Pergamon

Tetrahedron Letters, Vol. 35, No. 34, pp. 6347-6350, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01281-1

A Concise Synthesis of Chiral 2-methyl chroman-4-ones : Stereo selective Build-up of the Chromanol Moiety of Anti-HIV Agent, Calanolide A

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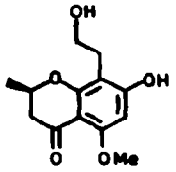
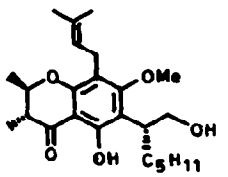
Abstract : Inter- and Intramolecular Houben-Hoesch reactions have been used for the first time for the enantioselective synthesis of both the antipodes of 5,7-dimethoxy-2-methyl chroman-4-one. (R)-7-Methoxy-2-methyl chroman-4-one has been diastereoselectively elaborated to the dimethylchromanol moiety of calanolide A.

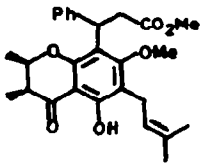
The chroman-4-one ring system occupies a prominent position among the heterocycles. It is found in several biologically active natural products[1] in enantiopure form with a variety of substituents at C-2, chief among them being the methyl group as exemplified by the compounds 1[2], 2[3], 3[4] below.



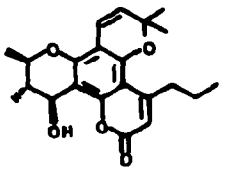
LL-Z53 DCL
1



Papuanic acid
2



3



Calanolide A
4

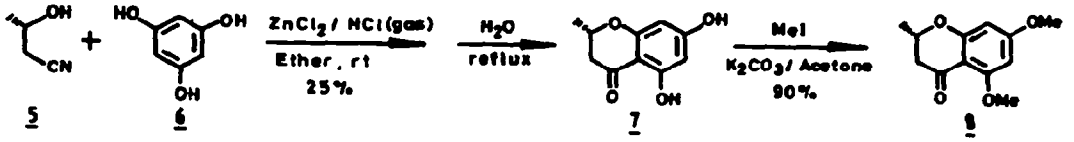
Chroman-4-ones are also important synthetic intermediates for chromans, chromenes chromanols etc., which have exhibited diverse pharmacological activities such as β-blockers, anti-convulsants, anti-microbials etc[1]. The recent isolation of calanolide A (4)[5] with impressive anti-HIV activity against even AZT-resistant strains has renewed the interest in these natural products. Widespread natural occurrence and highly useful biological activity notwithstanding, there is no simple and general method[6] available to obtain 2-substituted chroman-4-ones in optically pure form.

One of the frequently used methods to obtain chroman-4-ones is to treat phenols with α,β-unsaturated acids or their derivatives under acid-catalysis. This simple ditopic ring closure reaction can be a route also to chiral 2-substituted chroman-4-ones if appropriate reactants and reaction conditions are chosen. Homochiral lactates and 3-hydroxy butyrates have been used to alkylate arenes with moderate to excellent retention of chirality[7]. But the reaction parameters used have been such that only the hydroxyl function present in the electrophile could take part in the reaction while the carboxyl group remained dormant. Chosing (S)-3-hydroxy butyronitrile[8] as the chiral bifunctional electrophile and adopting Houben-Hoesch conditions[9], we present in this communication the first one-pot enantioselective synthesis of 5,7-dihydroxy-2-methyl chroman-4-one.

