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1,4-Remote Stereocontrol by Asymmetric Catalytic Carbonyl-Ene Reaction with Chiral Homoallylic Ethers: An Application to the Asymmetric Synthesis of (11*R*,14*S*)-*anti*- and (31*R*,34*S*)-*syn*-Segments of Immunosuppressant Rapamycin

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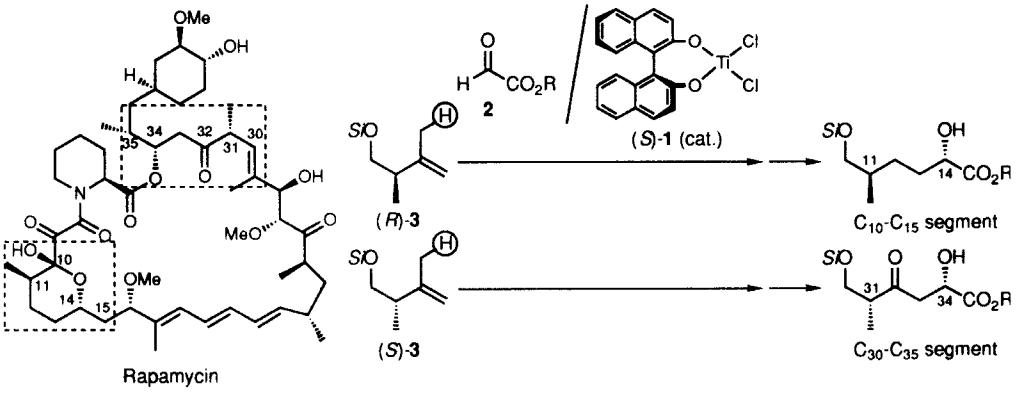
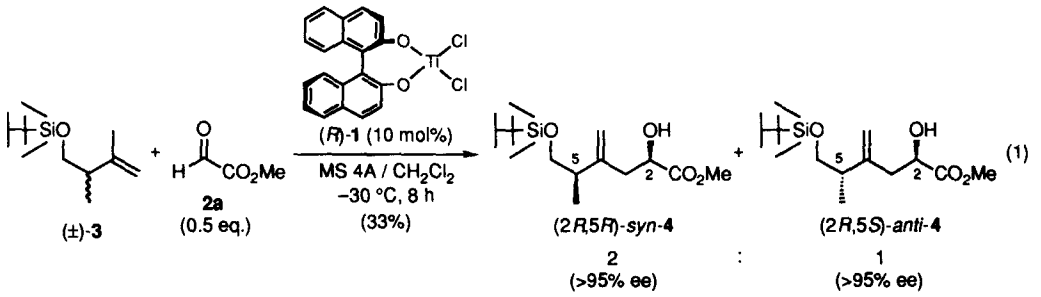
Abstract: *1,4-Remote stereocontrol is established through double asymmetric induction in asymmetric catalytic glyoxylate-ene reaction, by simple combination of the chirality of homoallylic ethers and binaphthol-titanium catalyst. The present approach to 1,4-remote stereocontrol can be applied to the asymmetric synthesis of the diastereomeric (11R,14S)-anti- and (31R,34S)-syn-fragments of an immunosuppressant rapamycin with remote relationships of Me and OH groupings.*

Currently, much attention has been focused on the development of efficient methods for stereocontrol over remote rather than adjacent stereogenic centers.[1] We now wish to report herein the 1,4-remote stereocontrol through the double asymmetric induction[2] in asymmetric catalytic carbonyl-ene reactions.[3] The basic strategy is the chiral binaphthol-titanium complex (**1**)-catalyzed carbonyl-ene reaction of glyoxylate **2** (glyoxylate-ene reaction)[4] with chiral homoallylic ethers **3** for the asymmetric synthesis of 1,4-*anti*- and 1,4-*syn*-diastereomers with remote relationships of Me and OH groupings. The diastereomers can be transformed to the C_{10}-C_{15} and C_{30}-C_{35} fragments of an immunosuppressant rapamycin with high potency and novel mechanism of action (Scheme 1).[5,6]

