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Stereocontrolled Radical Bicyclizations of Oxygenated Precursors Enable Short Syntheses of Oxidized Abietane Diterpenoids

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Abstract

The power of cation-initiated cyclizations of polyenes for the synthesis of polycyclic terpenoids cannot be overstated. However, a major limitation is the intolerance of many relevant reaction conditions toward the inclusion in the substrate of polar functionality, particularly in unprotected form. Radical polycyclizations are important alternatives to bioinspired cationic variants, in part owing to the range of possible initiation strategies, and in part for the functional group tolerance of radical reactions. In this article, we demonstrate that Co-catalyzed MHAT-initiated radical bicyclizations are not only tolerant of oxidation at virtually every position in the substrate, oftentimes in unprotected form, but these functional groups can also contribute to high levels of stereochemical control in these complexity-generating transformations. Specifically, we show the effects of protected or unprotected hydroxy groups at six different positions and their impact on stereoselectivity. Further, we show how multiply oxidized substrates perform in these reactions, and finally, we document the utility of these reactions in the synthesis of three aromatic abietane diterpenoids.

Graphical Abstract

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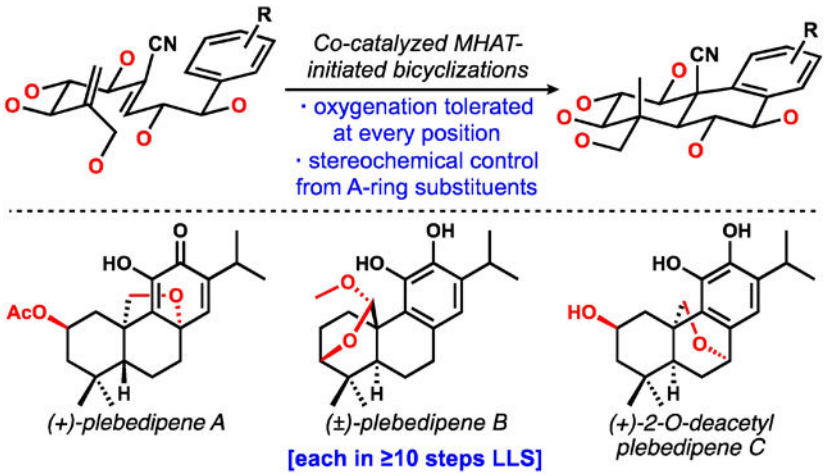
Author Contributions

The manuscript was written through contributions of all authors.

Supporting Information

Supporting Information including experimental procedures, characterization data, and NMR spectra for all new compounds is available free of charge on the ACS Publications website.



Introduction and Background

In nature, polyene cyclizations are mediated by terpene cyclase enzymes and proceed via cationic pathways[1] (Scheme 1a), as shown in low resolution for the aromatic abietane diterpenoids in Scheme 1b.[2] The resultant polycyclic frameworks are frequently decorated with oxygen functionality by cytochrome P450 oxygenases,[3] which in the cases of the abietanes leads to dozens of congeners that sample oxidation and/or dehydrogenation at every single carbon atom. Different combinations of oxidations result in vast structural diversity.[4] Some synthetic efforts to mimic this two-phase (cyclase/oxidase) strategy have been met with significant success, particularly by the Baran group,[5] but chemoselective late-stage oxidation remains a challenging task.[6,7] Reversing the order of operations by oxidizing the carbon skeleton prior to cyclization can be strategically risky, since polar cationic cascades tend to be sensitive to electronic effects and the presence of Lewis basic functional groups can interfere with many of the catalysts employed in these reactions.[8] Employing radical polycyclizations in highly oxidized contexts could be a viable alternative because they are generally more functional group tolerant and might be expected to perform better in sterically demanding situations.[9,10]

Since Breslow's seminal investigations of benzoyl radical addition to farnesyl acetate (Figure 1a),[11] a range of unique radical polyene cyclization methods have been described, in some cases offering new opportunities to deviate from canonical geraniol/farnesol/geranylgeraniol-derived starting materials.[12] Representative noteworthy advances include (1) acyl-radical-initiated polycyclizations[13] by the Boger and Pattenden labs, (2) Mn(III)-induced reactions of β-ketoesters[14] as described by the Snider and Zoretic groups, (3) photoinduced-electron-transfer-triggered polycyclizations from Demuth and co-workers,[15] (4) the use of Nugent/Rajanbabu-type single-electron epoxide reduction[16] to initiate ring closures[17] by the groups of Gansauer, Barrero, and Cuerva, and (5) the MacMillan lab's single electron oxidation of catalytically-generated chiral enamines.[18] A few years ago, Liu and co-workers used metal-catalyzed hydrogen atom transfer (MHAT)[19] to an alkene to initiate bicyclization in the context of their hispidanin A synthesis;[20] iron catalysis related to the previous work of Baran was key to this achievement.[21–23] Very recently, in efforts to

effect polyene cyclizations in which electron-deficient alkenes were competent reactants, we found that cobalt catalysis of MHAT[24–26] was uniquely effective in generating products with strategic oxidation at C20, in the form of the nitrile (see **10** to **11**, Figure 1b).[27]

Although stereocontrolled radical cyclizations have been utilized as key steps in many total syntheses, the stereochemical influence of pendent functionalities has not been investigated systematically in reactants leading to diterpenoid scaffolds. As already mentioned, Liu and co-workers reported an MHAT-initiated triene cyclization where high stereoselectivity was observed with respect to a C2 substituent that was later excised (**12** to **13**, Figure 1c).[20] In our investigations of Co(II)-catalyzed radical bicyclizations, we also observed excellent stereocontrol induced by a *t*-butyldimethylsilyloxy group at C2.[27] These results prompted us to further investigate the compatibility with and the stereodirecting role of oxygenated substituents at other positions in these reactants.

As part of our program to make use of prefunctionalized **π**-cyclization precursors to generate complex terpenoids,[27,28] we sought to systematically investigate the stereodirecting ability of pendant alkoxy substituents on cyclization substrates (Figure 2a). For this study, we focused on substrates with C20 in nitrile form, because many abietane and related diterpenoids are oxidized at this position, and the method is particularly adept at addressing this challenge. Prior work documented the unique suitability of the nitrile as electron-withdrawing group at this position, with no productive cyclizations observed with the corresponding esters.[27] Furthermore, examples are known with C20 oxidized and with further oxygenation at every position on the trans-decalin substructure (some examples shown in Figure 2b).[4,29,30] In this report, we describe the excellent functional group tolerance and often high stereoselectivity of these radical bicyclizations and establish the utility of these reactions with the total syntheses of three bioactive abietane diterpenoids bearing different oxidation patterns, as well as access to the complex oxygenation pattern found in a cassane diterpenoid.

