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Stereocontrolled synthesis of dihydroxycholecalciferol precursors

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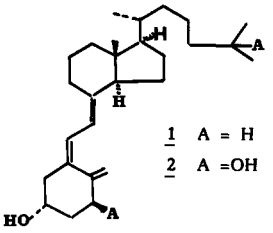
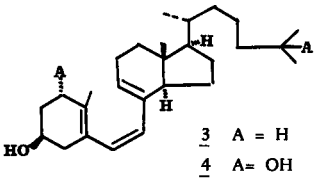
Abstract– The stereocontrolled synthesis of Des-AB-Cholestane and Cholestene 6[1] and 9[2] is described, starting from methyl-2 cyclopenten-2 one: These systems can be used as CD units for building vitamine D_3 hydroxylated metabolites (via the previtamine in the case of 9) by reaction with the suitable A ring.

The pionneering work of de Luca[1] and Kodicek[2] has shown that 1S,25-dihydroxycholecalciferol 2 is the active metabolite for physiological calcium translocation, after hydroxylation of vitamin D_3 1 at the 25 position in the liver and the 1 alpha position in the kidney. Consequently, this compound has received much attention in the last few years.

1S,25-dihydroxycholecalciferol can be formed via a 1-7 hydrogen shift of the triene moiety of a previtamin of type 4, as is the case for precholecalciferol 3, one of the classical examples of a sigmatropic shift permitted by the Woodward-Hoffmann rules.

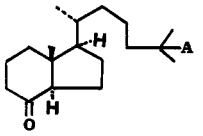


1 A = H
2 A =OH

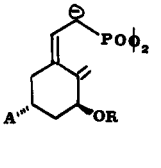


3 A = H
4 A= OH

Scheme 1



5 A =H
6 A = OSi^tBuMe_2



7 A = H
8 A = OSi^tBuMe_2

Cholecalciferol 1 itself can be prepared by partial synthesis from cholesterol[3], which is of course readily available. In the case of the 1S,25-metabolite 2, however, in which the two ends of the molecule are hydroxylated, a total synthesis would obviously be more useful than a partial one starting from cholesterol, since the latter molecule would have to be functionalized before carrying out the photochemical opening of ring B.

Among the many possible strategies available to effect the total synthesis of 1S,25-dihydroxycholecalciferol 2, two have been proposed by lythgoe[4] and used by him for the synthesis of vitamin D_3 1 itself, they are described in Schemes 1 and 2.

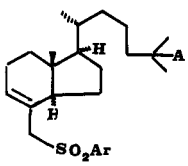
The first of these involves a Wittig reaction between the ylid of the phosphine oxide 7 and the carbonyl group of the CD unit 5 (5 + 7 ⟶ 1, scheme 1). This strategy has been used recently by the Hoffman-Laroche group[5] in the first stereoselective total synthesis of 1S,25-dihydroxycholecalciferol 2 (8 + 6⟶ 2, scheme 1) ; this strategy has the advantage of fixing the 7, 8 double bond in the right configuration, the configuration of the 5, 6 double bond being provided by the ring A precursors 7 or 8.

The second strategy proposed by Lythgoe leads not to cholecalciferol 1 itself but to the previtamin 3 via the hydroxy sulfone 12 and the tachysterol 13 (9 + 10 → 12 → 13 13 → 3 scheme 2).

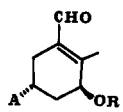
Our work on the total synthesis of hydroxylated metabolites of vitamin D_3 has been carried out according to the above two strategies proposed by Lythgoe, i.e. either through previtamins such as 4, or by convergent coupling, using the Wittig reaction, of the ylid 8 and the carbonyl group of a CD unit such as 6. In other words, we set out to prepare 2 either via the previtamin 4, or directly, while keeping in mind the possibility of using as far as possible the same intermediates in both cases. Both these strategies constitute an interesting challenge for a synthetic organic chemist, involving as they do the construction of CD units (6 and 9) containing four asymmetric carbon atoms and a functionality at position 8 (either a methylenesulfone as in 9, or a carbonyl as in 6), and A-ring units containing an aldehyde 11 or phosphine 8 function.

This lecture will only be concerned with our work directed towards the synthesis of the CD-ring components 5, 6, and 9.

