

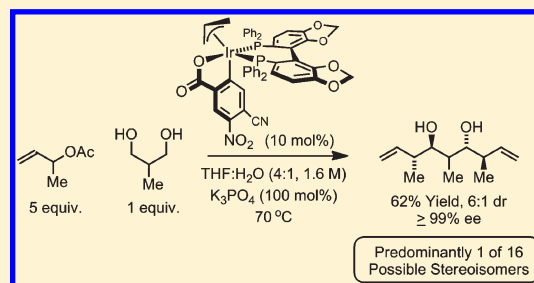
# Direct Generation of Acyclic Polypropionate Stereopolyads *via* Double Diastereo- and Enantioselective Iridium-Catalyzed Crotylation of 1,3-Diols: Beyond Stepwise Carbonyl Addition in Polyketide Construction

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Supporting Information

**ABSTRACT:** Under the conditions of transfer hydrogenation employing the cyclometalated iridium catalyst (*R*)-**I** derived from  $[\text{Ir}(\text{cod})\text{Cl}]_2$ , allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chiral phosphine ligand (*R*)-SEGPHOS,  $\alpha$ -methylallyl acetate engages 1,3-propanediol (**1a**) and 2-methyl-1,3-propanediol (**1b**) in double carbonyl crotylation from the alcohol oxidation level to deliver the  $C_2$ -symmetric and *pseudo*- $C_2$ -symmetric stereopolyads **2a** and **3a**, respectively, with exceptional control of *anti*-diastereoselectivity and enantioselectivity. Notably, the polypropionate stereopentad **3a** is formed predominantly as 1 of 16 possible stereoisomers. Desymmetrization of **3a** is readily achieved upon iodoetherification to form pyran **4**. The direct generation of **3a** enables a dramatically simplified approach to previously prepared polypropionate substructures, as demonstrated by the synthesis of C19–C27 of rifamycin S (eight steps, originally prepared in 26 steps) and C19–C25 of scytophycin C (eight steps, originally prepared in 15 steps). The present transfer hydrogenation protocol represents an alternative to chiral auxiliaries, chiral reagents, and premetallated nucleophiles in polyketide construction.

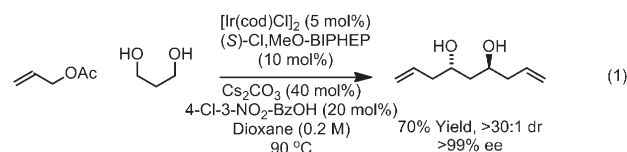


## INTRODUCTION

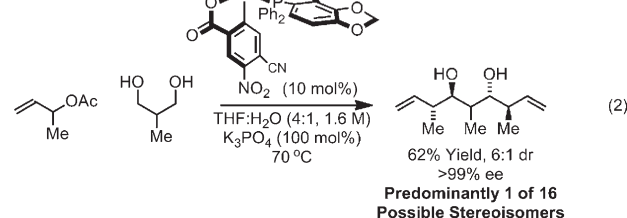
The complex issues of stereoselectivity posed by polyketide natural products are most often addressed through stepwise carbonyl addition reactions involving the use of chiral auxiliaries, chiral reagents, and premetallated nucleophiles.<sup>1,2</sup> In the course of exploring hydrogen-mediated C–C bond formation,<sup>3</sup> hydrogen exchange between primary alcohols and  $\pi$ -unsaturated reactants was found to trigger generation of electrophile–nucleophile pairs that combine to form products of carbonyl addition directly from the alcohol oxidation level.<sup>3–6</sup> A significant outcome of this approach resides in the ability to rapidly assemble polyacetate substructures through asymmetric double allylations of 1,3-diols (eq 1), as illustrated in dramatically simplified syntheses of the bryostatin A ring<sup>7a</sup> and the oxo-polyene macrolide roxatocin.<sup>7d</sup>