Results and Discussion

Stereochemical Control by Pendent Oxygen Functions

For the purpose of consistency and ease of synthesis, the 3,5-dimethoxyphenyl group was used as the terminator in investigations of stereochemical control by pendent oxygen-based functional groups. On the basis of our prior work, these results were expected to translate to substrates with a broad range of electron-rich arenes.[27] Further, the use of different terminators in the natural product syntheses are described in the latter half of this report. Systems with only one backbone oxygenated substituent at a time were examined initially, and it could be anticipated that these effects might be positively or negatively reinforcing depending upon the stereochemical arrangement in multiply substituted contexts. Interesting examples of this phenomenon are provided both in this section and in the natural product syntheses that follow.

A-Ring Oxygenation

Substrates bearing oxygenation at C3 (**22a–d**, Figure 3) were expected to cyclize with high diastereoselectivity via chair-like conformations from which the oxygenated substituent would emerge in an equatorial position. In this case, however, we found a significant protecting-group-dependence on stereochemical outcome. The stereoselectivity in the case of the free hydroxy group (**22a**) was moderate in favor of the equatorial isomer **23** (dr: 3:1), whereas TBS-protected alcohol **22d** showed a surprisingly strong preference for the axial product **24** (dr: 1:8). This outcome could prove quite useful since both polar and radical epoxypolyene cyclizations tend to be highly selective for equatorial orientation of the C3 hydroxy group. Ti(III)-catalyzed radical cyclizations of epoxypolyprenes only produce scaffolds with equatorial C3 hydroxyl group, presumably due to intermediacy of bulky titanoalkoxides.[31] The only direct way to access the axial C3 hydroxyl moiety was described by Corey et al. in their report on In(III)-catalyzed alkyne-initiated cationic cascades.[32] The incorporation of less bulky protecting groups like acetate (**22b**) and methoxymethyl (**22c**) resulted in negligible selectivity.

Oxygen substitution at C2 was associated with efficient bicyclization and exclusive selectivity for the equatorial group with both the free hydroxy group and the corresponding silyl ether (**25a** and **25b**). While both our previous work[27] and that of Liu[20] documented the use of C2 *t*-butyldimethylsilyloxy groups in these radical cyclizations, the efficiency of reactions with the free alcohol is a key point in this and many of the reactions that are described here. In this case, even though the OH/OTBDMS groups are not “large” (A values <1), the penalty for their axial disposition would be significant because of the axial methyl group that comprises C18, and the axial nitrile (despite an A value of only 0.17).

The substrate with a C1 hydroxy group (**28a**) cyclized efficiently in a 3:1 ratio favoring diastereomer **29a** with the alcohol equatorial. Interestingly, that is the same ratio as was observed with the C3 hydroxy group, perhaps simply reflecting the moderate steric bias against an axial OH group on the α-face in the transition structure for the first cyclization (no other axial substituents on that face). However, we expected significant impacts of steric interactions between the C1 substituent and the C11 methoxy group: (1) the two groups are in very close proximity in equatorial product **29**, and (2) we anticipated that these interactions of the hydroxy group in the axial configuration would hinder the B-ring cyclization, although post-cyclization these groups in **30** are not mutually encumbering. It is conceivable that hydrogen-bonding between the C1-OH and the C11-methoxy group facilitates the reaction leading to **30**. While we were somewhat surprised to observe any axial product **30** on kinetic grounds, this functional group arrangement (C1 axial acetoxy and C11 phenol) is found in the natural product euroabienol (**20**, Figure 2b).[30b] On the other hand, the stereochemical arrangement that places the C1 equatorial hydroxy group in very close proximity to the arene methoxy group (as in **29a**) is not known in the literature. We have obtained an X-ray crystallographic structure of **29a** that indicates hydrogen-bonding between the C1-OH and the C11 ether oxygen and an A-ring twist-boat conformation (see Supporting Information). Perhaps unsurprisingly, the silyl protected substrate **28b** did not react productively. To ascertain the potential importance of the steric and/or hydrogen bonding effects in **28a/b**, we evaluated *p*-methoxyphenyl substrates **31a–c**; this terminating

group also worked well in our previous studies.[27] In this case, substrate **31a** with the free hydroxy group did not proceed to tricyclic products, but the silyl-protected version **31b** was converted with low efficiency to **32** with apparent complete selectivity for the axial silyloxy group. The mass balance could not be characterized. It is difficult to ascertain the inherent stereoselectivity in the first ring closure in this case, because the equatorial stereoisomer might form selectively in the first cyclization, but fail to undergo the second ring formation. Finally, we evaluated the corresponding C1-acetoxy substrate, and found only cyclohexene nitrile **34** (32% + 35% recovered starting material), presumably resulting from elimination of acetoxy radical.

While oxidation on the terminal carbon of the substrate clearly cannot control the facial selectivity of π-cyclization, we wondered whether or not there would be an intrinsic preference for disposition of the resulting oxygenated carbon in the equatorial (C18) or axial (C19) position (Figure 4). We expected at best a modest preference for the slightly larger group to assume the equatorial position. However, we were surprised to observe complete selectivity (>20:1) for the equatorial diastereomer with both the TBS-protected and unprotected substrates (**35** and **40** respectively). In the case of silyl ether **35**, an efficient reaction resulted in the formation of **36** along with small and variable quantities of what we believe to be enoxysilane **39** (could not be purified to homogeneity for unambiguous structural determination). It is likely formed as a result of back-HAT to the Co(II) catalyst from the α-alkoxy methylene adjacent to the intermediary tertiary alkyl radical. Deprotection of **36** yielded neopentylic alcohol **38**, for which nOe experiments supported the stereochemical assignment. Interestingly, the desilylated substrate **40** cyclized to give a ~2:1 mixture of carbinol **38** and aldehyde **41**, both with the same relative configurations (**41** was reduced to **38** in aid of structural proof). The oxidation event likely occurs prior to the first cyclization since resubmitting carbinol **38** to reaction conditions did not give the oxidized product, and the ratio of **38**:**41** did not change appreciably with conversion. At this stage, we do not have a good explanation for the oxidation chemistry or the unanticipatedly high stereoselectivity. It is noteworthy that cationic epoxypolyene cyclizations involving terminal, 2,2-disubstituted epoxides lead to the same stereochemical preference but with moderate (4–5:1 selectivity), in the absence of other pendant stereodirecting groups.[28]

B-Ring Oxygenation

While oxygenation on the proto-A-ring portion of the bicyclization substrates often resulted in useful levels of stereoselectivity upon cyclization, we posited that substitutions at C6 or C7 (corresponding to the B-ring) would be less impactful. This hypothesis was based solely on the supposition that these cyclizations proceed stepwise, and that the impact of substitution at these positions on the conformational preferences for the first cyclization would be minimal. Nonetheless, we needed experimental validation of this hypothesis, which would simultaneously permit us to assess the efficiency of these cyclizations. Assuming that oxygenation was tolerated at these positions, then the possibility of stereochemical control in polyoxygenated systems could still be powerful (see below). Moreover, just the simple ability to use prefunctionalized substrates, even in the absence of stereochemical control, might offer strategic advantages in complex molecule synthesis.

