BINOL-Ti-Catalyzed Carbonyl-Ene Cyclization by Tuning the 6-Br-Ligand for the Synthesis of 2-Methyl-19-nor-22-oxa Vitamin D Analogue with Significant Differentiation Activity[1]

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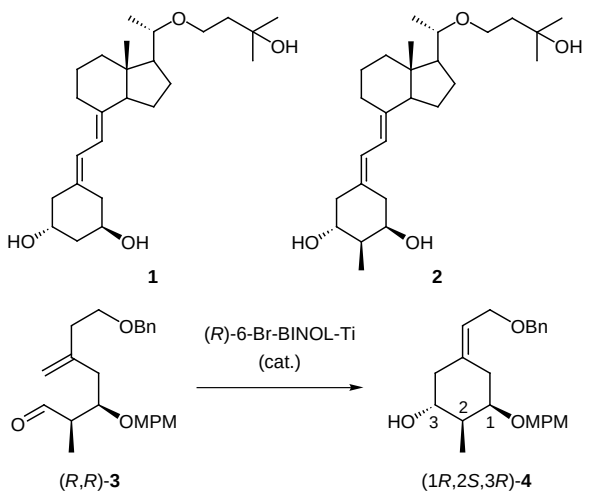
Abstract: Transition state control in BINOL-Ti-catalyzed asymmetric carbonyl-ene cyclization by tuning the 6-Br-BINOL ligand completes the synthesis of the A ring of the 2-methyl-19-nor-22-oxa D_3 analogue (**2**), which shows the significant activity in differentiation of HL-60 cell.

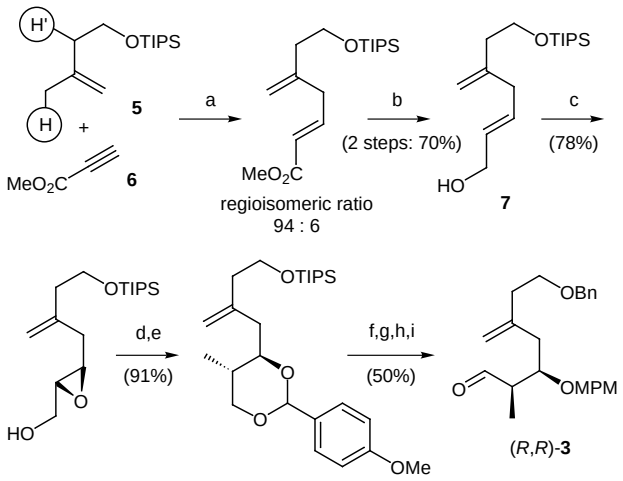
Key words: vitamin D, ene reaction, binaphthol, titanium complex, asymmetric catalysis

Basic research on the synthesis of analogues of the biologically active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], has brought about the development of an important new field in medicinal chemistry.[2] A number of analogues have been synthesized and used to clarify the mode of action of vitamin D hormones and find new therapeutically useful compounds. These analogues are useful not only for calcium metabolism disorder and bone diseases, but also for differentiation of myelocytic leukemias and the treatment of psoriasis.[3] 10-Oxo-19-nor-25$(OH)_2D_3$ has been reported to exhibit a selective activity for differentiation of myelocytic leukemias.[4] 19-Nor-1α,25$(OH)_2D_3$ also shows a selective activity profile, i.e., high potency in differentiation of malignant cells, but low calcitropic liability.[5] 22-Oxa-1α,25$(OH)_2D_3$ (OCT) shows a significant activity in the inhibition of cancer cell growth.[6] We have thus reported the hybridization analogue,[7] 19-nor-22-oxa-1α,25$(OH)_2D_3$ (**1**) on the basis of asymmetric carbonyl-ene cyclization[8b] catalyzed by a binaphthol-derived titanium (BINOL-Ti) complex.[9] Recent papers[10] prompt us to report the synthesis of 2-methyl-19-nor-22-oxa vitamin D_3 analogue (**2**)[1,11] by tuning the chiral ligands for the ene cyclization[12] (Scheme 1) and the significant activity in differentiation of myelocytic leukemia, HL-60 cell.