Corresponding double crotylations would enable the direct generation of  $C_2$ -symmetric polypropionate stereopentads (eq 2), which appear as substructures in diverse polyketide natural products, including rifamycin,<sup>8</sup> swinholide,<sup>9</sup> scytophycin,<sup>10</sup> saliniketol,<sup>11</sup> and reidispogiolide<sup>12</sup> (Figure 1). However, attempted double crotylations employing the catalyst generated *in situ* from  $[\text{Ir}(\text{cod})\text{Cl}]_2$ , 4-cyano-3-nitrobenzoic acid, allyl acetate, and (*R*)-SEGPHOS were unsuccessful. We recently observed that chromatographic isolation of the iridium precatalyst allows alcohol-mediated carbonyl crotylations to be conducted at a significantly lower temperature, resulting in enhanced levels of *anti*-diastereoselectivity and enantioselectivity.<sup>5c</sup> More significantly, the chromatographically purified precatalyst enables carbonyl crotylations that are not possible under previously reported conditions involving *in situ* generation of the catalyst.

### Previous Work (ref. 5d, 7a, 7d)



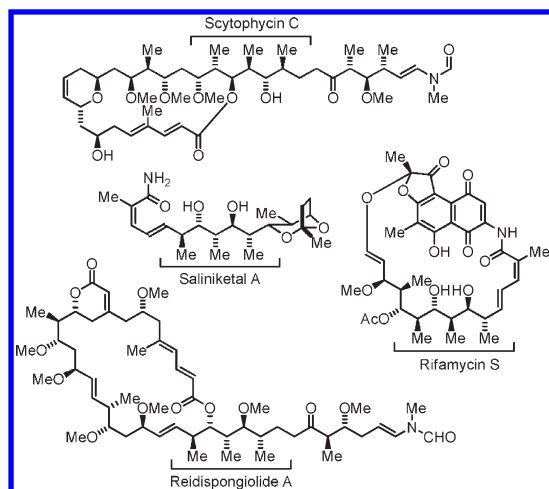
### This Work



In view of these findings, the generation of polypropionate stereopentads using *anti*-diastereoselective and enantioselective carbonyl double crotylation of 1,3-diols was revisited. Here we report that exposure of  $\alpha$ -methylallyl acetate to 1,3-propanediol (**1a**) and 2-methyl-1,3-propanediol (**1b**) in the presence of the chromatographically purified iridium precatalyst (*R*)-**I** results in double carbonyl crotylation from the diol oxidation level to deliver the  $C_2$ -symmetric and *pseudo*- $C_2$ -symmetric stereopolyads **2a** and **3a**, respectively, with exceptional control of the *anti* diastereoselectivity and enantioselectivity. *The present double crotylation process has*

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**Figure 1.** Representative polyketide natural products possessing *pseudo*-C<sub>2</sub>-symmetric polypropionate stereocenters.

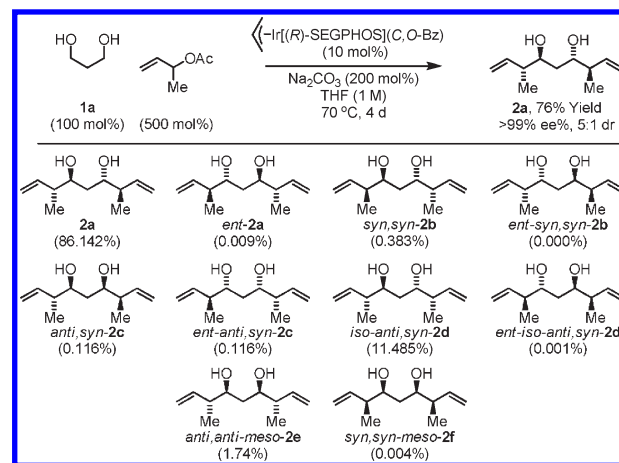
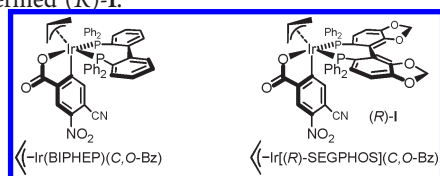
no counterpart in conventional crotylmetal chemistry and is unique in its ability to generate acyclic stereocenters from achiral reactants with control of the relative and absolute stereochemistry.<sup>13–15</sup>

