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Intramolecular Cyclopropanation Using Iodonium Ylides. The 3,5-Cyclovitamin D Ring A Synthon

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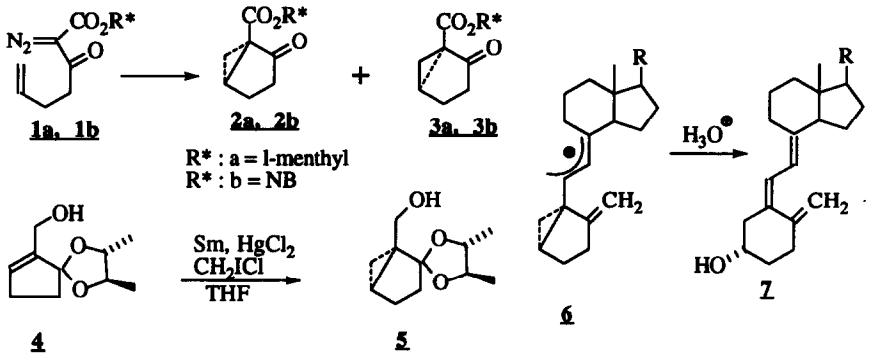
Abstract:
The key intermediate 2b for 3,5-cyclovitamin D ring A synthon 13 was prepared in 80% yield as a diastereomeric mixture (70:30) *via* intramolecular cyclopropanation from iodonium ylide 10b.

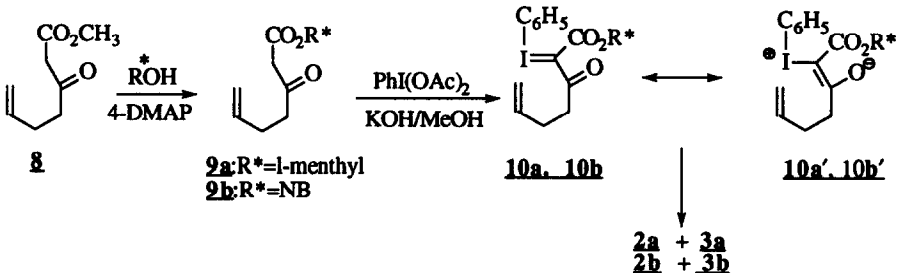
A valuable synthetic reaction is intramolecular cyclopropanation using appropriately unsaturated diazoesters.[1] This reaction has been applied to the synthesis of steroids[2], prostaglandins,[3,4] and the ring-A-synthon for 3,5-cyclovitamin D.[5-8] The latter example is of particular interest because of the emerging recognition that vitamin D analogs show powerful anti proliferative effects[9] and affect the differrentiation of various cell types.[10-12] Clinical results on psoriasis[13,14] and *in vivo* human cancer solid tumors have been reported.[15]

Vitamin D analog syntheses may be divided into three categories: (i) modification of the provitamin (5,7 cholestadiene system), (ii) modification of a truncated vitamin (typically from the C22-aldehyde 9,10 seco 7(8),5,6,10(19) triene) or a modular approach in which the A ring C-D rings (Grundmann ketone) and side-chain are synthesized separately and sequentially assembled.[16] Among the numerous A-ring synthons reported[17] an interesting system is the cyclovitamin one mentioned above, i.e. a 2-oxo -bicyclo[3.1.0]hexane-1-carboxylate such as 2a or 2b, which ultimately is converted to the 1α-hydroxyvitamin *via* the DeLuca Paaren homoallylic cycloreversion reaction.[18] The cyclovitamin A-ring has been obtained *via* intramolecular cyclopropanation using various Rh(III)TPP catalysts for decomposition of an optically active diazoester (1→2a, 2b; 3a, 3b)[8] or intermolecular cyclopropanation using an optically active cyclopentene derivative (4→5).[19]

Both methods yield the desired C_3,C_5-α-configuration of the cyclopropyl ring as in 2a, 2b, and 5. Using either of these synthons the 3α, 5-cyclovitamin D can be made and subsequent solvolytic cycloreversion yields 1α-hydroxyvitamin D analogs.(6→7).[18,21]



