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PALLADIUM-CATALYZED STEREOCONTROLLED CYCLIZATION OF 1,3-DIENE MONOEPOXIDE: A ROUTE TO A NEW SYNTHETIC INTERMEDIATE FOR DE-AB-CHOLESTANE DERIVATIVE.

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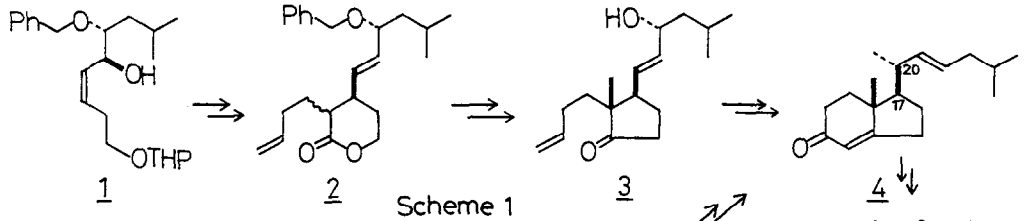
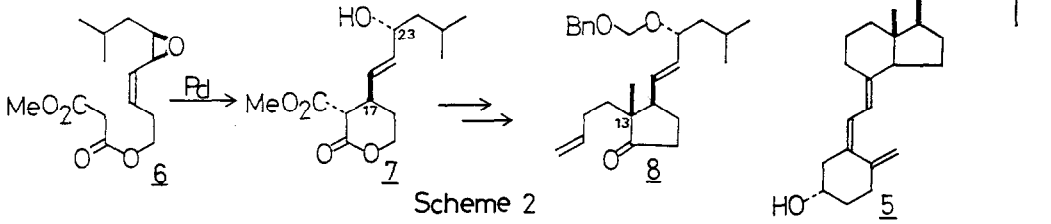
Summary: The optically active (2R,3R)-3-[(3R)-(E)-Benzyloxymethoxy-5-methyl-1-hexenyl]-2-(3-butenyl)-2-methyl-1-cyclopentanone (8) was synthesized as a precursor of vitamin D_3(5) by palladium-catalyzed syn-S_N2' cyclization of [Z,Z(22S,23R)]-ene oxide **6** as a key reaction.

1,3-Chirality transfer reactions such as [3,3]-sigmatropic rearrangements[1] and Pd-catalyzed allylations[2] are important and useful synthetic methods and have been studied extensively. The stereochemical outcomes in the Claisen rearrangement (supra-facial S_N2' alkylation) and the Pd-catalyzed cyclization (double inversion mechanism)[3] of allylic compounds are identical[4]. We have recently shown that the vicinal stereochemistry at C(17) and C(20) in the de-AB-cholestane **4** can be constructed by two Claisen rearrangements (1→2,3→4) as shown in Scheme 1[5]. We report here the stereoselective chiral synthesis of 2,2,3-trisubstituted cyclopentanone **8** as a precursor of Vitamin D_3(5) by Pd-catalyzed reaction of ene oxide and Claisen rearrangement.



