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Enantioselective Alcohol C-H Functionalization for Polyketide Construction: Unlocking Redox-Economy and Site-Selectivity for Ideal Chemical Synthesis

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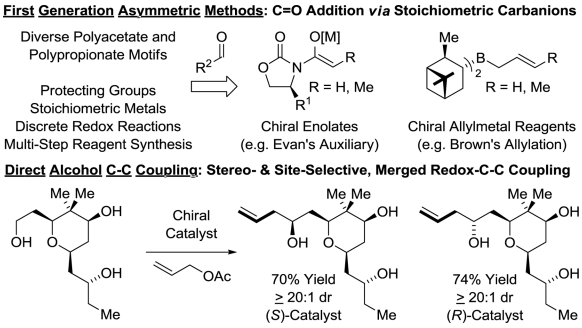
Abstract

The development and application of stereo- and site-selective catalytic methods that directly convert lower alcohols to higher alcohols are described. These processes merge the characteristics of transfer hydrogenation and carbonyl addition, exploiting alcohols and π-unsaturated reactants as redox pairs, which upon hydrogen transfer generate transient carbonyl-organometal pairs *en route* to products of C-C coupling. Unlike classical carbonyl additions, stoichiometric organometallic reagents and discrete alcohol-to-carbonyl redox reactions are not required. Additionally, due to a kinetic preference for primary alcohol dehydrogenation, the site-selective modification of glycols and higher polyols is possible, streamlining or eliminating use of protecting groups. The total syntheses of several iconic type I polyketide natural products were undertaken using these methods. In each case, the target compounds were prepared in significantly fewer steps than previously achieved.

Graphical Abstract



Introduction to Ideal Chemical Synthesis

The most authentic displays of efficient chemical synthesis are evident where economic selective pressure is greatest: the realm of commodity chemical manufacture. Thus, it is

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ASSOCIATED CONTENT

Supporting Information. Graphical summaries of prior total syntheses of neopeltolide, psymberin (irciniastatin A), mandelalide, oridamycins, xiamycin A, trienomycins, roxaticin, bryostatins, swinholide, erythromycins, cyanolide A, clavosolide A, zincophorin and cryptocaryol A. This material is available free of charge *via* the internet at http://pubs.acs.org

instructive to consider the two largest volume applications of homogenous metal catalysis (Figure 1), hydroformylation (the oxo-process)[1] and methanol carbonylation (the Monsanto/Cativa processes).[2] Both are C-C bond formations, both employ noble metal catalysts (rhodium and iridium), and both are byproduct-free. These processes speak to the fundamental significance of C-C bond construction in chemical synthesis, and reveal that a principal characteristic of a "process-relevant" method is the ability to transform an abundant, ideally renewable feedstock to a value-added product in the absence of stoichiometric byproducts.[3]

In multi-step chemical synthesis, an inverse correlation between complexity and efficiency is observed and may be quantified by E-factor analysis.[4] For example, dioctyl phthalate, a simple industrial plasticizer, is prepared through a 4-step linear sequence in which water is the only stoichiometric byproduct (Figure 1).[5] In contrast, the commercial manufacturing route for eribulin (Halaven), a highly complex polyketide-based therapeutic agent, comprises a total of 65 steps.[6] While the synthesis of eribulin represents an heroic milestone, half of the transformations are oxidation level adjustments and protecting group manipulations and nearly every step generates stoichiometric byproducts (Figure 1). The juxtaposition of these two syntheses reveals a technological gap and, more importantly, defines an opportunity for innovation: the development of stereo- and site-selective C-C bond formations accompanied by the addition, re-distribution or removal of hydrogen.

Redox-economic methods[7] for site-selective[8] skeletal assembly should dramatically impact synthetic efficiency, as they bypass discrete oxidation level adjustments and use of protecting groups.[9] As demonstrated by the benchmark provided by eribulin, in complex settings such transformations may represent over half the steps of a typical synthetic route even after intensive process optimization.[10] Hendrickson's view on synthetic efficiency[11] tacitly recognizes the significance of merged redox-construction events[7] and isomer-selective transformations,[12] including site-selective processes[8] for protecting group-free chemical synthesis.[9] Considerations of "process relevance," including atom-economy,[3] the minimization of preactivation (the degree of separation between reagent and feed-stock)[13] and the principles of green chemistry[14] provide a more complete perspective.

Guided by these concepts, we have developed a broad, new suite of catalytic methods for the direct stereo- and site-selective conversion of lower alcohols to higher alcohols.[15] These processes merge the characteristics of transfer hydrogenation with carbonyl addition, exploiting the native reducing ability of alcohols to drive generation of transient carbonyl-organometal pairs. Unlike classical synthetic sequences involving carbonyl addition, discrete alcohol-to-carbonyl redox reactions and use of premetalated *C*-nucleophiles are not required. Most remarkably, due to a kinetic preference for primary alcohol dehydrogenation, these methods may be applied to the site-selective (protecting group-free) modification of glycols and higher polyols.[16] In this perspective, we describe how this new technology has streamlined type I polyketide construction. Iconic type I polyketide natural products were targeted in order to obtain the highest number of benchmarks. As any given transformation is amenable to optimization, the fundamental metric of step count is applied as the primary indicator of strategic efficiency.[17]

Alcohol C-C Coupling for Polyketide Construction

The commercialization of erythromycin A (1952)[18] and subsequent discoveries of amphotericin B (1955)[19] and rifamycin B (1957)[20] comprise a turning point in both human medicine and synthetic organic chemistry. These natural products belong to the "polyketide" class of secondary metabolites - a broad and structurally diverse family of compounds that are used to treat a variety of indications (Figure 2).[21] Approximately 20% of the top-selling small molecule drugs are polyketides.[22] Remarkably, soil bacteria are the principal source of these compounds, yet less than 5% of soil bacteria are amenable to culture with many phyla having eluded culture completely.[23] Hence, one may assume that as methods for bacterial cultivation improve, polyketides will play an even more pervasive role in human medicine.

The impact of polyketides on synthetic organic chemistry has been profound. The challenges posed by these complex structures drove enormous advances in the development of stereoselective methods for carbonyl addition, culminating in a "first generation lexicon" largely centered on the use of asymmetric aldol reactions,[24] as exemplified by Evans' reagents,[25] and carbonyl allylmetalations,[26] as exemplified by Brown's allyl-/crotylboron reagents (Figure 3).[27] Despite the availability of this technology, all commercial polyketide-based drugs, with the exception of eribulin, are prepared by fermentation or semi-synthesis. *De novo* syntheses of polyketide-related structures that rely on these first-generation technologies are generally too lengthy for commercial application due in large part to (a) the separation of redox and skeletal construction events, and (b) the persistent requirement of protecting groups. As shown in this perspective, new capabilities inherent to direct alcohol C-H functionalization, namely, C-C coupling in the absence of protecting groups or discrete alcohol-to-carbonyl redox reactions (Figure 3), not only streamline polyketide construction, but evoke a shift in retrosynthetic paradigm.

Iridium[28] and ruthenium[29] complexes have found the greatest use in metal catalyzed transfer hydrogenation, and in our own asymmetric alcohol C-C couplings.[15] Novel cyclometalated π-allyliridium *ortho-C,O*-benzoate complexes derived from $[Ir(cod)Cl]_2$, allyl acetate, various 4-substituted-3-nitrobenzoic acids and axially chiral bis(phosphine) ligands have proven especially effective (Figure 4). These robust air stable iridium(III) complexes can be generated *in situ* from their components or can be isolated by precipitation or even conventional flash silica gel chromatography. As illustrated in the indicated catalytic mechanism, these complexes promote C-C coupling through one of two distinct reaction pathways wherein alcohol oxidation is balanced by (a) C-X reductive cleavage or (b) C=C π-bond hydrometalation. The former pathway is rendered more efficient upon use of catalysts that embody more electron deficient *ortho-C,O*-benzoate moieties, which enhance Lewis acidity at iridium and, in turn, accelerate turn-over limiting carbonyl addition. Consistent with this interpretation, single crystal X-ray diffraction analysis of a series of π-allyliridium *ortho-C,O*-benzoate complexes reveals a lengthening of the C-Ir, O-Ir, and P-Ir bonds for more inductive 4-substituents, suggesting enhanced Lewis acidity at iridium.[30e]

Hydrometalative pathways are promoted by more electron rich *ortho-C,O*-benzoate moieties, which may be attributed to stabilization of the intermediate iridium hydride with respect to deprotonation.