Intermolecular Houben-Hoesch reaction :

(S)-3-Hydroxy butyronitrile (5) and phloroglucinol (6) were treated (Scheme 1) with $ZnCl_2$

Scheme-1



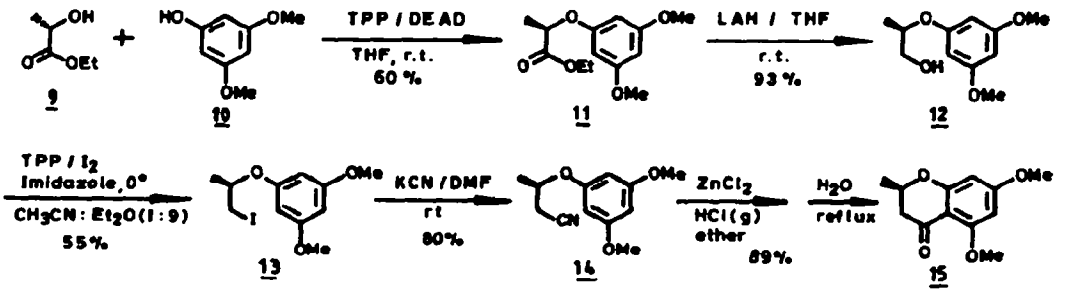
and HCl (gas) in ether. The product imine was hydrolysed in situ to the corresponding ketone. Chromatographic purification afforded the 5,7-dihydroxy-2-methyl chroman-4-one (7)[2] in 25% yield. $[\alpha]_D$ -58.6° (c 1, MeOH), m.p. 181°. The dimethyl ether (8)[10] had $[\alpha]_D$ -33.8° (c 1, $CHCl_3$). Although the yield is poor, the brevity, simplicity and the economy of the operation compensate for this drawback. The only other method[6a] reported in the literature for the synthesis of 2-methyl chroman-4-one involves seven steps and makes use of the asymmetric conjugate addition of methyl cuprate to the chiral sulfoxide of a chromone prepared from a salicylate. Exploratory experiments to improve the yield of our reaction are underway. However, we were gratified by the fact that several repetitions of the synthesis reproduced the same values for $[\alpha]_D$, indicating the formation of a single antipode. Since optically pure β-hydroxy nitriles[11] with a variety of substituents at C-3 are readily available, this reaction opens the way for several chiral 2-substituted chroman-4-ones.

Intramolecular Houben-Hoesch reaction :

To establish the absolute stereochemistry and to determine the enantiomeric excess, compound 8 was sought by an alternate but stereochemically predictable route. The reliable Mitsunobu[12] reaction was used for the stereospecific aryl ether bond formation and the intramolecular Houben-Hoesch for the acylative ring closure.

Thus (S)-ethyl lactate (9) and di-O-methyl phloroglucinol (10) were condensed to give the aryloxypropionate (11). Homologation to the butyronitrile (14) was done via a standard set of reactions as shown in the scheme 2. Intramolecular acylation using anhydrous $ZnCl_2$/HCl (g) in ether cleanly afforded the 5,7-dimethoxy chromanone (15) whose $[\alpha]_D$ +36.4° (c 1, $CHCl_3$) was comparable in magnitude to that of 8 (-33.8) but of opposite sign. The absolute stereochemistry of 8, the product from intermolecular Houben-Hoesch reaction is thus established

Scheme-2

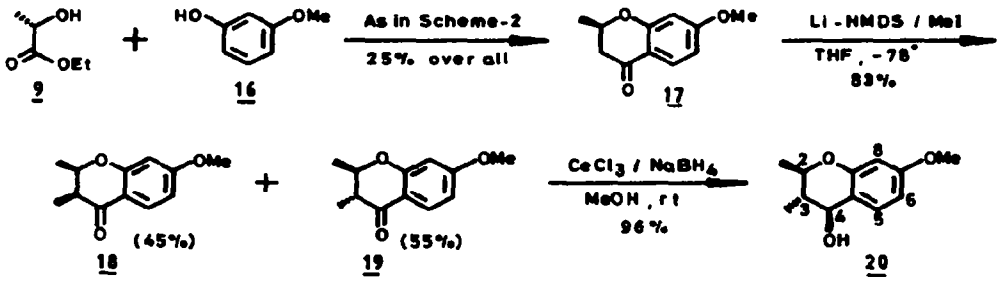


as (S), i.e. the reaction proceeded with the retention of configuration. Probably, the 3-OH of the butyronitrile (5) was first converted to the chloro by $ZnCl_2$/HCl (g) and then got displaced by the aryloxide resulting in net retention. Within the limits of experimental error in determining the specific rotations, (7) seems to be homochiral.

