A NEW INTERMEDIATE FOR METHYL JASMONATE AND PG'S FROM IRIDOID GLUCOSIDE AUCUBIN[1]

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Abstract - A synthetic approach to biologically active cyclopentanoids or their intermediates starting from natural heterocyclic precursors (iridoid glucosides) has been devised. Aucubin 1 was efficiently converted into chiral cyclopentenone 9 ,intermediate for synthesis of methyl jasmonate-type compounds and prostaglandins.

Iridoid glucosides are a widespread class of natural compounds with heterocyclic (cyclopenta[c]pyran) skeleton whose most common and abundant representative is aucubin 1 .

Starting by this natural chiral template we are running[3-6] a program of syntheses of biologically active cyclopentanoids or their intermediates. In continuation of our work we put now our attention upon isoeucommiol 3 whose unique utilization for synthetic purposes was the acid-catalyzed transformation into cis-2-oxa-bicyclo[3.3.0]-6,7-dihydroxymethyl-oct-7-ene 4 , a precursor of modified PG's.[3,7] The interest for the cyclopentenetetrol 3 is due also to its easy preparation by $NaBH_4$ reduction of the aglycone of 1 (aucubigenin 2) carried out at first on the isolated aglycone[8] and then directly "one-pot" on the enzymatic (β-glucosidase) hydrolizate of 1[3] ($y_{1\rightarrow 3}$ = 92%).

In this report we describe the conversion of 3 into bis-O-acetylcyclopentenone 9 , a chiral intermediate useful either for syntheses of PG's or of methyl dehydrojasmonate 13 and methyl jasmonate 14 , the latter identified as an insect sex-attractant pheromone[9] or a senescence promoting substance in some plants[10] and both used in perfume industry.[11]

Epoxidation of 3 with m-chloro perbenzoic acid in EtOH (12 h at r.t.) proceeded in a stereoselective way affording only the epoxide 5[12] with the oxirane ring in β configuration. This result was in agreement with the well known syn orienting effect[13] exerted by the allylic hydroxyl function in the epoxidation of 1-hydroxy-2-cyclopentenes. $LiAlH_4$ reduction of acetylepoxy derivative 6[14] in anhydrous DME afforded the cyclopentanepentol 7[15] (68% overall yield from 3), whose vic-diol function was

successively oxidized ($NaIO_4$) to give the β-hydroxy cyclopentanone derivative 8 (y = 48%).

In spite of literature data[16] describing the great tendence of similar cyclic β-ketols to be dehydrated to the corresponding enones by acid or basic catalysis, 8 resulted in rather stable compound under these conditions and the dehydration to the enone system was achieved only under acetylation conditions which transformed 8 into the acetylenone 9[17] (y = 61%).

This readily available cyclopentenone may be considered a useful chiral intermediate for the synthesis of jasmonate-type compounds and PG's.

In fact 9 can be easily converted, by routine methodologies, into diesters 11 and 12, in their turn reported precursors[18,19] of methyl jasmonate 14 and methyl dehydrojasmonate 13 respectively, through known and well established chemistry (C-alkylation of β-ketoester function with 2-pentynyl bromide followed by cis-hydrogenation of triple bond by Lindlar[19] or palladium-on-barium sulfate[18] catalyst and final acid-catalyzed decarboxylation[19] providing the thermodynamically stable trans isomer).

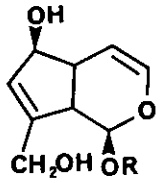
On the other side the Corey lactone analogue 15 should be obtained from γ,δ unsaturated carboxylic acid 10[20] by direct lactonization[21] or through iodolactonization procedure.[22]

Various attempts to obtain 7 (or its epimer at C-4) directly from 3 by Markownikoff hydration of double bond through classical oxymercuration-demercuration (OM-DM) procedure[23] (mercuric acetate in H_2O-THF) were unsuccessful.

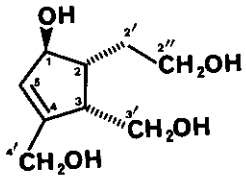
The lack of reactivity of 3 was absolutely unpredictable as OM-DM of trisubstituted cyclopentene double bonds (e.g. 2,4,5-trimethylcyclopentene[24] and 3-methyl-cis-bicyclo[3.3.0]oct-2-ene[25]) or of acyclic allylic alcohols[26] were described to give the expected hydration products.

This failure however could hide a positive aspect. In fact if the cyclopentene allylic 1,4-diol system of 3 would retain its unreactivity towards OM-DM also in the parent iridoid 1 , it could be possible to guess a chemoselective OM-DM reaction of the only enol-ether double bond of aucubin 1 , with results of predictable practical interest.

We are investigating at present the OM-DM reaction of 1 and the first results will be next published.