Numerous enantioselective iridium catalyzed C-C couplings based on these mechanisms have been developed.[15] Those most relevant to polyketide construction include alcohol C-H allylation[30] (site-selective,[16,30f,g] bidirectional[30c]), *anti*-crotylation[31] (bidirectional[31c]), methallylation,[32] propargylation,[33a] α-(methyl)propargylation,[33b] *tert*-prenylation[34a,b] and *tert*-(hydroxy)prenylation (Figure 4).[34c] Additionally, enantioselective ruthenium catalyzed alcohol C-C couplings for polyketide construction have been developed. The ruthenium catalyzed reactions are based solely on hydrometalative pathways, and include methods for alcohol C-H *syn*-crotylation[35a,c] and *anti*-crotylation (Scheme 1).[35b,d]

While additional process optimization will be required to realize the full potential of these methods, these protocols nevertheless define a distinct “second generation lexicon” for type I polyketide construction. 6-Deoxy-erythronolide B,[36] the “Proteus” of polyketides, biogenic precursor to all erythromycin family members, served as an ideal testing ground. When first discovered, *de novo* construction of the erythromycins was deemed insurmountable.[42] However, beginning with Corey’s landmark synthesis of erythronolide B in 1978,[40a] over 18 total syntheses of erythromycin family members are now reported (Scheme 2).[36–41] This large body of prior art provided a unique opportunity to benchmark the impact of our methods on synthetic efficiency. As 6-deoxy-erythronolide B comprises 7 propionate subunits, our synthesis[36f] manifested as an exposition in carbonyl crotylation technology. The propionate-based triketide motif spanning C1–C6, a stereoquintet, was directly assembled *via* iridium catalyzed *anti*-diastereo- and enantioselective iridium double crotylation of 2-methyl-1,3-propane diol.[31c] As the minor enantiomer of the *mono*-adduct is converted to the *meso*-diastereomer,[43] the double crotylation delivers a single enantiomer. The C10–C13 propionate-based diketide stereoquartet was prepared through ruthenium catalyzed C-C coupling of butadiene and propanol to form the indicated product of *syn*-crotylation.[35c] These fragments were combined through esterification and ring-closing enyne metathesis[44] to form the 14-membered macrolide, enabling access to 6-deoxy-erythronolide B in only 14 steps (LLS), nearly 10 steps shorter than the prior shortest routes, the most concise construction of any erythronolide reported, to date (Scheme 2).

The enantioselective bidirectional bis(*anti*-crotylation) of 2-methyl-1,3-propane diol[31c] provided a concise means of preparing diverse type I polyketide natural products. For example, application of this method to the construction of (+)-zincophorin methyl ester,[45] which bears 13 stereogenic centers, enabled a remarkably concise 13 step (LLS) synthesis.[46i] The 5 previously reported syntheses range between 21–49 steps in length (LLS) (Scheme 3).[46a–h] Similarly, the C19–C27 stereoheptet of rifamycin S[20,47] and the C19–C25 stereoquintet of scytophycin C[48,49] could be assembled in a fraction of the steps previously required, representing formal syntheses of these compounds.[31c] Finally, using diol double crotylation[31c] in combination with site-selective diol allylation,[30g] a stereopolyad common to the swinholides[50–54] and numerous other type I polyketides,[52i,54,57] including saliniketal,[55] reidispongiolide[56] and premisakinolide,[57] could be prepared in a relatively short number of steps, constituting a formal synthesis of the latter (Scheme 4).[58]

Polyacetate substructures in the form of 1,3-polyols also represent an important motif in type I polyketide natural products. Double C-H allylation of 1,3-propane diol enables direct formation of an acetate-based triketide motif,[30c] which forms as a single enantiomer due to

the aforementioned amplification effect.[43] Notably, the same C_2-symmetric diol was prepared through a 7 step sequence involving 3 protecting group manipulations, two alcohol-to-aldehyde redox reactions and two carbonyl allylboration reactions (Scheme 5).[59] This bidirectional chain elongation can be deployed iteratively to form 1,3-polyol substructures evident in numerous oxo-polyene macrolides.[30c] For example (+)-roxaticin[60] incorporates a C_2-symmetric polyol substructure that is readily formed using three iterations of bidirectional alcohol C-H allylation. Functionalization of the enantiotopic primary alcohol termini *via* dehydration-cross-metathesis and alcohol C-H crotylation, respectively, set the stage for installation of the polyene motif using a second cross-metathesis followed by Horner-Wadsworth-Emmons olefination. Finally, macrolactonization followed by global deprotection delivered (+)-roxaticin in 20 steps (LLS) from 1,3-propanediol.[61f] Nine of ten C-C bonds formed in the longest linear sequence are made *via* metal catalysis with 6 C-C bonds formed *via* iridium catalyzed alcohol C-H allylation. This synthesis of (+)-roxaticin is 9–25 steps shorter than previous routes that employ conventional carbanion chemistry (Scheme 6).[61]

The bidirectional C-H allylation of 1,3-diols has proven effective in total syntheses of several other type I polyketides (Scheme 7). In the total synthesis of the macrodiolide cyanolide A,[63g] double C-H allylation of neopentyl glycol[30c] followed by tandem cross-metathesis-oxa-Michael cyclization provides rapid access to the highly substituted pyran core with complete control of diastereo- and enantioselectivity, enabling access to the natural product in less than half the steps previously required.[63] Bidirectional C-H allylation of neopentyl glycol also was used by De Brabander in the total synthesis of psymberin (irciniostatin A).[64a,i] The Floreancig synthesis of this compound employs a strategically related iridium catalyzed *mono*-allylation reaction.[64g] These two routes to psymberin (irciniostatin A) are the shortest reported, to date (Scheme 7).[64] In She's total synthesis of neopeltolide,[65q] the C_2-symmetric diol derived upon bidirectional C-H allylation of 1,3-propane diol is subjected to palladium catalyzed oxypalladation-alkoxycarbonylation to form the trisubstituted pyran core as a single diastereo- and enantiomer. A total of 18 total syntheses of neopeltolide have been reported.[65] Hence, it is remarkably that She's route,[65q] which employs bidirectional double C-H allylation is the second shortest (Scheme 7). Fürstner's total synthesis of mandelalide A[66a,c] showcases yet another means of elaborating the C_2-symmetric diol derived upon bidirectional C-allylation. Here, iodoetherification differentiates the olefin termini to define the structure of a trisubstituted pyran (Scheme 7). Finally, in the total synthesis of cryptocaryol A,[67f] the product of enantioselective diol double C-H allylation is subjected to ring-closing metathesis-cross metathesis to form an α-pyrone, which is converted to the natural product *via* aldol addition. This 8-step (LLS) synthesis of cryptocaryol A is fewer than half the steps of any prior approach.[67]

From these data it can be seen that the direct assembly of triketide motifs *via* bidirectional enantioselective diol C-H allylation can be applied across diverse contexts, evoking especially efficient strategies. For polyketides that embody higher degrees of structural complexity, streamlining or eliminating redox reactions and protecting groups becomes more challenging, and the nuanced marriage of strategy and methodology plays an increasingly important role. The bryostatins,[68] a broad family of marine macrolides with impressive biological properties,[69] offered a more stringent testing ground for our methods,

as well as numerous benchmarks in the form of 8 previous syntheses.[70a–g,i–k] In our total synthesis of bryostatin 7,[70h] the natural product is convergently assembled through the union of the indicated fragments, which are of roughly equal complexity (Scheme 8). Fragment A is prepared through bidirectional C-H allylation of 1,3-propane diol, which assembles the polyacetate substructure spanning C1-C7.[30c,71a] The *gem*-dimethyl moiety at C8, a common motif in type I polyketides typically generated through the agency of SAM-dependent *C*-methyltransferases, is formed through asymmetric Ir-catalyzed *tert*-prenylation.[34a] Fragment B is prepared through hydrogen-mediated alkyne-carbonyl reductive coupling.[71b] Using these methods, bryostatin 7 was prepared in 20 steps (LLS), the most concise route to any bryostatin family member reported to date (Scheme 8).[70h] This strategy also enabled concise entry to bryostatin analogues.[71c]

Merged redox and C-C bond construction events in the form of both hydrogenative and transfer hydrogenative methods were used in the total synthesis of trienomycins A and F.[72] Specifically, enantioselective ruthenium catalyzed alcohol C-H-*syn*-crotylation[35a] followed by chelation-controlled carbonyl dienylation was used to prepare the C11–C13 stereotriad. Enantioselective rhodium catalyzed acetylene-aldehyde reductive coupling[73] mediated by gaseous hydrogen forms a diene that ultimately is subjected to diene-diene ring closing metathesis to form the macrocycle. This approach is 14 steps shorter (LLS) than the prior syntheses of trienomycins A and F, and 8 steps shorter (LLS) than any prior synthesis of a triene-containing C17-benzene ansamycin (Scheme 9).[72]

Finally, application of our methodology beyond the testing ground of type I polyketides is now underway. As illustrated in the total synthesis of the terpene alkaloid oridamycin A (Scheme 10),[74d] diastereo- and enantioselective iridium catalyzed *tert*-(hydroxy)prenylation[34c] converts a simple γ-hydroxy ketone to the indicated diol bearing an all-carbon quaternary stereocenter with exceptional control of relative and absolute stereochemistry. Using this transformation, oridamycin A was prepared in 7 steps (LLS), representing the first asymmetric synthesis of oridamycin A and shortest route to any member of this compound class.[74]

Conclusions

As organic molecules are compounds composed of carbon and hydrogen, C-C bond formations accompanied by the addition, redistribution or removal of hydrogen represent a natural endpoint in the evolution of methods for efficient chemical synthesis. This concept initially led us to develop hydrogen-mediated reductive couplings of carbonyl compounds[75] and, there-from, transfer hydrogenative C-C couplings that directly convert lower alcohols to higher alcohols:[15] two new classes of catalytic C-C bond formations that bypass use of preformed carbanions. To benchmark the utility of these methods, total syntheses of several iconic type I polyketide natural products were undertaken. As shown in this perspective, a uniform increase in step-economy was observed in each case. Thus, by harnessing the native reducing ability of alcohols for the generation of transient carbonyl-organometal pairs, stereo- and site-selective skeletal assembly may be achieved in a manner that streamlines or eliminates the use of protecting groups and discrete alcohol-to-carbonyl redox reactions.