To illustrate the utility of this methodology *vis-à-vis* polyketide construction, syntheses of key polypropionate substructures were executed with dramatic enhancement in step economy. Specifically, the ansa chain of rifamycin S spanning C19–C27 was prepared in eight steps, as opposed to 26 steps as originally described by Kishi.<sup>8c–f</sup> Additionally, the scytophycin C19–C25 stereocenter was prepared in eight steps, as opposed to 15 steps as described by Miyashita.<sup>10h,i</sup>

## RESULTS AND DISCUSSION

**Double Crotylation of 1,3-Propanediols 1a and 1b.** Enantioselective double crotylation of **1a** can potentially generate as many as 10 stereoisomers. Hence, quantitative evaluation of the product distribution represents a formidable challenge. A calculation of the theoretical distribution of stereoisomers based on a 99:1 enantiomeric ratio and 15:1 *anti*:*syn* diastereomeric ratio predicts a diastereomeric ratio (dr) of 6.2:1 for **2a** versus all of the other stereoisomers combined (Figure 2).

To quantitatively evaluate the product distributions obtained in the course of optimization, authentic samples of **2a**, *ent*-**2a**, and *anti*,*anti*-**2e** were prepared in a conventional stepwise manner involving successive monocrotylation.<sup>16</sup> Authentic samples of *anti*,*syn*-**2c** and *rac*-*iso*-*anti*,*syn*-**2d** were prepared conveniently *via* Mitsunobu inversion of **2a** and *anti*,*anti*-**2e**, respectively. These authentic standards were analyzed by chiral-stationary-phase GC, and the chromatograms were compared to those corresponding to the reaction mixtures arising upon exposure of 1,3-propanediol **1a** to  $\alpha$ -methyl allyl acetate in the presence of the iridium catalyst derived from [Ir(cod)Cl]<sub>2</sub>, allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chelating phosphine ligand BIPHEP (2,2'-bis(diphenylphosphino)-biphenyl), and the reaction mixture obtained using the chromatographically purified chiral complex modified by (R)-SEGPHOS, termed (R)-I.

