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Efficient Strategy for the Synthesis of Stereopentad Subunits of Scytophycin, Rifamycin S, and Discodermolide

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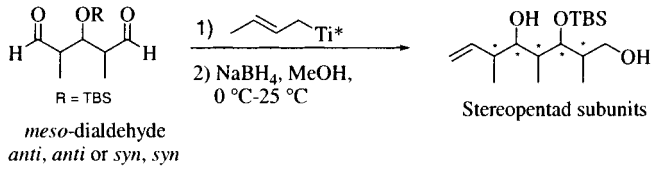
ABSTRACT



meso-dialdehyde
anti, *anti* or *syn*, *syn*

An efficient, simple method has been developed for the stereocontrolled synthesis of polypropionate stereopentads in high enantio- and diastereomeric purities.

The polypropionates (chains with alternating methyl−hydroxy−methyl substituents)[1] represent an important class of natural products such as the macrolides and the ionophores,[2] which are often associated with a broad spectrum of biological activity. Their name comes from their biogenesis, which entails the iterative condensation of propionate units.[3] Several stereoselective methods and strategies have been developed to provide access to these systems which possess a high density of stereogenic centers.[4,5]

The presence of more than one stereopentad encompassing multiple contiguous stereogenic centers and the control of absolute stereochemistry in a given molecule presents a major challenge in stereoselective synthesis. In looking for routes to prepare advanced stereopentad segments, our interest was drawn to *meso*-dialdehydes.[6] The asymmetric transformation of *meso* compounds by reaction with a chiral reagent is a generally useful strategy for asymmetric synthesis, and in recent years several reactions of this type involving either enzymatic catalysis or nonenzymatic reactions have been reported.[7]

We report here the direct transformation of *meso*-dialdehydes **1a** and **1b** to stereopentad subunits by using the cyclopentadienyldialkoxycrotyltitanium[8] complexes (*R*,*R*)-**II** and (*S*,*S*)-**II** and their further elaboration to common polypropionate subunits present in different natural products

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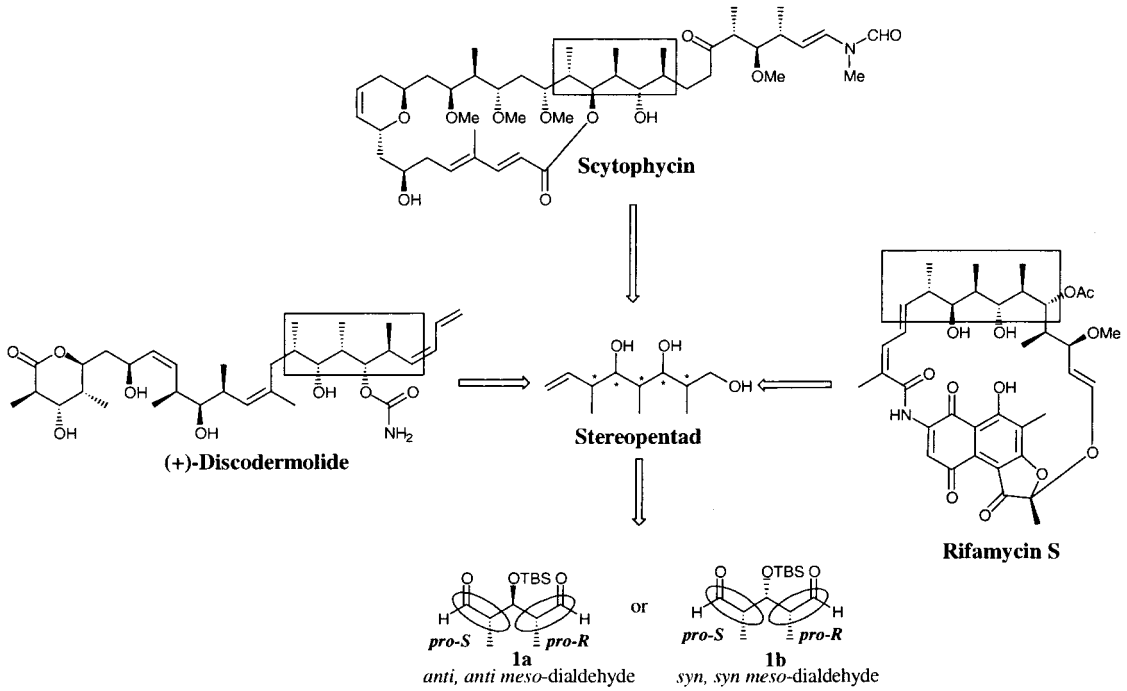


