An Effective Method for the Preparation of Optically Active Polyoxy 8-Membered Ring Enone Corresponding to the B Ring of Taxol

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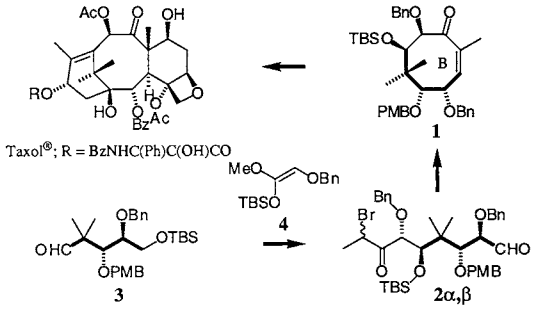
(Received July 6, 1999; CL-990598)

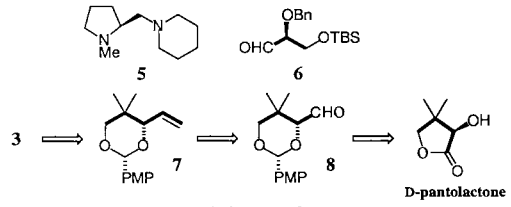
An effective method for the preparation of 8-membered ring enone **1** in sufficient quantities was developed. First, optically active trialkoxyaldehyde **3** was prepared by diastereoselective dihydroxylation of olefin **7** derived from D-pantolactone. Secondly, 8-chloro-7-oxoaldehydes **20**α,β were newly synthesized by the following reactions: namely, $MgBr_2 \cdot OEt_2$-mediated diastereoselective aldol reaction of the aldehyde **3** with ketene (trimethylsilyl) acetal **15**, direct 1,1-dichloroethylation of ester **17** with 1,1-dichloroethyllithium, and partial dehalogenation of the resulting α,α-dichloroethyl ketone **18** with $^nBu_3SnH$. Lastly, the chiral 8-chloro-7-oxoaldehydes **20**α,β were converted to the 8-membered ring enone **1** by SmI_2-mediated aldol cyclization.

The syntheses of Taxol and its analogues were recently reported from our laboratory.[1] In those synthetic sequences, the basic frameworks of taxoids were in the first place constructed from optically active polyoxy 8-membered ring enone **1** which corresponded to the B ring of Taxol. In order to prepare sufficient quantities of the optically active **1**, it was required to develop an effective method for the preparation of its precursor **3**.



Scheme 1.

In the previous papers, two routes for the synthesis of trialkoxyaldehyde **3** were reported by i) enantioselective aldol reaction of 3,3-dimethoxy-2,2-dimethylpropanal with ketene (*t*-butyldimethylsilyl) acetal **4** using tin(II) trifluoromethanesulfonate coordinated with chiral diamine **5** and ii) diastereoselective aldol reaction between optically active dialkoxyaldehyde **6** derived from L-serine and lithium enolate prepared from methyl isobutyrate.



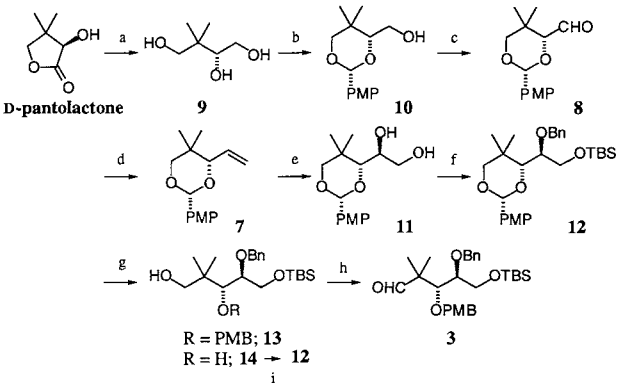
Scheme 2.

However, a problem of preparing aldehyde **3** in sufficient quantities yet remained to be solved; in other words, the former route needed to use a stoichiometric amount of chiral diamine **5** and the reaction was carried out carefully at low temperature. In the latter route, racemization of α-position of the carbonyl group took place slowly when dialkoxyaldehyde **6** was prepared over 10 g scale. Therefore, an alternative pathway was planned in which a dialkoxyaldehyde **8** was anticipated to resist toward racemization since this compound contained stable 6-membered ring in chair form with three equatorial functionalities. Also, the aldehyde **8** was prepared from commercially available D-pantolactone, and it would further be converted to the optically active key intermediate **3** by successive one carbon elongation and dihydroxylation through olefin **7**.

