Polyketide Construction *via* Hydrohydroxyalkylation and Related Alcohol C-H Functionalizations: Reinventing the Chemistry of Carbonyl Addition

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Abstract

Despite the longstanding importance of polyketide natural products in human medicine, nearly all commercial polyketide-based drugs are prepared through fermentation or semi-synthesis. The paucity of manufacturing routes involving *de novo* chemical synthesis reflects the inability of current methods to concisely address the preparation of these complex structures. Direct alcohol C-H bond functionalization *via* "*C-C bond forming transfer hydrogenation*" provides a powerful, new means of constructing type I polyketides that bypasses stoichiometric use of chiral auxiliaries, premetallated *C*-nucleophiles, and discrete alcohol-to-aldehyde redox reactions. Using this emergent technology, the total syntheses of 6-deoxyerythronolide B, bryostatin 7, trienomycins A and F, cyanolide A, roxaticin, and formal syntheses of rifamycin S and scytophycin C, were accomplished. These syntheses represent the most concise routes reported to any member of these respective natural product families.

1. Introduction

Polyketides are a broad class of secondary metabolites that display a diverse range of biological properties and are used extensively in human medicine.[1,2] Approximately 20% of the top-selling small molecule drugs are polyketides,[2,3] and it is estimated that polyketides are five times more likely to possess drug activity compared to other natural product families.[3] The first commercial polyketide drug, erythromycin A, a macrolide antibiotic isolated from soil bacteria from the Philippines, was marketed by Eli Lilly in 1952.[4] Later in 1955, amphotericin B, an important anti-fungal drug was discovered in soil samples taken from Venezuela,[5] and shortly thereafter, rifamycin B, which vanquished drug-resistant tuberculosis in the 1960s,[6] was isolated from soil samples taken from the south of France (Figure 1). While these and many other medicinally relevant polyketides derive from soil bacteria, it is estimated that less than 5% of soil bacteria are amenable to culture, and those that are do not represent the complete phylogenetic diversity of these organisms, as many bacterial phyla have eluded culture.[7] As methods for the culture of soil bacteria improve, the role of polyketide natural products in human medicine will surely broaden, as will the need for manufacturing routes to these complex structures and their derivatives.

Nearly all commercial polyketides are prepared through fermentation or semi-synthesis.[8] Polyketide construction by *de novo* chemical synthesis offers entry to otherwise inaccessible functional analogues; however, despite enormous strides, the current ensemble of synthetic methods does not permit concise access to such complex structures. To address this deficiency, our laboratory has developed a broad, new suite of catalytic processes that promote C-C bond formation *via* direct alcohol C-H functionalization.[9] In these processes, hydrogen exchange between alcohols and π-unsaturated reactants generates aldehyde-

organometal pairs that combine to form products of carbonyl addition. These methods streamline synthesis as they bypass discrete alcohol-to-aldehyde redox reactions, and the stoichiometric use of chiral auxiliaries or premetallated *C*-nucleophiles. Applications of this technology to the total syntheses of 6-deoxyerythronolide B, bryostatin 7, trienomycins A and F, cyanolide A, roxaticin are described in this review, as are formal syntheses of rifamycin S and scytophycin C. These syntheses represent the most concise routes to any member of these respective natural products families.

2. A New Lexicon of Catalytic Methods

Enantioselective carbonyl allylation and crotylation are important gateways to polyketide natural products.[10] Traditional methods for carbonyl allylation are not well suited for implementation on scale due to the frequent requirement of cryogenic conditions, multi-step synthesis of the requisite allylmetal reagents, generation of stoichiometric byproducts, the need for discrete alcohol-to-aldehyde oxidation, and the configurational and chemical lability of chiral α-stereogenic aldehydes. To address these shortcomings, our laboratory developed a series of *ortho*-cyclometallated iridium catalysts for the enantioselective C-H allylation of primary alcohols employing allyl acetate as the allyl donor.[11] Our initial studies employed cyclometallated iridium catalysts generated *in situ* from allyl acetate, 3-nitrobenzoic acid and a chiral *bis*-phosphine ligand.[11a,b] Aliphatic, allylic and benzylic alcohols couple with allyl acetate to form the corresponding homoallylic alcohols with consistently high levels of enantioselectivity. Under otherwise identical conditions, but in the presence of isopropanol, aldehydes are transformed to an equivalent set of homoallylic alcohols (Scheme 1).

This method was applied to the iterative elongation of 1,3-polyols to form polyacetate substructures evident in oxo-polyene macrolides.[11d] Complete levels of catalyst directed stereoselectivity were observed. Using the cyclometallated iridium complex purified by conventional silica gel flash chromatography, chemo- and stereoselective iridium catalyzed alcohol C-H allylation of polyols is achieved in the absence of protecting groups.[11f] Secondary alcohols present in the reactant and product remain unchanged due to a pronounced kinetic preference for primary alcohol dehydrogenation. Propane diol engages in two-directional chain elongation through successive generation and capture of transient mono-aldehydes to provide C_2-symmetric adducts in good yield.[11c] The minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer, amplifying the enantiomeric purity of the product.[12] The ability to engage polyols directly in a site-selective manner streamlines synthesis, as it removes steps otherwise required for protecting group installation-removal and it avoids discrete alcohol-to-aldehyde oxidation (Scheme 2).