These methods reinvent the chemistry of polyketide construction and, more broadly, the chemistry of carbonyl addition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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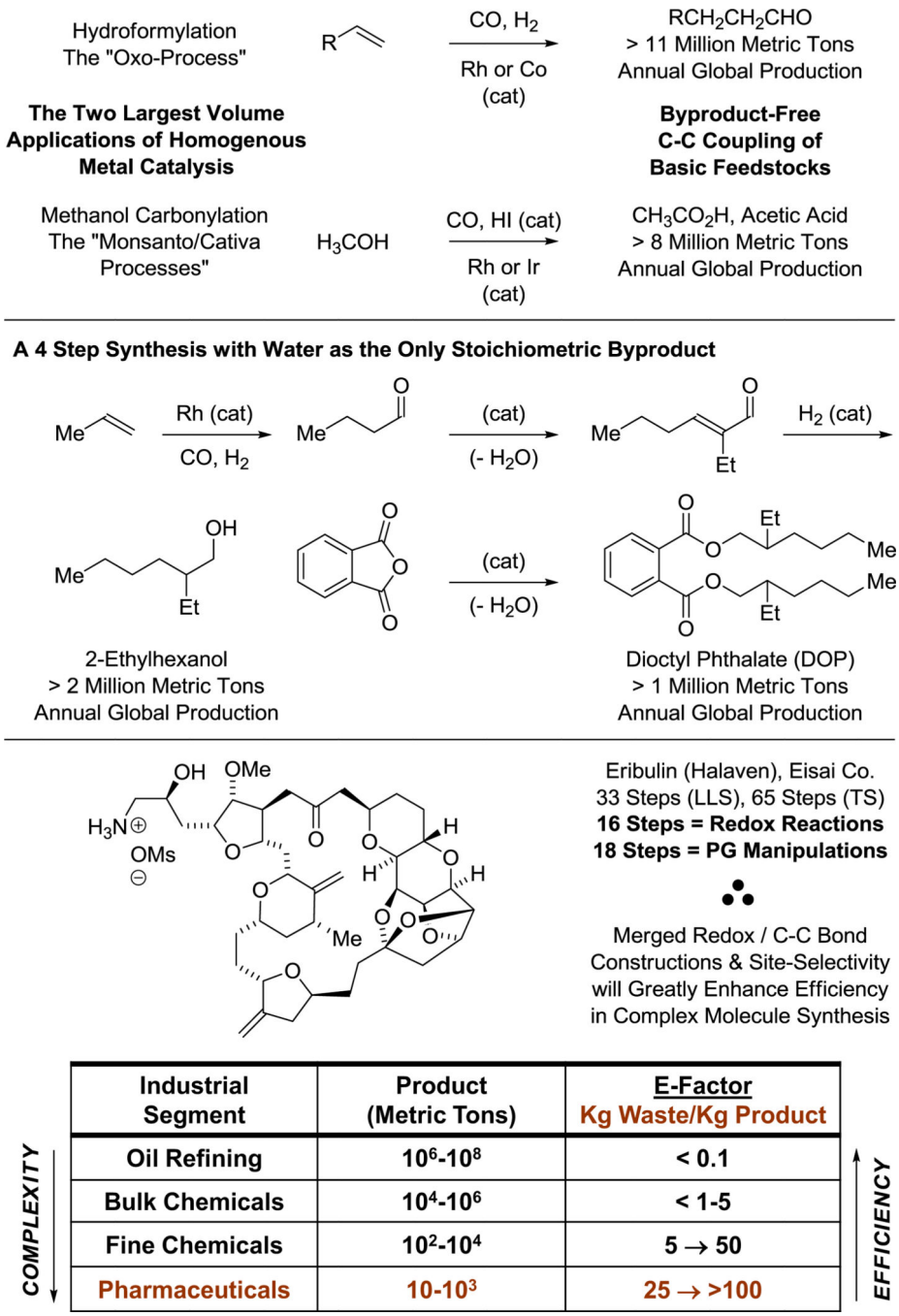


Industrial Segment	Product (Metric Tons)	E-Factor Kg Waste/Kg Product
Oil Refining	10^6-10^8	< 0.1
Bulk Chemicals	10^4-10^6	< 1-5
Fine Chemicals	10^2-10^4	5 → 50
Pharmaceuticals	10-10^3	25 → >100

Figure 1.

Economic selective pressure as a driver for synthetic efficiency and the technological gap *vis-à-vis* methods for complex molecule construction.

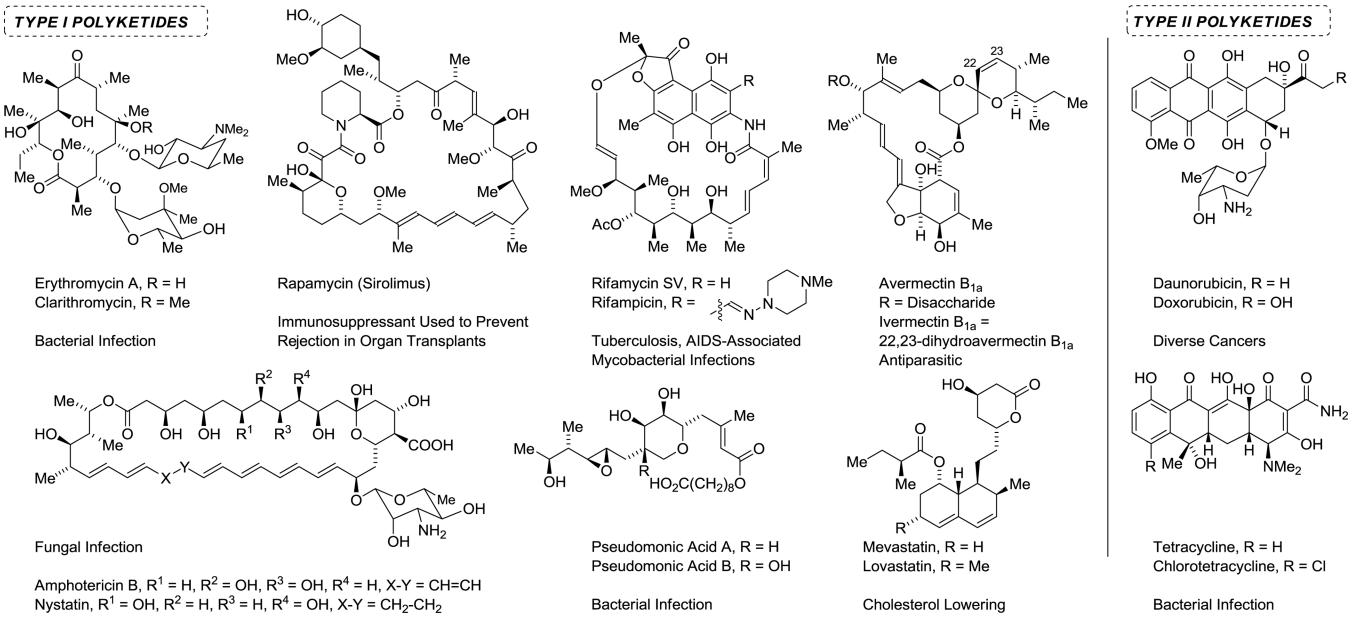


Figure 2.
Selected polyketide natural products and semi-synthetic congeners used in human medicine.