In this paper, we would like to report on an effective method for the preparation of optically active trialkoxyaldehyde **3** starting from D-pantolactone and further conversion to 8-membered ring enone **1** by the following reactions: i.e. an improved diastereoselective aldol reaction of the above aldehyde **3** with ketene (trimethylsilyl) acetal **15**, successive direct 1,1-dichloroethylation of ester **17** forming α,α-dichloroethyl ketone **18** which in turn was transformed to monochloroethyl ketones **19**α,β by partial dehalogenation, and facile 8-membered ring formation by treating 8-chloro-7-oxoaldehydes **20**α,β with SmI_2.

In the first place, D-pantolactone was reduced with $LiAlH_4$ in THF to give the corresponding optically active triol **9** in good yield, and then it was converted to *p*-methoxybenzylidene acetal **10** under thermodynamic conditions using camphorsulfonic acid (CSA).[2] The alcohol **10** was oxidized under Swern's conditions to afford the desirable α-alkoxyaldehyde **8**. The Wittig reaction of the aldehyde **8** furnished olefin **7** having five carbons backbone corresponding to that of trialkoxyaldehyde **3**. Dihydroxylation of the olefin **7** smoothly proceeded to yield *anti*-diol **11** with high diastereoselectivity (99%, *anti* / *syn* = 24 / 1) by using a catalytic amount of OsO_4 in the presence of NMO in acetone and water. When this reaction was carried out in the presence of AD-mix-α, a mixture of diols was obtained in 44% yield with lower stereoselectivity (*anti* / *syn* = 15 / 1) while the presence of AD-mix-β afforded the corresponding *anti*-diol **11** stereoselectively in moderate yield (51%, *anti* / *syn* = 33 / 1). Similar to the recently-published mechanism of diastereoselective dihydroxylation,[3] *anti*-diol **11** was formed through the model **7**α as shown in Figure 1, though the conformation of **7** in model **7**β is more stable than that in model **7**α.

Successive regioselective protection of primary and secondary hydroxy groups of **11** afforded *p*-methoxybenzylidene acetal **12** in quite high yield and HPLC analysis revealed that the optical purity of this compound was over 96% ee. Then, regioselective reductive cleavage of the acetal function was carried out with a stoichiometric amount of $BH_3 \cdot SMe_2$ in a sealed tube, and the desired primary alcohol **13** was obtained with perfect regioselectivity. Diol **14** formed along with **13** was



Scheme 3. Reagents and conditions: a) $LiAlH_4$, THF, 0 °C; b) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, rt (92%, 2 steps); c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C to rt; d) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C (86%, 2 steps); e) OsO_4, NMO, acetone, H_2O, ^{t}BuOH, rt (99%, *anti* / *syn* = 96 / 4); f) TBSCl, imidazole, DMF, rt (99%); BnBr, NaH, THF, DMF, rt (quant.); g) $BH_3{\cdot}SMe_2$, THF, 110 °C (83% of **13** plus 16% of **14**); h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C to rt (96%); i) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, 0 °C (90%).

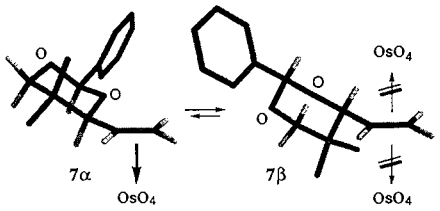
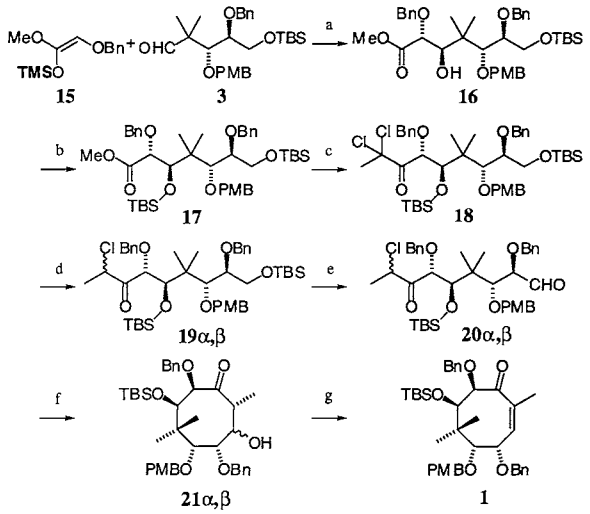