The cyclometallated π-allyliridium 3,4-dinitro-*C,O*-benzoate complex modified by (*R*)- or (*S*)-Cl,MeO-BIPHEP promotes the transfer hydrogenative coupling of allyl acetate to chiral β-stereogenic alcohols with good to excellent levels of catalyst-directed diastereoselectivity to furnish homoallylic alcohols that possess stereotriads found in numerous type I polyketides.[11e,13] This protocol bypasses discrete generation of configurationally labile chiral α-stereogenic aldehydes, which are used routinely in polyketide construction, yet often cannot be stored or subjected to silica gel chromatography without erosion of enantiomeric purity (Scheme 3).[14]

Related alcohol C-H crotylations employing α-methyl allyl acetate as the crotyl donor initially were achieved using the *ortho*-cyclometallated iridium *C,O*-benzoate prepared *in situ* from [Ir(cod)Cl]$_2$, α-methyl allyl acetate, 4-cyano-3-nitrobenzoic acid and the chiral phosphine ligand (*S*)-SEGPHOS.[15a] Although *in situ* generation of the catalyst is convenient and exceptional enantioselectivities were observed, moderate levels of *anti-*

diastereoselectivity were observed (5:1 – 11:1 dr). It was found that the cyclometallated π-allyliridium complex can be purified by conventional silica gel flash chromatography, and that the chromatographically purified catalyst functions at lower temperature (60 °C), resulting in enhanced levels of *anti*-diastereo- and enantioselectivity (Scheme 4).[15b]

A general catalytic mechanism has been proposed (Figure 2).[9a,11b] Mechanistic studies corroborate turnover limiting carbonyl addition.[11b] The pronounced influence of remote electron withdrawing groups at the 4-position of the *C,O*-benzoate moiety of the catalyst can be interpreted on this basis. For example, in C-H allylations of chiral β-stereogenic alcohols (Scheme 3), remote electron withdrawing groups were shown to minimize racemization of the transient chiral α-stereogenic aldehyde. Here, enhanced Lewis acidity at iridium may accelerate turnover limiting carbonyl addition with respect to aldehyde epimerization. Additionally, in the C-H crotylation of primary alcohols, kinetic selectivity observed in the generation of the (*E*)-σ-crotyliridium intermediate, which reacts stereospecifically to deliver the *anti*-diastereomer, is preserved when the rate of carbonyl addition is accelerated with respect to isomerization to the (*Z*)-σ-crotyliridium intermediate, which would react to form the *syn*-diastereomer. Increased Lewis acidity at iridium also may facilitate catalysis by strengthening the agostic interaction between iridium and the carbinol C-H bond to facilitate alcohol dehydrogenation. Deprotonation of the iridium(III) hydride obtained upon alcohol dehydrogenation and product-to-reactant alkoxide exchange also may be accelerated by enhanced Lewis acidity at iridium. As revealed in single crystal X-ray diffraction data of a series of π-allyliridium *C,O*-benzoate complexes,[11e] more electron deficient *C,O*-benzoates possess longer C-Ir, O-Ir, and P-Ir bonds, suggesting enhanced Lewis acidity (Figure 2).

Using these catalytic methods for enantioselective alcohol C-H allylation and crotylation, a total synthesis of the oxo-polyene macrolide (+)-roxaticin was accomplished in 20 steps (LLS) from 1,3-propanediol.[16f] In this approach, nine of ten C-C bonds formed in the longest linear sequence are made *via* metal catalysis, including 7 C-C bonds formed *via* iridium catalyzed alcohol C-C coupling. Notably, the present synthesis, which represents the most concise preparation of any oxo-polyene macrolide reported to date, is achieved in the absence of chiral reagents, chiral auxiliaries and premetallated *C*-nucleophiles (Scheme 5).

The rapid generation of polyacetate substructures *via* iterative double allylation of 1,3-propanediol prompted an investigation into related double crotylations of 2-methyl-1,3-propanediol.[15c] In the event, the chromatographically purified iridium precatalyst modified by (*R*)-SEGPHOS delivers the product of double crotylation as predominantly 1 of 16 possible stereoisomers due to the aforementioned amplification effect.[12] The resulting *pseudo-C2*-symmetric polypropionate stereoquintet possesses a chirotopic nonstereogenic center at the central carbon atom. Iodoetherification defines this stereocenter and differentiates the two terminal olefin and two secondary alcohol moieties. With the iodoether in hand, the C19–C27 stereoheptad of rifamycin S was rapidly assembled (Scheme 6).[18] In a similar fashion, the indicated iodoether was converted to a scytophycin C substructure in nearly half the number of steps previously required (Scheme 6).[19]

Our initial efforts to develop *syn*-diastereo- and enantioselective alcohol C-H crotylations relied on the use of 2-silyl-substituted butadienes prepared from chloroprene.[20a] Exposure of alcohols to such dienes in the presence of ruthenium complexes modified by (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS triggers generation of geometrically defined crotylruthenium-aldehyde pairs that engage in stereospecific carbonyl addition to form products of carbonyl crotylation in the absence of stoichiometric byproducts. In the presence of isopropanol under otherwise identical conditions, aldehydes are converted to an equivalent set of adducts (Scheme 7). Using this method for *syn*-crotylation, the triene-containing C17-benzene ansamycins trienomycins A and F were prepared in 16 steps (longest linear sequence, LLS)

and 28 total steps.[21] The present 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 ansamycins (Scheme 8).

