

A total synthesis of calcitriol

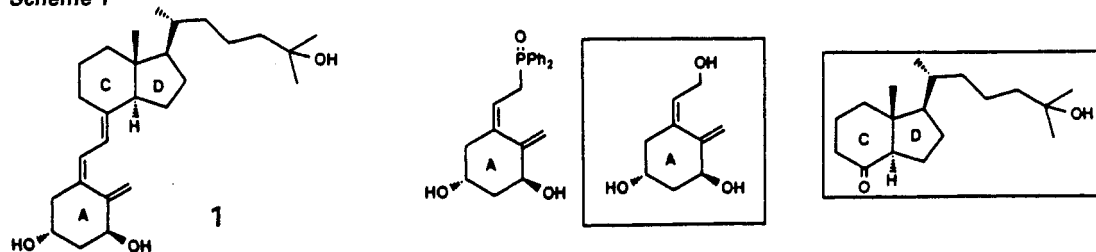
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Abstract - A total synthesis of calcitriol is reported. It involves the coupling of the C/D *trans* indanone system with the ring-A moiety. Both parts have been synthesized by two separate routes.

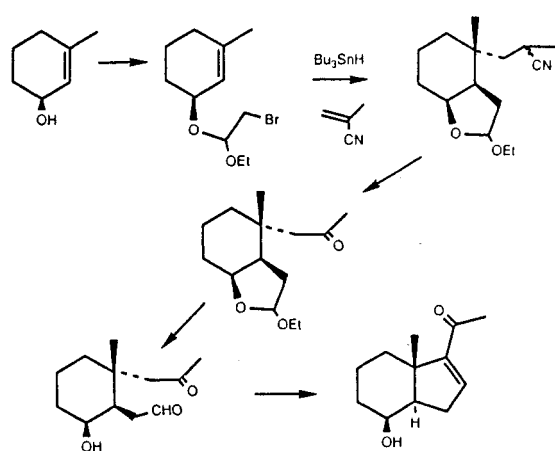
The following series of schemes illustrates the total synthesis of calcitriol in optically active form as we have carried it out at Columbia. We present two constructions of the C/D *trans* indanone system, as well as two constructions of the A-ring triol which are required for the final coupling to calcitriol 1. These two moieties are shown in the boxes in Scheme 1. The final coupling follows the procedure previously used by Uskokovic (ref. 1).

Scheme 1

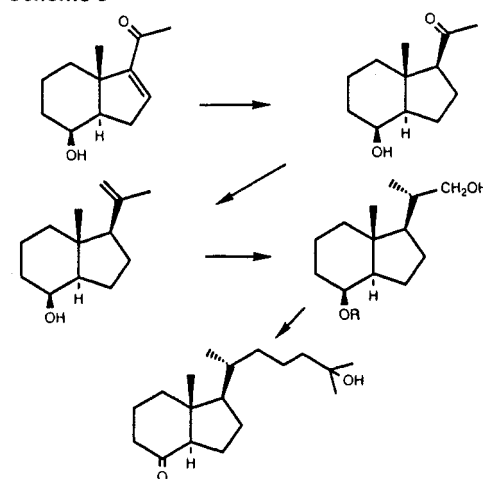


The first construction we show for the C/D system (Schemes 2 and 3) makes use of the free radical cyclization-trapping of mixed bromoacetals derived from 2-cycloalkenols, a process we have introduced earlier for the synthesis of stereocontrolled vicinally-substituted systems. The starting material for this short route is the optically active 3-methyl-2-cyclohexenol shown in Scheme 2. Its synthesis can be carried out in several ways, some of which are outlined in Scheme 4. The scheme is applied here to the stereospecific construction of a *trans* hydrindane