We first evaluated substrate **42a/b** with C6 oxygenation (Figure 5), and found that only the acetoxy derivative **42a** cyclized efficiently. As anticipated, this reaction occurred with essentially no stereochemical control, because the C6-configuration is unlikely to exert any control on facial selectivity in the first cyclization event. That the two diastereomeric intermediates cyclize with apparently similar efficiency to give axial and equatorial acetoxy products (**43** and **44**, respectively) might be understood by the fact that each reaction builds in a new *syn*-pentane-like interaction between the acetoxy group and either the C18 or C19 methyl groups. We were surprised that the silyloxy-substituted substrate did not lead to detectable quantities of bicyclized products, but rather underwent slower conversion to range of unidentified decomposition products. The unprotected C6-hydroxy substrate could not be evaluated because it proved unstable under the conditions for its formation by deprotection of either the acetate- or silicon-masked precursor. The C6-acetoxy-substituted reactant will become relevant in the context of multiply oxidized substrates (see below).

Both silyloxy and hydroxy substituents at C7 (see **45a/b**) were tolerated, and relatively efficient cyclization was observed in both cases, again with negligible stereochemical control from the preexisting stereogenic center. Showcasing the differences between cationic and radical polyene cyclizations, Chiba et al. reported that the presence of pendent ester groups (*C*-linked) in this benzylic position caused excellent stereocontrol in a protonative polyene cyclization.[33] There, the presumed concerted reaction with the substituent adopting the pseudoaxial orientation leads to high selectivity; in the case at hand, the stepwise radical bicyclization process ensures little impact of the distal stereogenic center on the first cyclization.

An interesting aspect of this work is that the formation of c*is*-decalin products is never observed. The second ring closure always favors the formation of the *trans*-decalin, irrespective of the necessary axial orientation of the C6/C7 oxygen-based group in roughly 50% of the material. Therefore, the configuration of the A-ring might generally control the stereochemical disposition of B-ring substituents, assuming that a diastereomerically pure precursor can be accessed (see below).

Doubly Oxygenated Precursors

We examined a select set of doubly oxygenated substrates (Figure 6). Terminally oxidized substrates with C7 and C6 oxygen groups (**48** and **51**, respectively) each cyclized with reasonable efficiency. We were unsurprised to find low levels of stereochemical control with **48**. However, because the C7 benzylic hydroxyl group is easily manipulated to make ether or lactone bridges (see Figure 2b for examples), or can be converted into either C7-epimer either via Mitsunobu inversion or oxidation/reduction,[34] this reaction still represents a powerful construction of compounds with this oxidation pattern, and further documents the reliability of the radical bicyclization in complex contexts.

Of more interest, substrate **51**, with the C6-acetoxy group, preferentially provided C6-axial diastereomer **52** (3:1 dr observed in the crude reaction mixture, but purified to a 14:1 mixture favoring **52**). We were unable to fully purify and characterize the minor product that we tentatively assign as stereoisomer **53**. The stereoselectivity of this reaction might arise from the avoidance of steric strain between the acetoxy group and the silyloxymethyl group

in the transition structure. However, we note the change relative to the reaction of **42a** (Figure 5), lacking C18 oxygenation, and that the size difference of silyloxymethyl and methyl groups might not be solely accountable for this change. It might be argued that the presence of an electronegative silyl ether proximal to the tertiary radical intermediate leads to a later transition state owing to diminished nucleophilicity of the radical species. As a result, this could lead to a preference for the C6-acetoxy group at C-6 to assume the pseudoaxial orientation necessary for hyperconjugative σ*-donation to the adjacent p-orbital of the electrophilic olefin. While the isolated yield of **52** is only 45%, this outcome is noteworthy for expedient access to the stereochemical and functional arrangement of the complex cassane diterpenoid 20-acetoxytaepeenin D[30c] (**21**, Figure 2b).

Finally, we wished to show that a resident stereogenic center in the A-ring area of the substrate could control the outcome with respect to B-ring stereogenic centers. We made diol **54** as an equimolar mixture of diastereomers in enantiopure form, starting from epichlorohydrin. Under standard conditions, this substrate generated an equimolar mixture of **55** and **56** in good yield, thus demonstrating that the C2 stereogenic center controls the outcome of the bicyclization reaction, and indicating that if a single diastereomer of substrate were made, a single diastereomer of product would result. The synthesis of a diastereomerically pure substrate should be accessible by catalyst-controlled diastereoselective reduction of the C7-ketone. However, we also note again that post-cyclization manipulation of the benzylic carbon should be facile. Of course, this reaction is also noteworthy for its efficiency in the presence of an unprotected diol. Further, this is a demonstrable case of A-ring substituents exerting influence over the equatorial/axial disposition of B-ring substituents. It is expected that the same type of control would arise from different combinations of substituents in a predictable way (A-ring C1, C2, or C3 oxygenation with B-ring C6 or C7 oxygenation), setting the stage for applications to highly oxidized terpenoid syntheses that are ongoing in our lab.

Total Synthesis of Abietane Diterpenoids

Inspired by the results described above and to showcase the utility of the Co(II)-catalyzed radical bicyclizations, we targeted several C20 oxidized abietane diterpenoids bearing different oxygenation patterns. Close to 100 aromatic abietane diterpenoids have been reported, and they include members that are oxidized at every carbon of their aliphatic architecture. Moreover, many are endowed with intriguing bioactivities.[4] Guo and co-workers recently reported the isolation of plebedipenes A, B, and C,[29] C20 oxidized abietanes with further oxygenation at either C2 or C3 (**15**, **16**, and **18** in Figure 2). The 2-*O*-deacetyl version of plebedipene A (**14**) was also reported, and the deacetyl analogue of plebedipene C (**17**) was previously reported by Fu and colleagues.[35] Based on results in Figure 3, we posited that stereocontrolled radical bicyclizations could grant quick access to the cores of these targets with appropriate oxygenation patterns and configurations.

(+)-2-O-Deacetyl Plebedipenes A and C

The synthesis of 2-*O*-deacetyl plebedipenes A (**15**) and C (**17**) began with known epoxide **57**,[36] which was opened with lithiated acetonitrile, the product of which was protected as silyl ether **58** (Scheme 2). Conversion to the phosphonate **59** was straightforward. To