Ideally, it would be desirable to perform direct regio- and stereoselective hydrohydroxyalkylations of butadiene itself. Ultimately, it was found that ruthenium catalysts modified by a chiral BINOL-derived phosphate counterion catalyze *anti*-diastereo- and enantioselective butadiene hydrohydroxyalkylation with benzylic alcohols.[20b] The chiral counterion is conveniently installed through the acid-base reaction of $H_2Ru(CO)$ $(PPh_3)_3$ and the corresponding BINOL-derived phosphoric acid. Remarkably, diastereoselectivity is inverted upon use of a TADDOL-derived phosphate counterion in combination with a chiral phosphine ligand, enabling *syn*-diastereo- and enantioselective butadiene hydrohydroxyalkylation with aliphatic alcohols (Scheme 9).[20c]

Using both iridium and ruthenium catalyzed alcohol C-H crotylation methodologies, a synthesis of 6-deoxyerythronolide B was undertaken (Scheme 10).[22f] Double *anti*-diastereo- and enantioselective crotylation of 2-methyl-1,3-propanediol is used to define the 5-contiguous stereogenic centers spanning C2–C6 of the indicated carboxylic acid fragment. Ruthenium catalyzed hydrohydroxyalkylation of butadiene with *n*-propanol is used to establish the C12 and C13 stereocenters found in the indicated acetylenic alcohol. Assembly of 6-deoxyerythronolide B from these two fragments was accomplished through esterification followed by ring-closing enyne metathesis to form the 14-membered macrolide. In this way, 6-deoxyerythronolide B was prepared in 14 steps (LLS) and 20 total steps. This route represents the most concise construction of any erythromycins family member reported, to date.[22]

Geminal dimethyl groups appear ubiquitously in type I polyketides. Such structural motifs are typically generated through the agency of SAM-dependent *C*-methyltransferases within PKS modules, which doubly methylate β-ketoacyl thioester intermediates. Using the indicated iridium *C,O*-benzoate complex modified by (*S*)-SEGPHOS,[15a] which was isolated by precipitation, hydrogen transfer from primary alcohols to 1,1-dimethylallene triggers generation of aldehyde-*n*-prenyliridium pairs that combine with allylic inversion to form products of *tert*-prenylation.[23] Notably, the enantiofacial selectivity in these processes is opposite to that observed in corresponding allylations and crotylations. Under otherwise identical conditions, but in the presence of isopropanol, aldehydes are transformed to an equivalent set of homoallylic alcohols (Scheme 11).

A total synthesis of marine macrolide bryostatin 7[24g] was accomplished using a convergent assembly of the core from Fragments **A** and **B** employing the Keck-Yu pyran annulation[25] and Yamaguchi macrolactonization (Scheme 12).[26] For the synthesis of Fragment **A**, the indicated hydrogen-mediated glyoxal-enyne reductive coupling was strategic,[27,28] as the key C20–C21 bond is formed with control of the C20 carbinol stereochemistry and C21 olefin geometry. The synthesis of Fragment **B**, which incorporates the A-ring,[29] takes advantage of three transfer hydrogenative processes: enantioselective double allylation of 1,3-propanediol to form the C_2-symmetric diol,[11c] subsequent aldehyde *tert*-prenylation[23] to establish the C7 carbinol stereochemistry and install the C8 *gem*-dimethyl moiety and, finally, allylation[11a,b] at C9 to introduce the C11 aldehyde. Using these methods, bryostatin 7 was prepared in 20 steps (LLS) and 36 total steps.

Through sequential application of the double allylation of 1,3-glycols[11c] and Fuwa's cascading cross-metathesis-oxa-Michael cyclization,[30] neopentyl glycol is transformed to the pyran core found in the cyanolide[31] and clavosolide[32] natural product families in only 2 steps (Scheme 13). This approach enabled the total synthesis of the C_2-symmetric

macrodiolide cyanolide A in 6 steps (LLS) and 10 total steps.[31g] Notably, the synthesis is accomplished in fewer than half the steps of any prior approach in the absence of any protecting groups, chiral auxiliaries or premetallated *C*-nucleophiles.

3. Conclusions

Whereas first-generation methods and strategies for the synthesis of polyketide natural products involving carbonyl addition by way of stoichiometric chiral auxiliaries and premetallated reagents represent important advances, they are clearly interim solutions to the challenge of *de novo* polyketide construction. As organic molecules are defined as compounds composed of carbon and hydrogen, the terminal solutions to this challenge will encompass stereoselective and atom-efficient methods for skeletal assembly involving the addition, removal or redistribution of hydrogen in the absence of protecting groups, discrete oxidation level adjustment, or non-constructive functional group interconversions.[33] As illustrated in syntheses of diverse type I polyketide natural products, the merged redox and C-C bond construction events developed in our laboratory have availed a step-function change in efficiency. This technology has been embraced by several other research groups engaged in the total synthesis of polyketide natural products.[34] Future studies will focus on the development of related alcohol C-H functionalizations, including the regio- and stereoselective hydrohydroxyalkylation of α-olefins.

