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Diastereoselective Hydroformylation of Acyclic Olefins: Efficient Construction of an all-*anti* Stereotriade Building Block for Polyketide Synthesis

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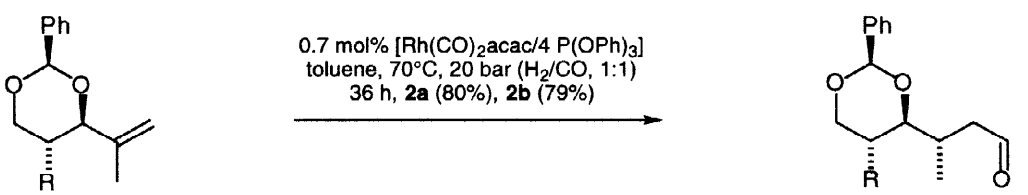
Abstract: The hydroformylation of 2-phenyl-4-(prop-2-enyl)[1,3]dioxanes has been studied. *anti*-Acetals **1a,b** were found to give extraordinarily high diastereoselectivity on hydroformylation, giving rise to the formation of the all-*anti* stereotriades **2a,b**. The origin of this stereoselectivity may be related to the preferred conformation of the actetals **3** in solution, as determined by 2D-NOESY NMR experiments and force field calculations (MM3). Hydroformylation of **1a** afforded an intermediate for a short and efficient synthesis of a key building block for the total synthesis of the macrolide antibiotic bafilomycin A_1.

Efficient transformations in organic synthesis require carbon carbon bond forming reactions giving rise to the selective formation of new stereogenic centers. In particular, transition metal catalyzed addition reactions have found increased attention,[1] as not only do they have an inherent potential for stereoselective carbon carbon bond formation, but also have the potential to be used in economically and ecologically sound processes. In this context diastereoselective rhodium catalyzed hydroformylation has become a major subject of interest. Whereas stereocontrol on hydroformylation of olefins incorporated in cyclic systems can be achieved rather easily,[2] the control of stereoselectivity upon hydroformylation of acyclic olefins is still a challenge.[3]

We report here, a special case in which stereoselective hydroformylation of an acyclic olefin could be achieved giving rise to the formation of an all-*anti* stereotriade, one of the central building blocks of the polyketide class of natural products.



1a R = Me
1b R = Et

2a, b
dr ≥99 : ≤1

Thus, hydroformylation of the benzylidene acetals **1a,b** employing 0.7 mol% of a rhodium/triphenylphosphite catalyst provided the all *anti* stereotriade[4] aldehydes **2a,b** in good yields and with *complete diastereoselecitvity* (≥99:≤1).

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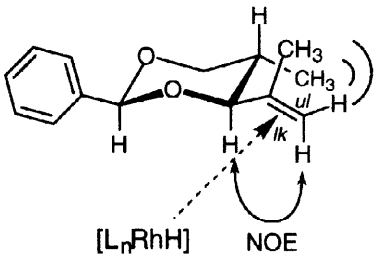
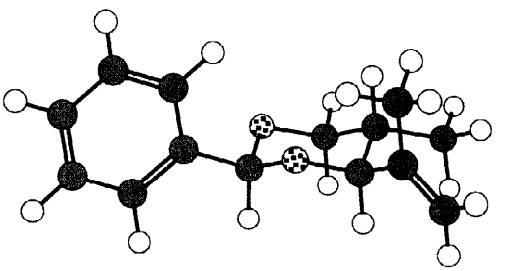
To rationalize this result the stereochemistry defining step of the hydroformylation reaction - the hydrometallation of the coordinated olefin in a trigonal bipyramidal rhodium(I) complex - had to be considered. This step has been shown to have a low activation barrier (≤ 10kJ/mol), and to be exothermic and irreversible for most Rhodium/triarylphosphine or phosphite catalysts.[5] For these reasons conformational preferences can become of major significance in determining the stereochemical result of this reaction.[6] As a consequence we investigated the preferred conformation of **1a** in solution, employing 2D-NOESY experiments. Accordingly, acetal **1a** has a preferred conformation **A** in solution at 25°C.

