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"Symmetry" in the Synthesis of the A-Ring of a Vitamin D Hybrid Analogue with Significant Transactivation Activity: A Combinatorial Sequence of Regioselective Propiolate-Ene, Catalytic Enantioselective Epoxidation and Carbonyl-Ene Cyclization Reactions@

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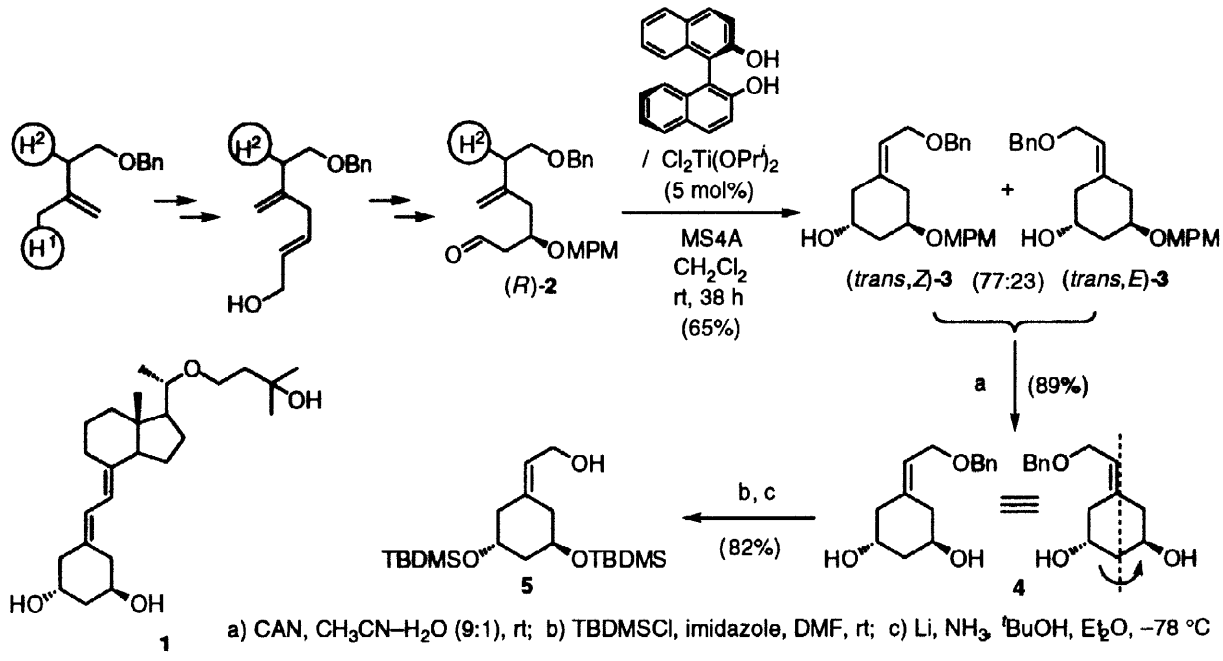
Abstract: The combination of the regioselective propiolate-ene reaction, catalytic enantioselective epoxidation and catalytic enantioselective carbonyl-ene cyclization completes the synthesis of the A ring of the hybrid 19-nor-22-oxa D_3 analogue (1), which shows the significant activity in transactivation.

Basic research on the synthesis of analogues of the biologically active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25(OH)$_2$D$_3$], has brought about the development of an important new field in medicinal chemistry.[1] 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.[2] 10-Oxo-19-nor-25(OH)D_3 has been reported to exhibit a selective activity for differentiation of myelocytic leukemias.[3] 19-Nor-1α,25(OH)$_2$D$_3$ also shows a selective activity profile, *i.e.*, high potency in differentiation of malignant cells, but low calcemic liability.[4] Furthermore, 22-oxa-1α,25(OH)$_2$D$_3$ shows a significant activity in the inhibition of cancer cell growth.[5] Therefore, we might design the hybridization analogue 19-nor-22-oxa-1α,25(OH)$_2$D$_3$ (**1**).



