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# 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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## Abstract

Under the conditions of transfer hydrogenation employing a cyclometallated 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-methyl allyl 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*-diastereo- and enantioselectivity. Notably, the polypropionate stereopentad **3a** is formed predominantly as 1 of 16 possible stereoisomers. Desymmetrization of polypropionate stereopentad **3a** is readily achieved upon iodoetherification to form pyran **4**. Direct generation of polypropionate stereopentad **3a** enables a dramatically simplified approach to previously prepared polypropionate substructures, as demonstrated by the synthesis of C19–C27 of rifamycin S (8 steps, originally prepared in 26 steps) and C19–C25 of scytophycin C (8 steps, originally prepared in 15 steps). The present transfer hydrogenative 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 use of chiral auxiliaries, chiral reagents and premetallated nucleophiles.[1,2] In the course of studies on hydrogen-mediated C-C bond formation,[3] 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.[3,4,5,6] A significant outcome of this approach resides in the ability to rapidly assemble polyacetate substructures through asymmetric double allylations of 1,3-diols (eqn. 1), as illustrated in dramatically simplified syntheses of the bryostatin A-ring[7a] and oxopolyene macrolide roxaticin.[7d]

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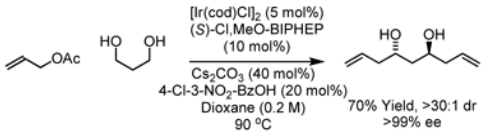
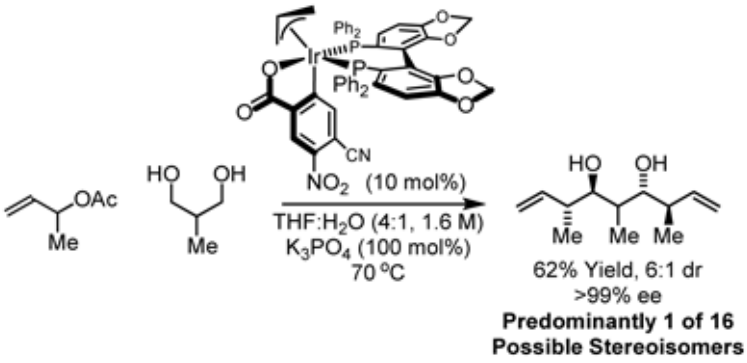
Supporting Information Available: Experimental procedures and spectral data for all new compounds ($^1$H NMR, $^{13}$C NMR, IR, HRMS). This material is available free of charge *via* the internet at http://pubs.acs.org.




(eqn. 1)




(eqn. 2)

Corresponding double crotylations would enable direct generation of $C_2$-symmetric polypropionate stereoquintets (eqn. 2), which appear as substructures in diverse polyketide natural products, including rifamycin,[8] swinholide,[9] scytophycin,[10] saliniketal[11] and reidispongiolide[12] (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. Recently, we observed that chromatographic isolation of the iridium precatalyst allows alcohol mediated carbonyl crotylations to be conducted at significantly lower temperature, resulting in enhanced levels of *anti*-diastereo- and enantioselectivity.[5e] More significantly, the chromatographically purified precatalyst enables carbonyl crotylations that are not possible under previously reported conditions involving *in situ* generation of the catalyst.

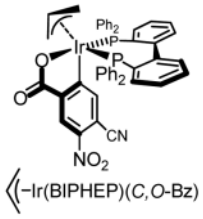
Given these findings, the generation of polypropionate stereoquintets using *anti*-diastereo- and enantioselective carbonyl double crotylation of 1,3-diols was revisited. Here, we report that exposure of α-methyl allyl acetate to 1,3-propanediols **1a** or **1b** in the presence of the chromatographically 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 *anti*-diastereo- 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 relative and absolute stereochemistry*.[13,14,15]

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 8 steps *versus* 26 steps, as originally described by Kishi.[8c–f] Additionally, the scyotphycin C19–C25 stereoquintet was prepared 8 steps *versus* 15 steps, as described by Miyashita.[10h,i]

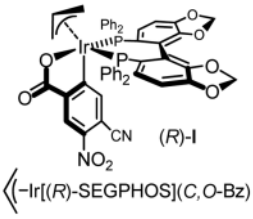
## Results and Discussion

Enantioselective double crotylation of 1,3-propanediol **1a** potentially generates as many as ten 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 diastereomeric ratio (*anti:syn*) predicts a diastereomeric ratio of 6.2:1 dr (**2a** versus all other stereoisomers combined) (Figure 2).