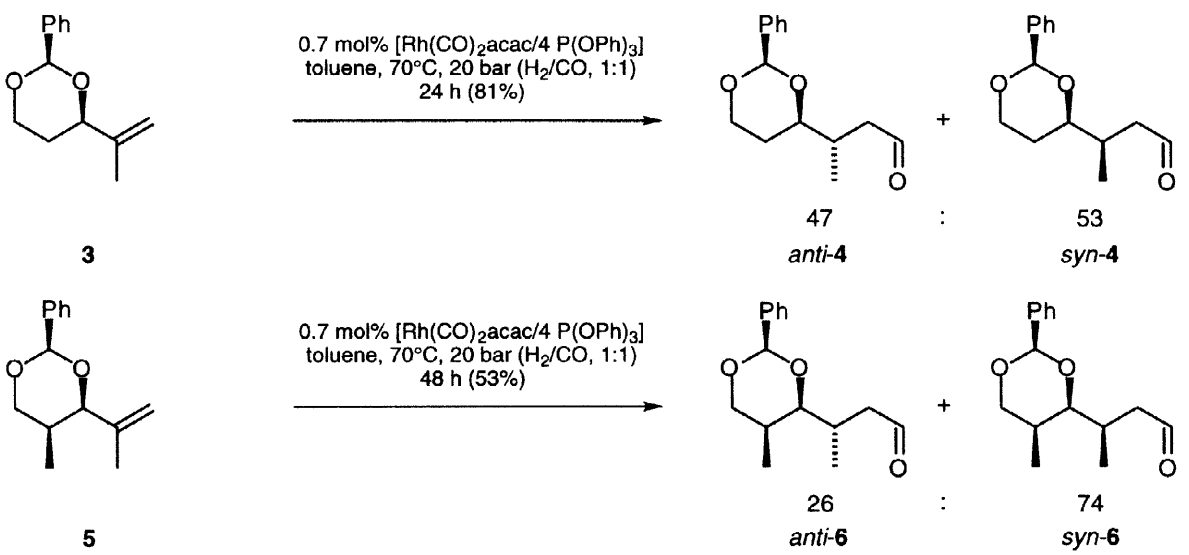


Preferred conformation **A** of **1a** according to 2D NOESY experiments.

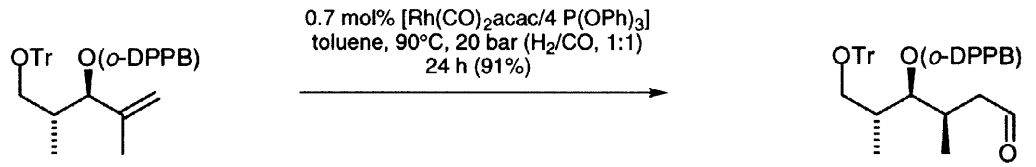


Energetically preferred conformation **A** of **1a** according to MACROMODEL/MM3.

This observation was confirmed by MACROMODEL/MM3 calculations indicating conformation **A** to be populated to almost 90% at 25°C.[7] Such a strong conformational preference stems mainly from a minimization of a repulsive *syn*-pentane interaction [8a] between the two methyl substituents, as well as minimization of 1,3 allylic strain [8b] within the alkene moiety. Those two repulsive interactions orientate the acyclic olefin into a single defined position. The origin of the exclusive attack of the Rhodium catalyst from the *lk* face of the double bond seems to be the spatial shielding of the *ul* face by the equatorial methyl substituent. Further support of this interpretation was provided by the hydroformylation of derivatives **3** and **5**. In these cases the conformation controlling and shielding methyl group is either missing or in an axial position. Accordingly, the hydroformylation of **3** and **5** proceeded in a stereorandom fashion. Thus, the diastereoselective hydroformylation of the acetals **1** represents a special case, which allows the stereoselective construction of the all-*anti* stereotriade only.