Acknowledgments

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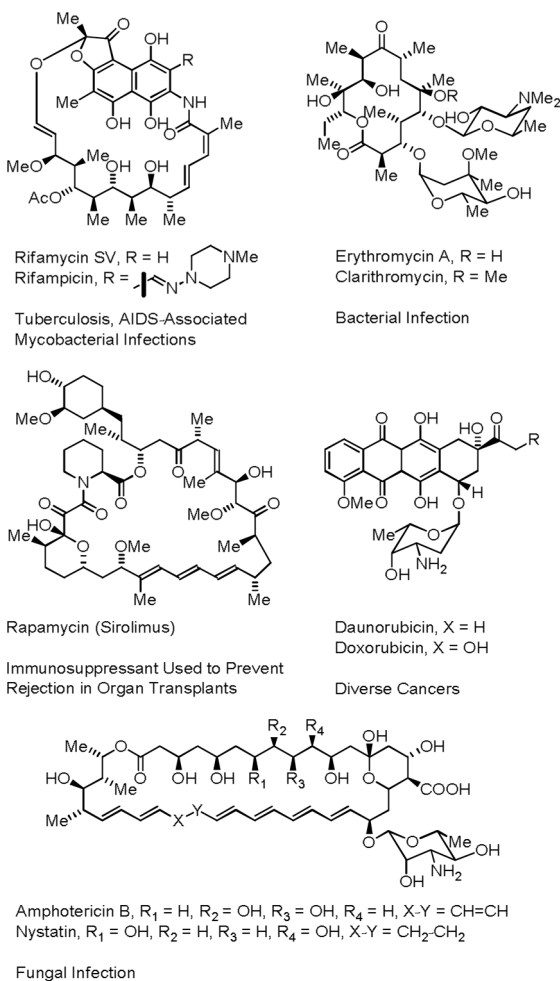
Figure 1.
Representative polyketide natural products isolated from soil bacteria used in human medicine.
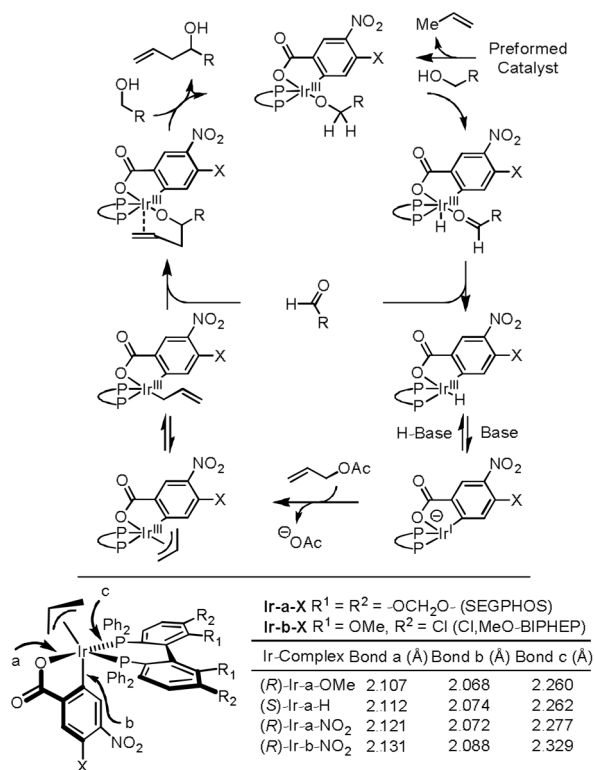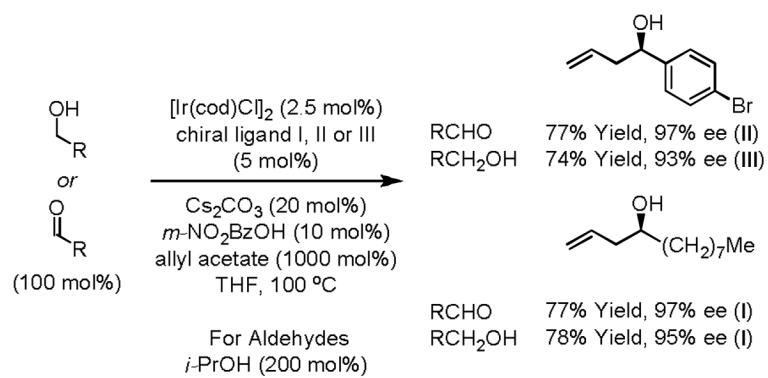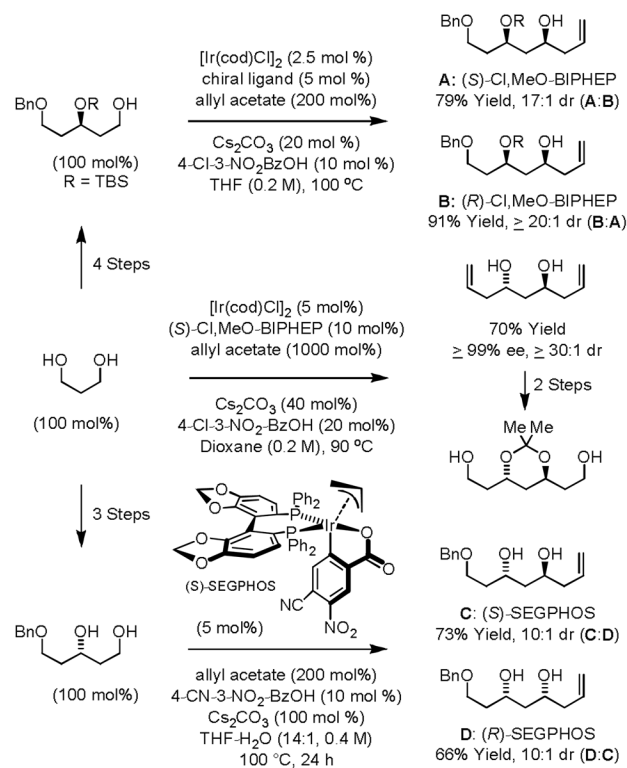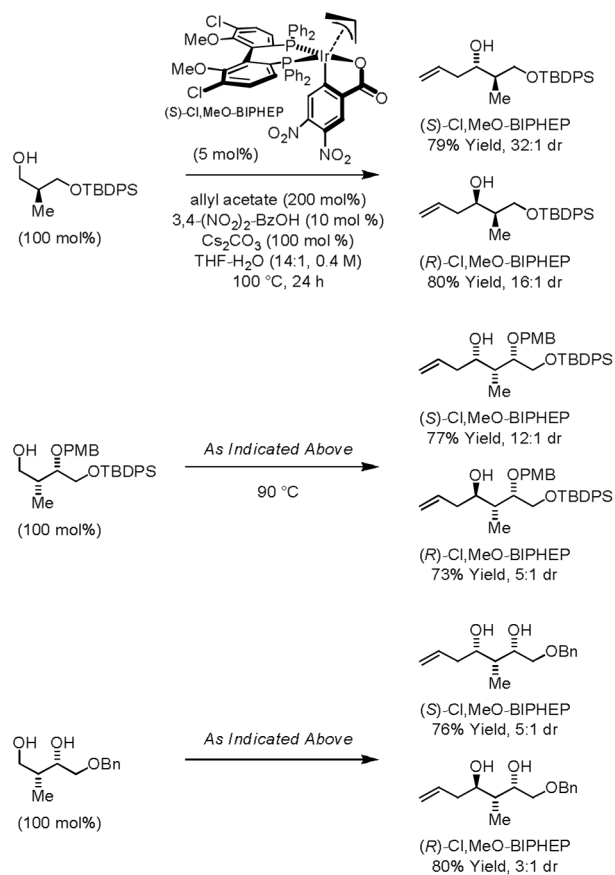
Figure 2.