To quantitatively evaluate product distributions obtained in the course of optimization, authentic samples of **2a**, *ent*-**2a**, *anti,anti-meso*-**2e** were prepared in a conventional stepwise manner involving successive *mono*-crotylation.[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 a comparison to the reaction mixture obtained 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(diphenylphosphino)biphenyl), as well as the product distribution obtained using the chromatographically purified chiral complex modified by (*R*)-SEGPHOS, termed (*R*)-**I**.




⟨–Ir(BIPHEP)(*C,O*-Bz)




⟨–Ir[(*R*)-SEGPHOS](*C,O*-Bz)

For the reaction mixture obtained using the BIPHEP-modified catalyst, chiral stationary phase GC analysis reveals ten distinct species, presumably the ten stereoisomers indicated in Figure 2. Indeed, good correlation in GC retention time is 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 in product distribution is observed in the enantioselective reaction employing the chiral catalyst (*R*)-**I**.[17] Chiral stationary phase GC and $^1$H NMR analysis reveal predominantly two stereoisomers: the $C_2$-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 delivers **2a** in 76% yield as a single enantiomer as a 5:1 mixture of diastereomers. Thus, an acyclic array of four stereogenic centers is generated in a single manipulation from achiral reactants with control of relative and absolute stereochemistry (Figure 3).

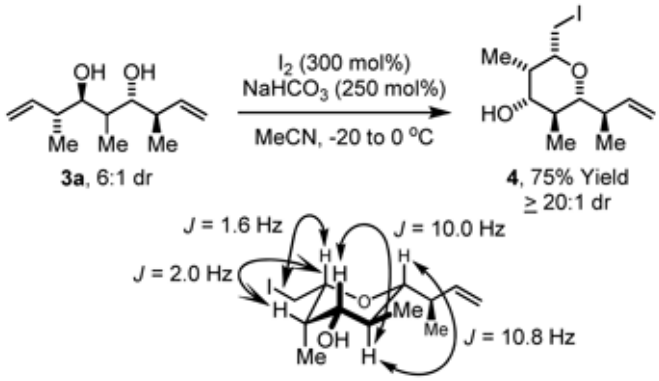
Given these favorable results, the double crotylation of 2-methyl-1,3-propanediol **1b** was explored. Here, generation of the *pseudo*-$C_2$-symmetric contiguous polypropionate stereoquintet **3a** is potentially achieved in a single manipulation. However, sixteen stereoisomeric adducts potentially arise (Figure 4). The calculated theoretical distribution of stereoisomers obtained upon use of the chiral catalyst (*R*)-**I** suggests only three stereoisomers will be generated in significant proportion: the desired $C_2$-symmetric adduct **3a** (86.1%), *s,s,a,a*-**3b** (5.7%) and *s,a,s,a*-**3b** (5.7%). Accordingly, authentic samples of these components and *ent*-**3a** were prepared in a conventional stepwise manner involving successive mono-crotylation.[16]

Chiral stationary phase GC analysis of the mixture obtained in the double crotylation of 2-methyl-1,3-propanediol **1b** using the BIPHEP-modified catalyst reveals over ten distinct species. However, chiral stationary phase GC and $^1$H NMR analysis of the reaction mixture

obtained using chiral catalyst (*R*)-**I** reveals that the desired $C_2$-symmetric adduct **3a** is formed predominantly, along with small quantities of *s*,*s*,*a*,*a*-**3b** and *s*,*a*,*s*,*a*-**3b** (Figure 5). This outcome is in excellent agreement with the predicted stereoisomeric ratios. Isolation by silica gel chromatography delivers **3a** in 62% yield as a single enantiomer as a 6:1 mixture of diastereomers. Thus, a contiguous acyclic array of five stereogenic centers is generated in a single manipulation from achiral reactants with control of relative and absolute stereochemistry (Figure 4). In attempted double crotylations of the higher congener, 2,2-dimethyl-1,3-propanediol, only mono-adducts were formed. Presumably, steric crowding prohibits formation of the double crotylation product.