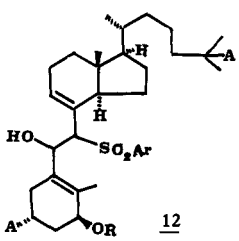
Scheme 2



9 A=H



10 A = H
11 A = $OSi^{t}BuMe_2$



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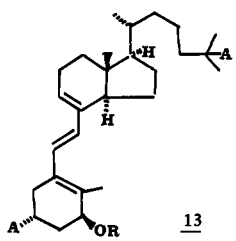

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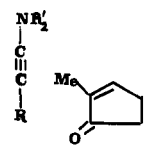
Scheme 3



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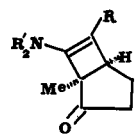

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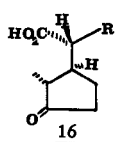

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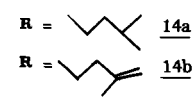
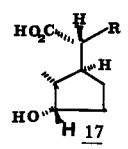


14a
14b



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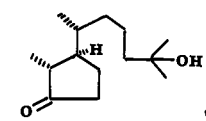

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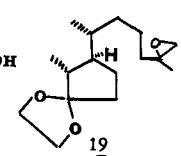

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One of the difficulties which must be overcome in the synthesis of these units is the stereochemical control of their chiral centers, and in particular of the chiral center on the flexible side chain (position 20). It so happens that, some years ago, we developed a method which solves this problem, since it fixes the stereochemistry of an asymmetric center on a flexible side chain adjacent to a five[6] or six[7] membered ring. This is made possible by the stereochemical control of the hydrolysis of the bicyclic enamines (e.g., 15) formed from the cycloaddition between the ynamines 14 and cycloalkenones (scheme 3).

Used as a key step to fix the stereochemistry of the asymetric centers in the side chain of the CD units 5, 6, and 9, this method consists in the hydrolysis of the adducts 15 formed by cycloaddition of the ynamines 14 with, 2-methylcyclopentenone, the five-membered ring of which will eventually constitute the D-ring of the CD unit. And indeed, using our method, the thermodynamically controlled hydrolysis of the bicyclic enamine 15 afforded the keto-acid 16, which was then readily converted into the desired cyclopentanone 18, after resolution which leads to the pure enantiomer*.

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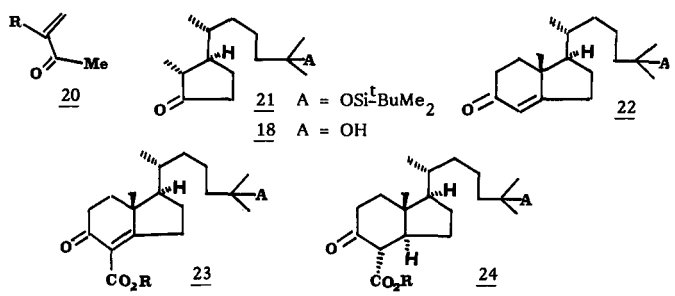
*The resolution of the dl keto-acid 16 was accomplished via hydroxy-acid 17 by fractional crystallization of its diastereoisomeric ammonium salts [(-) ethyl-naphtylamine] in 80% yield of pure enantiomer 17. The (-) methyl ester of 16 derived from the (+) methyl ester of optically pure 17 was then used in the subsequent steps of the synthesis, and all structures in this paper are shown in the correct absolute configuration.

This conversion requires that the carboxyl group in 16 should become the methyl group in 18, and that the group R in the original ynamine 14 should be such that it comprises the six carbon atoms of the side chain and the possibility of introducting the hydroxyl group at position 25. The latter requirement was fulfilled by preparing[8] the ynamine 14b with R = 4-methyl pent-4-enyl, the double bond being the precursor of the hydroxyl group[9] (the ynamine 14a with a saturated R group was also prepared as a model for the 25H series[10]).

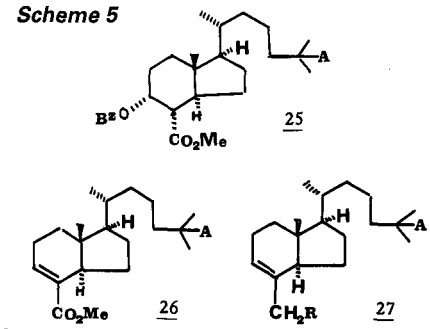
The conversion of the carboxyl group in 16 into a methyl group was carried out by a classical route : protection of the carbonyl group (dioxolane) of the methylester of 16 was followed by reduction of the ester group ($LiAlH_4$), epoxydation of the double bond, and mesylation to afford 19. The latter compound was treated with lithium triethylborohydride (2 eq.), to lead in a single step to the hydroxycylopentanone 18 (overall yield from 16 : 72%). This compound, which constitutes the D ring of the CD unit, already comprises a side chain with the correct number of carbon atoms, the correct stereochemistry, the correct functionality, and the correct chirality.