General catalytic mechanism and survey of selected bond lengths from a series of π-allyliridium *C,O*-benzoate complexes.
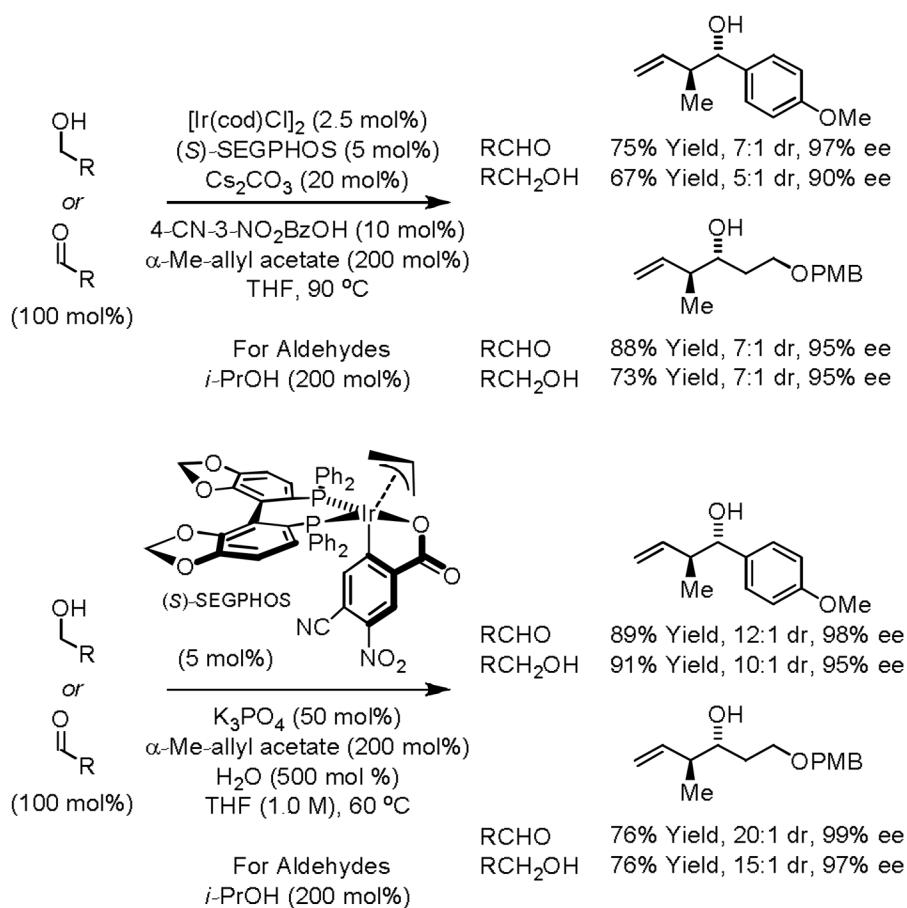
Scheme 1.
Enantioselective iridium catalyzed alcohol C-H allylation.[a]
[a]I = (*R*)-Cl,MeO-BIPHEP, II = (*R*)-TMBTP, III = (*R*)-BINAP
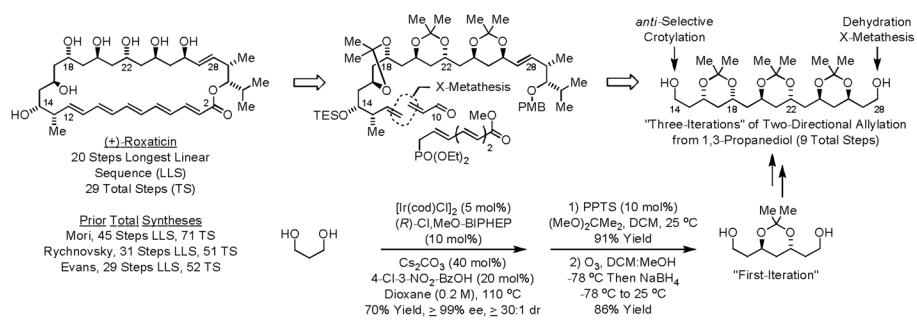
Scheme 2.
Generation of polyacetate substructures *via* 1- and 2-directional chain elongation.

