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RETROSYNTHETIC STUDIES WITH FORSKOLIN

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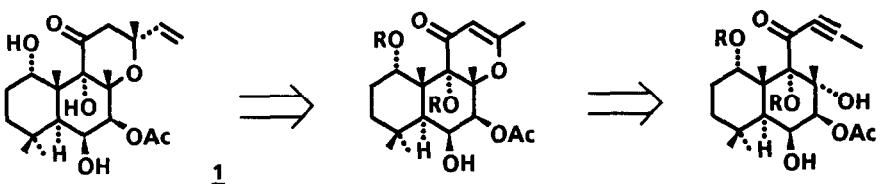
ABSTRACT : New preparations of some dihydro- γ-pyrones derived from forskolin 1 are reported. Conjugate addition of cuprates is shown to occur on these compounds , in good yield, in the presence of BF_3-Et_2O : dimethyl and vinyl cuprates add with major α stereoselectivity, whereas dibutylcuprate adds mostly β . Some other reaction conditions or copper reagents failed.

Forskolin 1, a labdane diterpene isolated from the roots of the Indian herb Coleus forskohlii, has been shown to have a very promising biological and medical potential (1). Therefore a considerable interest has been found in its chemical modifications and total synthesis.

Forskolin is indeed a fascinating target for total synthesis since its very peculiar structural features often result in an unusual chemical reactivity, as shown by some remarkable rearrangements (2). The recent report of a stereocontrolled synthesis of (±)-1,6,7-trideoxy forskolin 2 by IKEGAMI and coworkers (3) prompts us to disclose some of our results concerning the C ring elaboration, from the following retrosynthetic scheme.



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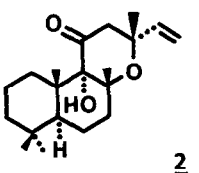

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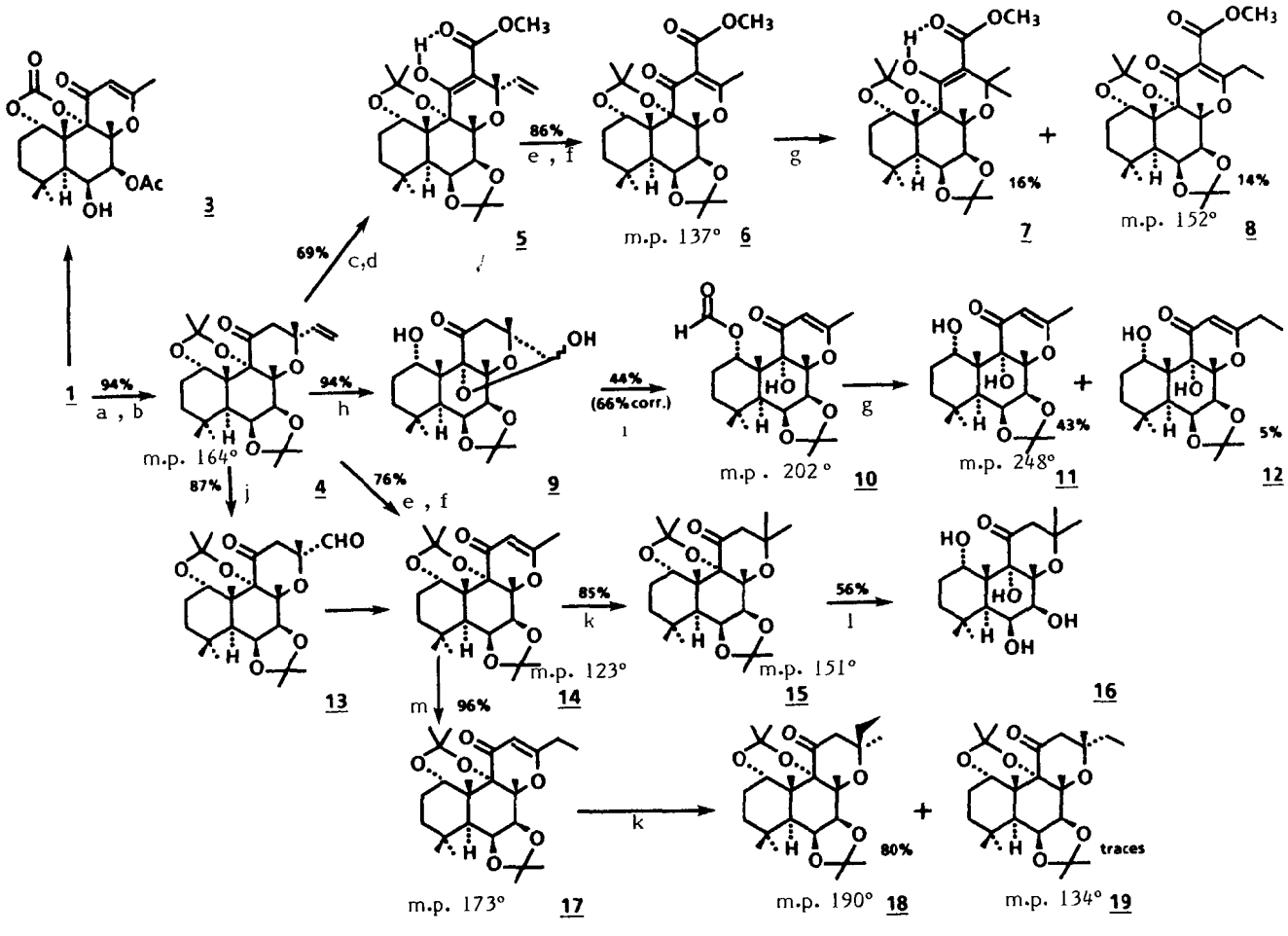