generate the electrophile for the convergent Horner–Wadsworth–Emmons (HWE) reaction, we began with regioselective oxidation of known iodophenol **60**.[37] The crude catechol was protected as orthoformate **61**, because of the need for a readily removable group in the late stages of the synthesis. Heck coupling with allyl alcohol gave aldehyde **62**, which was reacted with phosphonate **59** in a Z-selective (9:1) HWE alkenylation to give bicyclization precursor **63** as an inconsequential mixture of diastereomers with respect to the orthoformate carbon (*). Co(II)-catalyzed bicyclization in the presence of 1 equiv. of 2,6-di-*tert*-butylpyridine (DTBP, needed because of the sensitive orthoformate) delivered **64** with excellent stereochemical control in 75% yield on gram scale. The unusual catechol protective group was chosen after the dimethylated catechol analogue of **63** failed to undergo radical bicyclization. This failure was explained by a likely gearing effect of the three contiguous substituents causing the C11 methoxy group to orient itself in a way that sterically shielded the desired reaction site. Surprisingly, NMR data indicated that **64** was isolated as a single diastereomer, suggesting that the orthoformate is equilibrated to its more stable diastereomer (unassigned) under the reaction conditions. Reduction of the hindered nitrile using DIBAL-H in toluene delivered the corresponding imine which was hydrolyzed on silica gel and further reduced using $NaBH_4$ in MeOH to give carbinol **65**. Removal of the silyl and orthoformate protecting groups with TMSCl in MeOH gave tetraol **66** which was concentrated and directly used in the next step without purification. We envisioned that the tetrahydrofuran ring could be constructed via oxidative cyclization of the pendent primary alcohol to C8 of the catechol. Screening a variety of conditions revealed that the inclusion of an acid source in the optimal hypervalent-iodine-mediated oxidation is critical[38] (see Supporting Information). This observation suggests that the intermediary orthoquinone needs to be protonated for the hydroxyl group to attack C8. The result of this oxidative THF formation is the synthesis of (+)-2-*O*-deacetyl plebedipene A (**14**).[39] Subjection of tetraol **66** to an alternate oxidation protocol using silver oxide, as reported in a related context by Majetich and co-workers,[38] delivered (+)-2-*O*-deacetyl plebidepene C (**17**)[35] after heating the intermediate *o*-quinone in toluene overnight.[39]

(±)-Plebedipene B

An analogous convergent approach to the one described above was utilized for synthesis of plebedipene B. Cyclization precursor **71** (Scheme 3) was generated by HWE alkenylation of the same aldehyde **62** with a different cyanophosphonate reagent (see Supporting Information). The results from studies above (Figure 3) suggested that to access scaffolds bearing equatorial oxygenation at C3 in reasonable yield, the stereodirecting moiety should be a free hydroxyl group. With this in mind, **71** was treated with TBAF and submitted to bicyclization conditions in the presence of DTBP to furnish the desired scaffold **73** (3:1 dr at C3, as anticipated, purified to C3 stereochemical homogeneity in 45% yield). Interestingly, and in contrast to **64** (Scheme 2), **73** was isolated as an inconsequential 2:1 mixture of orthoformate diastereomers. It was necessary to reprotect the free hydroxyl group prior to reduction of the hindered nitrile to avoid formation of a hydrolysis-resistant cyclic aminal. Treatment of **73** with TBSOTf in DCM followed by reduction with DIBAL-H in toluene furnished a critical aldehyde intermediate in excellent yield over two steps. Curiously, when the reduction is performed on a single orthoformate diastereomer of **73**, the orthoformate stereogenic center is equilibrated to a 4:1 mixture (unnassigned) in this sequence. Cleavage

of the orthoformate and silyl ether protecting groups with TMSCl in methanol resulted in concomitant acetalization to deliver (±)-plebedipene B[29] (**16**) in quantitative yield.

Conclusions

The ability of pendent oxygen substituents to control the stereochemical outcome of radical bicyclizations was systematically investigated to explore the possibility of using preoxidized polyene precursors to access highly oxidized terpenoids. The degree of stereoselectivity was often high, but varied with oxygenation locus, with free hydroxy groups performing well in most contexts. The stereochemical outcomes of cyclizations of dioxygenated polyenes were dictated by aliphatic chain oxygenation closest to the initiating, 1,1-disubstituted alkene. Simple analyses of non-bonding interactions in the putative cyclization transition states were sufficient to rationalize stereochemical outcomes in most cases. Moreover, in the most complex methodological example, we selectively accessed the functional group arrangement unique to the complex cassane diterpenoid 20-acetoxytaepeenin D. To further validate this proposed approach to bioactive diterpenoid synthesis, we completed the first total syntheses of (+)-2-*O*-deacteyl plebedipene A, (±)-plebedipene B, and (+)-2-*O*-deacetyl plebedipene C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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39. We made (+)-14, and (+)-17, which are the unnatural enantiomers of these natural products, only because we had large quantities of the corresponding enantiomer of epichlorohydrin in our laboratories. Both enantiomers of starting material are readily available.