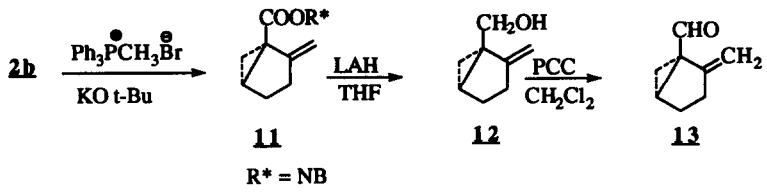
We have shown earlier that iodonium ylides derived from an unsaturated β-ketoesters upon reaction with a catalytic amount of Cu(I)Cl yield cyclopropyl products.[20] A comparison of intramolecular cyclopropanation using the diazoester versus iodonium ylide can be made with respect to chemical and stereochemical yield as applied to the synthesis of 2a, 2b. Accordingly, methyl-3-oxo-6-heptenonate 8 was converted to the enantiomerically pure β-ketoesters 9a and 9b using 4-(dimethylamino)pyridine (4-DMAP) catalyzed exchange[22] with the two chiral auxiliary alcohols l-menthol (8→9a)[23] and 1(S)-3(S)-exo-hydroxy-2(S)-exo-naphthylbornane (NB) (8 → 9b).[24]



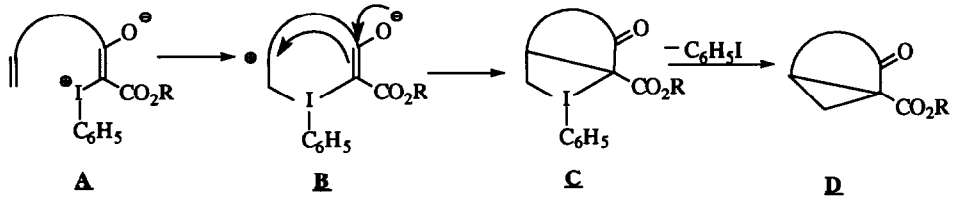
Iodonium ylide 10a , (R*=l-menthyl) formed using $PhI(OAc)_2$ in methanolic KOH upon decomposition catalysed by Cu(I)Cl in CH_2Cl_2[20] yielded a 1:1 mixture of 2a and 3a. By contrast, iodonium ylide 10b (R*= NB)[24] yielded a 70:30 ratio of 2b and 3b.[24] These diastereomers were separated by column chromatography (ΔRf=0.1) to yield crystalline 2b (56%) and 3b (24%), m.p 152-153°C, and m.p 135-137°C, respectively.[24]

The potential C19 methylene group was introduced (2b→11) (85%),[8] LAH reduction yielded 12 (91%) and the

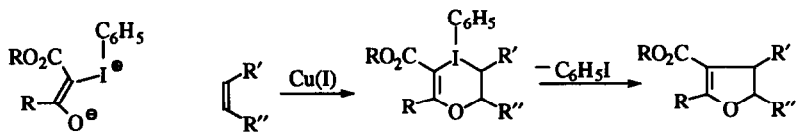
recovered chiral auxilliary NB. PCC oxidation of 12 yielded 13 which can be attached to a C-D part and converted to vitamin D (13→6→7).[5]



The iodonium ylide cyclopropanation probably is a stepwise electrophilic addition of the iodonium center to the double bond A→B followed by transannular alkylation of the thus formed carbocation by the enolate B→C followed by reductive elimination and ligand coupling C→D.



In agreement with this description is the fact that the bimolecular reaction between the β-dicarbonyl ylides and olefins yields dihydrofurans and not cyclopropanes since the analogous intramolecular reaction for 10b would incur a Bredt's rule violation.



Acknowledgement

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24. 9b: FT-IR (film) 2957, 1740, 1716,1394, 1244 cm^{-1} MS(EI) 404 (M^+, 13.5%); HRMS (EI) calcd 404.2351, obsd 404.2361; 10b: FT-IR ($CDCl_3$) 1734, 1649 cm^{-1}; 3b: $[a]_D^{24}$=+131.6°; R_f=0.21 (15% EtOAc in hexanes); m.p=135-137°C; FT-IR (KBr) 2957, 1738, MS (EI) 402 (M^+, 17.3%); HRMS (EI) calcd 402.2194, obsd 402.22. 2b: $[a]_D^{24}$= +95.7°; R_f=0.11 (15% EtOAc in Hexanes); m.p=152-155°C; FT-IR (KBr) 2957, 1739,1262 cm^{-1}; MS (EI) 402 (M^+, 11.8%); HRMS (EI) calcd 402.2194, obsd 402.2182. 11: $[a]_D^{24}$= -50°; FT-IR (film) 3343, 2938, 2868, 1014 cm^{-1}. 13: $[a]_D^{24}$=-59°; FT-IR (film) 2965, 1690, 1022 cm^{-1}; MS (CI) 123 (M^++1, 100%).

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