Scheme 3.
Asymmetric iridium catalyzed C-H allylation of chiral β-stereogenic alcohols.

OH
R

or

O
R

(100 mol%)

[Ir(cod)Cl]$_2$ (2.5 mol%)
(S)-SEGPHOS (5 mol%)
Cs$_2$CO$_3$ (20 mol%)
→
4-CN-3-NO$_2$BzOH (10 mol%)
α-Me-allyl acetate (200 mol%)
THF, 90 °C

For Aldehydes
i-PrOH (200 mol%)

RCHO   75% Yield, 7:1 dr, 97% ee
RCH$_2$OH   67% Yield, 5:1 dr, 90% ee

RCHO   88% Yield, 7:1 dr, 95% ee
RCH$_2$OH   73% Yield, 7:1 dr, 95% ee

OH
R

or

O
R

(100 mol%)

(S)-SEGPHOS
(5 mol%)
→
K$_3$PO$_4$ (50 mol%)
α-Me-allyl acetate (200 mol%)
H$_2$O (500 mol %)
THF (1.0 M), 60 °C

For Aldehydes
i-PrOH (200 mol%)

RCHO   89% Yield, 12:1 dr, 98% ee
RCH$_2$OH   91% Yield, 10:1 dr, 95% ee

RCHO   76% Yield, 20:1 dr, 99% ee
RCH$_2$OH   76% Yield, 15:1 dr, 97% ee

Scheme 4.
Enantioselective iridium catalyzed alcohol C-H crotylation.