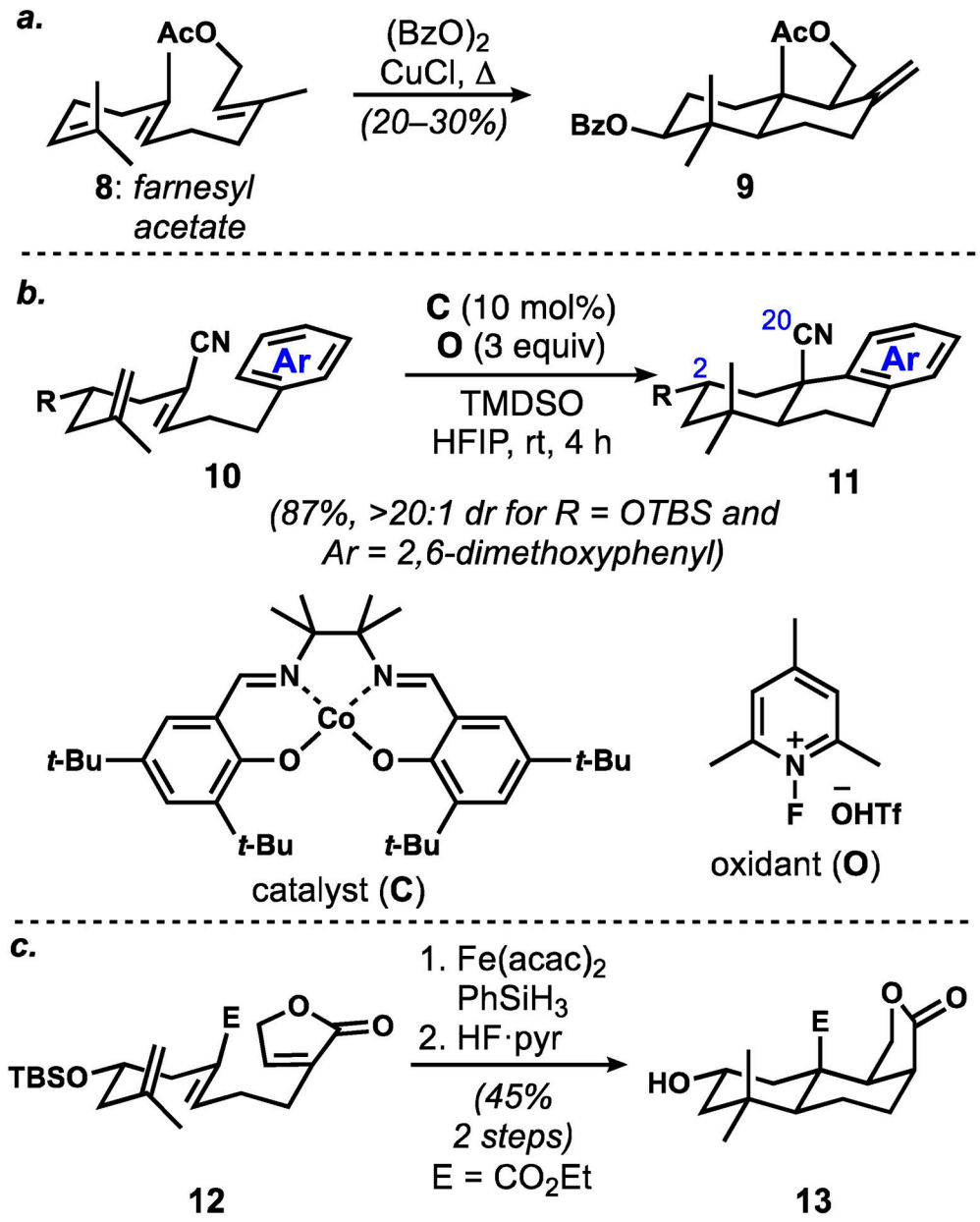


Figure 1.

a. Breslow's pioneering radical bicyclization of farnesyl acetate. ***b.*** Our previous report of MHAT-initiated radical bicyclizations that tolerated an oxidized C20 (as the nitrile). ***c.*** Liu's use of the C2 silyloxy group to control diastereoselectivity in an MHAT-initiated bicyclization.

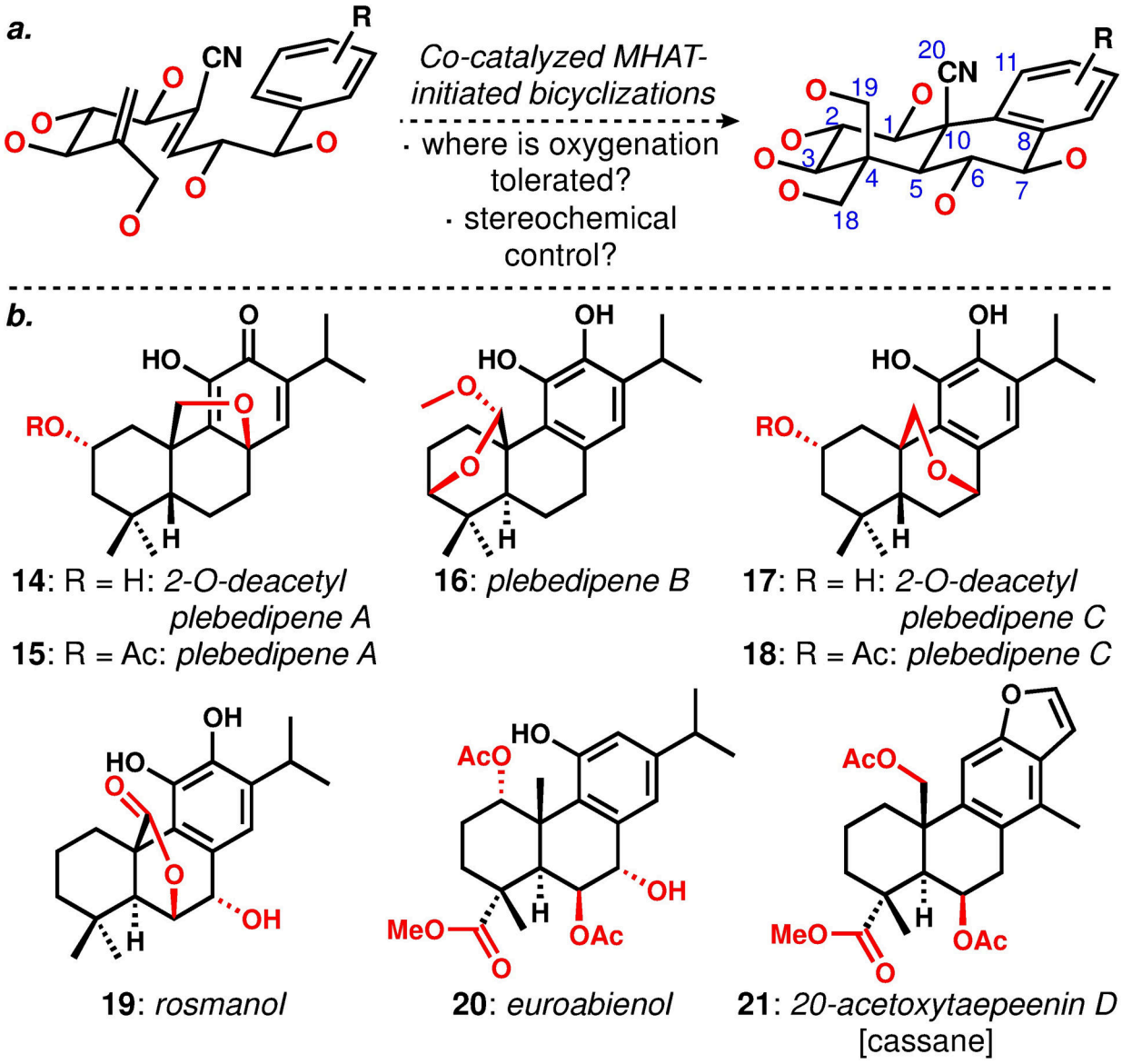
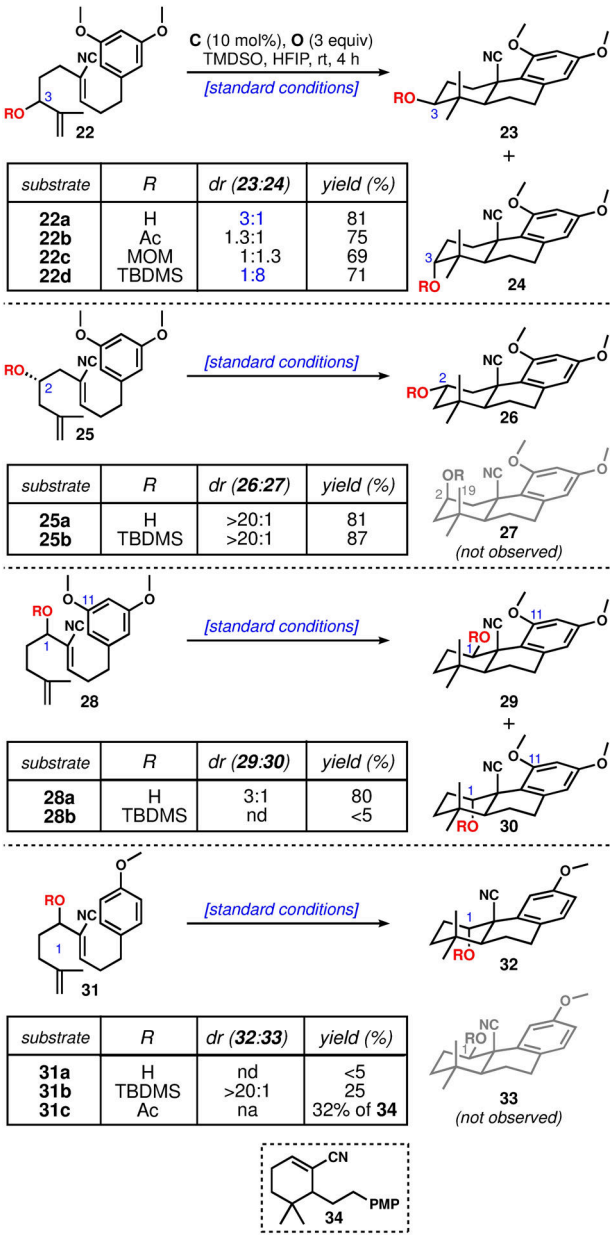