## Formal Synthesis of the Rifamycin S and Synthesis of the Scyotphycin C19–C25 Stereoquintet

To explore the utility this methodology in polyketide construction, the product of double crotylation **3a** was applied in a synthetic approach to the *ansa* chain of rifamycin S, the C19–C27 stereoheptad. A key objective involves differentiation of the diastereotopic hydroxyl moieties and olefinic termini of **3a**. Additionally, the latent stereocenter residing on the *pseudo*-$C_2$-axis must be defined. These goals are achieved in a single operation through the conversion of **3a** to iodoether **4**. As corroborated by $^1$H NMR analysis of the pyran spin system, the substituents attached to the two newly formed stereocenters of iodoether **4** are equatorially disposed (eqn. 3).




(eqn. 3)

Elaboration of iodoether **4** to the *ansa* chain of rifamycin S is accomplished in a straightforward manner. Ozonolytic cleavage of iodoether **4** delivers the aldehyde **5**, which is subjected to Batey's crotylation conditions[19] to furnish the homoallylic alcohol **6** as a single stereoisomer (>20:1 dr), as determined by $^1$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[20] and Cram-Reetz[21] models, respectively, account for the high level of stereoselectivity.[22] Ozonolytic cleavage of the terminal olefin followed by $NaBH_4$-mediated reduction of the ozonide delivers the primary alcohol **7** (not shown). Exposure of **7** to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage to reveal the polypropionate stereohepted **8**. Conversion of tetraol **8** to the *bis*-acetonide **9** and, finally, ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by $NaBH_4$, delivers the protected C19–C27 stereohepted **10**, which is identical in all respects to previously reported material.[7] This eight step preparation of the *ansa* chain constitutes a formal total synthesis of rifamycin S from 2-methyl-1,3-propanediol **1b** (Scheme 1).[8c–f]

Paterson reports a 10 step synthesis of the same C19–C27 segment of rifamycin S using asymmetric aldol reactions mediated by (+)- and (−)-$(Ipc)_2BOTf$.[23]

To further illustrate the generality of this approach, a synthesis of the scyotphycin C C19–C25 stereoquintet was undertaken. Ozonolytic cleavage of the terminal olefin of iodoether **4** with $NaBH_4$-mediated reduction of the ozonide delivers the primary alcohol **11** (not shown), which is converted to the pivalate **12**. Exposure of an ethanolic solution of **12** to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage to reveal the 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 $NaBH_4$, delivers the primary alcohol **15** (not shown), which is converted to the benzylic ether **16** (Scheme 1). Ether **16** is identical in all respects to previously reported material.[9h–i]

## Conclusion

In summary, we report a powerful new process for the direct generation of polypropionate stereoquintets *via* iridium catalyzed *anti*-diastereo- and enantioselective carbonyl double crotylation of 1,3-propanediols **1a** and **1b**. Based on this methodology, syntheses of the rifamycin S C19–C27 stereoheptad and the scytophycin C C19–C25 stereoquintet were executed with dramatic enhancement in step economy. To our knowledge, the efficiency associated with the conversion of the achiral/chiral racemic materials **1b** and α-methyl allyl acetate to stereoquintet **3a** is without precedent. Future studies will focus on the development and application of other alcohol C-C couplings of relevance to polyketide construction.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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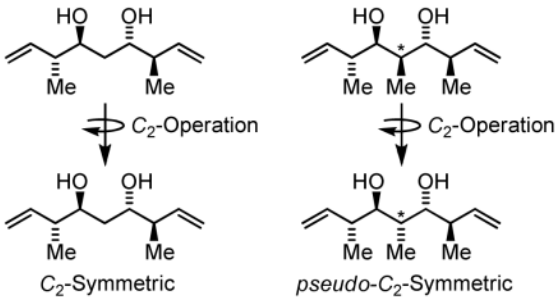


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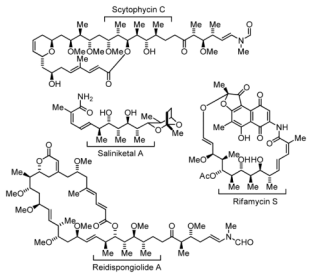



**Figure 1.**
Representative polyketide natural products possessing pseudo-$C_2$-symmetric polypropionate stereoquintets.