Scheme 5.
Total synthesis of the oxo-polyene macrolide (+)-roxaticin.
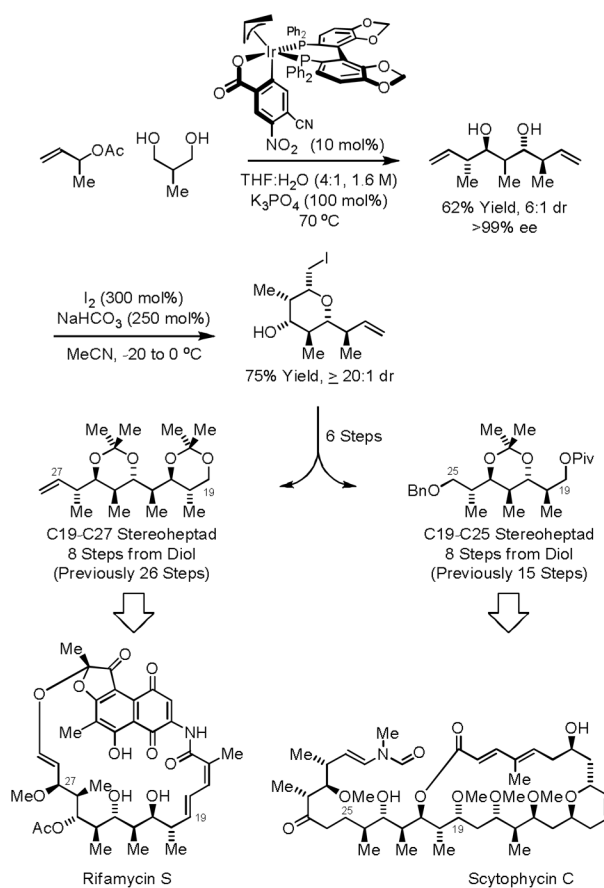
Scheme 6.
Asymmetric double *anti*-crotylation of 2-methyl-1,3-propanediol: formal syntheses of rifamycin S and scytophycin C.
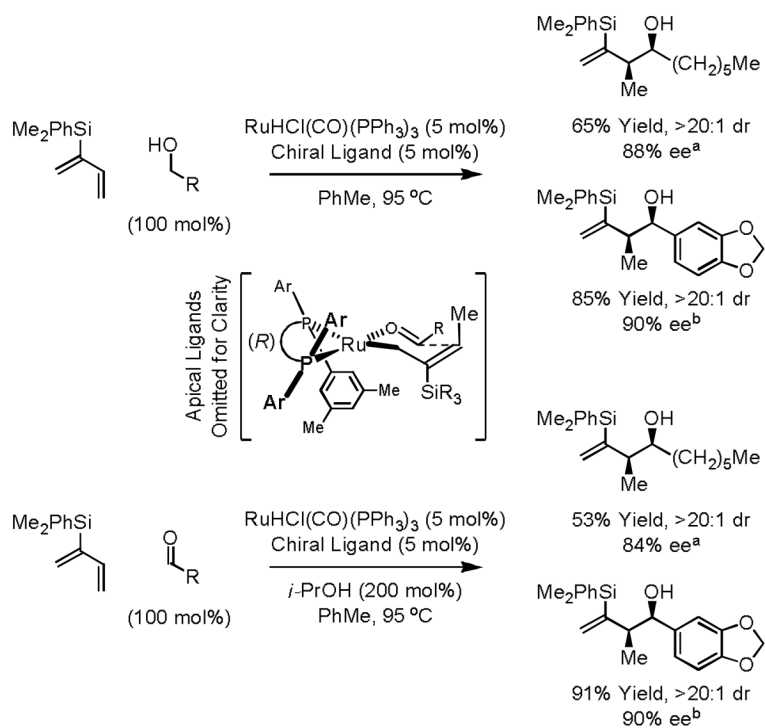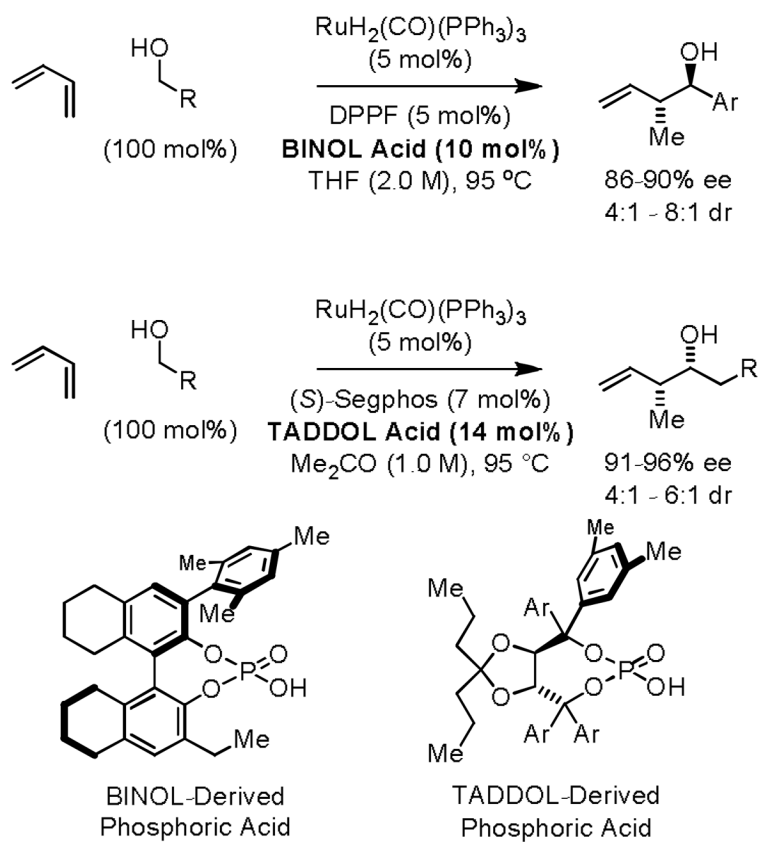
Scheme 7.
Ruthenium catalyzed *syn*-diastereo- and enantioselective crotylation *via* hydrohydroxyalkylation of 2-silyl-butadienes.
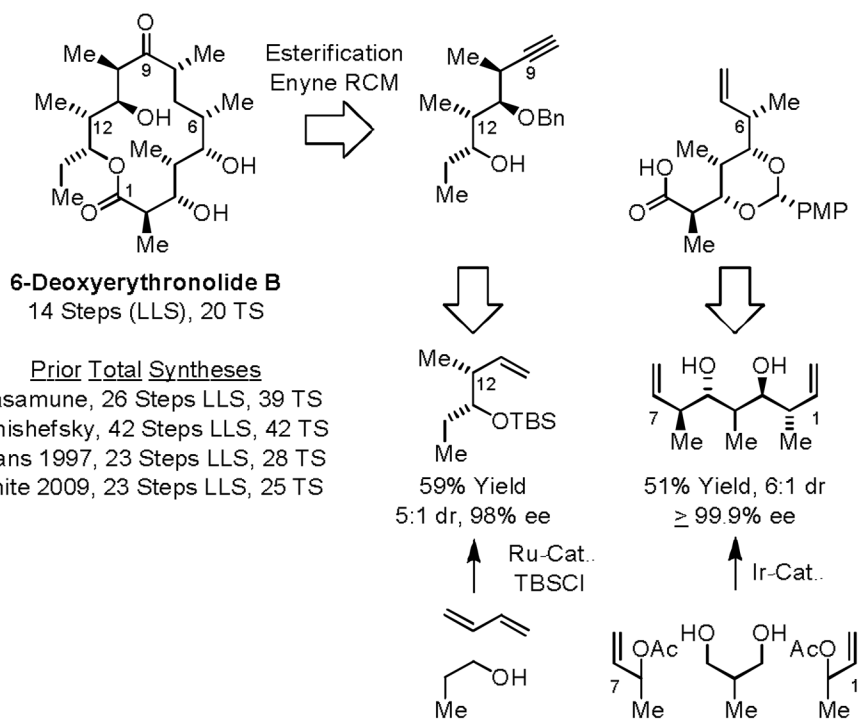[a] Chiral Ligand = (*R*)-DM-SEGPHOS. [b] Chiral Ligand = (*R*)- SEGPHOS.
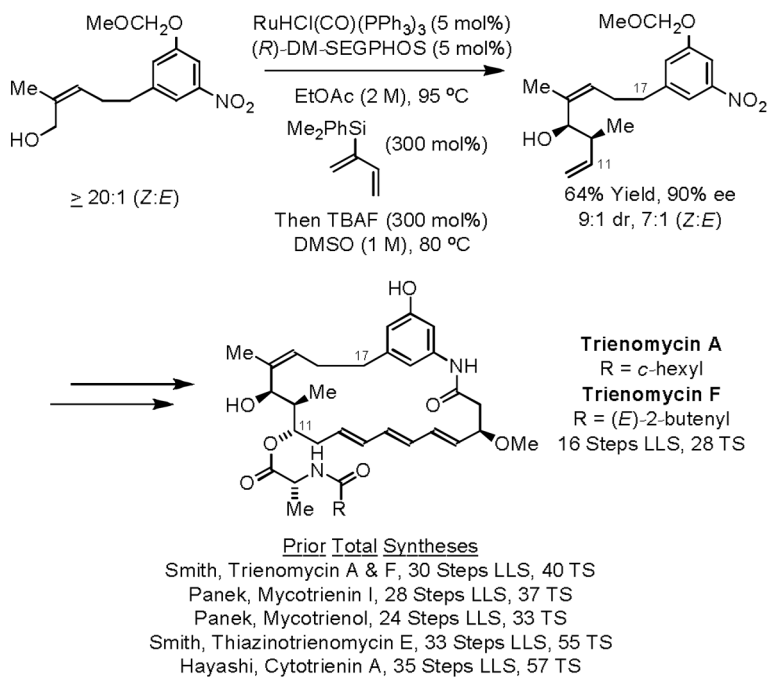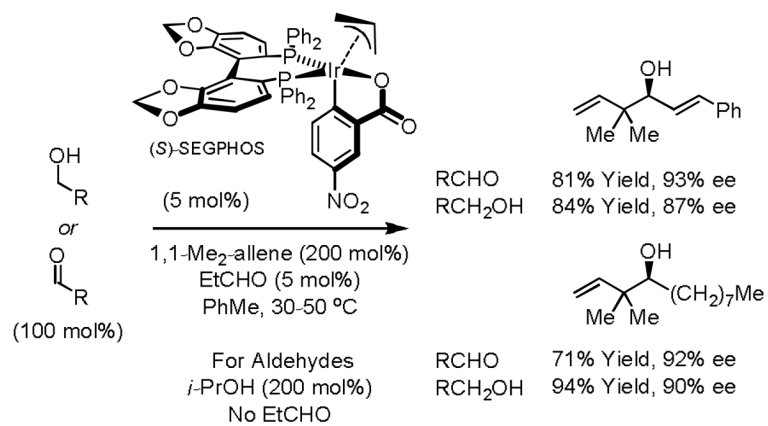
Scheme 8.