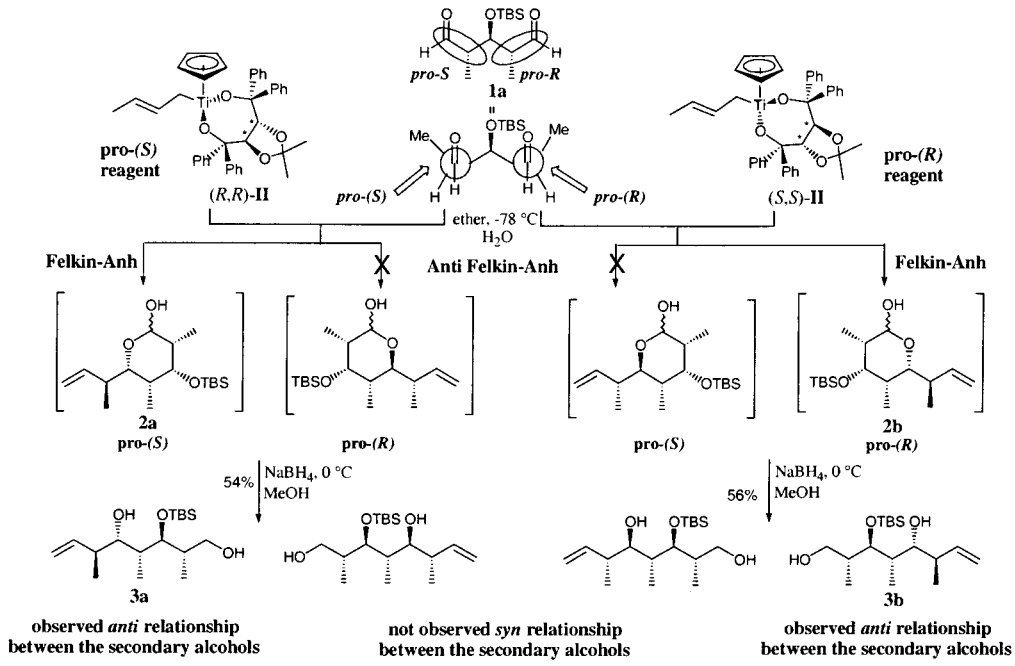
Figure 1.

such as scytophycin,[9] rifamycin S,[10] and discodermolide[11] (Figure 1).

Treatment of dialdehyde **1a** with one equivalent of crotyltitanium complex (*R*,*R*)-**II** and (*S*,*S*)-**II** was first examined. The hemiketals **2a** and **2b** were respectively obtained, and these crude products were treated with $NaBH_4$ to produce stereopentads **3a**[12] (54% from **1a**) and **3b**[12] (56% from **1a**). It is worth noting that in these experiments the double addition products were not observed (Scheme 1).

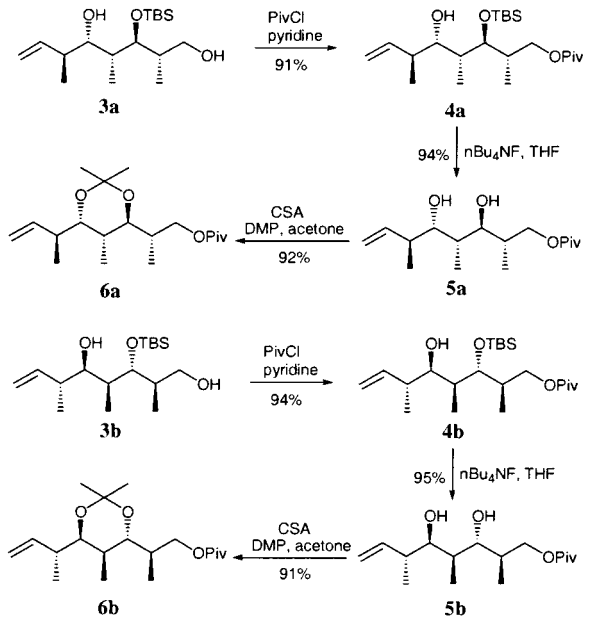
The relative stereochemistry between the different groups present in **3a** and **3b** was determined after transformation of these compounds to the corresponding acetonides **6a** and

Scheme 1



6b. Esterification of the primary alcohol **3a** with pivaloyl chloride led to **4a** in 91% yield, followed by treatment of compound **4a** with tetra-*n*-butylammonium fluoride (*n*Bu_4NF) (94%). Subsequent protection of diol **5a** with 2,2-dimethoxypropane in the presence of CSA in acetone afford the acetonide **6a** in 92% yield. A similar reaction sequence was applied to stereopentad **3b** to afford acetonide **6b** (Scheme 2). The relative stereochemistry of the *anti*-1,3-

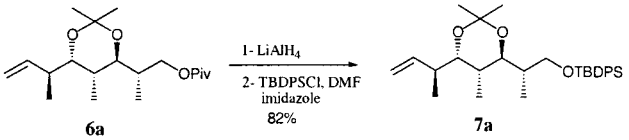
Scheme 2



diol in **6a** and **6b** was confirmed by analyzing the ^{13}C NMR chemical shift (δ = 25.0, 23.2 for Me_2C).[13] The only product obtained in each case was the Felkin−Anh product.