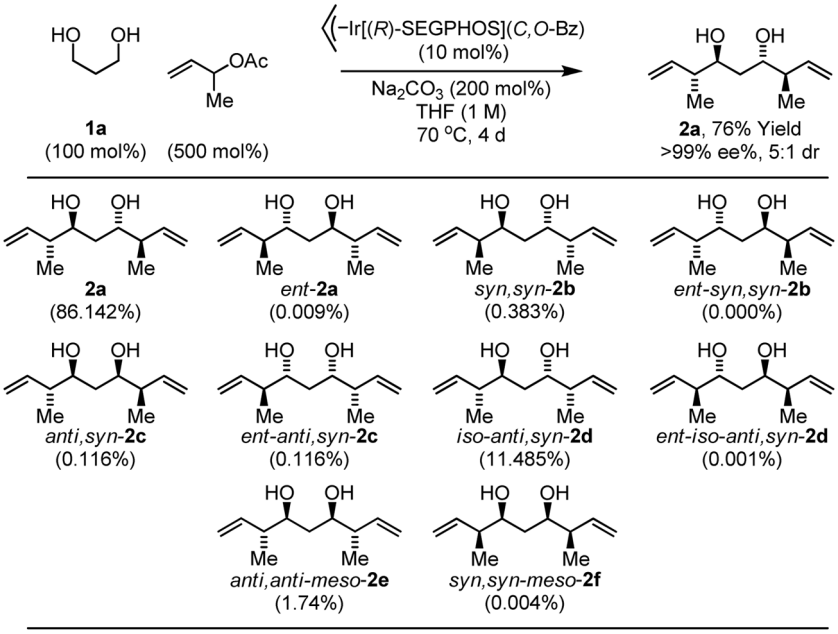



**Figure 2.**

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 dr (*anti:syn*) and observed experimental results.[a]

[a]Yields are of combined isomeric materials. Regio- and stereoselectivities were determined by $^1$H NMR analysis of crude reaction mixtures. Diastereomeric ratios refer to the proportion of **2a** and **3a** with respect to all respective stereoisomers combined.

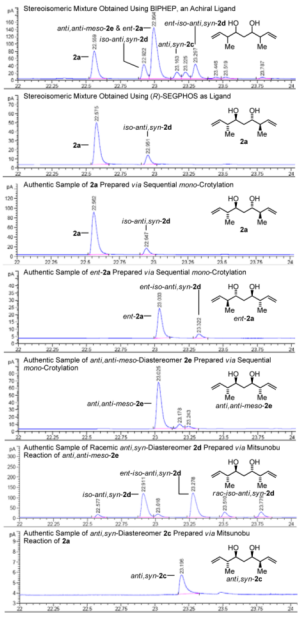



**Figure 3.**

Characterization of the product distribution obtained upon *anti*-upon diastereo- and enantioselective double *C*-crotylation of 1,3-propanediol **1a**.[a]

[a]Reaction products were isolated by silica gel chromatography and analyzed by chiral stationary phase GC analysis using authentic samples of the indicated stereoisomers. See Supporting Information for details.

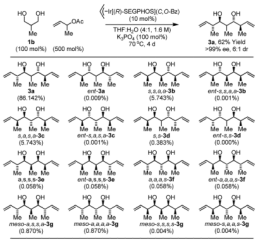


**Figure 4.**

Calculated theoretical distribution of stereoisomers **3** obtained in the double crotylation of 2-methyl propanediol **1b** based on 98% ee for both *syn*- and *anti* -crotylation events and a 15:1 dr (*anti*:*syn*) and observed experimental results.[a]

[a]Yields are of combined isomeric materials. Regio- and stereoselectivities were determined by $^{1}$H NMR analysis of crude reaction mixtures. Diastereomeric ratios refer to the proportion of **2a** and **3a** with respect to all respective stereoisomers combined.

