (4 equiv.), THF, 40 °C, then $PdCl_2$(dppf), TlOEt, $AsPH_3$. THF/DMF/H_2O (6:3:1), 60 °C; then TBAF, THF,0 °C; b) TBAF, THF 0 °C, 95%; c) PPTs MeOH, rt, 99%;d) 9-BBN (1.2 equiv.), THF,0 °C to rt., then $PdCl_2$(dppf), TlOEt, $AsPh_3$, THF/DMF/H_2O (6:3:1), 60 °C.



Scheme 9.

Optimization of B-Alkyl Suzuki Cyclization.a

[a]Reagents and Conditions: a) 9-BBN (1.5 quiv.), THF, rt,12 h, then $Pd(PPh_3)_4$ (0.5 equiv.), NaOH (5.0 equiv.), CH_3CN/H_2O (15:1) [0.005M], 85 °C, 18 h; then aq. AcOH, THF, 85 °C, 66%, *dr = 80:20 at* C_{19}; b) TPAP, NMO, **4** Å mol. sieves, CH_2Cl_2, 79%.



Scheme 10.

Completion of the Total Synthesis of **4**.a

[a]Reagents and Conditions: a) LDA, THF, −78 °C, then PhSeBr; b) *m*CPBA, CH_2Cl_2, −78 °C, then Et_3N, then warm to rt., 89% (2 steps); c) TBAF, THF, 40 °C, 83%; d) LDA, THF, −78 °C, then PhSeBr; e) *m*CPBA, CH_2Cl_2, −78 °C, then Et_3N, then warm to rt., 55% (2 steps).