Figure 2.

a. The possibility of using preoxidized bicyclization precursors to access highly oxidized abietane-type scaffolds. ***b.*** Representative oxidized aromatic abietane diterpenoids and one exemplary cassane.



substrate	R	dr (**23**:**24**)	yield (%)
22a	H	3:1	81
22b	Ac	1.3:1	75
22c	MOM	1:1.3	69
22d	TBDMS	1:8	71

substrate	R	dr (**26**:**27**)	yield (%)
25a	H	>20:1	81
25b	TBDMS	>20:1	87

substrate	R	dr (**29**:**30**)	yield (%)
28a	H	3:1	80
28b	TBDMS	nd	<5

substrate	R	dr (**32**:**33**)	yield (%)
31a	H	nd	<5
31b	TBDMS	>20:1	25
31c	Ac	na	32% of **34**

Figure 3.

Stereochemical outcomes of bicyclization reactions using substrates with proto-A-ring oxygen functional groups

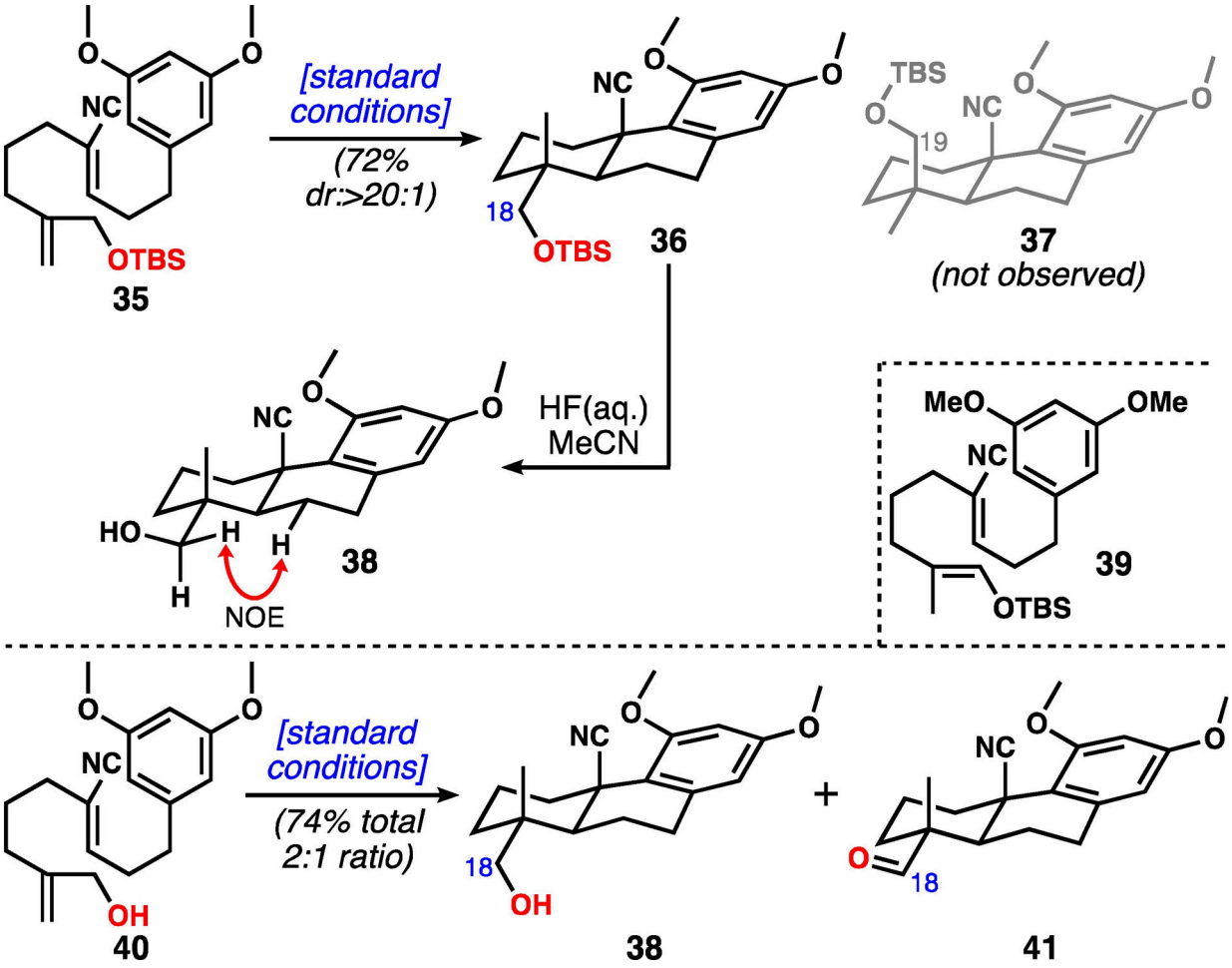
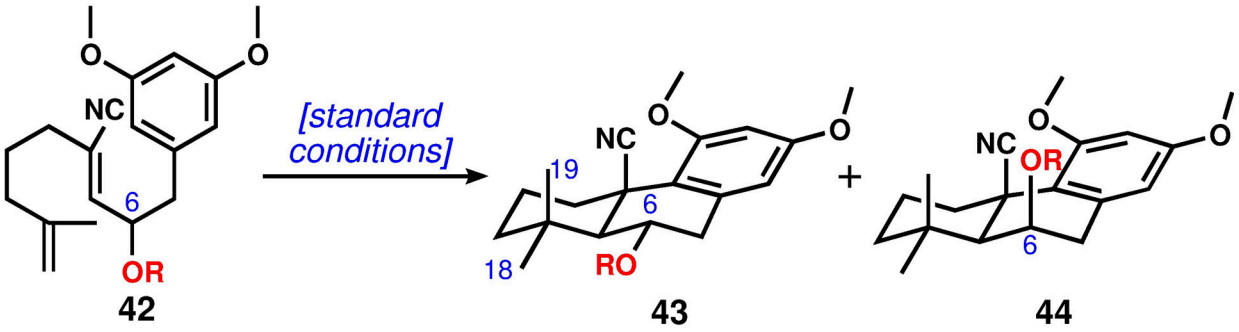


Figure 4.