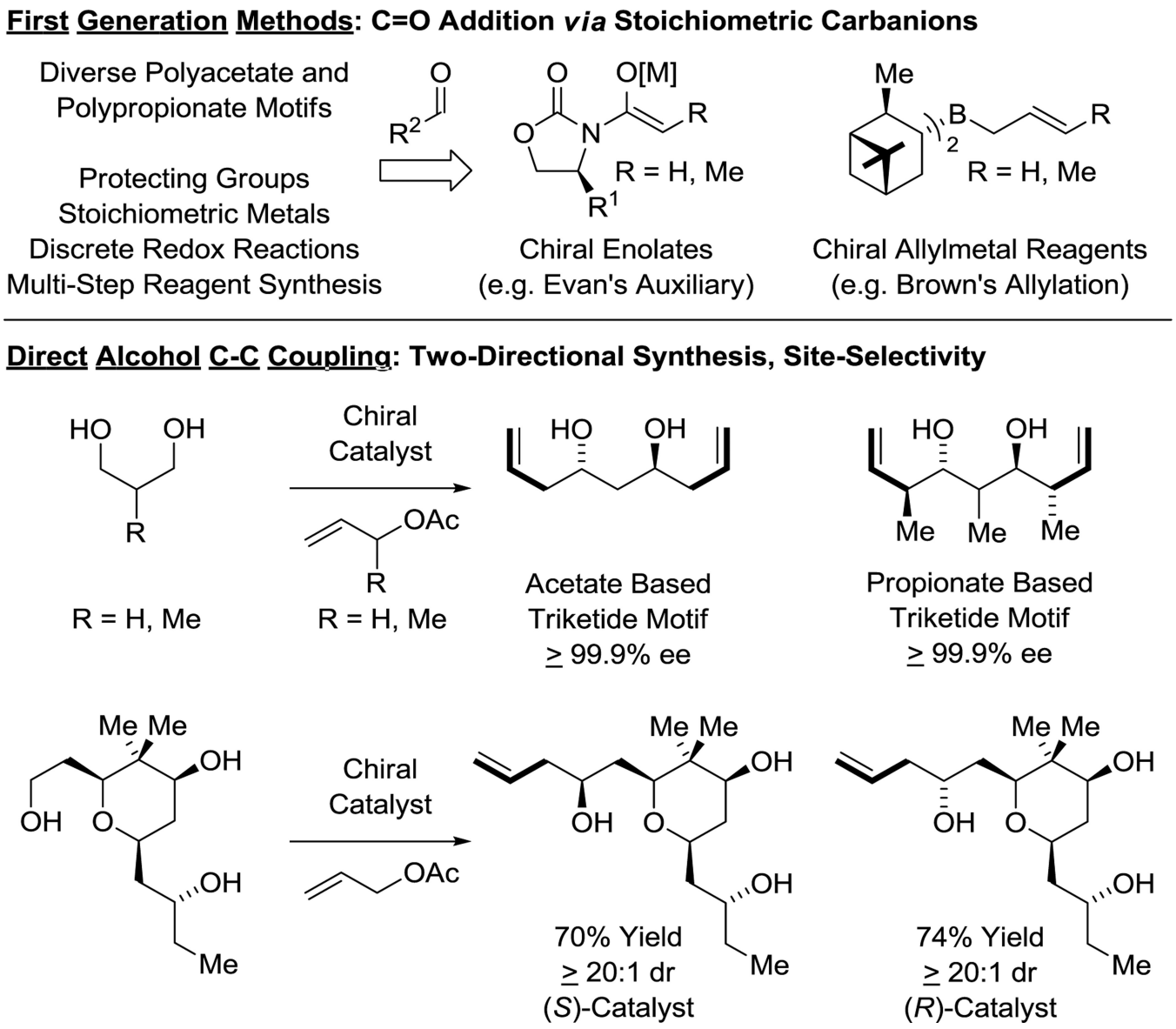


Figure 3.

First-generation methods for polyketide construction and new capabilities availed by direct alcohol C-C coupling.

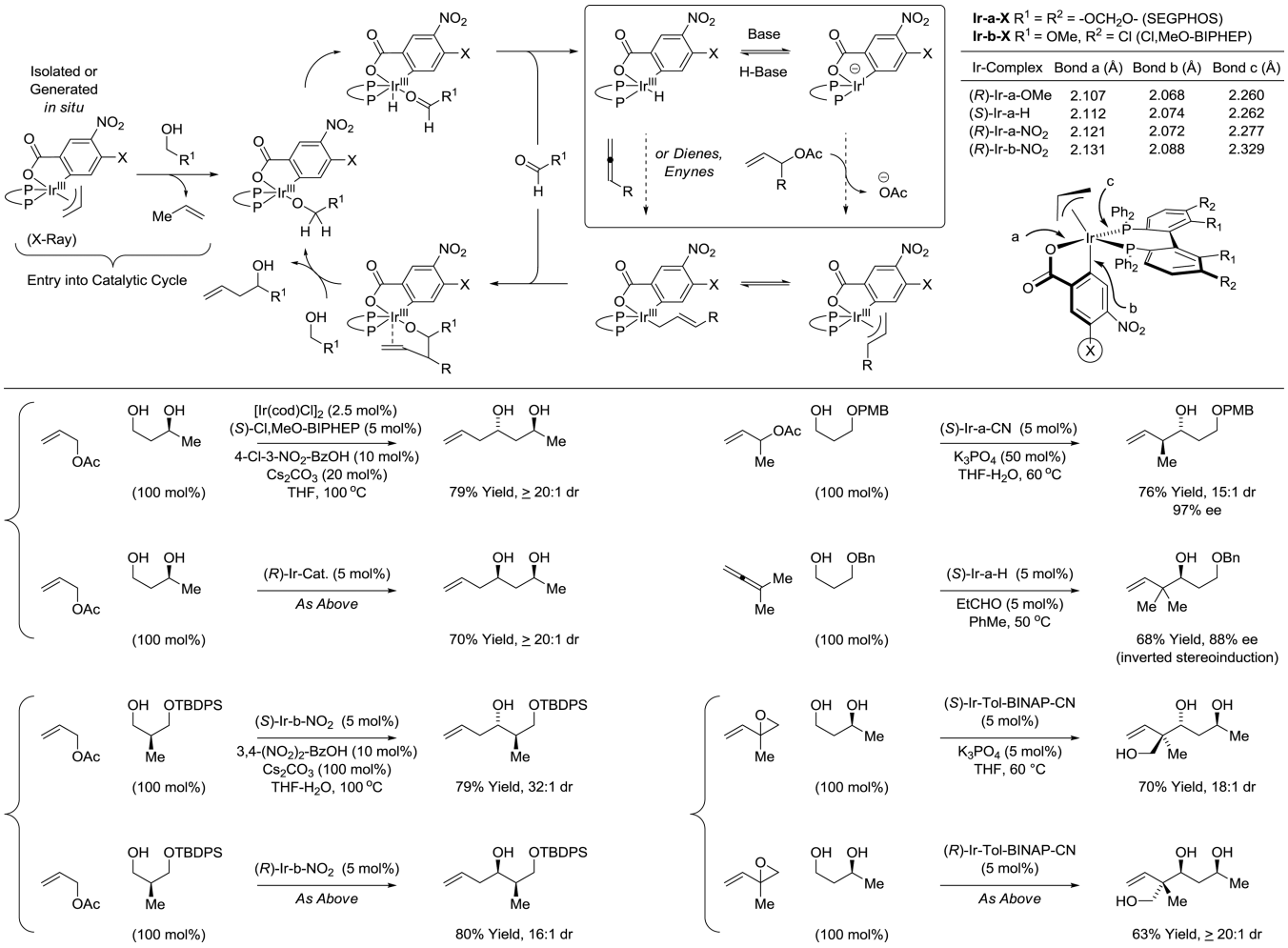


Figure 4.

General mechanism for iridium catalyzed C-C coupling of primary alcohols and selected transformations applicable to polyketide construction: allylation, crotylation, *tert*-prenylation and *tert*-(hydroxy)prenylation.