a) NaOH, H_2O-CH_3OH ; b) 2-methoxypropene, pTsOH, CH_2Cl_2 ; c) MMC, DMF, 140° ; d) CH_2N_2, CH_2Cl_2

e) $RuCl_3$-$NaIO_4$, CCl_4-CH_3CN-H_2O ; f) $Pb(OAc)_4$-$Cu(OAc)_2$, benzene-pyridine ; g) Me_2CuLi , Et_2O , -78° to r.tp.

h) O_3, CH_2Cl_2-CH_3OH, -78°, then Me_2S ; i) $Pb(OAc)_4/CaCO_3$, benzene, 80° ; j) O_3, CH_2Cl_2-CH_3OH, pyridine, -78° ;

k) Me_2CuLi, BF_3-Et_2O, -78° to r.tp. ; l) aq. HCl/THF ; m) LDA/HMPA, then CH_3I, -78° to r.tp.

Starting from 1, we first prepared 3 according to SAKSENA et al. (4). Our preliminary experiments of vinyl copper reagents conjugate addition failed, possibly due to heterogeneous conditions and thermal instability of these cuprates (5, 6). Therefore, we examined the reaction of 3 with dimethylcuprate which is known to give homogeneous and quite stable solutions. However, attempts of conjugate addition with $(CH_3)_2CuLi$ / Et_2O (- 78° to r.tp.) failed also with 3 : only products of hydrolysis of the 1,9-carbonate and (or) the 7β -OAc, and 7β to 6β acetate transposition, were obtained (72% yield of isolated compounds).

Conjugate cuprate additions on γ-pyrones (chromones) (7), dihydro-γ-pyrones (8) or thiin-4-ones (9) are indeed generally difficult. Moreover, in the formation of 1 or 2, stereoelectronic control of the conjugate addition implies that β-CC bond formation creates a 1,3-diaxial interaction in the pre half-chair transition state leading to the enolate; on the other hand α-CC bond formation gives a pre-twist transition state in which a 1,4-diaxial interaction between the incoming group and the C-9/O-9 bond is generated (10).

In order to avoid the partial hydrolysis and 7β -OAc migration we met with 3, we next prepared the bis-acetonide dihydro-γ-pyrone 6. In 6, introduction of the 12-$COOCH_3$ group was thought to facilitate the cuprate conjugate addition, as such an effect by an electron withdrawing group has already been shown for chromones (7) or thiin-4-ones (9).