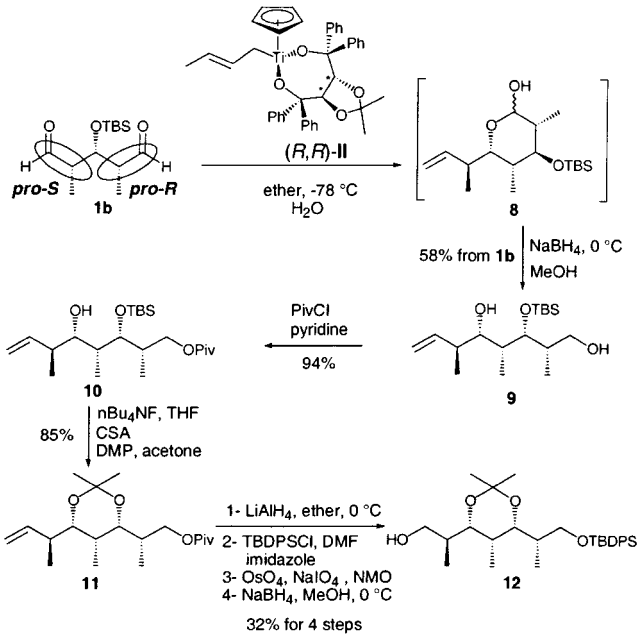
The absolute configuration at C2, C3, C4, C5, and C6 in **3a** was determined after transformation of compound **6a** to the corresponding acetonide **7a** (Scheme 3). After reduction

Scheme 3



of **6a** with $LiAlH_4$ and protection of the primary alcohol by using TBDPSCl (DMF, imidazole), compound **7a** was obtained in 82% yield ($[\alpha]^{22}_D$ = +16.1, *c* 1.1, $CHCl_3$; lit.[14] $[\alpha]^{22}_D$ = +18.1, *c* 1.4, $CHCl_3$). This chemical correlation allowed us to attribute the configuration 2*S*,3*S*,4*S*,5*S*,6*S* to compound **3a**. The stereopentad **3a** corresponds to the C19−C25 fragment of scytophycin and to the C4−C10 fragment of rifamycin S.

Scheme 4



The stereopentad **9** present in the C15−C21 fragment of (+)-discodermolide was synthesized from the *meso*-dialdehyde **1b**[15] by using the cyclopentadienyldialkoxycrotyltitanium complex (*R*,*R*)-**II**. When dialdehyde **1b** was treated with (*R*,*R*)-**II**, lactol **8** was obtained and directly reduced with $NaBH_4$ (MeOH, 0 °C) to afford the stereopentad **9** in 58% yield. This compound was then transformed to acetonide **11** in three steps. After protection of the primary alcohol by using pivaloyl chloride (PivCl, pyridine, 25 °C), ester **10** was treated with *n*Bu_4NF and the diol was protected under the standard conditions (CSA, acetone, DMP) to produce the acetonide **11** in 85% yield. The *syn* relative configuration of the hydroxy groups at C3 and C5 was confirmed by the analysis of the ^{13}C NMR spectra (δ = 19.2, 29.8 for Me_2C).[13] The absolute configuration of the stereogenic centers was determined after transformation of **11** to **12** and by comparison of the $[\alpha]_D$ ($[\alpha]^{22}_D$ = +21, *c* 1.4, $CHCl_3$; lit:[16] $[\alpha]^{22}_D$ = +23.4, *c* 1.37, $CHCl_3$) (Scheme 4).

As previously observed in the desymmetrization of *meso*-dialdehydes by cyclopentadienyldialkoxyallyltitanium com-

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plexes,[17] the cyclopentadienyldialkoxycrotyltitanium complexes (*R*,*R*)-**II** and (*S*,*S*)-**II** discriminate respectively the *pro*-(*S*) and the *pro*-(*R*) faces of *meso*-dialdehydes. The desymmetrization of *meso*-dialdehydes by the complexes (*R*,*R*)-**II** and (*S*,*S*)-**II** allow a short and efficient synthesis of stereopentads which are present in biologically active natural products.

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Supporting Information Available: Experimental procedure, analytical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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