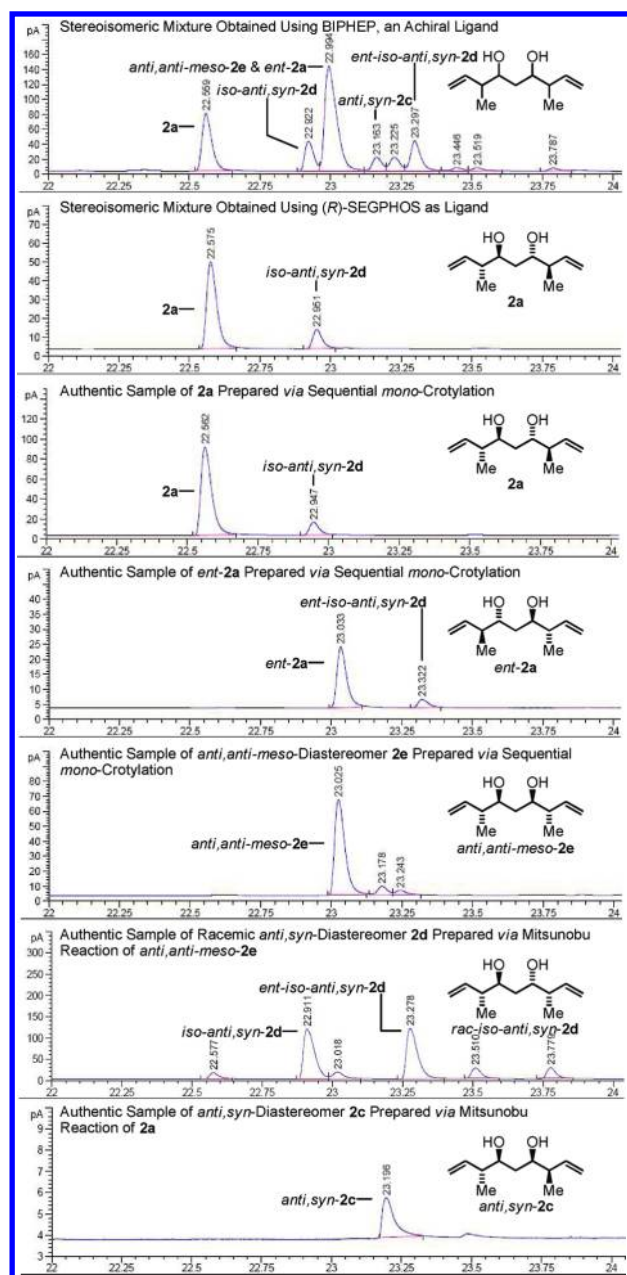


**Figure 2.** Calculated theoretical distribution of stereoisomers **2** obtained in the double crotylation of 1,3-propanediol (**1a**) based on 98% ee for both *syn*- and *anti*-crotylation events and a 15:1 *anti*:*syn* dr. The observed experimental results are also shown. Yields are of combined isomeric materials. Regio- and stereoselectivities were determined by chiral stationary phase GC analysis. Diastereomeric ratios refer to the proportion of **2a** relative to the combination of all of the stereoisomers.

For the reaction mixture obtained using the BIPHEP-modified catalyst, chiral-stationary-phase GC analysis revealed 10 distinct species, presumably the 10 stereoisomers indicated in Figure 2. Indeed, a good correlation of GC retention times was observed with the six authentic samples of **2a**, *ent*-**2a**, *anti*,*syn*-**2c**, *anti*,*anti*-**2e**, *iso*-*anti*,*syn*-**2d**, and *ent*-*iso*-*anti*,*syn*-**2d**. A dramatic simplification of the product distribution was observed for the enantioselective reaction employing the chiral catalyst (R)-I.<sup>17</sup> Chiral-stationary-phase GC and <sup>1</sup>H NMR analysis revealed predominantly two stereoisomers: the C<sub>2</sub>-symmetric adduct **2a** and a minor stereoisomer identified as *iso*-*anti*,*syn*-**2d**. These data are in excellent agreement with the predicted stereoisomeric ratios. Isolation by silica gel chromatography delivered **2a** in 76% yield as a single enantiomer and a 5:1 mixture of diastereomers. Thus, an acyclic array of four stereogenic centers was generated in a single manipulation from achiral reactants with control of the relative and absolute stereochemistry (Figure 3).

Given these favorable results, the double crotylation of **1b** was explored. Here, generation of the *pseudo*-C<sub>2</sub>-symmetric<sup>18</sup> contiguous polypropionate stereocenter **3a** could potentially be achieved in a single manipulation. However, 16 stereoisomeric adducts could potentially arise (Figure 4). The calculated theoretical distribution of stereoisomers obtained upon use of the chiral catalyst (R)-I suggested that only three stereoisomers would be generated in significant proportion: the desired *pseudo*-C<sub>2</sub>-symmetric adduct **3a** (86.1%), *syn*,*syn*,*anti*,*anti*-**3b** (5.7%), and *syn*,*anti*,*syn*,*anti*-**3b** (5.7%). Accordingly, authentic samples of these components and *ent*-**3a** were prepared in a conventional stepwise manner involving successive monocrotylation.<sup>16</sup>