Surprisingly high diastereoselectivity for equatorial (C18) disposition of oxygenation in bicyclizations of allylic alcohol derivatives



42 43 44

substrate	R	dr (**43**:**44**)	yield (%)
42a	Ac	1:1.1	64
42b	TBDMS	nd	<5

45 46 47

substrate	R	dr (**46**:**47**)	yield (%)
45a	H	1:1.3	65
45b	TBDMS	1:1	73

Figure 5.

Proto-B-ring oxygenation is tolerated, but has little impact on overall reaction diastereoselectivity

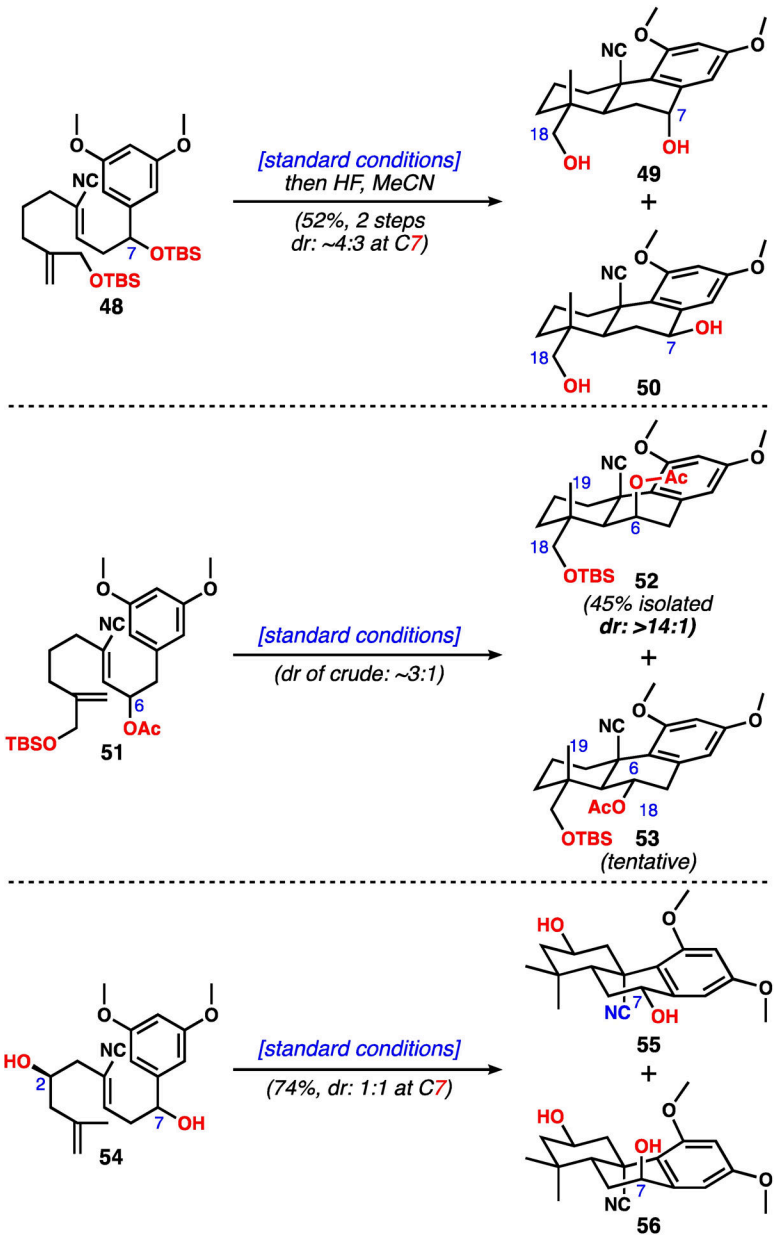
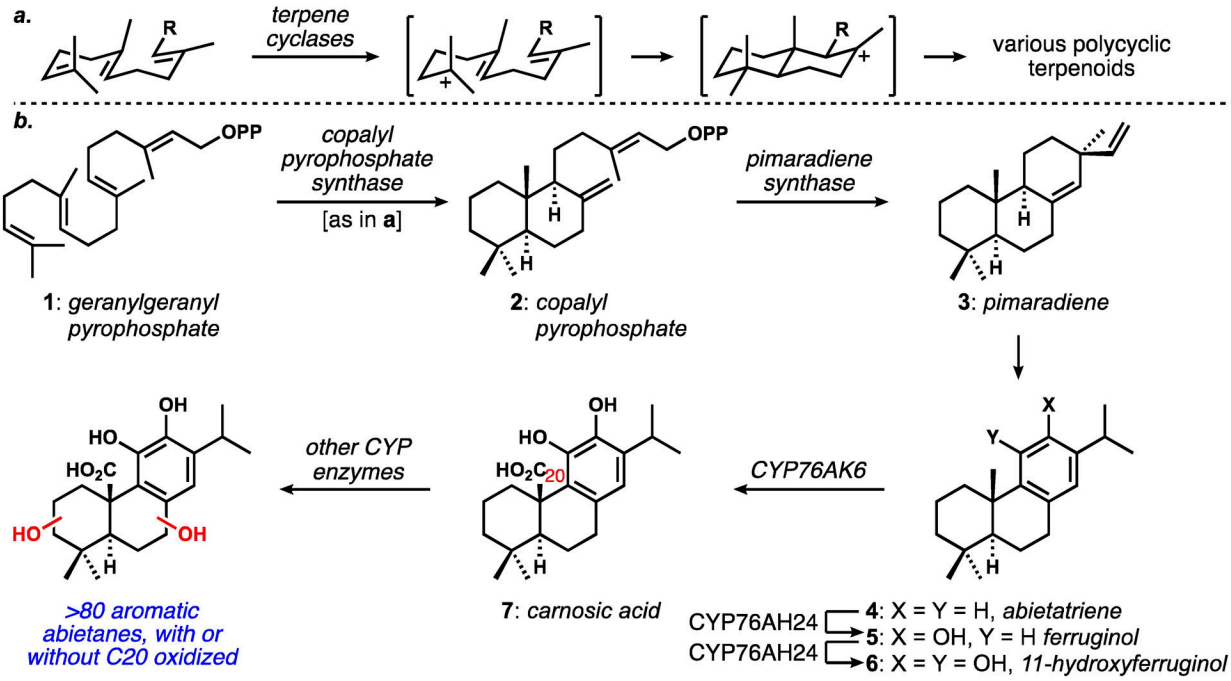
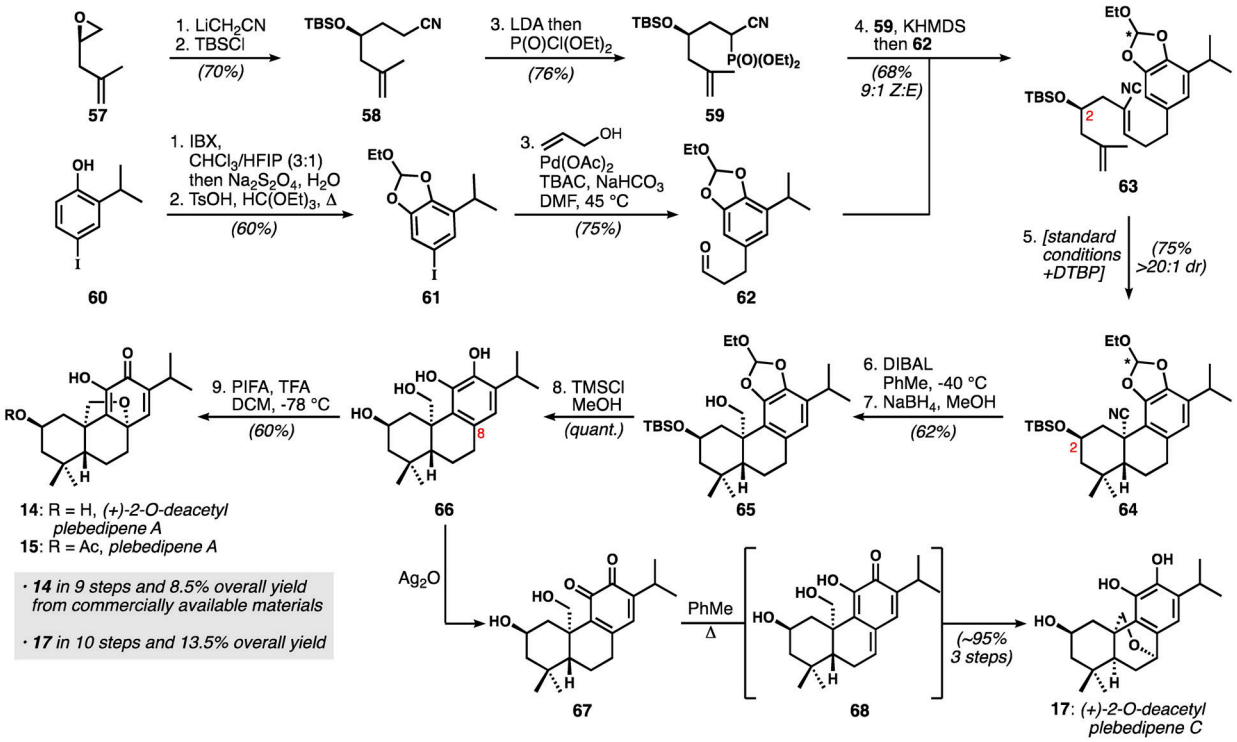