Scheme 2

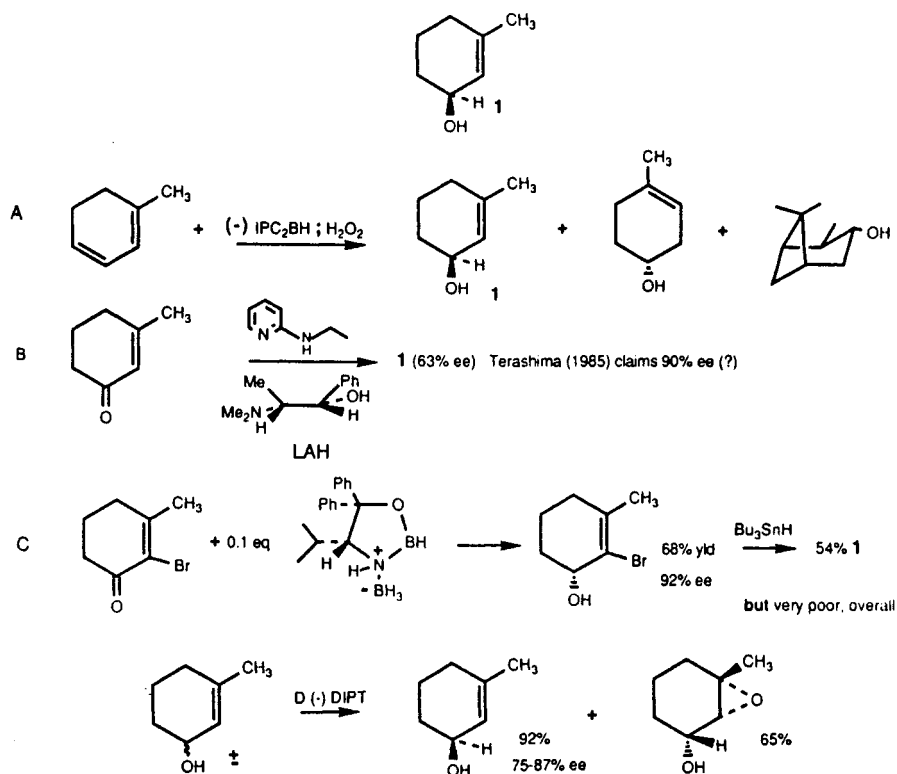


Scheme 3



Scheme 4

Synthesis of (S)-3-Methyl-2-cyclohexenol

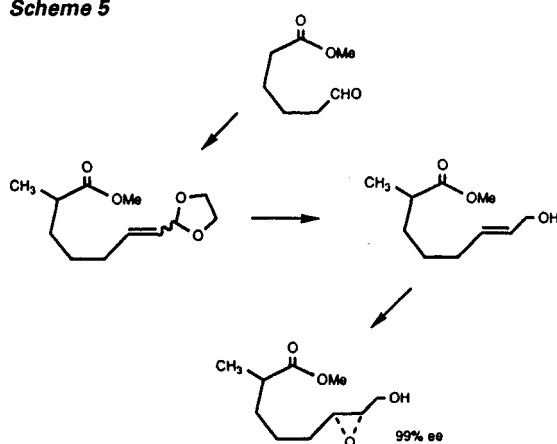


(see ref. 2). The second method (Schemes 5 and 6) makes use of another stereocontrolled synthesis, of vicinally substituted cyclohexanols in this case, the cyclization of allylic epoxides with carbanions (ref. 3).

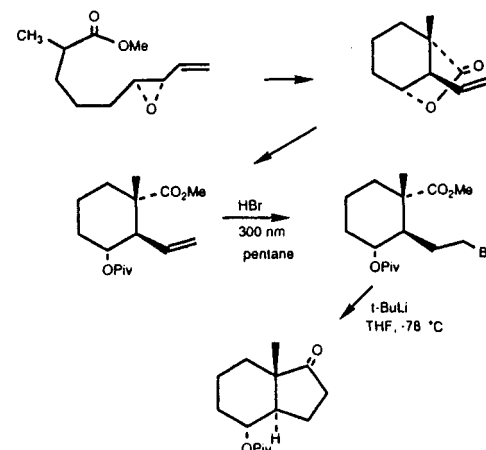
The completion of the finished C/D system from the optically active hydroxyindanone of Scheme 6 is shown in Scheme 7, starting with the usual Z-product of the Wittig reaction with ethylidene triphenyl phosphorane.