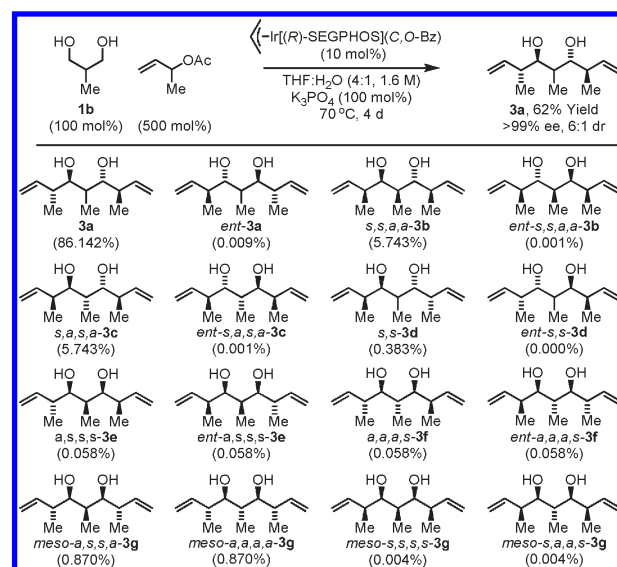
Chiral-stationary-phase GC analysis of the mixture obtained in the double crotylation of **1b** using the BIPHEP-modified catalyst revealed more than 10 distinct species. However, chiral-stationary-phase GC and <sup>1</sup>H NMR analysis of the reaction mixture obtained using chiral catalyst (R)-I revealed that the desired *pseudo*-C<sub>2</sub>-symmetric adduct **3a** was formed predominantly, along with small quantities of *syn*,*syn*,*anti*,*anti*-**3b** and *syn*,*anti*,*syn*,*anti*-**3b** (Figure 5). This outcome is in excellent agreement



**Figure 3.** Characterization of the product distribution obtained upon *anti*-diastereoselective and enantioselective double C-crotylation of **1a**. Reaction products were isolated by silica gel chromatography and analyzed by chiral-stationary-phase GC analysis using authentic samples of the indicated stereoisomers (see the Supporting Information for details).

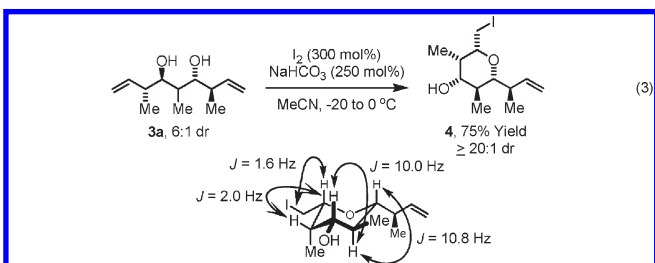
with the predicted stereoisomeric ratios. Isolation by silica gel chromatography delivered **3a** in 62% yield as a single enantiomer and a 6:1 mixture of diastereomers. Thus, a contiguous acyclic array of five stereogenic centers was generated in a single manipulation from achiral reactants with control of the relative and absolute stereochemistry (Figure 5). In attempted double crotylations of the higher congener 2,2-dimethyl-1,3-propanediol, only monoadducts were formed. Presumably, steric crowding prohibits formation of the double-crotylation product.

