

# Total Synthesis of (+)-Roxaticin via C–C Bond Forming Transfer Hydrogenation: A Departure from Stoichiometric Chiral Reagents, Auxiliaries, and Premetalated Nucleophiles in Polyketide Construction

Soo Bong Han, Abbas Hassan, In Su Kim, and Michael J. Krische\*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712

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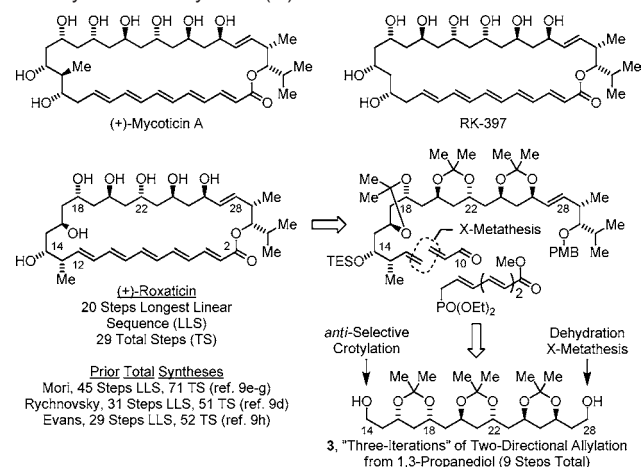
**Abstract:** A total synthesis of the oxo-polyene macrolide (+)-roxaticin is achieved in 20 steps from 1,3-propanediol. In this approach, 9 of 10 C–C bonds formed in the longest linear sequence are made *via* metal catalysis, including 7 C–C bonds formed by iridium catalyzed alcohol C–C coupling. Notably, 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 and chiral auxiliaries with minimal use of premetalated C-nucleophiles.

Polyketide natural products represent a broad class of secondary metabolites used extensively in human medicine.<sup>1,2</sup> Approximately 20% of the top-selling small molecule drugs are polyketides,<sup>2,3</sup> and it is estimated that polyketides are five times more likely to possess drug activity compared to other natural product families.<sup>3</sup> As investigations into polyketide biosynthesis<sup>4</sup> and chemical biology continue to uncover important biochemical pathways and novel therapeutic targets, the design of synthetic<sup>5</sup> and bioengineered<sup>6</sup> methods for polyketide construction remains at the forefront of research.

The complex issues of stereoselectivity posed by polyketides are most often addressed through the use of chiral auxiliaries, chiral reagents, and premetalated nucleophiles.<sup>5</sup> Although such methods are highly effective, their use often mandates multistage preactivation and excessive byproduct generation. Inspired by the atom economy of catalytic hydrogenation, we have developed a broad family of enantioselective “C–C bond forming hydrogenations,”<sup>7</sup> which provide an alternative to stoichiometric organometallic reagents in certain carbonyl and imine additions. Here, we showcase the utility of this methodology in a total synthesis of the oxo-polyene macrolide (+)-roxaticin.<sup>8,9d–h,10</sup>

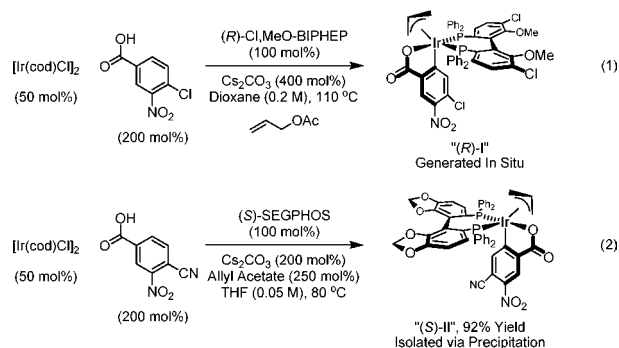
Our approach takes advantage of carbonyl allylation<sup>7f,11a–d</sup> and crotylation<sup>7f,11e</sup> protocols recently developed in our laboratory, wherein primary alcohol dehydrogenation concurrently triggers aldehyde formation and reductive generation of allyliridium nucleophiles, enabling asymmetric carbonyl allylation and crotylation directly from the alcohol oxidation level. Iterative two-directional carbonyl allylation of 1,3-diols<sup>11c,d,12</sup> was envisioned to deliver the requisite C<sub>2</sub>-symmetric 1,3-polyol substructure spanning C14–C28. Elaboration of the protected 1,3-polyol **3** to (+)-roxaticin requires differential elongation of the homotopic diol termini, which is potentially achieved *via* sequential dehydration–cross-metathesis at C28 and direct carbonyl crotylation from the alcohol oxidation level at C14. Installation of the oxo-pentaene fragment takes advantage of a sequence involving cross-metathesis–Horner–Wadsworth–Emmons olefination. Subsequent macrocyclization and global deprotection would deliver (+)-roxaticin (Scheme 1).