1 R= β-D-Gluc
2 R= H



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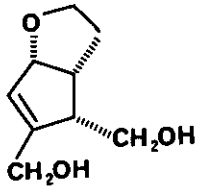

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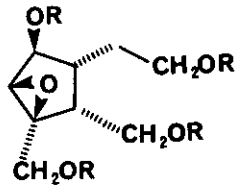
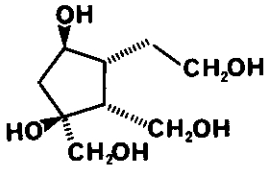


5 R = H
6 R = Ac



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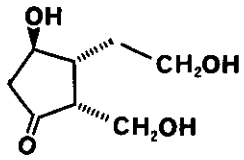

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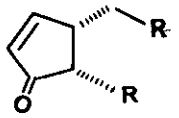
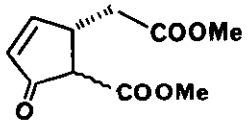


9 R=CH_2OAc
10 R=COOH



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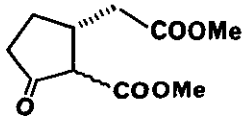

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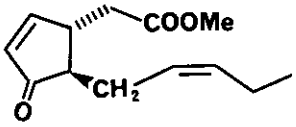

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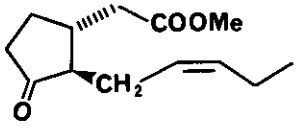

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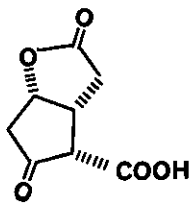

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14. ^{1}H-nmr (300 MHz, $CDCl_3$): δ 4.91 (d, 1H, H-1, $J_{1,5}$= 9.0 Hz), 4.51 (d, 1H, H_A-4', J_{AB}= 12.0 Hz), 4.21 (octet, 2H, 2H-3', AB part of an ABX), 4.06 (d, 1H, H_B-4', J_{AB}= 12.0 Hz), 4.03 (dt, 2H, 2H-2"), 3.69 (s, 1H, H-5), 2.63 (d, 1H, H-3),2.20 (m, 1H, H-2), 2.10-2.03 (12H, 4 AcO signals), 1.69 (q, 2H, 2H-2', J = 9.0 Hz); ^{13}C-nmr (75 MHz, $CDCl_3$): δ 78.51 (d, C-1), 70.40 (s, C-4), 62.70 (d, C-5),62.50 (t, C-4'), 60.20 (t, C-2"), 59.37 (t, C-3'), 39.62 (d, C-3), 36.43 (d, C-2), 26.64 (t, C-2'); AcO signals: 171.20, 170.79, 170.30 (C=O) and 20.97, 20.61 (CH_3).
15. ^{1}H-nmr (300 MHz, D_2O): δ 3.91 (sextet, 1H, H-1, J = 3.6 Hz), 3.65-3.40 (m, 6H, 2H-2", 2H-3', 2H-4'), 2.26 (p, 1H, H-2, J = 6.9 Hz), 2.16 (dd, 1H, H_B-5, J_{AB}= 15.0 Hz, $J_{1,5B}$= 8.4 Hz), 2.05 (bq, 1H, H-3), 1.59 (m, 2H, 2H-2'), 1.43 (dd,

1H,H_A-5, J_{AB}= 15.0 Hz, $J_{1,5A}$ = 4.5 Hz); ^{13}C-nmr (75 MHz, D_2O): δ 83.02 (s, C-4), 76.67 (d, C-1), 66.71 (t, C-4'), 61.73 (t, C-2"), 58.53 (t, C-3'), 52.25 (d, C-3), 45.91 (d, C-2), 44.25 (t, C-5), 31.34 (t, C-2').

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17. ^{1}H-nmr (300 MHz, $CDCl_3$): δ 7.66 (dd, 1H, H-1, $J_{1,5}$ = 6.3 Hz, $J_{1,2}$ = 2.4 Hz),6.23 (dd, 1H, H-5), 4.2-3.8 (m, 4H, 2H-2", 2H-3'), 2.91 (t, 1H, H-2), 2.34 (m, 1H, H-3), 2.00-1.75 (m, 2H, 2H-2'), 2.04 and 2.03 (6H, 2 AcO signals); ^{13}C-nmr (75 MHz, $CDCl_3$): δ 207.13 (s, C-4), 166.41 (d, C-1), 133.57 (d, C-5), 63.04(t,C-3'), 62.35 (t, C-2"), 50.82 (d, C-3), 42.76 (d, C-2), 32.81 (t, C-2'); AcO signals: 170.88, 170.83 (C=O) and 20.94, 20.75 (CH_3).
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