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A NOVEL *o*-QUINODIMETHANE STRATEGY FOR AN ACTIVE METABOLITE OF VITAMIN D_3. A TOTAL SYNTHESIS OF 25-HYDROXY WINDAUS-GRUNDMANN KETONE

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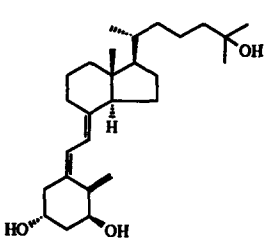
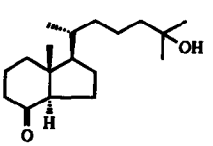
Abstract : A highly diastereoselective total synthesis of 25-hydroxy Windaus-Grundmann ketone (**2**) was achieved *via* a novel regiocontrolled C-C bond formation by an intramolecular epoxide ring opening reaction of the bissulfonyl epoxide (**19**) as a key step, which was derived stereoselectively by the thermolysis of olefinic benzocyclobutene (**8**) as a key step.

Over the past decade, there has been intense interest[1] in the development of methodology for the stereocontrolled construction of the CD-ring system and side chain of vitamin D_3 and steroids. Of these steroidal compounds, 1α,25-dihydroxyvitamin D_3 (**1**) has emerged at present time as one of the most important compounds because of its increasing biological importances.[2,3] On the basis of Lythgoe's methodology[4] for the synthesis of calciferols via convergent routes, 25-hydroxy Windaus-Grundmann ketone (**2**) has proven useful in the synthesis of **1**. Here we report a new and general strategy for the diastereoselective synthesis of steroid side chains including CD-ring system based on the highly stereoselective intramolecular [4+2] cycloaddition reaction of *o*-quinodimethane[5] and strictly regiocontrolled C-C bond formation by intramolecular epoxide ring opening reaction.[6]

Scheme 1



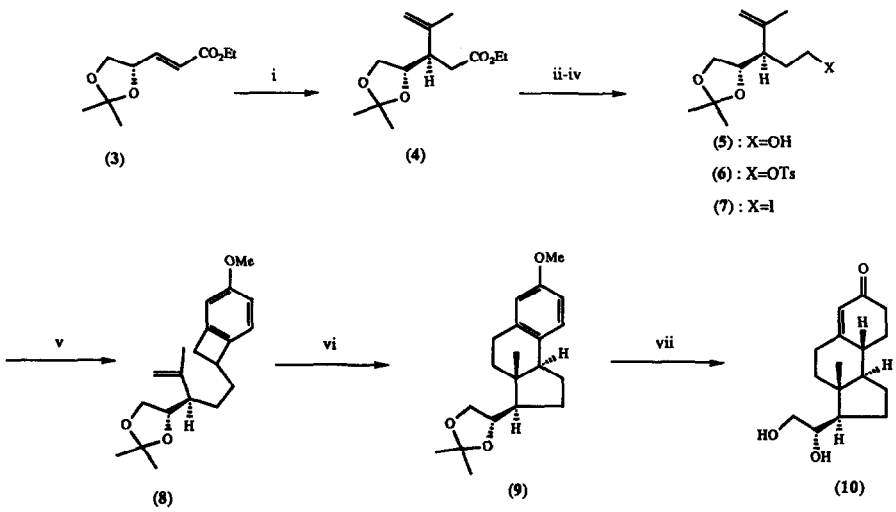
(1)



(2)

The preparation[7] of **10**, which has all the required chiral centers of **2**, was initiated by a stereoselective 1,4-addition of isopropenyl group to **3**[8] readily available from D-mannitol to give **4** ($[\alpha]_D$ +3.7°) (61%). Reduction of **4**, tosyla-