Synthesis of the chiral chromanol moiety of calanolide A :

Encouraged by the success in carrying out both inter- and intramolecular Houben-Hoesch reactions on phloroglucinol, we tried to extend it to resorcinol. While the intermolecular reaction failed to give the desired product, the intramolecular reaction with resorcinol monomethyl ether (16) was as smooth and efficient. (R)-7-Methoxy-2-methyl chroman-4-one (17)[13], $[\alpha]_D$ +53.2 (c 1, MeOH), m.p. 69.5°, thus obtained was elaborated to the chiral chromanol moiety of calanolide A (4). C-Methylation of 17, with Li-HMDS/MeI in THF neatly afforded a well separable approximately 1:1 mixture of cis and trans-dimethyl compounds 18[14a], $[\alpha]_D$ +21.7° (c 0.9, $CHCl_3$), m.p. 74.0° and 19[14b], $[\alpha]_D$ +94.6° (c 0.9, CH_2Cl_2), m.p. 76.8°, in a combined yield of 83% (scheme 3) in contrast to the literature reports of the difficulties encountered due to the anomalous behaviour of the active methylene group of the 2-substituted chroman-4-

Scheme - 3



ones[15]. $J_{2,3}$ value of 3.4 Hz for 18 and 11.5 Hz for 19 formed the basis for the assigned configurations. Luche reduction[16] of the 2,3-trans dimethyl compound 19 resulted in the chromanol (20)[14c] $[\alpha]_D$ +123° (c 0.6, $CHCl_3$), m.p. 99° in excellent (>95%) diastereoselectivity. The formation of the β-equatorial alcohol is indicated by the diaxial coupling of 9.2 Hz between H_3 and H_4. Asymmetric synthesis of calanolide A and some of the biologically active chiral 2-methyl chroman-4-ones is actively being pursued in the light of these findings.

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14. ^{1}H NMR (200 MHz, $CDCl_3$-TMS) data in ppm and Hz.
a) **18**: 1.1 (d, J=7.0, 3H, C_3-Me), 1.4 (d, J=7.1, 3H, C_2-Me), 2.6 (dq, J=3.4 and 7.0, 1H, H-3), 3.8 (s, 3H, OCH_3), 4.62 (dq, J=3.4 and 7.1, 1H, H-2), 6.4 (d, J=2.8, 1H, H-8), 6.6 (dd, J=2.8 and 8.0, 1H, H-6), 7.8 (d, J=8.0, 1H, H-5).
b) **19**: 1.2 (d, J=7.1, 3H, C_3-Me), 1.5 (d, J=7.0, 3H, C_2-Me), 2.48 (dq, J=11.5 and 7.1, 1H, H-2), 3.8 (s, 3H, OCH_3), 4.2 (dq, J=11.5 and 7.0), 6.35 (d, J=2.6, 1H, H-8), 6.55 (dd, J=2.6 and 8.0, 1H, H-6), 7.8 (d, J=8.0, 1H, H-5).
c) **20** : 1.1 (d, J=6.9, 3H, C_3-Me), 1.4 (d, J=6.9, 3H, C_2-Me), 1.6 (ddq, J=6.9, 9.2, 11.3, 1H, H-3), 3.75 (s, 3H, OCH_3), 3.9 (dq, J=6.9, 11.3, 1H, H-2), 4.3 (d, J=9.2, 1H, H-4), 6.33 (d, J=2.8, 1H, H-8), 6.53 (dd, J=2.8 and 8.0, 1H, H-6), 7.35 (d, J=8.0, 1H, H-5).
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IICT Communication No. 3397

(*Received in UK* 9 *May* 1994; *revised* 28 *June* 1994; *accepted* 1 *July* 1994)