Scheme 1

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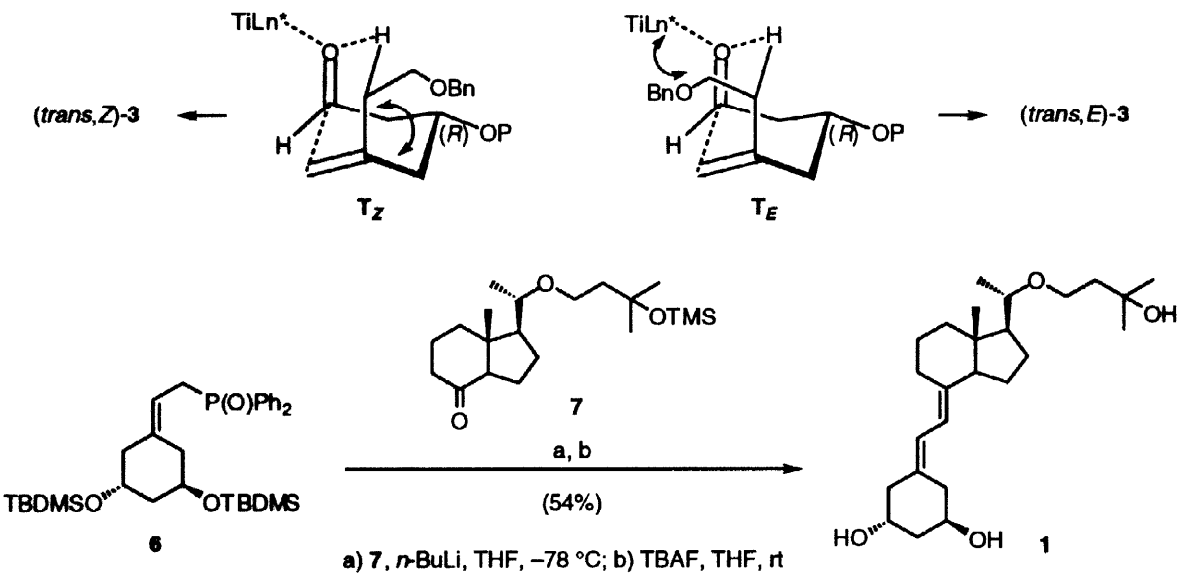
Reported herein is a "symmetry"-based enantiospecific synthesis of the A-ring. This is accomplished by a sequence of regioselective[6] propiolate-ene reaction[7] of a homoallylic alcohol followed by catalytic enantioselective Katsuki-Sharpless epoxidation[8] of the resultant allylic alcohol and then catalytic enantioselective carbonyl-ene cyclization[9a] (Scheme 1). The hybrid analogue (1) thus synthesized is found to possess a greater ability than 1α,25(OH)$_2$D$_3$ to transactivate a rat 25-hydroxyvitamin D$_3$ 24-hydroxylase gene despite an extremely low binding affinity for the nuclear calf-thymus vitamin D receptor, VDR.