## Scheme 1. Representative Oxo-polyene Macrolides and Retrosynthetic Analysis of (+)-Roxaticin<sup>a</sup>

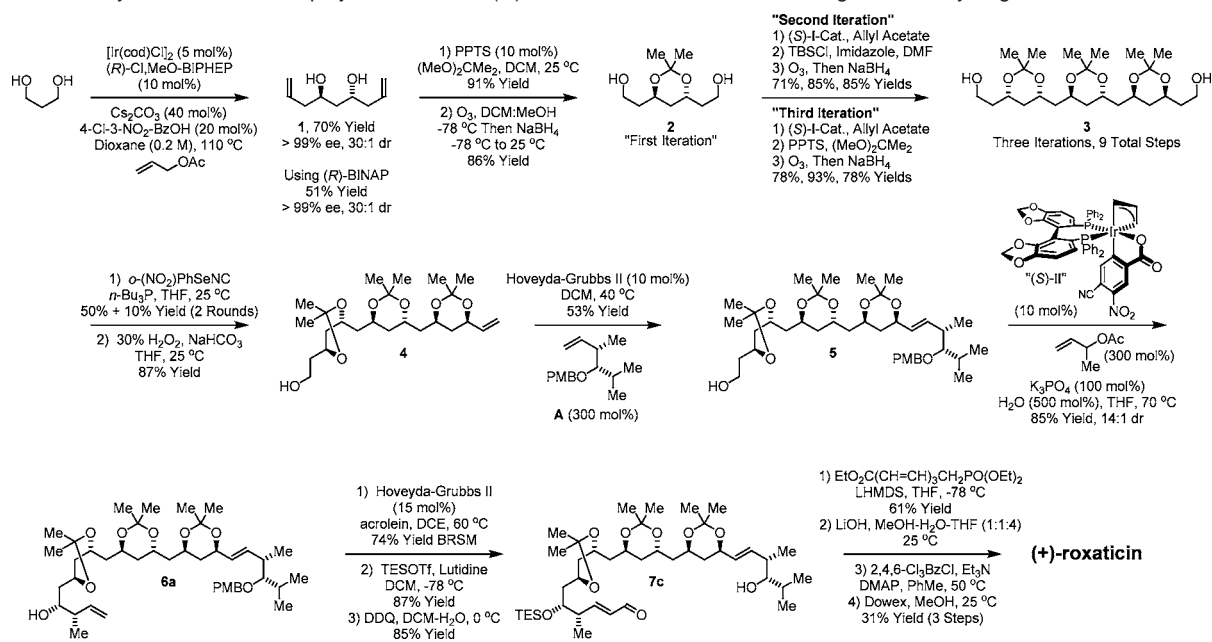


<sup>a</sup> See Supporting Information for a graphical summary of prior syntheses.

Double C-allylation of 1,3-propanediol was accomplished as previously described using the *ortho*-cyclometalated iridium C,O-benzoate generated *in situ* from [Ir(cod)Cl]<sub>2</sub>, (*R*)-Cl<sub>2</sub>MeO-BIPHEP, 4-chloro-3-nitrobenzoic acid, and allyl acetate (eq 1).<sup>11c,d</sup> The C<sub>2</sub>-symmetric product of double allylation **1** is obtained in 70% yield and >99% ee, as the minor enantiomer of the monoadduct is converted to the *meso*-diastereomer of **1**.<sup>13,14</sup> On a larger scale (20 mmol), to mitigate cost, double allylation reactions were conducted using the corresponding (*R*)-BINAP complex, which provides **1** in 51% yield with equivalent levels of absolute stereocontrol.



Conversion of **1** to the acetonide followed by ozonolysis of the olefinic termini provides the homologous diol **2**, constituting “one iteration” of two-directional carbonyl allylation from the alcohol oxidation level. In principle, subsequent iterations of two-directional carbonyl allylation could be performed from the diol or dialdehyde oxidation level. However, the  $\beta$ -alkoxy aldehydes were found to

Scheme 2. Total Synthesis of the Oxo-polyene Macrolide (+)-Roxaticin via C–C Bond Forming Transfer Hydrogenation<sup>a</sup>

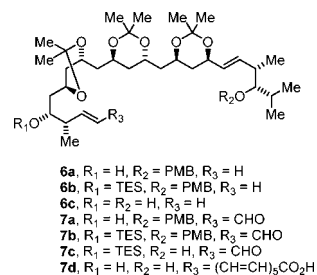
<sup>a</sup> Yields are of material isolated by silica gel chromatography and represent the average of two runs. Enantiomeric excess of **1** was determined by chiral stationary phase HPLC analysis. See Supporting Information for preparation of homoallylic ether **A** and other experimental details.