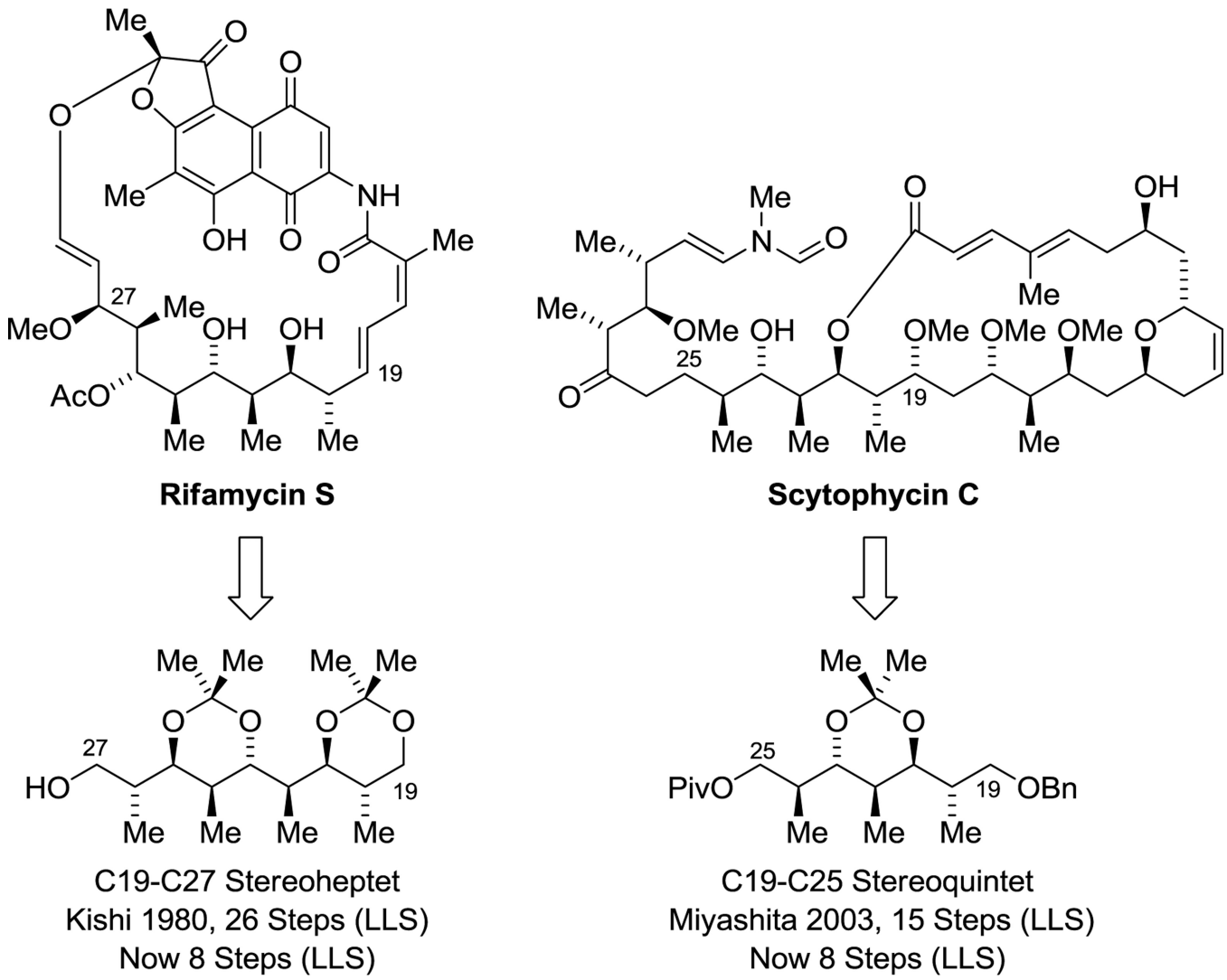
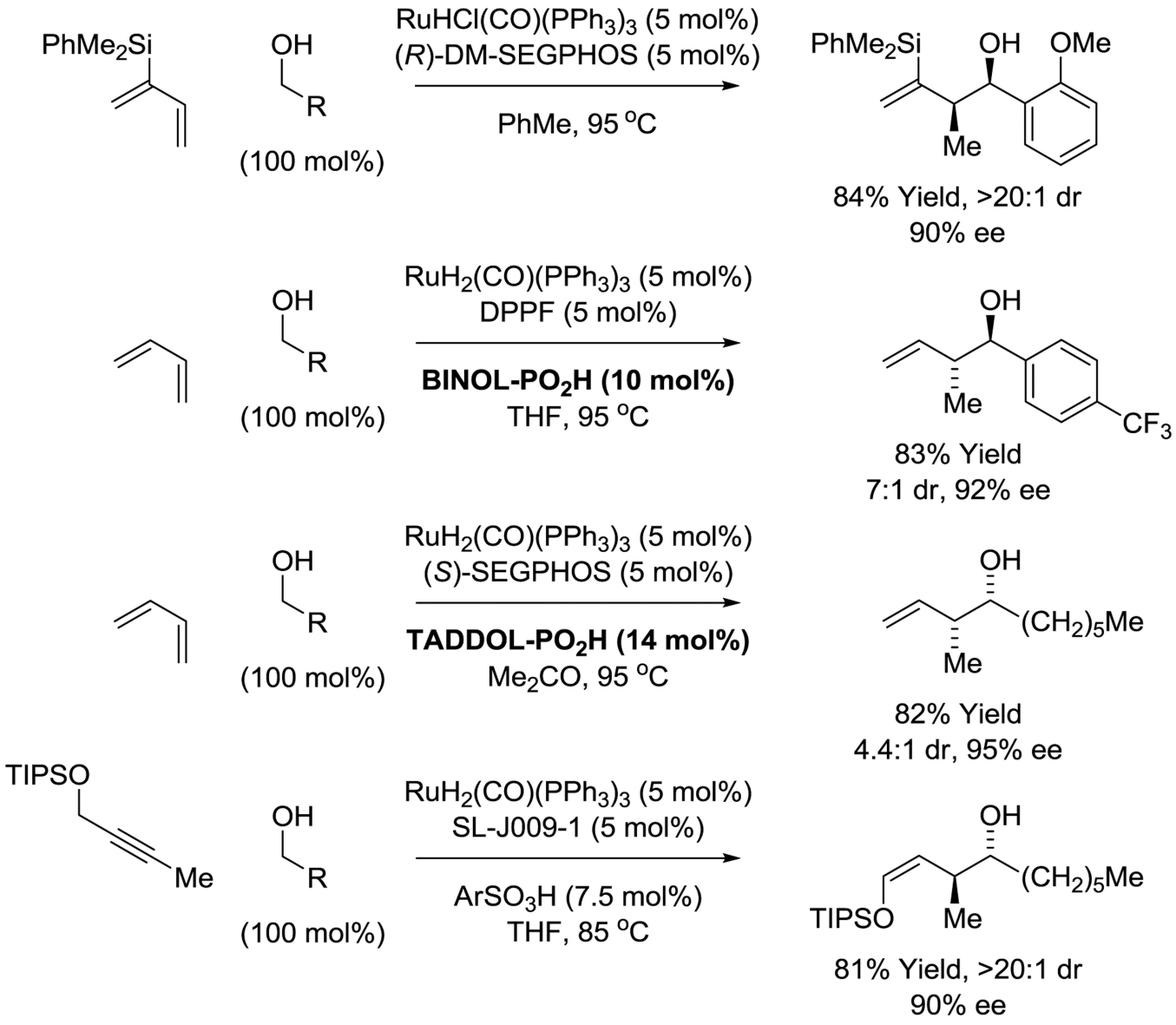


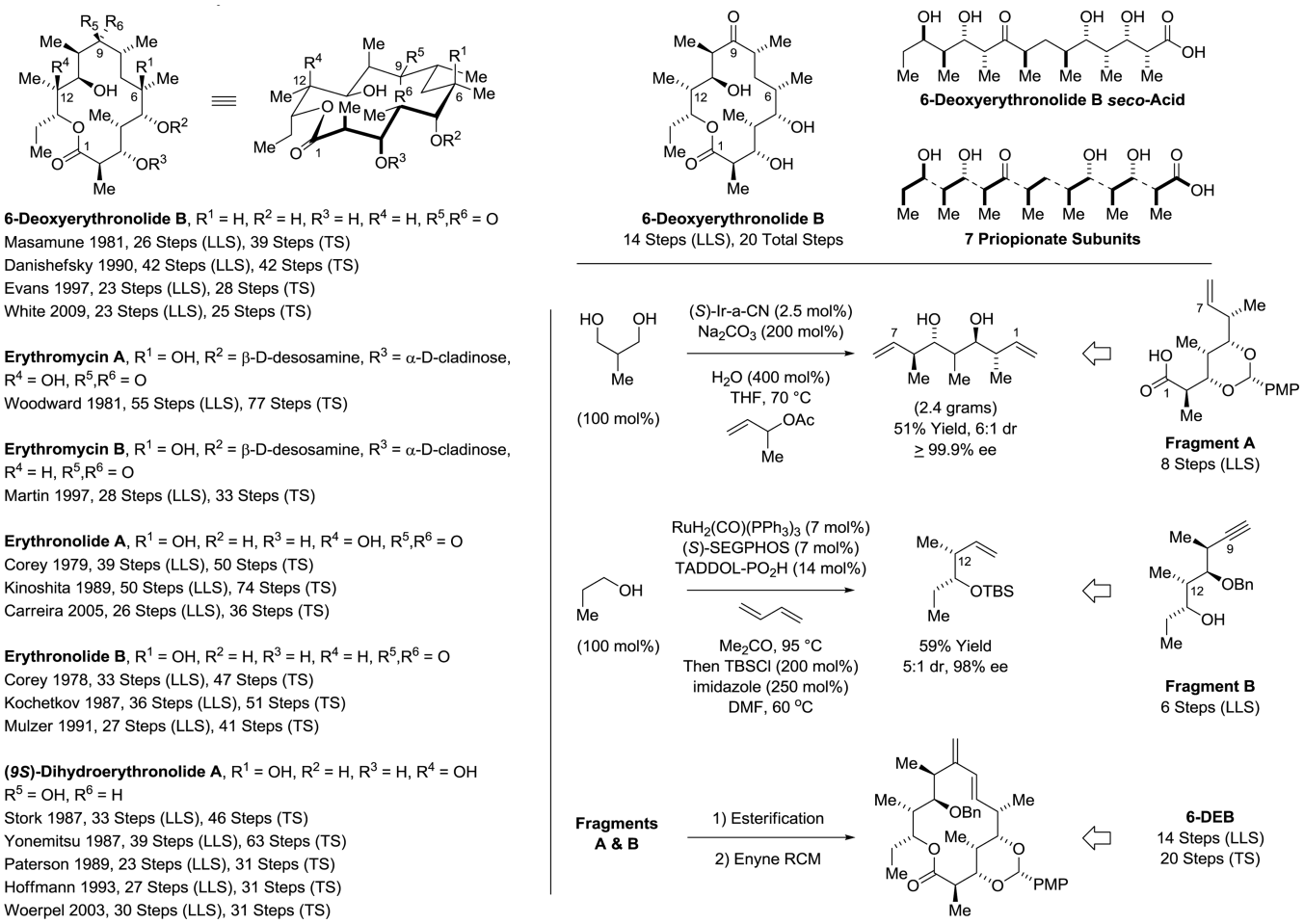
Figure 5.