Two synthetic routes are also reported for the ring-A moiety. In both cases our goal was to achieve the direct synthesis of the required (Z) diene, as well as the stereospecific synthesis of the cyclohexanediol array. The two routes are conceptually related but the first one, shown in Scheme 8, requires starting with the difficultly accessible (at this time) 4-methyl-3-cyclohexenol of high optical purity. The advantage of the second (Schemes 10, 11, 12) is that it starts with the readily available, optically pure 4-methyl-3-cyclohexenecarboxylic acid.

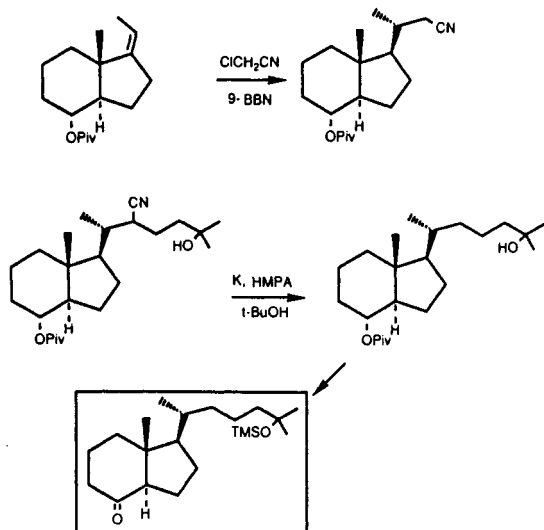
Scheme 5



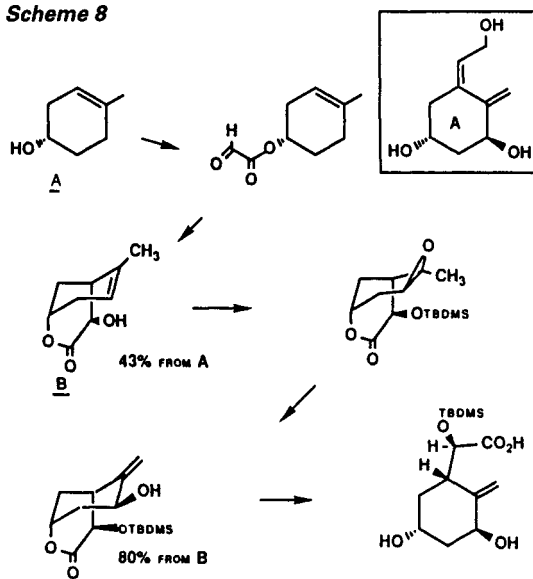
Scheme 6



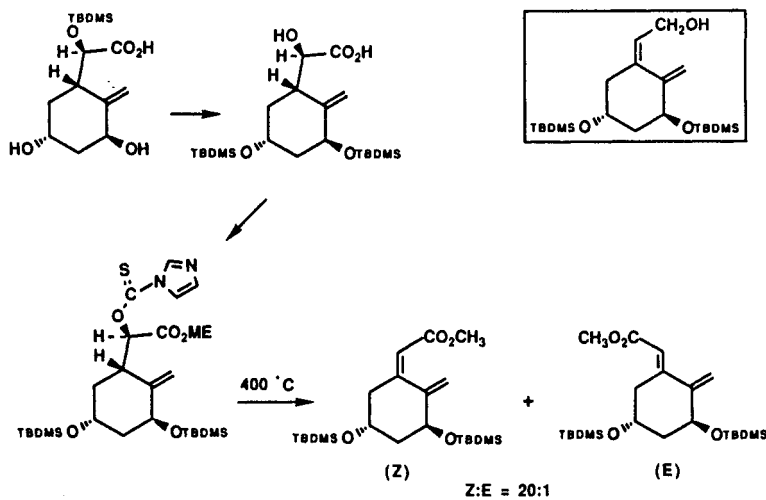
Scheme 7



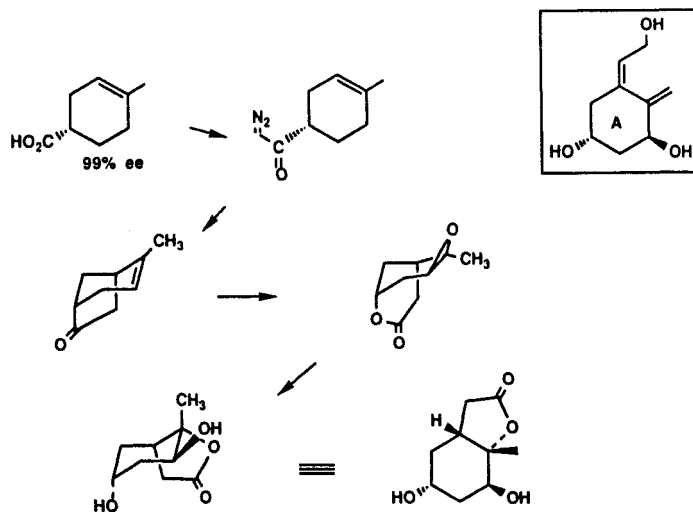
Scheme 8



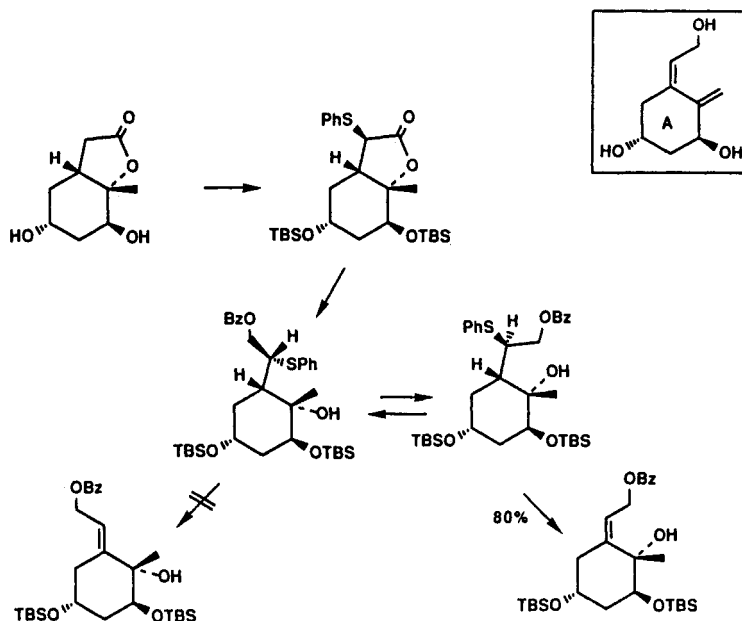
Scheme 9



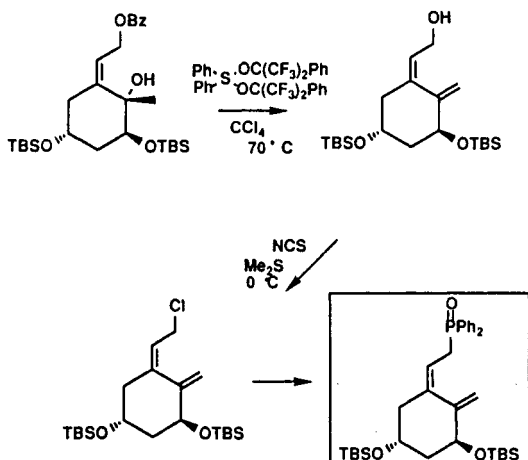
Scheme 10



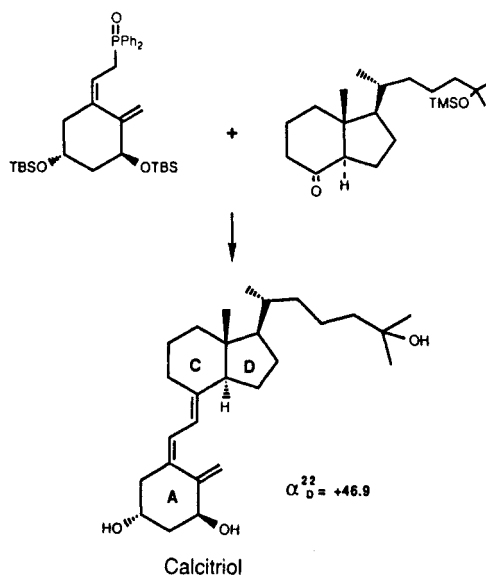
Scheme 11



Scheme 12



Scheme 13



Finally, the two halves are joined to product calcitriol in the usual way (ref. 1), as shown in Scheme 13.

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