The preparation of the 2-methyl ene-cyclization substrate ((*R*,*R*)-**3**) is worth mentioning (Scheme 2). The allylic alcohol (**7**) was obtained through highly regioselective propiolate-ene reaction using triisopropylsilyl ethers (**5**)[13] (regioisomer ratio = 94:6)[14] with methyl propiolate (**6**) using $EtAlCl_2$ as the promoter. The ene substrate **3** was prepared in 96% ee via catalytic enantioselective epoxidation of allylic alcohol[15] (**7**) with (*S*,*S*)-diethyl tartrate (DET),



Scheme 1



a) $EtAlCl_2$, CH_2Cl_2, rt; b) DIBAL-H, toluene, –78 °C; c) (–)-DET / $Ti(OPr^i)_4$ (20 mol% each), TBHP, MS 4A, CH_2Cl_2, –30 °C; d) MeMgCl, CuBr•Me_2S (10 mol%), THF/Et_2O, –40 °C to –20 °C; e) *p*-anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, rt; f) TBAF, THF; g) BnBr, NaH, TBAI; h) DIBAL-H, CH_2Cl_2, 0 °C to rt; i) PCC, MS 3A, CH_2Cl_2, rt

Scheme 2

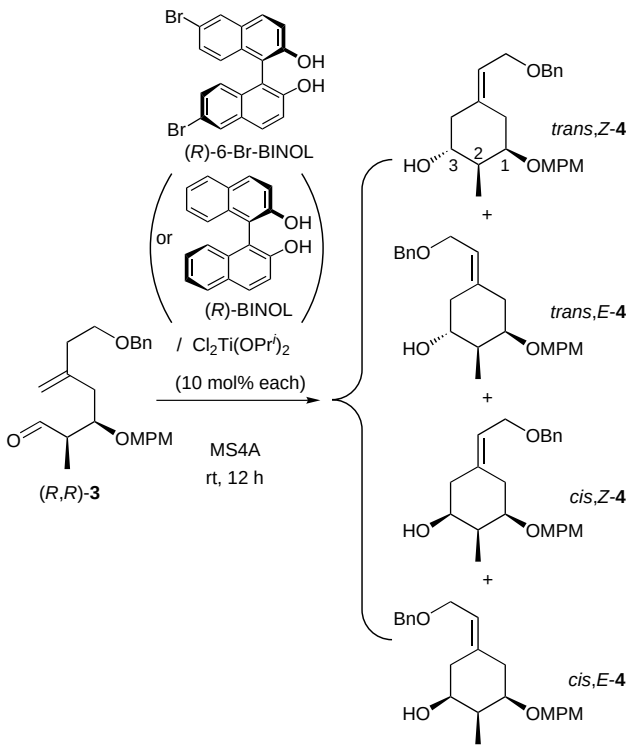


Table Asymmetric carbonyl ene-cyclization catalyzed by BINOL-Ti or 6-Br-BINOL-Ti complex.

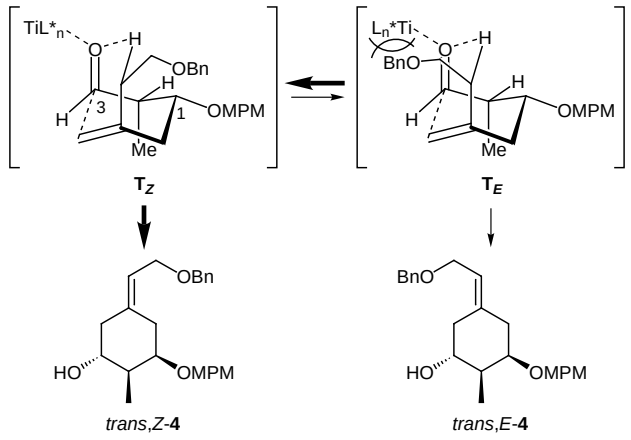
Run	**3**	Cat	yield	*trans*,*Z*-**4**	*trans*,*E*-**4**	*cis*,*Z*-**4**	*cis*,*E*-**4**
1[a]	(*R*,*R*)	(*R*)-BINOL-Ti	76%	68	28	4	–
2[b]	(*R*,*R*)	(*S*)-BINOL-Ti	63%	53	29	17	1
3[a]	(*R*,*R*)	(*R*)-6-Br-BINOL-Ti	83%	82	16	2	–
4[a,c]	(*S*,*S*)	(*S*)-6-Br-BINOL-Ti	84%	83	15	2	–
5	(*R*,*R*)	Me_2AlCl (1.0 eq.)	60%	66	8	26	–

[a] 4% of *endo* olefin was obtained as by-products. [b] 27% of *endo* olefin was obtained as by-products. [c] The opposite enantiomers were obtained.

titanium tetraisopropoxide, and *tert*-butyl hydroperoxide (TBHP) and the following regioselective ring-opening with methylcopper reagent prepared from methyl chloride-derived Grignard reagent.[16]