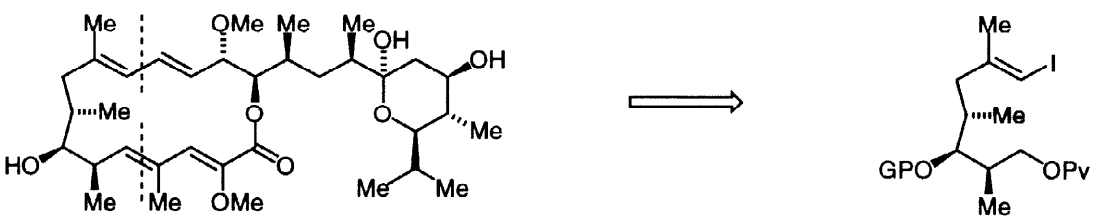
Conversely, to gain access to the *anti-syn* stereotriade by means of the hydroformylation reaction, one can make use of the *ortho*-diphenylphosphanylbenzoate group (*o*-DPPB) as a catalyst directing group (CDG).[9] Thus, hydroformylation of the *o*-DPPB-ester **7** provided in 91% yield aldehyde **8** in a diastereomer ratio of 96:4.



7 **8**

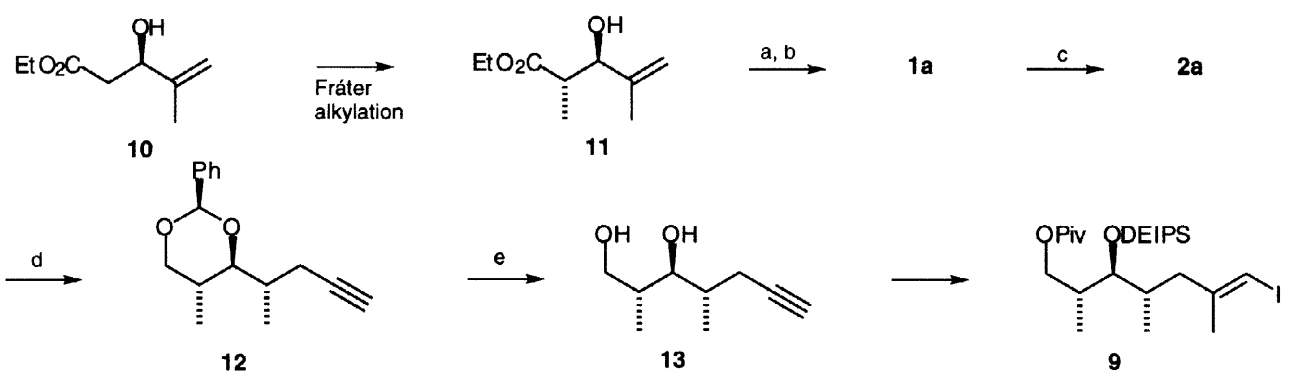
dr 96 : 4

The macrolide antibiotic bafilomycin A_1 constitutes an attractive target to explore the synthetic utility of this methodology. Following the convergent retrosynthetic analysis, according to Toshima *et al.*, the major building block **9** became of primary interest.[10] This building block **9** has been synthesized employing a rather long sequence, consisting of 13 steps.[10]



bafilomycin A_1 **9**

Our synthesis of **9** started from the β-hydroxyester **10**. Its resolution employing Sharpless epoxidation has been described.[11] Subsequent Fráter alkylation gave the methallylic alcohol **11**.[12] Reduction and protection as the benzylidene acetal provided **1a**, which was hydroformylated to give **2a**.[13] Subsequent Corey-Fuchs chain elongation furnished the terminal acetylene **12**,[14] which was deprotected to afford the 1,3-diol **13**. Transformation of this diol into the key building block **9** within 3 steps has been reported previously.[10] Thus, our hydroformylation methodology provides an efficient and short access to the central building block **9** for the total synthesis of the macrolide bafilomycin A_1. Further extension of this methodology is in progress.