be quite unstable, whereas diol intermediates, such as **2**, are highly tractable and may be stored for long periods of time under ambient conditions without decomposition. Therefore, in subsequent iterations of two-directional carbonyl allylation, ozonolysis reactions were quenched with NaBH<sub>4</sub> to furnish the homologous diols.<sup>15</sup> In the following two double allylation reactions, complete levels of catalyst-directed diastereoselectivity were observed, providing rapid access to the acetonide-protected C<sub>2</sub>-symmetric 1,3-polyol **3** as a single diastereomer. Thus, *tris*-acetonide **3**, which possesses six stereocenters, is prepared in only nine steps from 1,3-propanediol (Scheme 2).

Differential elongation of the diol termini of *tris*-acetonide **3** begins with Grieco's two-step method for primary alcohol dehydration.<sup>16</sup> Because the diol termini of **3** are homotopic, the product appears as a component of a statistical mixture. The resulting allylic ether was exposed to the previously prepared homoallylic ether **A**<sup>17</sup> in the presence of the second generation Hoveyda–Grubbs catalyst to furnish the product of cross-metathesis **5** in 53% yield with complete (*E*)-selectivity, as determined by <sup>1</sup>H NMR.<sup>18</sup> Direct carbonyl crotylation from the alcohol oxidation level at C14 using the preformed iridium *C,O*-benzoate complex (S)-II (eq 2) delivers the desired adduct **6a** in 85% yield with 14:1 *anti*-diastereoselectivity.

With homoallylic alcohol **6a** in hand, installation of the polyene substructure was undertaken. The unprotected homoallylic alcohol **6a** was subjected to cross-metathesis with acrolein to deliver the corresponding enal **7a** in 68% yield with complete (*E*)-selectivity, as determined by <sup>1</sup>H NMR.<sup>19</sup> Subsequent protection of the C14 alcohol to provide the triethylsilyl (TES) ether **7b** was followed by oxidative removal of the *para*-methoxybenzyl ether to furnish hydroxy enal **7c**. This specific sequence of functional group interconversions was essential as the TES-ether **6b** does not participate in cross-metathesis, presumably due to the sterically demanding environment at the homoallylic olefin. Additionally, selective protection of the C14 and C30 diol **6c** was not possible under a variety of conditions. Finally, attempted macrolactonization

of **7d**, which lacks a C14 hydroxyl protecting group, was unsuccessful.



Elaboration of hydroxy enal **7c** to (+)-roxaticin was accomplished as follows. Exposure of **7c** to the previously reported Horner–Wadsworth–Emmons reagent, EtO<sub>2</sub>C(CH=CH)<sub>3</sub>CH<sub>2</sub>PO(OEt)<sub>2</sub>,<sup>20</sup> delivered the polyunsaturated ester in 61% yield. This transformation, which involves LHMDS mediated lithium enolate generation, represents the sole use of a premetallated C-nucleophile in the longest linear sequence. Ester hydrolysis followed by Yamaguchi lactonization<sup>21</sup> and global deprotection, as practiced in prior syntheses by Mori<sup>9c–g</sup> and Evans,<sup>9h</sup> delivers (+)-roxaticin in 31% yield over the three-step sequence. The last step of the longest linear sequence, which involves hydrolysis of three acetonide moieties and a TES-ether, was particularly daunting, as in Evan's synthesis<sup>9h</sup> acetonide protecting groups could not be removed and were abandoned for cyclopentylidene ketals, which are hydrolytically more labile. Hence, in the present macrolactonization–global deprotection sequence, it is possible that even higher efficiencies would be observed were cyclopentylidene ketals employed as protecting groups.

In summary, in this initial application of our “C–C bond forming hydrogenation” methodology, (+)-roxaticin is prepared from 1,3-propanediol in 20 steps (longest linear sequence), with a total number of 29 manipulations. Notably, 9 of 10 C–C bonds formed in the longest linear sequence are made via metal catalysis (7 hydrogen-mediated C–C couplings, 2 cross-metatheses) in processes that exploit “native functionality” (alcohols, olefins). This

approach circumvents additional manipulations associated with the use of non-native functional groups or substructures to mediate bond construction, as evident in the use of chiral auxiliaries, and minimizes (re)functionalizations, especially redox manipulations. Indeed, as demonstrated in carbonyl additions from the alcohol oxidation level, as in the conversion of **5** to **6a**, the union of oxidation–construction events allows one to bypass discrete alcohol oxidation while gaining access to more tractable synthetic intermediates in the form of alcohols. These features are in line with longstanding ideals of synthetic efficiency.<sup>22,23</sup>

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**Supporting Information Available:** Detailed experimental procedures, spectral data for new compounds, including scanned images of <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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