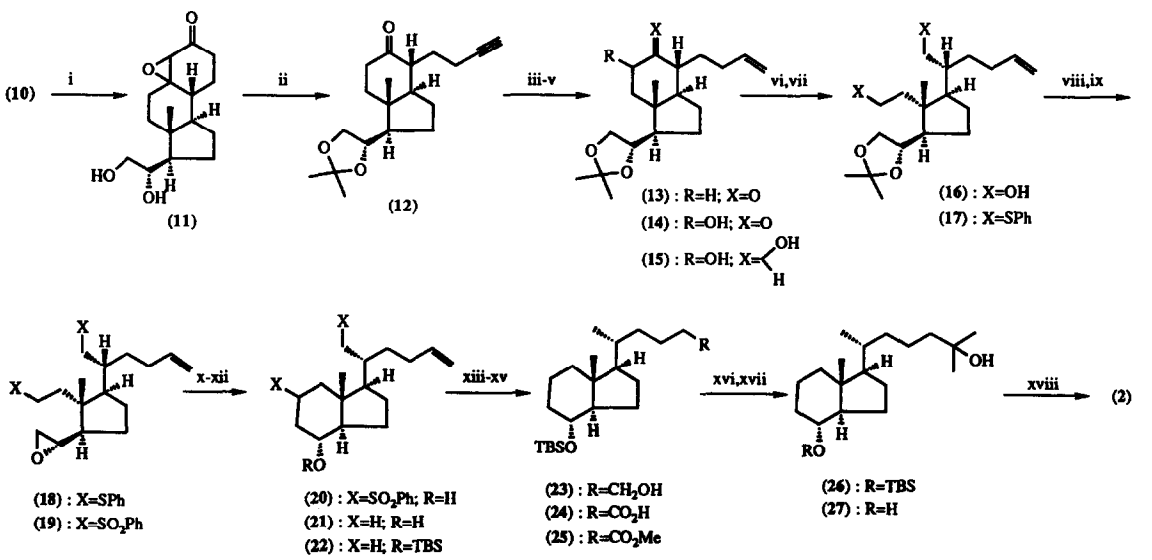
tion of **5**, followed by iodination of **6** afforded the iodide (**7**) ($[\alpha]_D$ -41.3°) (79% overall from **4**). Condensation of **7** with 1-cyano-4-methoxydihydrobenzocyclobutene[9] followed by a removal of cyano group gave **8** ($[\alpha]_D$ -6.4°) [95% overall from the iodide (**7**)], and the thermolysis of **8** at 190 °C in *o*-dichlorobenzene gave stereoselectively[5] the tricyclic compound (**9**) (m.p. 90-91 °C; $[\alpha]_D$ +1.6°) (90%) through *in situ* generated *o*-quinodimethane. Birch reduction of **9** followed by an acid catalyzed isomerisation afforded the enone (**10**) ($[\alpha]_D$ +14.6°) (78% overall from **9**).



Scheme 2. *Reagents and conditions* : i, CH_2=C(Me)MgBr , CuBr Me_2S, THF, - 78 °C, 1 h ; ii, $LiAlH_4$, THF, 0 °C,30 min ; iii, TsCl, DMAP, pyridine, 25 °C, 2 h ; iv, NaI, acetone, 25 °C, 10 h ; v, 1-cyano-4-methoxybenzocyclobutene, $NaNH_2$, liq. NH_3, THF, - 40 °C, 1 h; then Na, -78 °C, 30 min ; vi, *o*-dichlorobenzene, 190 °C, 12 h; vii, Li, liq. NH_3, THF, - 78 °C, 1 h ; 10% HCl, MeOH, 25 °C, 10 h, ; then reflux, 1 h.

