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Enantioselective allyltitanations. Synthesis of optically active 1,2-diol units: useful intermediates for the preparation of biologically active compounds

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Abstract

1,2-Diol units were synthesized with excellent enantiomeric excess by using an enantioselective allyltitanation of α-alkoxy-substituted aldehydes.

For developing more efficient drugs, the synthesis of analogues or isosteric compounds has been the focus of intense research synthetically and medicinally.[1] For example, a new structural class of protein kinase C inhibitors related to the naturally occuring staurosporine, such as LY 333531, has been developed and synthesized from **A** and the bis-alkylating agent derived from triol derivative **1**.[2–4] In the case of the isosteric phosphonate (IP) of ganciclovir monophosphate (GMP), which is an effective in vitro and in vivo inhibitor of human cyto-megalovirus (HCMV) replication, its synthesis was performed from **B** and chlorodiol derivative **2**.[5]

In support of these studies, a synthetic route that would be useful for the preparation of compounds (−)-**1** and (+)-**2** is required. For our part, we used an enantioselective allyltitanation of aldehydes to synthesize these two compounds.

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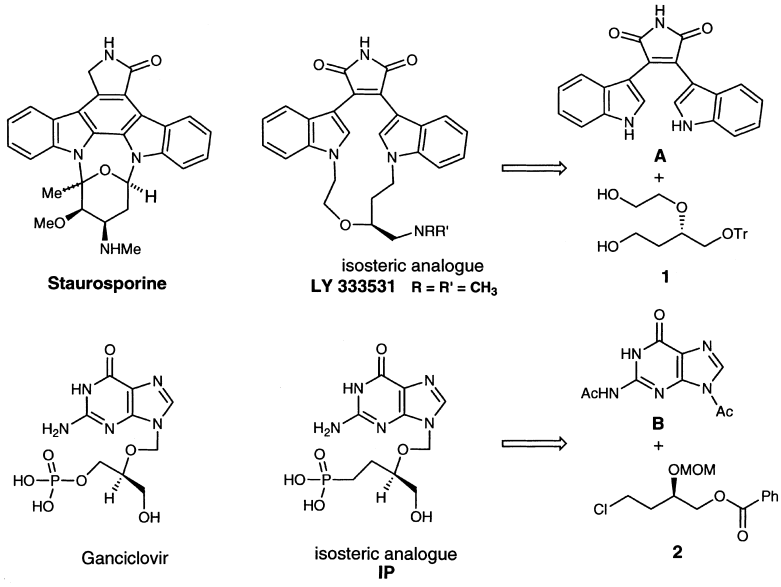
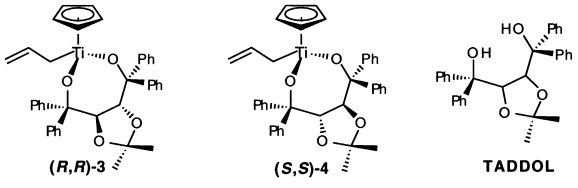
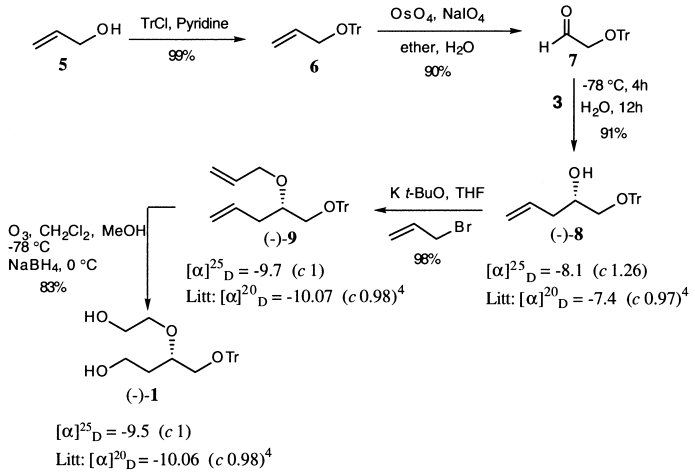


Compound (−)-**1** was first synthesized from the expensive (*R*)-1-chloro-2,3-propanediol (ee=98%) in five steps with an overall yield of 45–55%.[2,4] In the case of compound (+)-**2**, a limited number of methods exist for the construction of this synthon. For example, it can be synthesized from L-arabinose in eight steps with an overall yield of 4%.[5] Here, we report a simple synthesis of compound (−)-**1** and (+)-**2** from the inexpensive allylic alcohol **5**, with high yield and with excellent enantiomeric excess, by using an enantioselective allyltitanation of an aldehyde with optically active cyclopentadienyl dialkoxyallyltitanium complexes (*R*,*R*)-**3** or (*S*,*S*)-**4**.[6]