Figure 6.
Radical bicyclizations of doubly oxygenated substrates



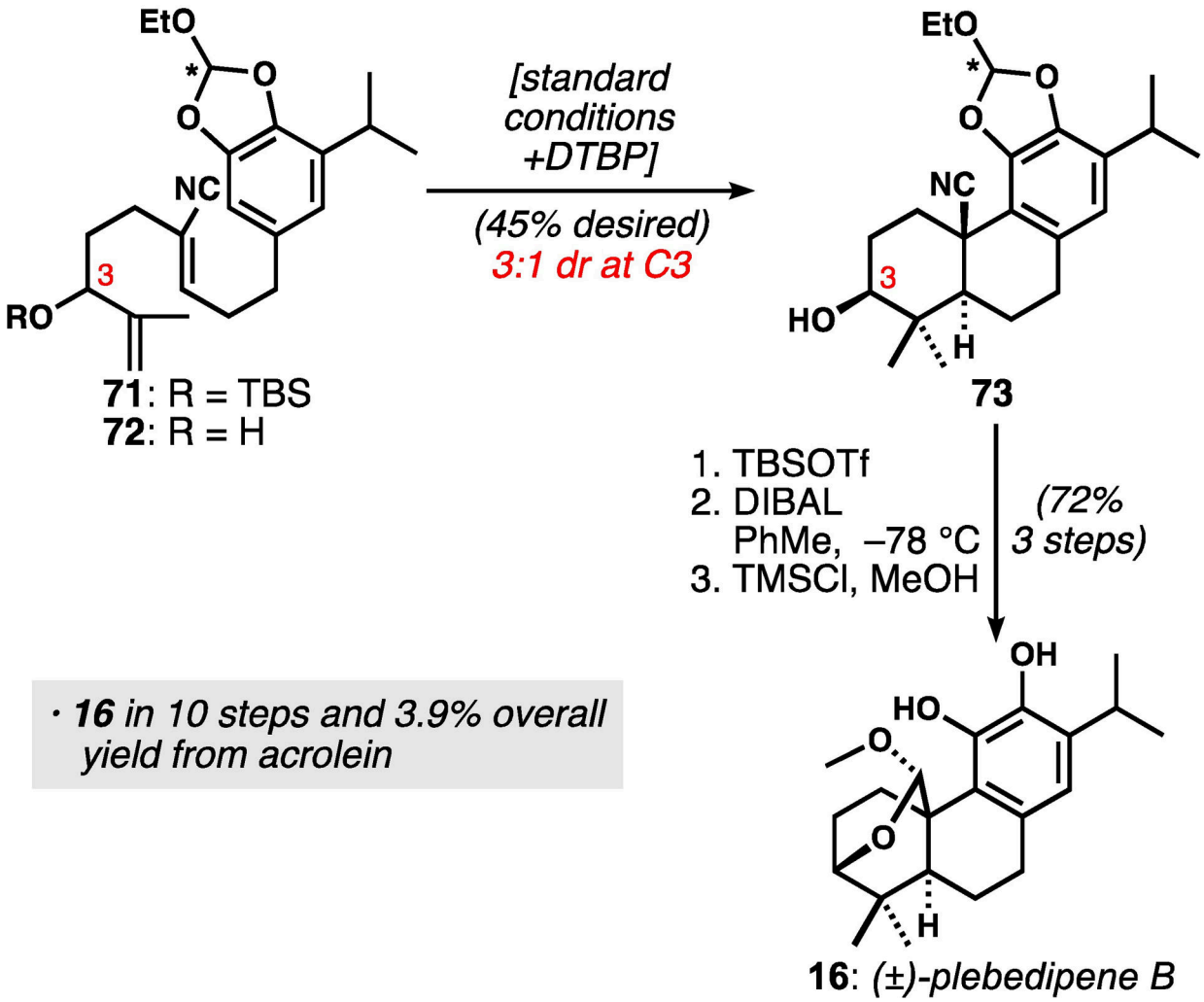
Scheme 1.

a. Typical *trans*-decalin formation by cationic bicyclizations of oligoisoprenes. ***b.*** Overview of the biosynthesis of oxidized aromatic abietane diterpenoids.



Scheme 2.

Enantiospecific, stereoselective syntheses of (+)-2-*O*-deacetyl plebedipenes A and C[35]



Scheme 3.
Synthesis of (±)-plebedipene B