Formal syntheses of rifamycin S and scytophycin C *via* enantioselective C-H crotylation of 2-methyl-1,3-propane diol.a

[a]For graphical summaries of prior total syntheses, see Supporting Information.



Scheme 1.
Enantioselective ruthenium catalyzed alcohol C-H crotylation.



6-Deoxyerythronolide B, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5,R^6 = O
Masamune 1981, 26 Steps (LLS), 39 Steps (TS)
Danishefsky 1990, 42 Steps (LLS), 42 Steps (TS)
Evans 1997, 23 Steps (LLS), 28 Steps (TS)
White 2009, 23 Steps (LLS), 25 Steps (TS)

Erythromycin A, R^1 = OH, R^2 = β-D-desosamine, R^3 = α-D-cladinose, R^4 = OH, R^5,R^6 = O
Woodward 1981, 55 Steps (LLS), 77 Steps (TS)

Erythromycin B, R^1 = OH, R^2 = β-D-desosamine, R^3 = α-D-cladinose, R^4 = H, R^5,R^6 = O
Martin 1997, 28 Steps (LLS), 33 Steps (TS)

Erythronolide A, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH, R^5,R^6 = O
Corey 1979, 39 Steps (LLS), 50 Steps (TS)
Kinoshita 1989, 50 Steps (LLS), 74 Steps (TS)
Carreira 2005, 26 Steps (LLS), 36 Steps (TS)

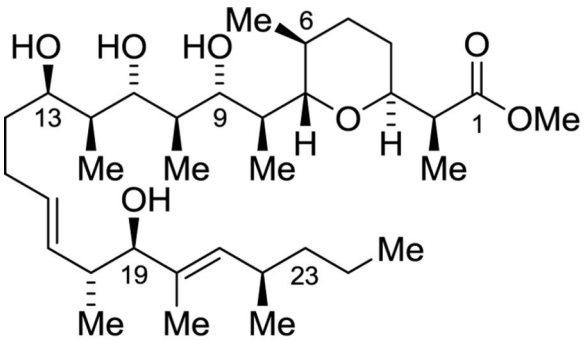
Erythronolide B, R^1 = OH, R^2 = H, R^3 = H, R^4 = H, R^5,R^6 = O
Corey 1978, 33 Steps (LLS), 47 Steps (TS)
Kochetkov 1987, 36 Steps (LLS), 51 Steps (TS)
Mulzer 1991, 27 Steps (LLS), 41 Steps (TS)

(*9S*)-Dihydroerythronolide A, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH R^5 = OH, R^6 = H
Stork 1987, 33 Steps (LLS), 46 Steps (TS)
Yonemitsu 1987, 39 Steps (LLS), 63 Steps (TS)
Paterson 1989, 23 Steps (LLS), 31 Steps (TS)
Hoffmann 1993, 27 Steps (LLS), 31 Steps (TS)
Woerpel 2003, 30 Steps (LLS), 31 Steps (TS)

Scheme 2.

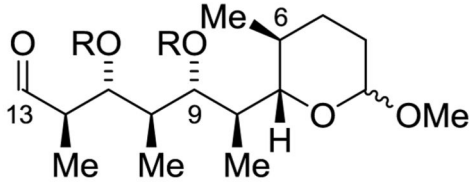
Prior total syntheses of selected erythromycin family members and total synthesis of 6-deoxyerythronolide B *via* enantioselective alcohol C-H crotylation.a

[a]For graphical summaries of prior total syntheses, see Supporting Information. LLS = Longest Linear Sequence; TS = Total Steps.

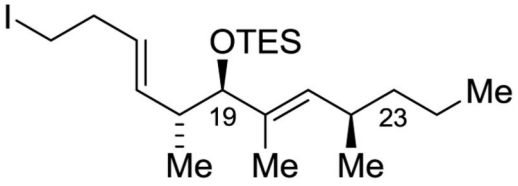


Zincophorin Methyl Ester
13 Steps (LLS), 25 Steps (TS)

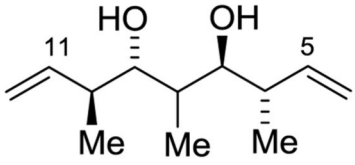
Danishefsky 1987, 35 Steps (LLS), 61 Steps (TS)
Cossy 2003, 30 Steps (LLS), 56 Steps (TS)
Miyashita 2004, 38 Steps (LLS), 53 Steps (TS)
Leighton 2011, 21 Steps (LLS), 33 Steps (TS)
Guindon 2015, 49 Steps (LLS), 70 Steps (TS)



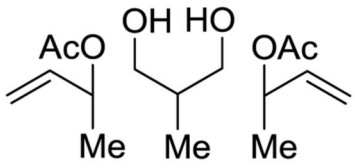
Fragment A (R= TES)
10 Steps (LLS)

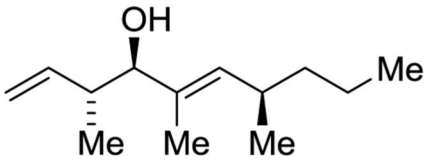


Fragment B
8 Steps (LLS)

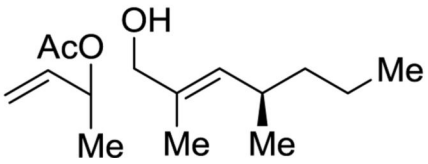


(*S*)-Ir-a-CN ↑ (cat)





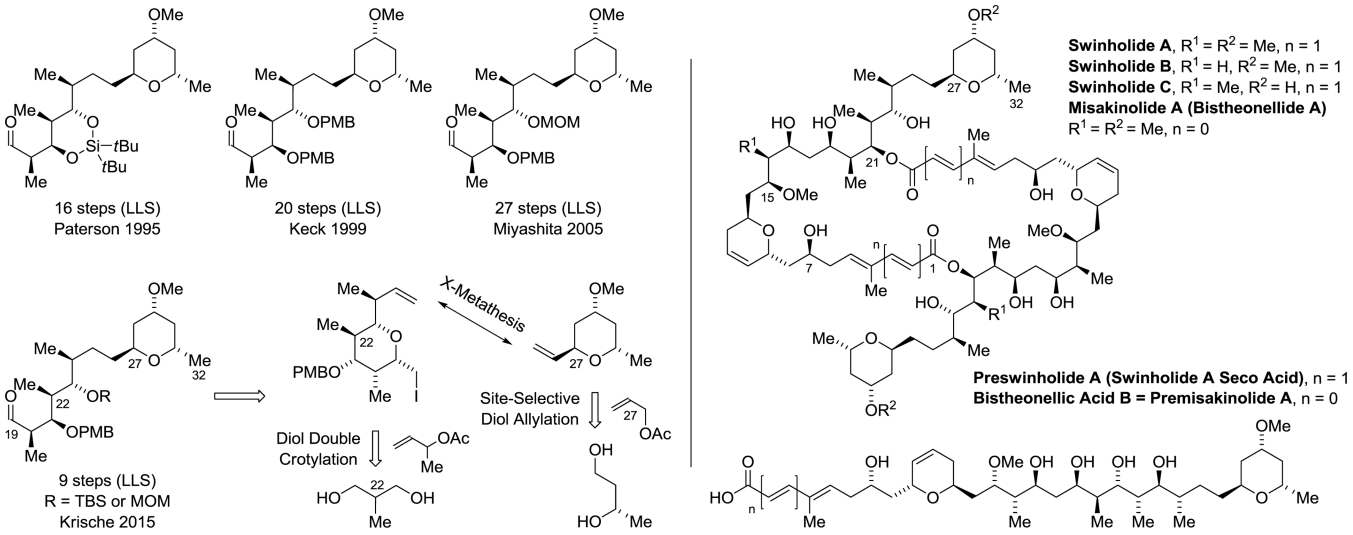
(cat) ↑ (*R*)-Ir-a-CN



Scheme 3.

