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 [Ir(cod)Cl]₂, allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chiral phosphine ligand (R)-SEGPHOS, α-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 C₂-symmetric and pseudo-C₂-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 premetalated 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 premetalated nucleophiles. In the course of exploring hydrogen-mediated C–C bond formation, hydrogen exchange between primary alcohols and π-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. 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 and the o xo-polyene macrolide roxaticin.

Corresponding double crotylations would enable the direct generation of C₂-symmetric polypropionate stereoquintets (eq 2), which appear as substructures in diverse polyketide natural products, including rifamycin, swinholide, saliniketal, and redispongiolide (Figure 1). However, attempted double crotylations employing the catalyst generated in situ from [Ir(cod)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. More significantly, the chromatographically purified precatalyst enables carbonyl crotylations that are not possible under previously reported conditions involving in situ generation of the catalyst.

In view of these findings, the generation of polypropionate stereoquintets using anti-diastereoselective and enantiomeric carbonate double crotylation of 1,3-diols was revisited. Here we report that exposure of α-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 C₂-symmetric and pseudo-C₂-symmetric stereopolyads 2a and 3a, respectively, with exceptional control of the anti diastereoselectivity and enantioselectivity. The present double crotylation process has
no counterpart in conventional crotylmetal chemistry and is unique in its ability to generate acyclic stereoquintets from achiral reactants with control of the relative and absolute stereochemistry.13–15

To illustrate the utility of this methodology vis-à-vis polypetide construction, syntheses of key polypetide 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.8c–f Additionally, the scytophycin C19–C25 stereoquintet was prepared in eight steps, as opposed to 15 steps as described by Miyashita.10u

RESULTS AND DISCUSSION

Double Crotylation of 1,3-Propanediol 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-meso-2e were prepared in a conventional stepwise manner involving successive monocrotylation.16 Authentic samples of anti,syn-2c and rac-iso-anti,syn-2d were prepared conveniently via Mitsunobu inversion of 2a and anti,anti-meso-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 α-methyl allyl acetate in the presence of the iridium catalyst derived from [Ir(cod)Cl]2, allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chelating phosphine ligand BIPHEP (2,2-bis(di phenylphosphino)-biphenyl), and the reaction mixture obtained using the chromatographically purified chiral complex modified by (R)-SEGPHOS, termed (R)-I.

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-meso-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.17 Chiral-stationary-phase GC and 1H NMR analysis revealed predominantly two stereoisomers: the C2-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-C2-symmetric10 contiguous polypetide stereoquintet 3a could potentially be achieved in a single manipulation. However, 16 stereoisomeric adducts could potentially arise (Figure 4). The calculated theoretical distribution of stereoisomers observed upon use of the chiral catalyst (R)-I suggested that only three stereoisomers would be generated in significant proportion: the desired pseudo-C2-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.16

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 1H NMR analysis of the reaction mixture obtained using chiral catalyst (R)-I revealed that the desired pseudo-C2-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
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 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-C2-axis had to be defined. These goals were achieved in a single operation through the conversion of 3a to iodoether 4. As corroborated by 1H 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 to furnish homoolallylic alcohol 6 as a single stereoisomer (>20:1 dr), as determined by 1H NMR analysis. Here, synergistic 1,2- and 1,3-asymmetric induction associated with the R- and β-stereocenters of the aldehyde, as described by the Felkin/Anh 20 and Cram-Reetz 21 models, respectively, account for the high level of stereoselectivity. 22 Ozonolytic cleavage of the terminal olefin followed by NaBH4-mediated reduction of the ozonide delivers...
primary alcohol 7 (not shown). Exposure of 7 to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage, affording polypropionate stereoheptad 8. Conversion of tetrrol 8 to bis-acetonide 9 and, finally, ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by NaBH₄, delivers primary alcohol 11, which is converted to pivalate 12. Exposure of an ethanolic solution of 12 to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage, affording polypropionate stereoheptad 13. Conversion of the diol to the acetonide followed by ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by NaBH₄, delivers primary alcohol 15 (not shown), which is converted to benzylic ether 16. Ether 16 is identical in all respects to previously reported material.⁹h,i

![Figure 5. Characterization of the product distribution obtained upon anti-diastereoselective and enantioselective double C-crotylation of 1b.](image)

**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.”

**Scheme 1. Formal Synthesis of Rifamycin S via Construction of the C19-C27 Stereoheptad**

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**

Yields are of material isolated by silica gel chromatography. See the Supporting Information for experimental details.

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.

**CONCLUSION**

![Scheme 1. Formal Synthesis of Rifamycin S via Construction of the C19—C27 Stereoheptad⁹](image)

![Scheme 2. Synthesis of the C19—C25 Stereoquintet of Scytophycin C⁹](image)


(16) See the Supporting Information for the preparation of the authentic standards employed in the chiral-stationary-phase GC analyses.


(18) The term "pseudo-C$_2$-symmetric" has been used to characterize stereopolyads that would be C$_2$-symmetric if they did not contain a central chirotopic, nonstereogenic center. See: Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* 1994, 27, 9.