**Formal Synthesis of the Rifamycin S Ansa Chain and the Synthesis of the Scytophycin C19–C25 Stereoquintet.** To



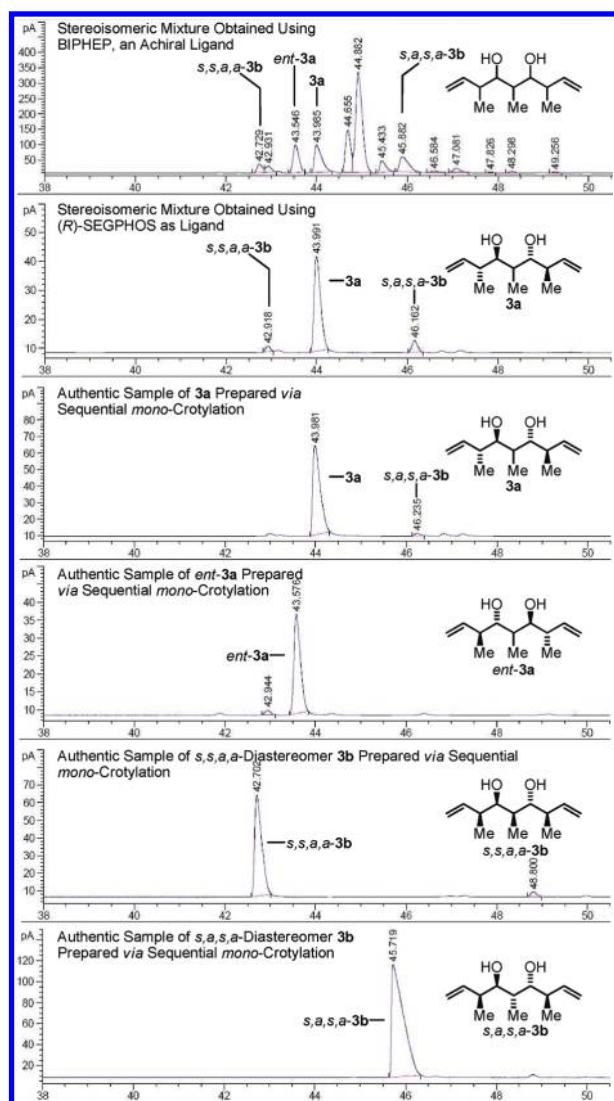
**Figure 4.** Calculated theoretical distribution of stereoisomers **3** obtained in the double crotylation of 2-methyl-1,3-propanediol (**1b**) based on 98% ee for both *syn*- and *anti*-crotylation events and a 15:1 *anti:syn* dr. The observed experimental results are also shown. Yields are of combined isomeric materials. Regio- and stereoselectivities were determined by chiral stationary phase GC analysis. Diastereomeric ratios refer to the proportion of **3a** relative to the combination of all of the stereoisomers. In the compound labels, “s” denotes “*syn*” and “a” denotes “*anti*”.

explore the utility of this methodology in polyketide construction, the double-crotylation product **3a** was applied in a synthetic approach to the ansa chain (C19–C27 stereoheptad) of rifamycin S. A key objective was differentiation of the diastereotopic hydroxyl moieties and olefinic termini of **3a**. Additionally, the latent stereocenter residing on the *pseudo*-C<sub>2</sub>-axis had to be defined. These goals were achieved in a single operation through the conversion of **3a** to iodoether **4**. As corroborated by <sup>1</sup>H NMR analysis of the pyran spin system, the substituents attached to the two newly formed stereocenters of **4** were equatorially disposed (eq 3).



Elaboration of iodoether **4** to the ansa chain of rifamycin S was accomplished in a straightforward manner (Scheme 1). Ozonolytic cleavage of iodoether **4** delivered aldehyde **5**, which was subjected to Batey's crotylation conditions<sup>19</sup> to furnish homoallylic alcohol **6** as a single stereoisomer (>20:1 dr), as determined by <sup>1</sup>H NMR analysis. Here, synergistic 1,2- and 1,3-asymmetric induction associated with the α- and β-stereocenters of the aldehyde, as described by the Felkin–Anh<sup>20</sup> and Cram–Reetz<sup>21</sup> models, respectively, account for the high level of stereoselectivity.<sup>22</sup> Ozonolytic cleavage of the terminal olefin followed by NaBH<sub>4</sub>-mediated reduction of the ozonide delivers



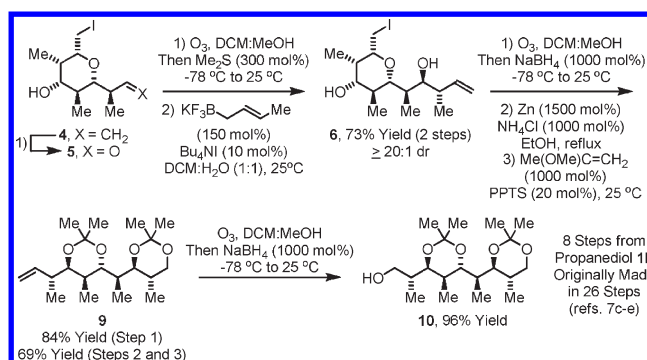


**Figure 5.** Characterization of the product distribution obtained upon *anti*-diastereoselective and enantioselective double C-crotylation of **1b**. Reaction products were isolated by silica gel chromatography and analyzed by chiral-stationary-phase GC analysis using authentic samples of the indicated stereoisomers (see the Supporting Information for details). In the compound labels, “*s*” denotes “*syn*” and “*a*” denotes “*anti*”.