Total syntheses of trienomycins A and F *via* ruthenium catalyzed *syn*-diastereo- and enantioselective hydrohydroxyalkylation of 2-silyl-butadienes.
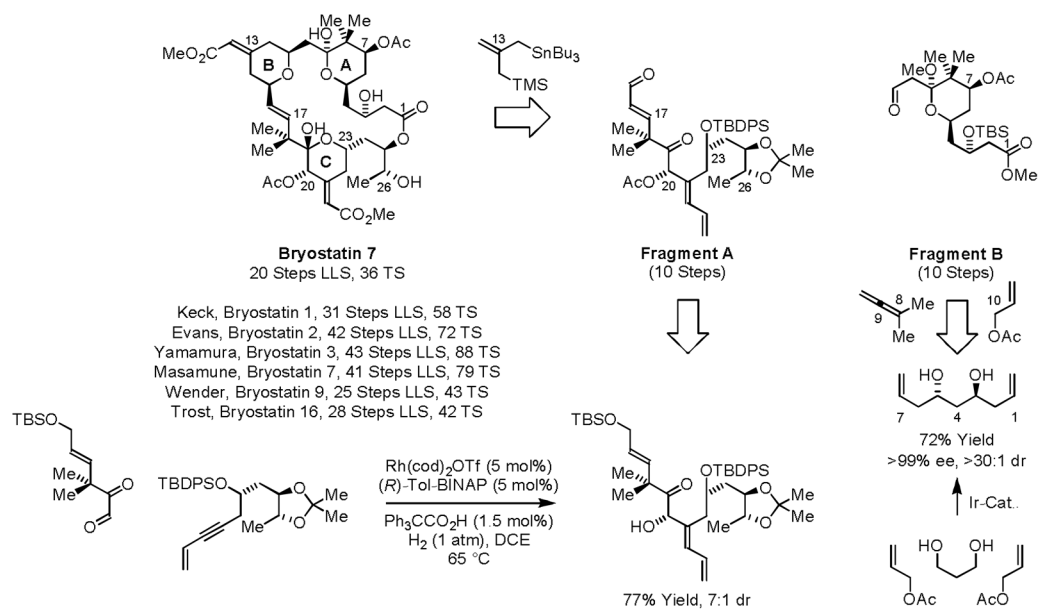
Scheme 9.
Inversion of diastereoselectivity in enantioselective ruthenium catalyzed crotylation *via* butadiene hydrohydroxyalkylation.
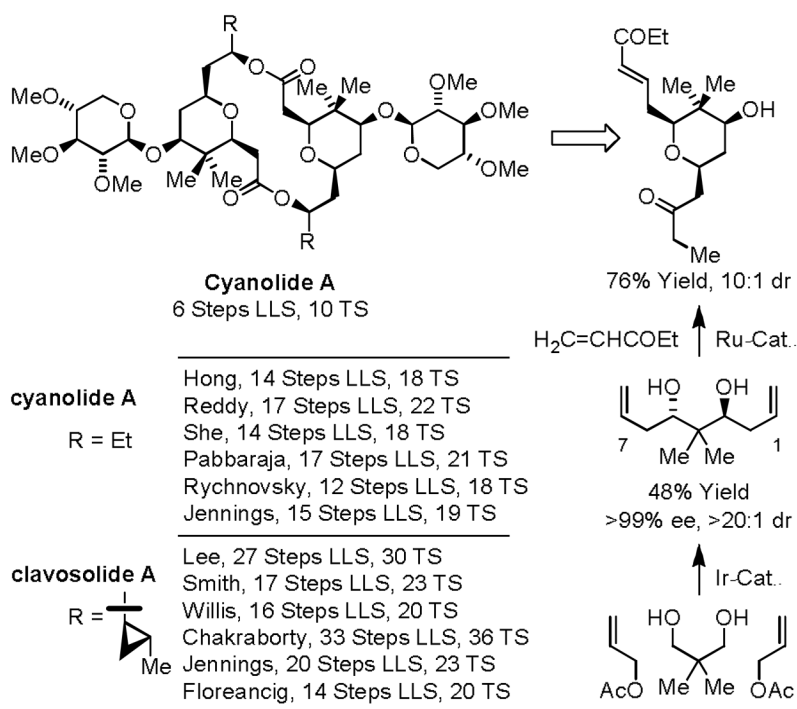
Scheme 10.
Total synthesis of 6-deoxyerythronlide B *via* diastereo- and enantioselective alcohol C-H crotylation.

Scheme 11.
Enantioselective iridium catalyzed alcohol C-H reverse prenylation.

Scheme 12.
Total synthesis of bryostatin 7 *via* C-C bond forming hydrogenation and transfer hydrogenation.

Scheme 13.
Total synthesis of cyanolide A *via* enantioselective double allylation of neopentyl glycol.