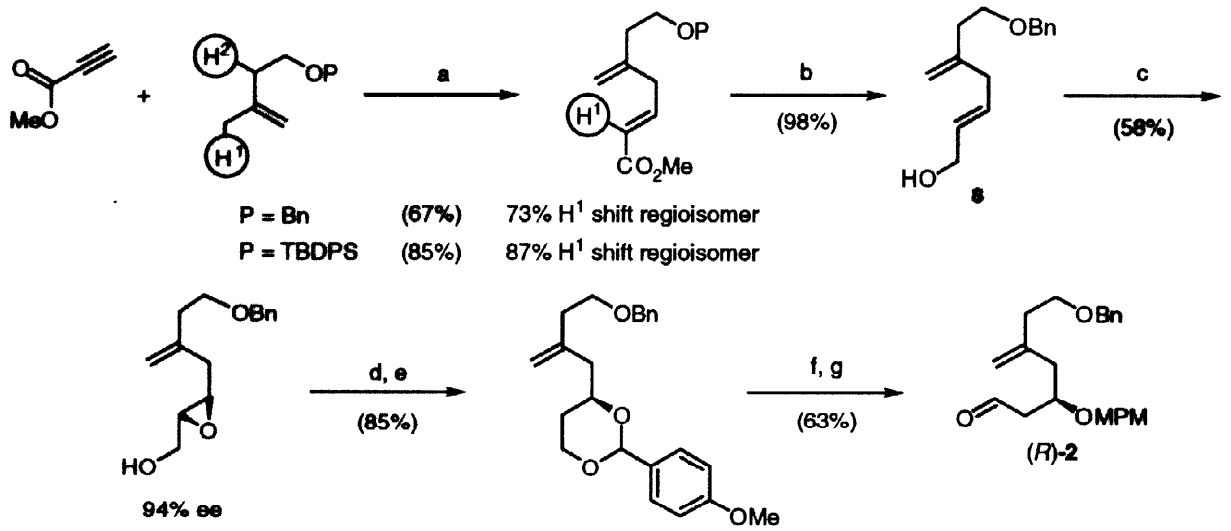
It occurred to us that the intramolecular 6-(2,4)[9a] carbonyl-ene cyclization of (*R*)-MPMoxy[10] (benzyloxyethyl)hexenal (**2**) catalyzed by a (*R*)-binaphthol-derived titanium (BINOL-Ti) complex would provide the desired cyclohexanediol with high enantiomeric purity (Scheme 1). Because the pseudo C_2-symmetry[11] of the (*E*)- and (*Z*)-isomers of the ene cyclization product (**3**) could afford the same single compound **4** after deprotection. As expected, the carbonyl-ene cyclization of **2** by the (*R*)-BINOL-Ti catalyst[12] (5 mol%) took place at room temperature[13] to give the ene cyclization product (**3**) with extremely *R,R* stereochemistry, though as a geometrical mixture [(*trans, Z*), (*trans, E*), (*cis, Z/E*) = 75 : 23 : 2 as determined by GLC (OV-1701, 270 °C) analysis], in 65% isolated yield. Both geometrical isomers (*E*)- and (*Z*)-**3** can be transformed to the identical DeLuca intermediate (**5**)[4,14] after deprotection of MPM ether. In contrast, the enantiomeric form of (*S*)-BINOL-Ti catalyst gave four possible isomers (*trans, Z*), (*trans, E*), (*cis, Z*), and (*cis, E*) in a ratio of 32 : 8 : 32 : 28.

The Lewis acid-catalyzed carbonyl-ene cyclization would proceed via 6-membered transition states[15] to provide the (*trans, Z*)- and (*trans, E*)-**3** depending on the balance of acyclic allylic 1,2-strain[16] (T_Z) and repulsion between the sterically demanding BINOL-Ti catalyst and benzyloxymethyl group (T_E).[17] Further transformation of the (*trans, Z*)- and (*trans, E*)-**3** to the Wittig reagent (**6**)[4] for olefination of 22-oxa-C,D ring (**7**) lead to the hybrid analogue of 19-nor-22-oxa-1α,25(OH)$_2$D$_3$ (**1**) (Scheme 2).



Scheme 2

1α,25(OH)$_2$D$_3$ mediates its biological activities through specific binding to VDR which forms a hetero conjugate with a nuclear accessary factor (NAF) *i.e.*, retinoid X receptor (RXR) and subsequently the hetero conjugate 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. However, we have found a counter example to this principle that our hybrid analogue (**1**) thus synthesized has a greater ability to transactivate a rat 25-hydroxyvitamin D$_3$ 24-hydroxylase gene (twice as active as 1α,25(OH)$_2$D$_3$) in spite of a 33-fold reduction in binding affinity for VDR.



a) $EtAlCl_2$, CH_2Cl_2, rt; b) DIBAL-H, toluene, –78 °C; c) (–)-DET / $Ti(OPr^i)_4$ (30 mol% each), TBHP, MS 4A, CH_2Cl_2, –20 °C; d) Red-Al, MeOH, THF, rt; e) *p*-anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, rt; f) DIBAL-H, CH_2Cl_2, 0 °C to rt; g) PCC, MS 3A, CH_2Cl_2, rt

Scheme 3

The preparation of the ene-cyclization substrate ((*R*)-**2**) is worth mentioning. The ene substrate **2** was prepared in 94% ee *via* catalytic enantioselective epoxidation[8] of allylic alcohol (**8**) which was in turn obtained through regioselective propiolate-ene reaction of homoallylic ethers with methyl propiolate using $EtAlCl_2$[6a] as the promoter (Scheme 3). Thus, the combination of the regioselective propiolate-ene reaction, catalytic enantioselective epoxidation and catalytic enantioselective carbonyl-ene cyclization completes the synthesis of the A ring of the hybrid 19-nor-22-oxa D_3 analogue (**1**). Furthermore, the present synthesis exploits the latent C_2-symmetry in the A-ring of **1**, which shows the significant activity in transactivation.

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