For preparing 6 by a sequence analogous to that reported for 3 (4), ozonolysis of 5 was found to be unsatisfactory. However, compound 6 was obtained in 86% yield from 5 ($RuCl_3$ / $NaIO_4$, followed by $Cu(OAc)_2/Pb(OAc)_4$). Reaction of 6 with $(CH_3)_2CuLi$(3 eq,Et_2O,0°) gave the 1, 4-addition product 7, but in 16% yield only - and, quite unexpectedly, 14% of 8 which probably originated from a radical process. Starting material was also recovered (17%), possibly due to some enolization of 6 by the cuprate reagent as observed with some chromones (7a) or α, β-unsaturated ketones having a methyl group in the β-position (11).

Due to the low yield of 7, we next tried to prepare the protected dihydro-γ-pyrone 14. However, ozonolysis of 4 in CH_2Cl_2/CH_3OH gave the lactol 9 (94%) and not the expected aldehyde 13. The lactol 9 was converted into 10 with $Pb(OAc)_4/CaCO_3$ (44%, 66% corrected from recovered 9) (12). Further reaction of 10 with $(CH_3)_2CuLi$ was attempted to involve a 9α-alkoxy cuprate which, if formed (13), might facilitate and direct an intramolecular CC bond formation at C-13. However, reaction of 10 with $(CH_3)_2CuLi$ (Et_2O, -78° to r.tp) gave no conjugate addition -but, interestingly again, 5% of compound 12 were isolated.

The aldehyde 13 was obtained (87%) by ozonolysis of 4 in CH_2Cl_2/CH_3OH in the presence of pyridine, allowing the preparation of 14 by the sequence developed by SAKSENA et al (4). However, we found that 14 was also conveniently prepared (76%) in two steps from 4 ($RuCl_3/NaIO_4$; $Cu(OAc)_2/Pb(OAc)_4$), with no intermediate purification, like for the conversion of 5 into 6.

Many attempts of conjugate addition - with methyl, ethyl or vinyl copper reagents - failed completely with 14 in diethyl ether or THF (-78° to r.tp). In all these experiments, starting material was always recovered in good yield (90% to almost quant.) (14).

In contrast, dimethylcuprate (from CH_3Li/Et_2O and CuI), in the presence of BF_3-Et_2O (15), reacted with 14 to yield the 1,4-addition product 15 (85%). Subsequent hydrolysis at 20° with aqueous HCl in THF afforded 16 (56%).

Our next goal was then to determine the stereochemistry of the reaction for the planning of a total synthesis of forskolin. As we were unable to achieve vinyl or ethyl conjugate addition in the foregoing experiments, we prepared 17 (96%) by alkylation of 14 (LDA/HMPT, CH_3I at -78°). Methyl conjugate addition occurred on 17 in the same conditions, with BF_3-Et_2O, yielding 18 (80%) and only traces of 19. The structure of the major product was shown unambiguously to be 18, by comparison with the hydrogenation product 19 of 4 (H_2, Pd/C, EtOH, r.tp).

More recently, we were also able to achieve the conjugate addition of vinyl cuprate (from vinyl tri n-butyl tin and n-butyl lithium in situ, and CuI), with added BF_3-Et_2O, and obtained 4 as the major product (59%) together with the C-13 epimer (14%).

To sum up, 1,4-addition of methyl or vinyl cuprate has been achieved in the presence of BF_3-Et_2O and shown to occur stereoselectively α at C-13. Consequently, at least in these examples, 1,4-cuprate addition appears to involve preferentially an intermediate twist type transition state. However, one has to be cautious in any generalization to either other dihydro-γ-pyrones or other copper reagents : we observed that 14 reacts with nBu_2CuLi in the same conditions to afford the major β-1,4 addition product (61%) together with the α-adduct (23%), as shown by identification with the compound prepared by the following sequence (13 + $Ph_3P{=}CH{-}CH_2{-}CH_3$, THF, r.tp; H_2, Pd/C).

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