Compound 18 was used as a building block in the next stage of the synthesis, which is the attachement of ring C by a Robinson annelation (21→22). The product of the annelation, the hydrindenone 22 was stereochemically pure (^{13}C NMR) since, as expected, the Michael acceptor approaches from the side of the molecule opposite from the side chain. This stage of the synthesis which controls the stereochemistry of the third asymmetric center of the CD unit (position 13), was carried out by reaction of the thermodynamic enolate of 21 on the alpha-silyl butenone 20 (R=$SiMe_3$)[11] followed by intramolecular aldolisation of the resulting dione (scheme 4).

Scheme 4



Scheme 5



The carboxyl group was then introduced[12] to form the keto-acid 23 (R=H); this key intermediate is a precursor of both the desired CD units 6 and 9. The carboxyl group plays a dual role. On the one hand it controls the stereochemistry of the catalytic reduction of the 12-13 double bond and hence of the fourth asymmetric center (position 14) of the hydrindanone 24 ; in the absence of the carboxyl group, the CD ring junction would be cis rather than trans. On the other hand, the carboxyl group regioselectivity attached to carbon atom 8, will be used to build, at will, the functionnalities of CD units 5, 6 and also 9 which, are different, but in all cases substituents at position 8.

The catalytic reduction (H_2, Pt) of 23 (R=H) leads in excellent yields to keto-acid 24 (R=H) as a single isomer (as shown by ^{13}C, ^1H, NMR of the corresponding ester 24 [R=Me]). This catalytic reduction step, thus controlled the fourth asymetric center (position 14).

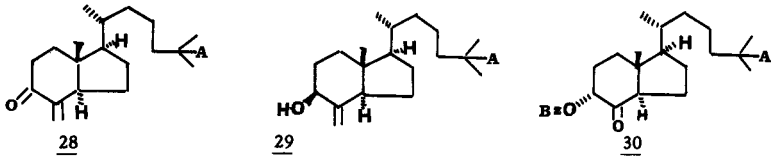
Sulfone 9 which was prepared from the keto-ester 24 (R=Me) can lead to the hydroxy-previtamine 4 by reaction with 11, whereas the hydrindanones 6 and 9 which were prepared from keto-acid 24 (R=H) can lead directly to dihydroxy vitamine 2 via reaction with 8.

The transformation of keto-ester 24 (R=Me) into the sulfone 9 was performed with no particular problems via ethylenic ester 26. This ester 26 was reduced into the corresponding alcohol 27 (R=OH) precursor of chloro compound 27 (R=Cl) which was displaced by sodium sulfinate to give the sulfone 9 (scheme 5).

The ethylenic ester 26 was prepared by elimination of the benzoate of hydroxy-ester 25 (using lithium isopropylamid, 1 eq., -78°, 25°C) obtained by reduction (L selectride) of keto-ester 24 (R=Me).

It is, on the other hand, the keto-acid 24 (R=H) and not its methyl ester 24 (R=Me) which was used to synthetize the hydrindanones 5 and 6. This transformation was performed according to the following steps (scheme 6): first, a decarboxylativ Mannich reaction leads from 24 (R=H) to ketone 28 which is then reduced (Dibal) to the alcohol 29. The methylene of this alcohol 29, later becomes the crucial carbonyl of hydrindanones 5 and 6 by ozonolysis (29→30) followed by reductiv elimination (Ca in NH_3) of benzoate 30. This benzoate led to the desired hydrindanones 5 and 6 in the last step : (30→ 5 and 30→ 6).

Scheme 6



CONCLUSION AND ACKNOWLEDGEMENTS

The synthesis of Des-AB-cholestene 9 and Des-AB-cholestanones 5 and 6 from methyl-cyclopentenone which is described here, constitutes part of our research directed towards the total stereocontrolled synthesis of vitamine D_3 metabolites, particularly the 1S-2S Dihydroxycholecalciferol 2.

It is a pleasure to acknowledge the contributions of my very able collaborators Claude Barbara, Isabelle Daoust-Maleval, Didier Desmaële, Philippe Kahn. Their names are cited in the appropriate references. We all thank the Ministry of Education and science, the C.N.R.S. and Rhône-Poulenc S. A. for financial support.

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