Scheme 1

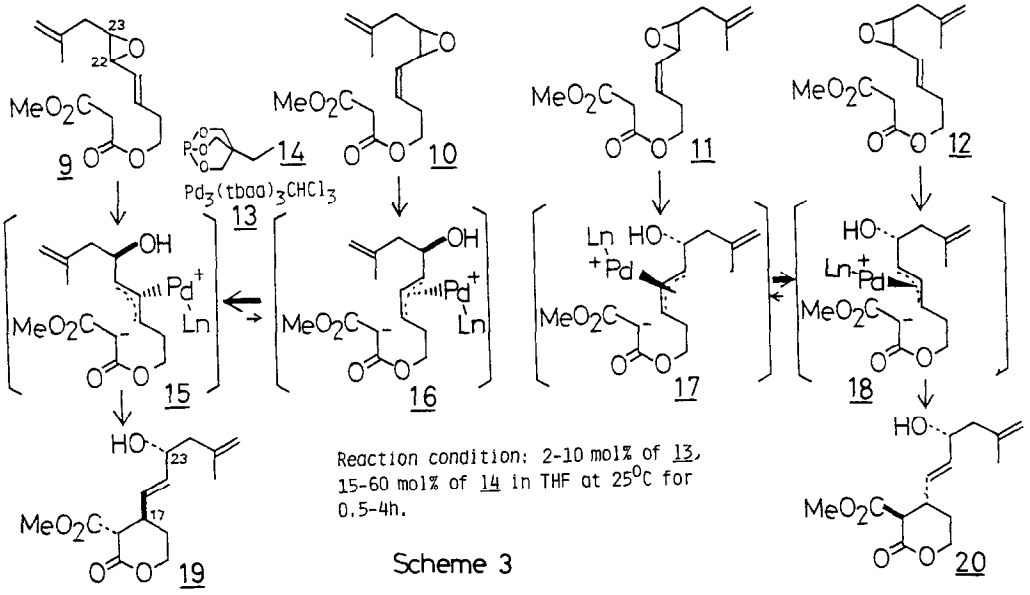


Scheme 2

As outlined in Scheme 2, the key step in our synthesis is the Pd-catalyzed stereocontrolled cyclization of the ene oxide **6** to introduce the desired relative stereochemistry at C(17) and C(23) as well as the geometry of the [20,(22)E]-olefin in the lactone **7**. This allylic system can be utilized to introduce the C(20)-methyl stereoselectively by combination of Claisen rearrangement and decarbonylation promoted by a rhodium complex as described before[5]. The formal 3-butenylation of the lactone **7** by the Pd-catalyzed

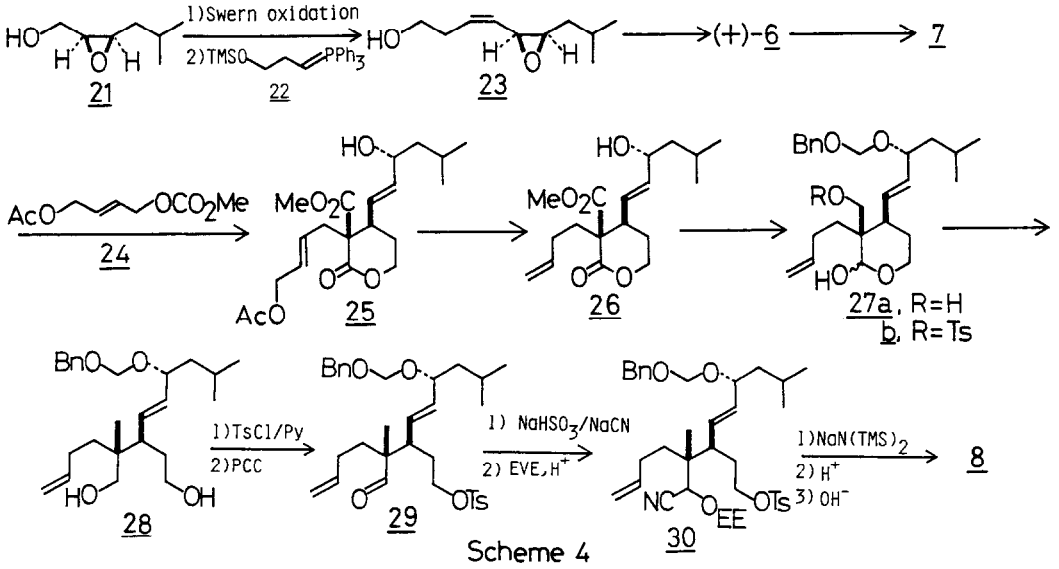
alkylation with allylic carbonate **24** followed by hydrogenolysis with formate[6], the transformation of methoxy carbonyl group to the C(13)-methyl and the conversion of δ-lactone to the cyclopentanone by applying the protected cyanohydrin method afford the ketone **8**.

We have reported[7] that Pd-catalyzed cyclizations of (E,E)- and (Z,E)-ene oxides such as **9** and **11** proceeded in the absence of a base, to give the δ-lactones **19** and **20**, respectively, with high regio-and stereoselection by double inversion mechanism (inversions in the Pd-assisted ionization and in the nucleophilic addition). Recently we have also found[4] crucial effects of a base and the catalyst concentration on the racemization of π-allylpalladium formed from allylic carbonates; the higher concentration of palladium and absence of a base induced the partial racemization of π-allylpalladium. Therefore, at first, we reexamined whether the racemization of the π-allylpalladium developed from ene oxides-**9**,**10**,**11** and **12** would arise under the neutral condition. Cyclizations were carried out as previously described[7]. Reactions of **9** and **12** gave the δ-lactones **19** and **20** in 70-80% yield with extremely high stereoselectivity (>98%)[8] via syn, syn-Pd complexes **15** and **18** respectively. Cyclizations of **10** and **11** proceeded through either Pd complex **16** (anti, syn) or **15** (syn, syn) drived from **16** via π-σ-π interconversion in the case of **10** and Pd complex **17** (anti, syn) or **18** (syn, syn) in the case of **11**, respectively, to give the δ-lactones **19** and **20**[8]. The chemical yield and stereoselectivity in the cyclizations of **10** and **11** were almost same as those in cyclizations of **9** and **12**. In all cyclizations, the eight-membered lactone[9] and the Z-olefinic isomer were not formed. Moreover the racemization of π-allylpalladium formed from ene oxides was not dependent on catalyst concentration(5-20 mol%) . The higher stability of the π-allylpalladium formed from ene oxides than that formed from allylic carbonates can be explained by neighboring-group effect of the hydroxy as shown in **15**,**16**,**17** and **18**.