Total synthesis of (+)-zincophorin methyl ester *via* enantioselective alcohol C-H crotylation.a

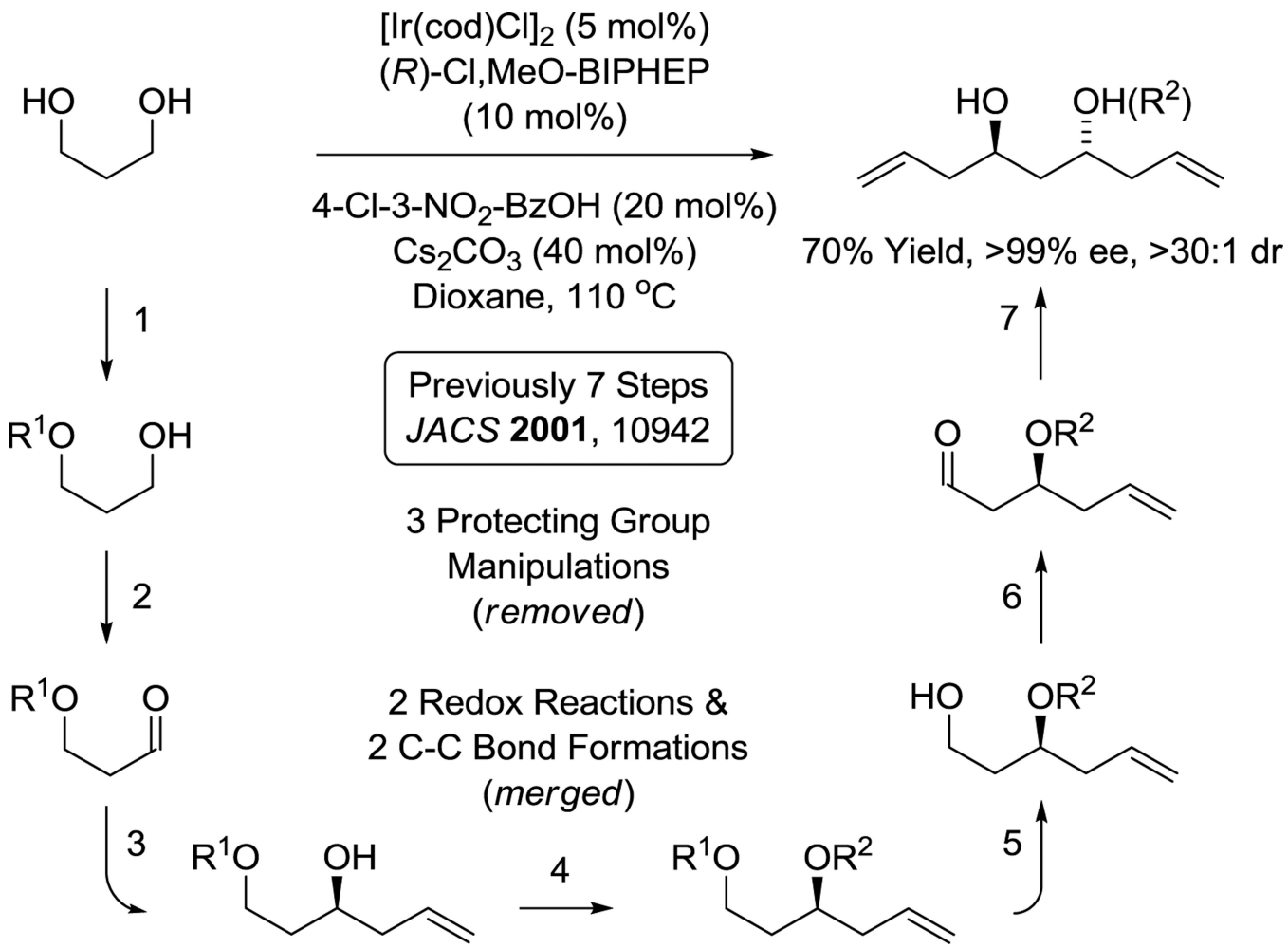
[a]For graphical summaries of prior total syntheses, see Supporting Information.



Scheme 4.

Formal synthesis of premisakinolide A and C(19)–C(32) of swinholide A *via* site-selective C-H allylation and crotylation of unprotected diols.a

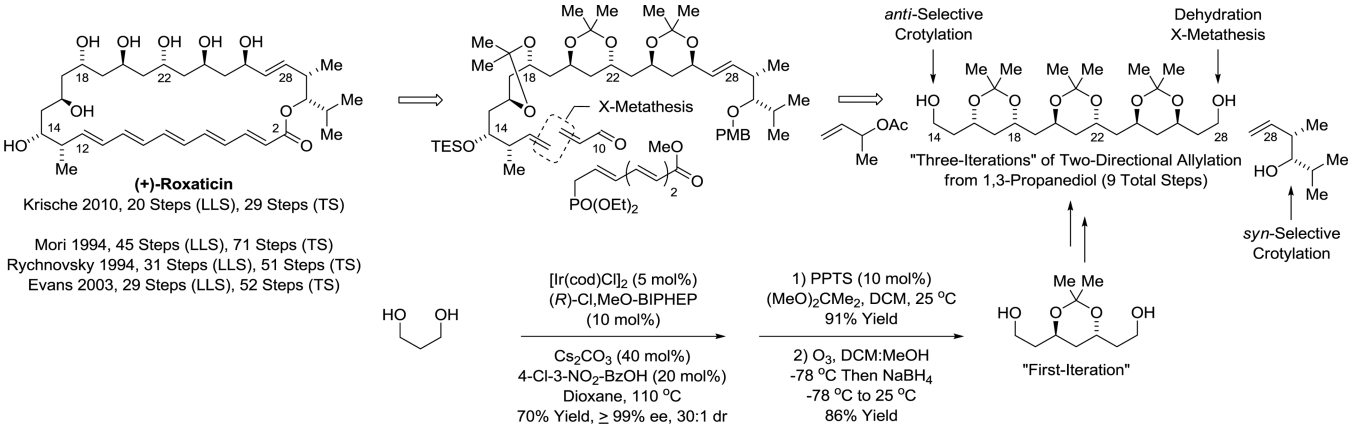
[a]For graphical summaries of prior syntheses, see Supporting Information.



Scheme 5.

Direct generation of an acetate-based triketide motif *via* bidirectional enantioselective C-H allylation of 1,3-propane diol.a

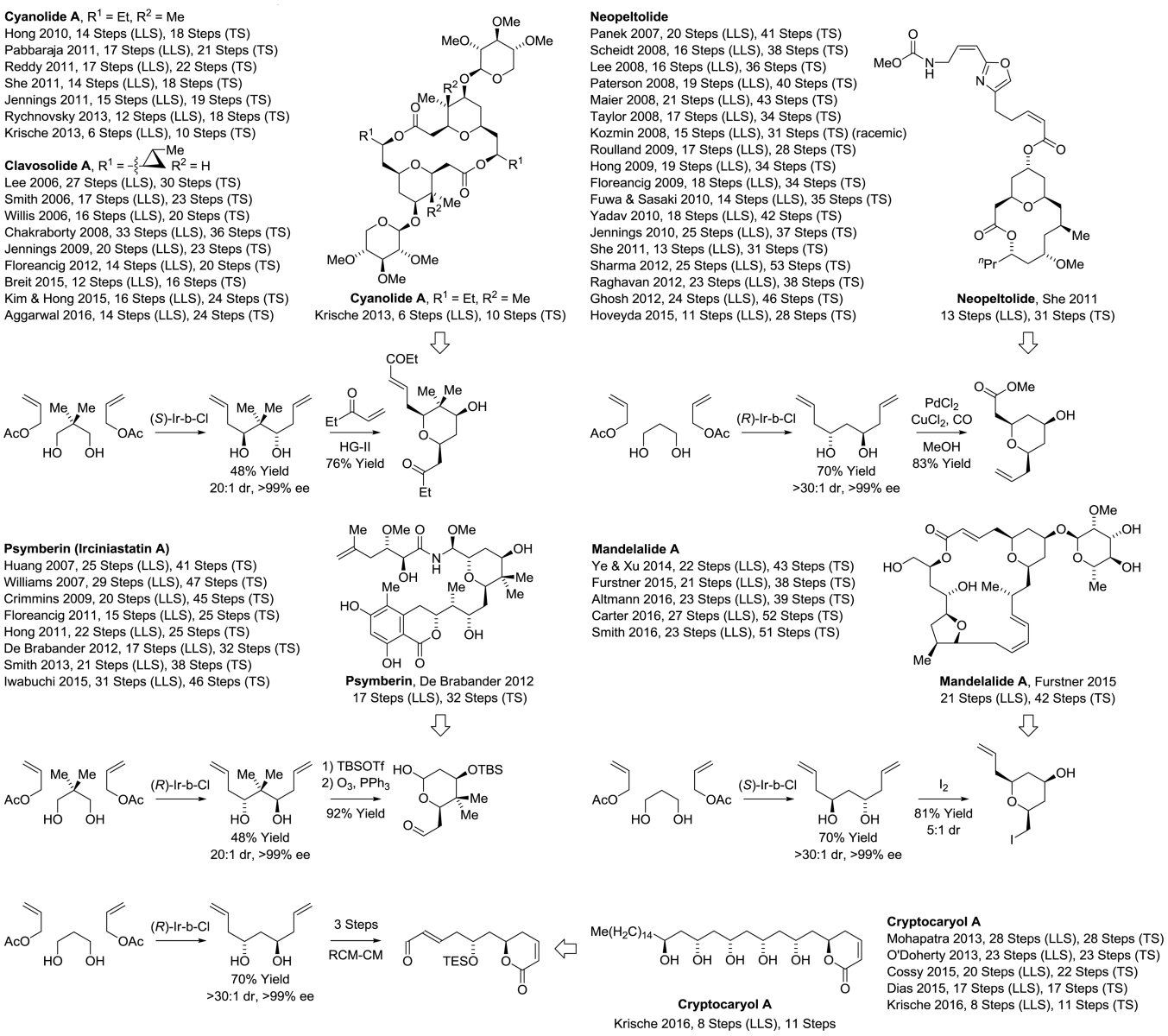
[a]For further experimental details, see references 30c, 61f, 67e, 70h.