The preparation of the substrate (**19**) for cyclization and the conversion of the cyclised product (**20**) into **2** were straightforward and as follows. Eschenmoser ring cleavage of the epoxide (**11**) obtained by epoxidation of **10**, followed by acetonide formation gave the acetylenic ketone (**12**) ($[\alpha]_D$ -8.2°) (51% *overall from* **10**). Catalytic hydrogenation of **12**, regioselective oxidation of **13**, and then reduction of **14** gave the diol (**15**) (71% overall from **12**). Cleavage of the diol (**15**), followed by reduction afforded the monocyclic diol (**16**) ($[\alpha]_D$ +14.4°) (87% overall from **15**) which was converted to the bis(phenyl sulfide) (**17**) ($[\alpha]_D$ +48.4°) (67%). Transformation of the acetonide (**17**) into the epoxide (**18**), followed by oxidation gave the substrate (**19**) ($[\alpha]_D$ +44.8°) (78% overall from **17**). A complete regiocontrolled cyclisation of **19** was effected by the base treatment with lithium diisopropylamide to give the bicyclic alcohol (**20**) (76%) which was then subjected to reductive removal of phenylsulfonyl groups to afford the alcohol (**21**)[10] ($[\alpha]_D$ +21.3°) (49%). Protection of the hydroxy compound (**21**) gave **22** ($[\alpha]_D$ +9.6°) (95%) which was then subjected to hydroboration-oxidation process to afford the alcohol (**23**) ($[\alpha]_D$ +11.1°) (79%

overall). The acid (**24**) obtained by oxidation of **23** was converted to the ester (**25**) ($[\alpha]_D$ +10.4°) (73% overall from **23**) which was treated with methylmagnesium bromide to yield the alcohol (**26**) ($[\alpha]_D$ +11.2°) (93%). Finally deprotection of **26**, followed by oxidation furnished our aimed 25-hydroxy Windaus-Grundmann ketone (**2**)[12] ($[\alpha]_D$ +5.3°) (96% overall from **26**), which was identical with the data of the authentic sample in all aspects including optical behavior.



Scheme 3. *Reagents and conditions* : i, 30 % H_2O_2, 10 % NaOH, MeOH, 0 °C, 1 h ; ii, $TsNHNH_2$, AcOH, - 20 °C, 20 h ; 25 °C, 4 h ; then $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 25 °C, 2 h ; iii, H_2, Lindlar Cat., AcOEt, 25 °C, 30 min ; iv, $PhSO_2$-N-CHPh, $KN(SiMe_3)_2$, - 78 °C, 20 min ; v, $NaBH_4$, MeOH, CH_2Cl_2, 25 °C, 30 min ; vi, $NaIO_4$, MeOH, 25 °C, 12 h ; then v ; vii, $(PhS)_2$, $^nBu_3P$, pyridine, 25 °C, 48 h ; viii, TsOH, MeOH, 25 °C, 15 h ; MsCl, Et_3N, CH_2Cl_2, 25 °C, 0 min ; then NaH, EtOH, 25 °C, 10 min ; ix, MCPBA, CH_2Cl_2, 25 °C, 1 h ; x, LDA, THF,- 78 °C, 30 min ; 0 °C, 1 h ; xi, Na-Hg, Na_2HPO_4, MeOH, 25 °C, 1 h ; xii, TBSCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 5 h ; xiii, BH_3Me_2S, THF, 0 °C, 30 min ; then 30% H_2O_2, 10% NaOH, MeOH, 0 °C, 30 min ; xiv, PDC, DMF, 25 °C, 20 h ; xv, CH_2N_2, Et_2O, 10 min ; xvi, MeMgBr, THF, 25 °C, 1 h ; xvii, nBu_4NF, THF, 25 °C, 20 h ; xviii, PCC, Molecular Sieves 4Å, CH_2Cl_2, 25 °C, 1 h.

The synthetic route described above makes use of a novel approach to diastereoselective construction of CD-ring system including acyclic portion of steroid, making possible the synthesis of various types of biologically important steroids.

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10 At this stage, the structure including absolute configuration of all the chiral centers of **21** was confirmed unambigously by comparing with the authentic *sample* prepared starting with Inhoffen-Lythgoe diol[11] and the details will be described elsewhere.

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