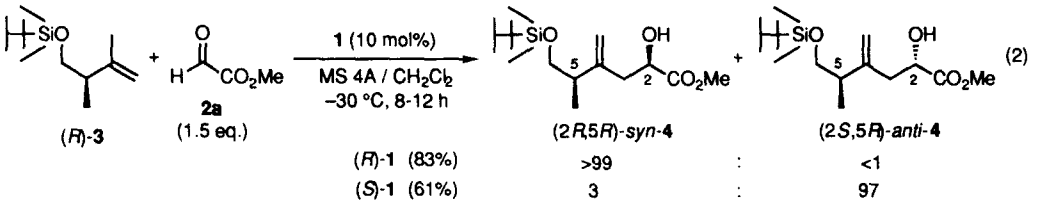
Scheme 1



Recently, we reported that the kinetic optical resolution[7] of racemic allylic ethers by the asymmetric catalytic glyoxylate-ene reaction exhibited a high level of *syn*-diastereoselection along with a remarkably high enantiomeric excess (>95% ee).[8] We have now found, by contrast, that the kinetic resolution of racemic homoallylic ether **3** by the catalysis of (*R*)-binaphthol-titanium dichloride **1** (BINOL-$TiCl_2$) provides only a low level of diastereoselection (*syn* / *anti* = 2 : 1),[9] however, with a remarkably high enantiomeric excess (>95% ee, 2*R*) for both diastereomers (eq. 1). Thus, the ene reaction of methyl glyoxylate **2a** with racemic homoallylic ether **3** did proceed smoothly in dichloromethane at –30 °C for 8 h by the catalysis of (*R*)-BINOL-$TiCl_2$ **1** (10 mol%) to give the *syn*- and *anti*-diastereomers of **4** in a ratio of 2 : 1. The enantiomeric purities are virtually complete for both the diastereomeric products **4** as measured by the LIS ^{1}H-NMR analysis after conversion to its methyl ether derivatives.[4] The absolute configuration of both products was thus determined to be *R* by the similarity in the LIS ^{1}H-NMR spectra.[4]

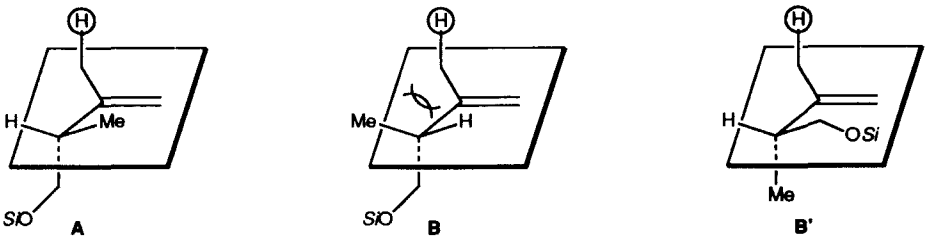


These observations suggest that the enantiocontrol over the prochiral glyoxylate **2a** would be achieved essentially independent of the reactant chirality of homoallylic ethers **3**. Indeed, we found that the glyoxylate-ene reaction with (*R*)-**3** using (*R*)-BINOL-$TiCl_2$ (**1**) or (*S*)-**1** gave the (2*R*,5*R*)-*syn*- and (2*S*,5*R*)-*anti*-diastereomers **4**, respectively, in high diastereoselectivity (>95% ds) (eq. 2). Therefore, we can synthesize the four possible diastereomers with 1,4-remote relationships of Me and OH groupings in highly enantiomeric form at will, by the proper combination of the chirality of the catalyst and the ene substrate. However, in the "mis-matched" reaction of (*R*)-**3** catalyzed by (*S*)-**1**, the regioisomer, 2-hydroxy-4,5-dimethyl-6-siloxy-4-hexenoate, was obtained in 19% yield.[10] Of particular interest is that the present homoallylic cases are different in nature from the allylic counterpart,[8] wherein the efficient remote diastereocontrol is achievable only by the matched pair of the (*S*)-allylic ether / (*R*)-catalyst or (*R*)-allylic ether / (*S*)-catalyst.