Figure 1. Stable conformations of olefin **7**. Some atoms have been omitted for clarity.

reused after having been treated with *p*-methoxybenzaldehyde dimethylacetal and CSA. The primary alcohol **13** was oxidized under Swern's conditions to produce initially targeted aldehyde **3** in quite high yield. Thus, a new pathway to prepare sufficient quantities of optically active trialkoxyaldehyde **3** that starts from D-pantolactone was established.

Next, a convenient method for the synthesis of 8-membered ring enone **1** in sufficient quantities from the trialkoxyaldehyde **3** was studied. The aldol reaction of **3** with ketene (trimethylsilyl) acetal **15**,[4] a highly reactive nucleophile, in stead of previously reported ketene (*t*-butyldimethylsilyl) acetal **4** was tried in the presence of 3 molar equiv. amount of $MgBr_2{\cdot}OEt_2$. This addition reaction proceeded smoothly at -19 °C, and the desired 2,3,5-*anti,anti*-aldol **16** was obtained in better yield with excellent diastereoselectivity (98%, 98 / 2 / 0 / 0) compared to the case of using **4** as a nucleophile (77%, 82 / 18 / 0 / 0). After converting the aldol **16** to the corresponding silyl ether **17**, direct alkylation of the ester function using 1,1-dichloroethyllithium was tried.[5] When the ester **17** in a mixed solvent of Et_2O and THF was treated with 1,1-dichloroethyllithium prepared from 1,1-dichloroethane and a solution of ^{n}BuLi in hexane at -100 °C, the desired monoalkylated α,α-dichloroethyl ketone **18** was exclusively formed in good yield. Although complete dehalogenation of α,α-dichloroethyl ketone **18** with $^n Bu_3SnH$ and AIBN combined system took place giving the corresponding ethyl ketone, partial dehalogenation of **18** affording a mixture of monochloroethyl ketones **19**α,β was carried out in high yield by using only $^n Bu_3SnH$. After removal of TBS groups at C9, 8-chloro-7-oxoaldehydes **20**α,β, precursors of 8-membered ring



Scheme 4. Reagents and conditions: a) $MgBr_2{\cdot}OEt_2$, toluene, -19 °C (98%, 98 / 2 / 0 / 0); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (99%); c) CH_3CHCl_2, ^{n}BuLi, Et_2O, THF, -100 °C to -78 °C (77%); d) $^n Bu_3SnH$, benzene, reflux (90%, diastereomeric ratio = ca. 7 / 1); e) 1N HCl, THF, rt (94%); DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C to rt (92%); f) SmI_2, THF, 0 °C (65%); g) Ac_2O, DMAP, pyridine, rt (α / β = 83 / 17); then DBU, benzene, 60 °C (82%).

compounds, were obtained by Swern oxidation. Similar to the case of a mixture of 8-bromo-7-oxoaldehydes **2**α,β mentioned in the previous paper, intramolecular aldol reaction of **20**α,β also proceeded smoothly to produce a diastereomeric mixture of 8-membered ring aldols **21**α,β in good yield.[1,6] Finally, the desired 8-membered ring enone **1** was obtained in high yield from **21**α,β by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

An effective method for the preparation of 8-membered ring enone **1**, a key intermediate of Taxol synthesis, that starts from D-pantolactone, was accomplished by the following successive reactions: namely, diastereoselective dihydroxylation of olefin **7**, regioselective cleavage of *p*-methoxybenzylidene acetal **12**, diastereoselective aldol reaction of **3** with ketene (trimethylsilyl) acetal **15**, conversion of the ester **17** to α-chloroethyl ketones **19**α,β, and 8-membered ring formation by aldol-type cyclization of 8-chloro-7-oxoaldehydes **20**α,β with SmI_2.

This work was supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture.

References and Notes

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