The synthesis of compound (−)-**1** was achieved from allylic alcohol **5** in five steps (Scheme 1). The allylic alcohol was transformed to the trityl ether **6** (TrCl, pyr, yield 99%) and oxidized to the aldehyde **7** (yield 90%) by oxidative cleavage of the double bond, using $NaIO_4/OsO_4$ in ether/H_2O. Cyclopentadienyl[(4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]-2-propenyltitanium (*R*,*R*)-**3**[6] was then added to aldehyde **7** (ether, −78°C) to produce the homoallylic alcohol (−)-**8** with an (*S*)-configuration and with an enantiomeric excess up to 95%.[7] The allylation of (−)-**8** by allyl bromide under basic conditions ($KOBu^t$/THF) afforded (−)-**9**[4] in 98% yield. Ozonolysis of (−)-**9** in a 1:1 mixture of CH_2Cl_2/MeOH at −50°C followed by the treatment of the reaction mixture with a 0.05 N solution of $NaBH_4$ in NaOH gave diol (−)-**1**[4] in 83% yield. Compound (−)-**1** was thus synthesized from allylic alcohol with an overall yield of 66.6% and with an enantiomeric excess up to 95%.

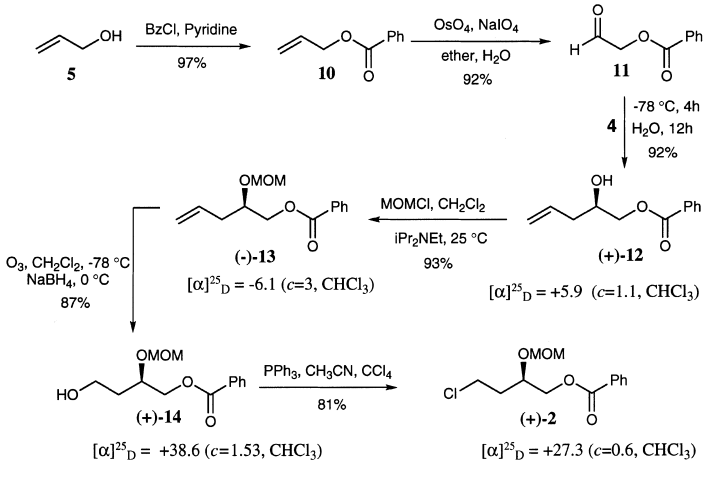
The synthesis of compound (+)-**2** was also achieved from allylic alcohol **5** in six steps (Scheme 2). After treatment of the allylic alcohol with benzoyl chloride in pyridine at 25°C the corresponding ester **10** was obtained (97%) and converted to aldehyde **11** by using $NaIO_4/OsO_4$ (ether/H_2O, 25°C, yield: 92%). Treatment of aldehyde **11** with the cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-



a) Specific rotations were recorded in MeOH at 25°C

Scheme 1. Synthesis of the 1,2-diol unit used in the synthesis of LY 333531[a]

tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]-2-propenyltitanium (*S*,*S*)-**4**[6] (ether, −78°C) afforded the homoallylic alcohol (+)-**12**[8] with an (*R*)-configuration and with an enantiomeric excess up to 96%.[7] It is worth noting that this allyltitanation is chemoselective as the ester functionality is not reactive under these conditions. Treatment of (+)-**12** with dimethoxymethane in methylene chloride in the presence of diisopropylethylamine provided the methoxymethyl ether (−)-**13**[8] in a 93% yield. At this point, compound (−)-**13** was transformed to the primary alcohol (+)-**14**[8] by oxidative cleavage of the unsaturation (O_3, CH_2Cl_2, −78°C), and the in situ reduction of the resulting aldehyde ($NaBH_4$, 0°C). Conversion of the primary alcohol (+)-**14** to the chloride (CCl_4, PPh_3, CH_3CN) gave compound (+)-**2**[5] in 81% yield. Chloride (+)-**2**, which is used in the synthesis of IP, was synthesized in six steps with an overall yield of 54% and with an enantiomeric excess up to 96%.



Scheme 2. Synthesis of the 1,2-diol unit used in the synthesis of IP[a]

The use of optically active allyltitanium reagents for the allylation of aldehydes is a very versatile approach as (*S*)- or (*R*)-allylic alcohols can be obtained with good yield and with high enantiomeric excess. This is illustrated by the synthesis of compounds (−)-**1** and (+)-**2** which were obtained in a few steps from a very inexpensive starting material. We have to point out that sensitive functional groups are

tolerated when the allytitanation reaction is used due to the selectivity of the reagents and to the neutral aqueous conditions employed in the work-up. Furthermore, the chiral ligand, TADDOL, can be recovered and recycled to synthesize the titanium complexes (*R*,*R*)-**3** and (*S*,*S*)-**4**.[6]

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7. The enantiomeric excess of **8** and **12** was determined by HPLC analysis, Chiralcel-AD_2 column (hexane/isopropanol).
8. All new compounds exhibited satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, MS).