The carbonyl-ene cyclization of (*R*,*R*)-**3** by the parent *(R)*-BINOL-Ti catalyst (10 mol%) took place at room temperature in CH_2Cl_2 to give the ene cyclization product (**4**) in extremely high (1*R*,2*S*,3*R*)-stereochemistry with moderate geometrical selectivity [(*trans, Z*) : (*trans, E*) = 68:28 as determined by HPLC analysis[17]], in 76% isolated yield (Table, Run 1). Although the absolute configuration of the newly created stereogenic center at C-3 is primarily controlled by the chirality of the ene substrate **3** (Runs 1, 2), the combination of (*R*,*R*)-**3** and *(R)*-BINOL-Ti catalyst resulted in higher *trans* (1*R*,3*R*)-selectivity than the combination with *(S)*-BINOL-Ti catalyst (Run 1 *vs.* 2). It is noteworthy that the use of electronically withdrawing and sterically demanding 6-bromo-binaphthol (6-Br-BINOL)[18] ligand leads to the significant increase in chemical yield and *(Z)*-geometrical selectivity up to 83% and 82%, respectively (Run 3). Likewise, the opposite combination of the enantiomeric *(S)*-6-Br-BINOL-Ti catalyst and (*S*,*S*)-**3** lead to the opposite enantiomer (1*S*,2*R*,3*S*)-**4** preferentially (Run 4). The importance of the chirality of BINOL-Ti catalysts should be emphasized in comparison with the lower *trans* selectivity observed in the reaction promoted by Me_2AlCl as an equimolar reagent (Run 5).

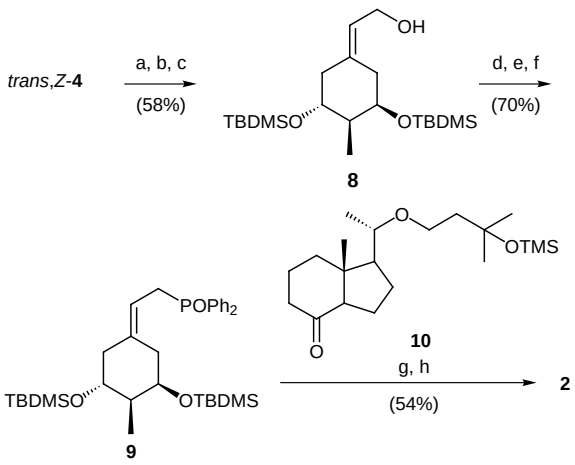
The 6-(2,4)[8b] carbonyl-ene cyclization of **3** catalyzed by a *(R)*-BINOL-Ti complex would proceed via chair-like transition states (Scheme 3),[19] where 1-MPMO group occupied an equatorial position and carbonyl group at C-3 position oriented to the axial direction to provide the desired *(Z)*-cyclohexanediol **4** in high *trans* (1*R*,3*R*)-selectivity. This β-form like transition state may be in close resemblance to the binding conformation of 1α,25$(OH)_2D_3$.[20] *Z*/*E* stereochemistry is critically dependent on the balance of acyclic allylic 1,2-strain[21] in $\mathbf{T}_Z$ and repulsion between the bulky BINOL-Ti catalyst and benzyloxymethyl group ($\mathbf{T}_E$). By tuning the electron withdrawing and sterically demanding 6-Br-BINOL ligand, *(Z)*-geometrical selectivity significantly increases to 83%, presumably because of the steric repulsion between 6-Br-BINOL-Ti complex with the benzyloxymethyl moiety.



Scheme 3

The (*trans, Z*)-**4** can be easily separated from the geometrical isomer (*trans, E*)-**4** and transformed to the A-ring intermediate **8**. Further transformation of the (1*R*,2*S*,3*R*)-**8** to the Wittig reagent **9** for olefination with 22-oxa-C,D ring **10** lead to the hybrid analogue of 2-methyl-19-nor-22-oxa-1α,25$(OH)_2D_3$ (**2**) (Scheme 4).

1α,25$(OH)_2D_3$ mediates its biological activities through specific binding to VDR which forms a hetero dimer with a nuclear accessary factor (NAF) i.e., retinoid X receptor (RXR) and subsequently the hetero dimer binds to the vitamin D responsive element (VDRE) to induce gene transcriptions. Therefore, a high binding affinity for VDR has been considered necessary for analogues to possess high biological activity. By contrast, we found a counter example to this principle that our hybrid analogue (**2**) thus synthesized has an equally high activity to active 1α,25$(OH)_2D_3$ in cell differentiation activity of HL-60



a) CAN, CH_3CN, rt; b) TBDMSCl, imidazole, DMF, rt; c) Li, NH_3, –78 °C; d) NCS, Me_2S, CH_2Cl_2, –20 °C to rt; e) PhPLi, THF, 0 °C; f) H_2O_2, THF/H_2O, rt; g) **10**, *n*-BuLi, THF, –78 °C; h) TBAF, THF, rt

Scheme 4

myelocytic leukemia cell in spite of significantly low binding affinity for VDR by three order of magnitude (0.008 relative to 1α,25(OH)$_2$D$_3$).

In summary, we have reported the transition state control in BINOL-Ti-catalyzed asymmetric carbonyl-ene cyclization by tuning the 6-Br-BINOL ligand for the synthesis of the A ring of the 2-methyl-19-nor-22-oxa D analogue **2**, which shows the significant activity in cell differentiation activity of HL-60 myelocytic leukemia.

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