Scheme 6.

Total synthesis of the oxo-polyene macrolide (+)-roxaticin *via* enantioselective alcohol C-H allylation and crotylation.a

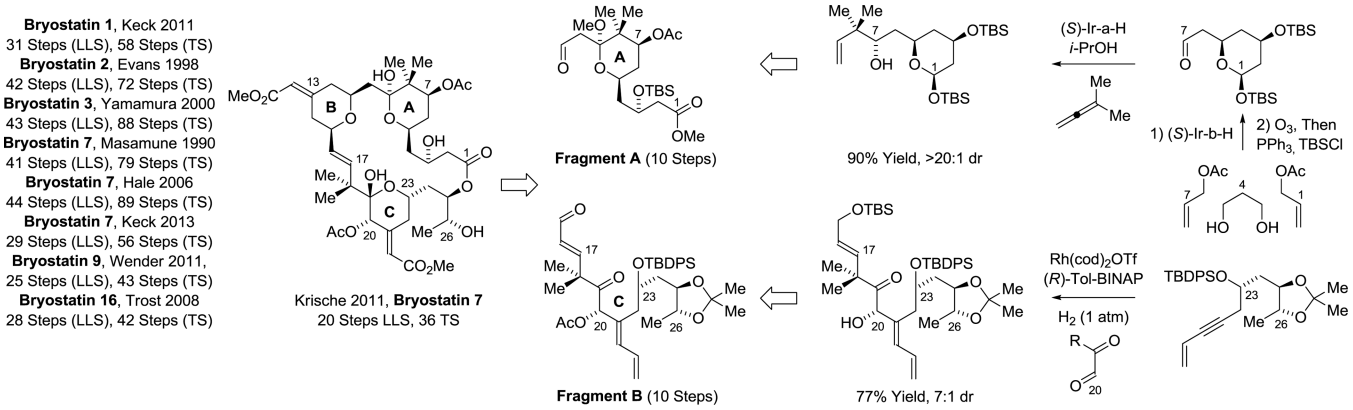
[a]For graphical summaries of prior total syntheses, see Supporting Information.



Scheme 7.

Total syntheses of cyanolide A, neopeltolide, psymberin (irciniastatin A), mandelalide and cryptocaryol A *via* bidirectional enantioselective alcohol C-H allylation.a

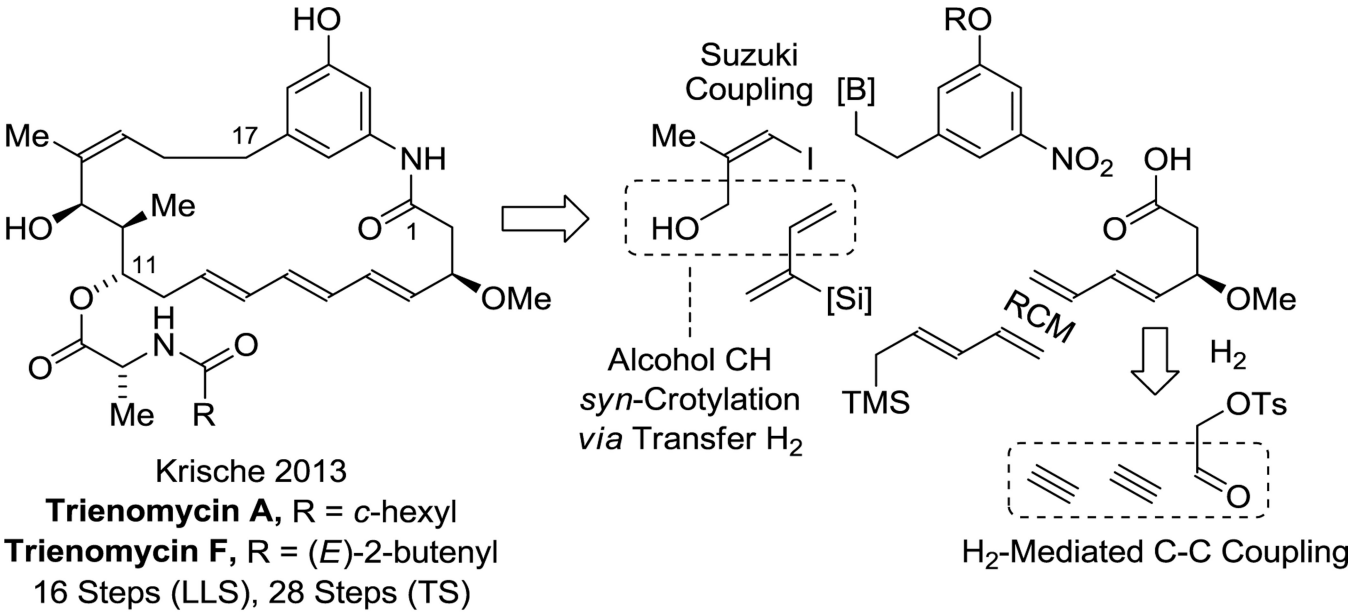
[a]For graphical summaries of prior total syntheses, see Supporting Information.



Scheme 8.

Total synthesis of bryostatin 7 *via* hydrogenative and transfer hydrogenative carbonyl addition.a

[a]For graphical summaries of prior total syntheses, see Supporting Information.



Trienomycin A & F, Smith 1995, 30 Steps (LLS), 40 Steps (TS)
Mycotrienin I, Panek 1998, 28 Steps (LLS), 37 Steps (TS)
Mycotrienol, Panek 1998, 24 Steps (LLS), 33 Steps (TS)
Thiazinotrienomycin E, Smith 1999, 33 Steps (LLS), Steps (55) TS
Cytotrienin A, Hayashi 2008, 35 Steps (LLS), 57 Steps (TS)

Scheme 9.

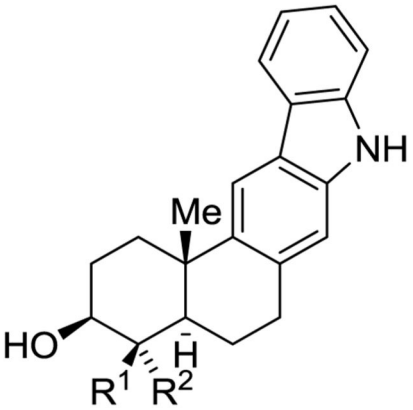
Total synthesis of trienomycin A and F *via* hydrogenative and transfer hydrogenative carbonyl addition.a

[a]For graphical summaries of prior total syntheses, see Supporting Information.

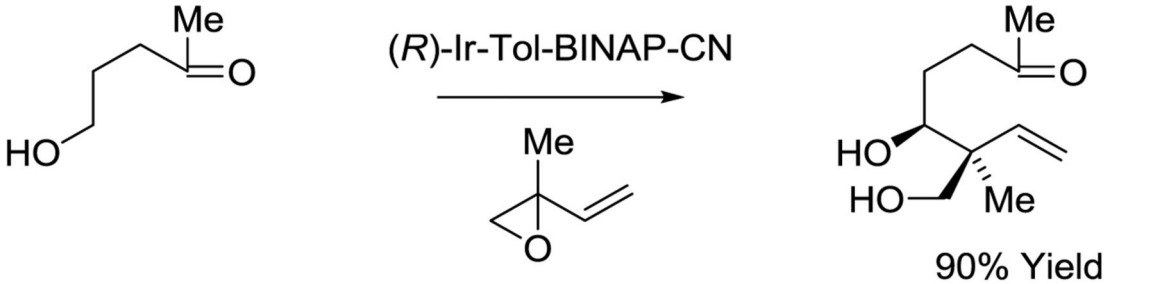
Oridamycin A, $R^1 = CO_2H$, $R^2 = Me$
Krische 2016, 7 Steps (LLS), 7 Steps (TS)
Li 2015, 10 Steps (LLS), 12 Steps (TS) (racemic)
Trotta 2015, 11 Steps (LLS), 14 Steps (TS) (racemic)

Oridamycin B, $R^1 = CO_2H$, $R^2 = CH_2OH$
Li 2015, 14 Steps (LLS), 16 Steps (TS) (racemic)
Trotta 2015, 13 Steps (LLS), 16 Steps (TS) (racemic)

Xiamycin A, $R^1 = Me$, $R^2 = CO_2H$
Baran 2014, 14 Steps (LLS), 14 Steps (TS)
Li 2015, 9 Steps (LLS), 12 Steps (TS)



Krische 2016, **Oridamycin A**
7 Steps (LLS), 7 Steps (TS)



90% Yield
30:1 dr, 98% ee

Scheme 10.
Total synthesis of oridamycin A *via* enantioselective alcohol C-H *tert*-(hydroxy)prenylation.a
[a]For graphical summaries of prior total syntheses, see Supporting Information.