Scheme 3

Results of these cyclizations predict that [E,E(22R,23R)]-**9** and [Z,Z(22S,23R)]-**10** should provide the desired chiral lactone **7** with 17(R) and 23(R) configuration. We prepared herein [Z,Z(22S,23R)]-**6** as follows. Sharpless epoxidation[10] [(+)-DET/Ti(O^iPr)$_4$/TBHP] of 5-methyl-(2Z)-hexene-1-ol gave the epoxy alcohol **21** ; $[\alpha]_D^{25}$ -5.2°,(c 1.76, $CHCl_3$), 95%e.e., in 80% yield. Swern oxidation [Me_2SO,$(COCl)_2$ in CH_2Cl_2 then Et_3N] of **21**, followed by Wittig reaction[11] of the resulting aldehyde with ylide **22**, prepared from $HOCH_2CH_2CH_2PPh_3Br$ /n-BuLi then Me_3SiCl , gave the (Z,Z)-ene oxide **23** in 47% overall yield. The (E,Z)-isomer of **23** was formed in less than 5% yield. Esterification of **23** with methyl hydrogen malonate by Mitsunobu method[12] gave the (+)-ester **6** ; $[\alpha]_D^{25}$ +55.2°, (c 0.99, $CHCl_3$), in 80% yield. Pd-catalyzed cyclization [2.4mol% of $Pd_2(tba)_3CHCl_3$, 11 mol% of dppe in THF at 25°C for 10h] of **6** gave the lactone **7** in 80% yield. The direct 3-butenylation[13] of **7** with 3-butenyl iodide under a basic condition [K_2CO_3/acetone reflux] was unsuccessful. Then we attempted the indirect butenylation as follows. Pd-catalyzed alkylation of **7** with the allylic carbonate **24** proceeded stereoselectively to give the lactone **25** in 51% yield. The C(13)-stereoisomer of **25** was not found in the crude mixture[14]. Pd-catalyzed hydrogenolysis of the resulting allylic acetate **25** with formic acid and Et_3N gave the lactone **26** in 98% yield[6]. The resulting terminal olefin in **26** can be used as the methyl ketone[15] which is necessary to construct C-ring in the last step of the synthesis. Carbonyl groups of ester and lactone in **26** were simultaneously reduced with diisobutylaluminium hydride to give the hemiacetal **27a** in 76% yield. Selective monotosylation of **27a** and synchronous reductions of the tosyl and lactol groups with lithium aluminium hydride gave the diol **28**; $[\alpha]_D^{25}$ +68.2°, (c 1.45, $CHCl_3$), ^1H, NMR δ 0.79(18-Me), in 61% yield. Transformation of **28** to **8** was carried out in a similar manner as



Scheme 4

reported before[5]. Selective monotosylation of the diol **28** and oxidation of the residual alcohol with pyridium chlorochromate gave the aldehyde **29** in 64% overall yield. Cyanohydrin formation of **29** in two steps (85% yield), cyclization[16] of the protected cyanohydrin **30** with $NaN(SiMe_3)_2$ (90% yield) and conversion of the cyclized product to the cyclopentanone with acid and base gave the ketone **8**; $[\alpha]_D^{25}$ +52.6°, (c 0.31, $CHCl_3$), ^1H, NMR δ 0.83(18-Me).

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8) In all cyclizations, the relative stereochemistry at C(17) and C(23) was completely controlled as shown in lactons **19** and **20**, whereas the C(13)-stereochemistry was uncontrollable and lactones **19** and **20** contained about 10% of C(13)-stereoisomer;HPLC, **19**, Rt=7-9min: **20**, Rt=9-10min.

9) Trost reported an unusual effect of palladium on the rules for ring closure in the cyclization of 1-acetoxy-(2E)-penten-5-yl benzenesulfonyl-acetate to give the larger eight-membered ring rather than six-membered ring; B.M.Trost, T.R.Verhoeven, J. Am. Chem. Soc., **1979**, 101, 1595.

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13) Usually, alkylation of ketone with 3-butenyl iodide is not easy because of an easy β-elimination of HI under basic conditions; G. Stork, Excerpta Med. Int. Congr. Ser., **1971**, 219, 101.

14) In our privious synthesis[5], C(13)-β-methyl was introduced by alkylation of the lactone **2** with moderate stereoselectivity (4:1).

15) As another way to construct C(13)-stereochemistry as well as C-ring, 1,4-addition of **7** to methyl vinyl ketone was carried out and the desired product **i** was obtained in 80% yield.

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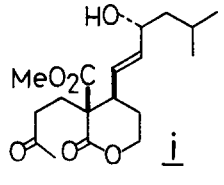

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