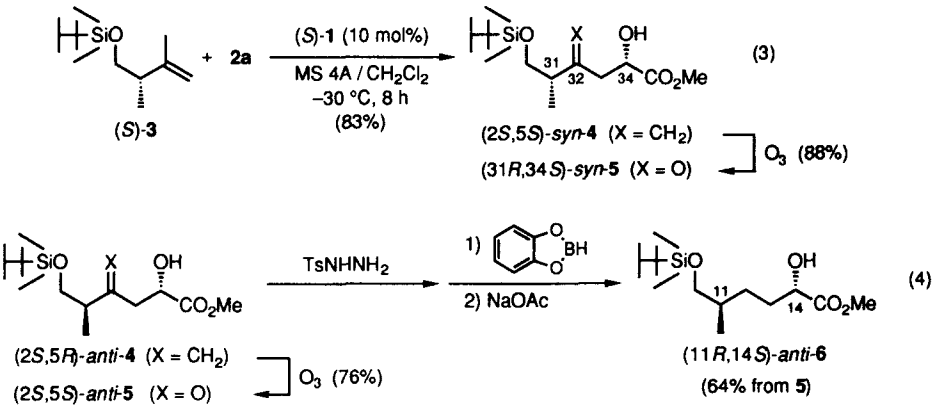


In the "matched" reaction of (*R*)-**3** catalyzed by (*R*)-**1**, the most reactive conformer (**A**) of **3**, wherein the highly electron-donating alkoxymethyl group[11] is in perpendicular to the π-face of **3**, would be involved. However, in the "mis-matched" reaction of (*R*)-**3** catalyzed by (*S*)-**1**, the conformer (**B**) might be operative in

spite of the $A^{(1,2)}$ acyclic allylic strain or another conformer (**B'**), wherein the less electron-donating Me group is in perpendicular to the π-face of **3**, might be involved. Thus, the regioisomeric product was obtained to some extent in the "mis-matched" catalytic system *via* the methine-hydrogen shift.



Thus, the diastereomeric C_{10}-C_{15} and C_{30}-C_{35} fragments of an immunosuppressant rapamycin[5,6] with (11*R*,14*S*)-*anti*- and (31*R*,34*S*)-*syn*-Me,OH-relationship can be synthesized by the (*S*)-BINOL-$TiCl_2$-catalyzed carbonyl-ene reaction with (*R*)- and (*S*)-**3**,[12] respectively (eq. 3 and 4). The (2*S*,5*S*)-*syn*-**4** was obtained in diastereo- and enantiomerically pure form through the double asymmetric induction *via* asymmetric catalytic glyoxylate-ene reaction with (*S*)-**3**. Ozonolysis of (2*S*,5*S*)-*syn*-**4** afforded the desired 32-keto segment (31*R*,34*S*)-*syn*-**5**[13] in good yield. Similarly, (2*S*,5*R*)-*anti*-**4** was transformed *via* ozonolysis to the diastereomeric γ-keto ester (2*S*,5*S*)-*anti*-**5**.[14] Furthermore, the desired 12-deoxy segment (11*R*,14*S*)-*anti*-**6**[15] was obtained *via* tosylhydrazone by reduction with catecholborane.[16]



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(9) With 1 equivalent each of $SnCl_4$ and methyl glyoxylate **2a**, *syn*- and *anti*-**4** were obtained in a ratio of 3 : 2 in 93% yield.

(10) In the "matched" reaction, no regioisomer was obtained.

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(13) $[\alpha]_D^{23}$ –25.5 ° (c 1.30, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 4.51 (dd, *J* = 3.6, 6.6 Hz, 1H, C<u>H</u>(OH)CO_2Me).

(14) $[\alpha]_D^{27}$ +32.3 ° (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 4.46 (dd, *J* = 4.0, 5.9 Hz, 1H, C<u>H</u>(OH)CO_2Me).

(15) $[\alpha]_D^{27}$ +6.82 ° (c 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 4.19 (dd, *J* = 4.3, 7.0 Hz, 1H, C<u>H</u>(OH)CO_2Me).

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