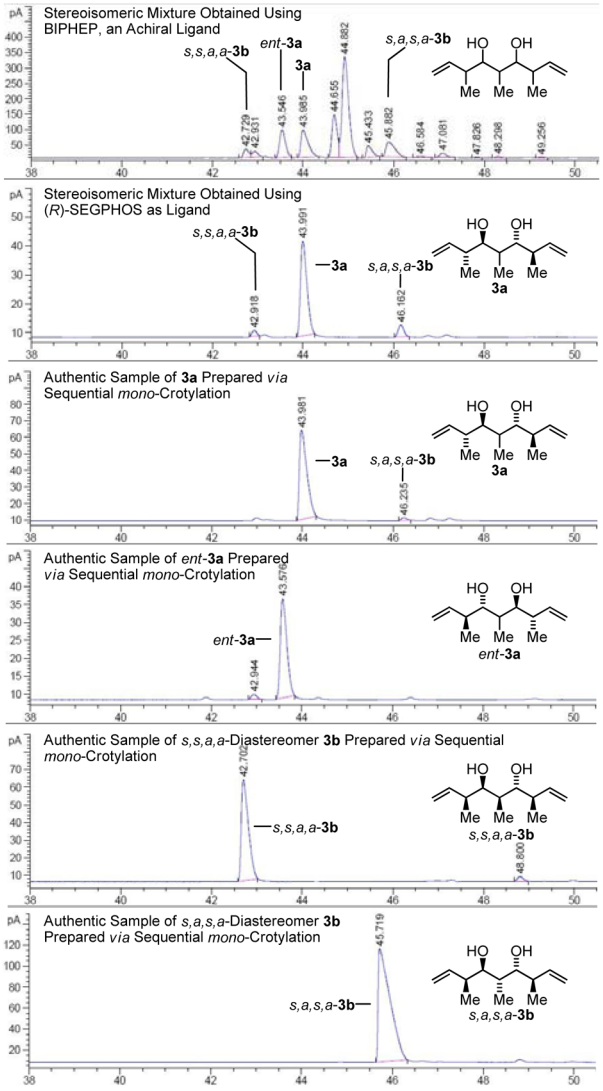
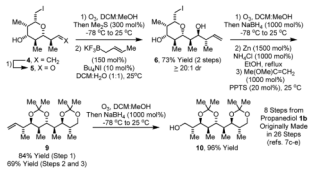



**Figure 5.**

Characterization of the product distribution obtained upon *anti*-upon diastereo- and enantioselective double *C*-crotylation of 2-methyl-1,3-propanediol **1b**.[a]

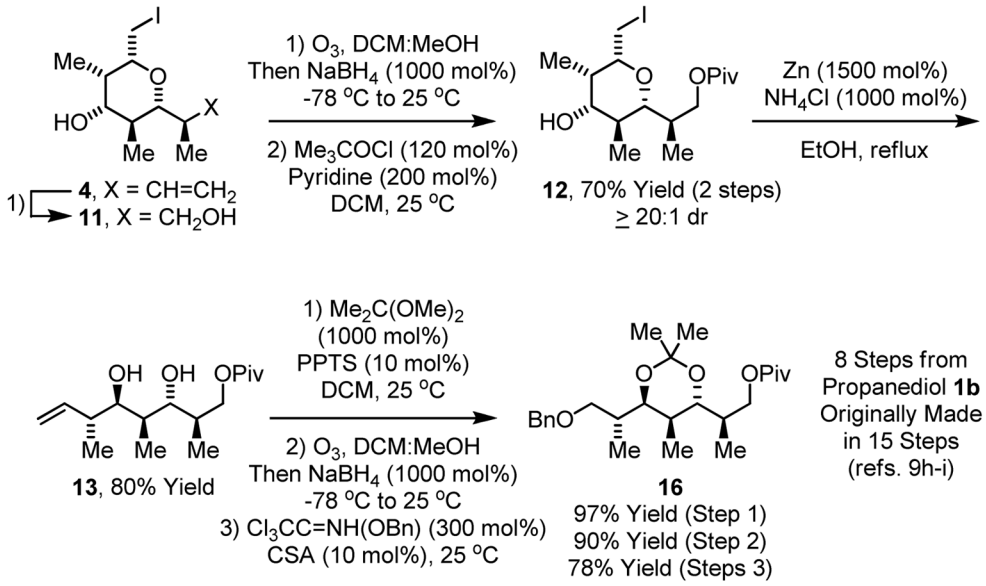
[a]Reaction products were isolated by silica gel chromatography and analyzed by chiral stationary phase GC analysis using authentic samples of the indicated stereoisomers. See Supporting Information for details.



**Scheme 1.**

Formal synthesis of rifamycin S via construction of the C19–C27 stereoheptad.[a]

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




**Scheme 2.**

Synthesis of the scytophycin C C19–C25 stereoquintet.[a]

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