primary alcohol **7** (not shown). Exposure of **7** to zinc dust in the presence of ammonium chloride induces  $\beta$ -iodoether cleavage, affording polypropionate stereohepted **8**. Conversion of tetraol **8** to *bis*-acetonide **9** and, finally, ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by  $\text{NaBH}_4$ , delivers the protected C19–C27 stereohepted **10**, which is identical in all respects to previously reported material.<sup>7</sup> This eight-step preparation of the ansa chain constitutes a formal total synthesis of rifamycin S from **1b**.<sup>8c–f</sup> Paterson reports a 10-step synthesis of the same C19–C27 segment of rifamycin S using asymmetric aldol reactions mediated by (+)- and (–)-(Ipc)<sub>2</sub>BOTf.<sup>23</sup>

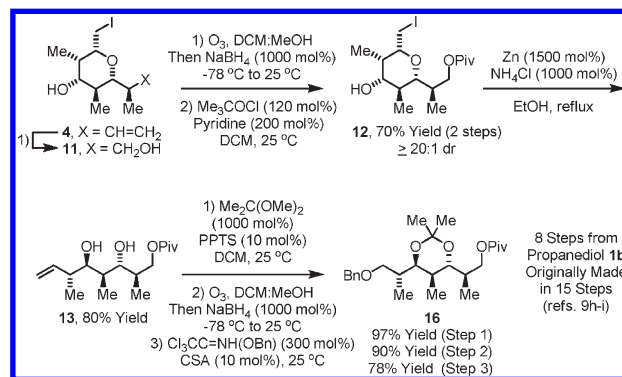
To further illustrate the generality of this approach, a synthesis of the C19–C25 stereoquintet of scytophycin C was undertaken (Scheme 2). Ozonolytic cleavage of the terminal olefin of iodoether **4** with  $\text{NaBH}_4$ -mediated reduction of the ozonide delivers primary alcohol **11**, which is converted to pivalate **12**. Exposure of an ethanolic solution of **12** to zinc dust in the presence of

### Scheme 1. Formal Synthesis of Rifamycin S via Construction of the C19–C27 Stereoheptad<sup>a</sup>



<sup>a</sup> Yields are of material isolated by silica gel chromatography. See the Supporting Information for experimental details.

### Scheme 2. Synthesis of the C19–C25 Stereoquintet of Scytophycin C<sup>a</sup>



<sup>a</sup> Yields are of material isolated by silica gel chromatography. See the Supporting Information for experimental details.

ammonium chloride induces  $\beta$ -iodoether cleavage, affording polypropionate stereoquintet **13**. Conversion of the diol to the acetonide followed by ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by  $\text{NaBH}_4$ , delivers primary alcohol **15** (not shown), which is converted to benzylic ether **16**. Ether **16** is identical in all respects to previously reported material.<sup>9h,i</sup>

## CONCLUSION

In summary, we report a powerful new process for the direct generation of polypropionate substructures *via* iridium catalyzed *anti*-diastereoselective and enantioselective carbonyl double crotylation of 1,3-propanediols **1a** and **1b**. With this methodology, syntheses of the C19–C27 stereoheptad of rifamycin S and the C19–C25 stereoquintet of scytophycin C were executed with dramatic enhancements in step economy. To our knowledge, the direct stereoselective generation of acyclic stereoquintets from achiral/chiral racemic starting materials, as in the formation of **3a**, is without precedent. Future studies will focus on the development and application of other alcohol C–C couplings of relevance to polyketide construction.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Experimental procedures and spectral data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, HRMS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## ■ ACKNOWLEDGMENT

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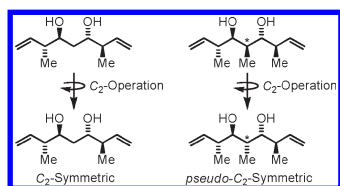
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