10 **11** **12** **13** **9**

Reagents and Conditions: a) $LiAlH_4$, ether, 0°C (83%); b) $PhCH(OMe)_2$, PTS, CH_2Cl_2 (86%); c) 0.7 mol % $[Rh(CO)_2acac/4\ P(OPh)_3]$, toluene, 70°C, 20 bar, 36 h (80 %); d) i, CBr_4, PPh_3 (71%); ii, *n*-BuLi, THF (90%); e) 80% AcOH, THF, 50°C (70%).

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13. All new compounds gave satisfactory analytical data. Spectrosopic data of selected new compounds. **1a**: ^{1}H-NMR (200.133 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 6.7 Hz, 3H), 1.81 (s, 3H), 2.05 (m_c, 1H), 3.55 (pt, *J* = 11.1 Hz, 1H), 3.87 (d, *J* = 10.0 Hz, 1H), 4.18 (dd, *J* = 11.2, 4.7 Hz, 1H), 4.96-4.99 (m, 2H, =CH_2), 5.54 (s, 1H, H2), 7.31-7.35 (m, 3H, Ar-H), 7.47-7.52 (m, 2H, Ar-H); ^{13}C-NMR (50.323 MHz, $CDCl_3$): δ = 12.28, 17.47, 31.20, 73.08, 88.19, 101.13, 114.89, 126.19 (2 C) 128.15 (2 C) 128.72, 138.59, 142.59. **2a**: ^{1}H-NMR (300.133 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.89 (m_c, 1H), 2.41-2.55 (m, 2H), 2.60-2.70 (m, 1H), 3.38 (dd, *J* = 10.1, 1.3 Hz, 1H), 3.49 (pt, *J* = 11.1 Hz, 1H), 4.10 (dd, *J* = 11.2, 4.8 Hz, 1H), 5.46 (s, 1H), 7.31-7.39 (m, 3H), 7.43-7.47 (m, 2H), 9.82 (m_c, 1H); ^{13}C-NMR (75.469 MHz, $CDCl_3$): δ = 12.11, 18.31, 28.90, 31.24, 44.90, 72.91, 86.66, 101.21, 125.97 (2 C), 128.11 (2 C), 128.64, 138.66, 202.30. **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 1.9 (dd, *J* = 17.6, 8.3 Hz, 1 H), 2.1 (m, 1 H), 2.22 (dd, *J* = 17.6, 5.1 Hz, 1 H), 2.46 (m, 1 H), 2.96 (pseudo t, *J* = 8.3 Hz, 1 H), 3.15 (dd, *J* = 8.7, 3.0 Hz, 1 H), 4.97 (dd, *J* = 9.0, 2.3 Hz, 1 H), 6.92 (m, 1 H), 7.12-7.46 (m, 27 H), 7.76 (m, 1 H), 9.46 (s, 1 H, CHO). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ = 13.50, 14.86, 28.86, 36.04, 48.02, 64.94, 78.27, 86.63, 126.90 (3 C), 127.74 (6 C), 128.18, 128.48 (2 C), 128.57 (d, $J_{C,P}$ = 6.9 Hz, 4 C), 128.81 (6 C), 130.80, 132.00, 133.58 (d, $J_{C,P}$ = 16.9 Hz), 133.83 (d, $J_{C,P}$ = 20.4 Hz, 2 C), 134.22, 134.36 (d, $J_{C,P}$ = 21.6 Hz, 2 C), 137.92 (d, $J_{C,P}$ = 13.5 Hz), 138.53 (d, $J_{C,P}$ = 20.9 Hz), 141.18 (d, $J_{C,P}$ = 28.1 Hz), 144.17 (3 C), 166.19, 201.44; ^{31}P NMR (161.978 MHz, $CDCl_3$): δ = -3.5.
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