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AN EFFICIENT SYNTHESIS OF 13(S)-HYDROXY-9Z,11E-OCTADECADIENOIC (CORIOLIC) ACID.

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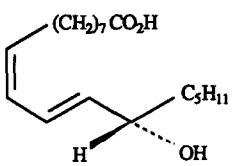
Abstract : *An efficient and highly selective total synthesis of 13(S)-hydroxy-9Z,11E octadecadienoic (coriolic) acid is described, starting from an optically active lactol easily available through an enantioselective enzymatic hydrolysis.*

(+)-Coriolic acid **1** [13(S)-hydroxy-9Z,11E octadecadienoic acid or 13(S)-HODE], a metabolite of linoleic acid, has been isolated from a resistant cultivar of rice plant and has been shown to play a role as a self defensive substance against the rice blast disease [1]. Furthermore during the last four years a number of interesting biological properties of this metabolite have been reported in the literature and recent studies indicate that 13-HODE may be involved in modulating cellular functions. In particular it has been found that the intracellular level of 13-HODE is associated with limited (or no) adhesive interactions between platelets, leukocytes or malignant cells and endothelial cells [2]. Thus, this acid may have significant effects on the adhesive events involved in the pathogenesis of thrombosis, inflammation and metastasis [3].

Synthetic approaches to coriolic acid as well as analogs were required in order to further evaluate their biological properties and several total syntheses have been described in the literature either in racemic [4] or optically active [5] form. We report here a flexible and highly selective route to (+)-coriolic acid **1**, starting from the chiral lactol **2**, available in two steps from the hemiester obtained by an enantioselective enzymatic (pig liver esterase) hydrolysis [6] of the exo adduct of furan and dimethyl maleate.



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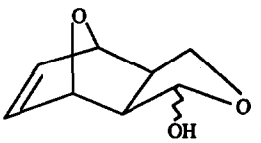

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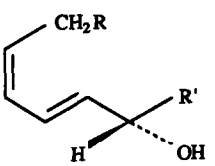

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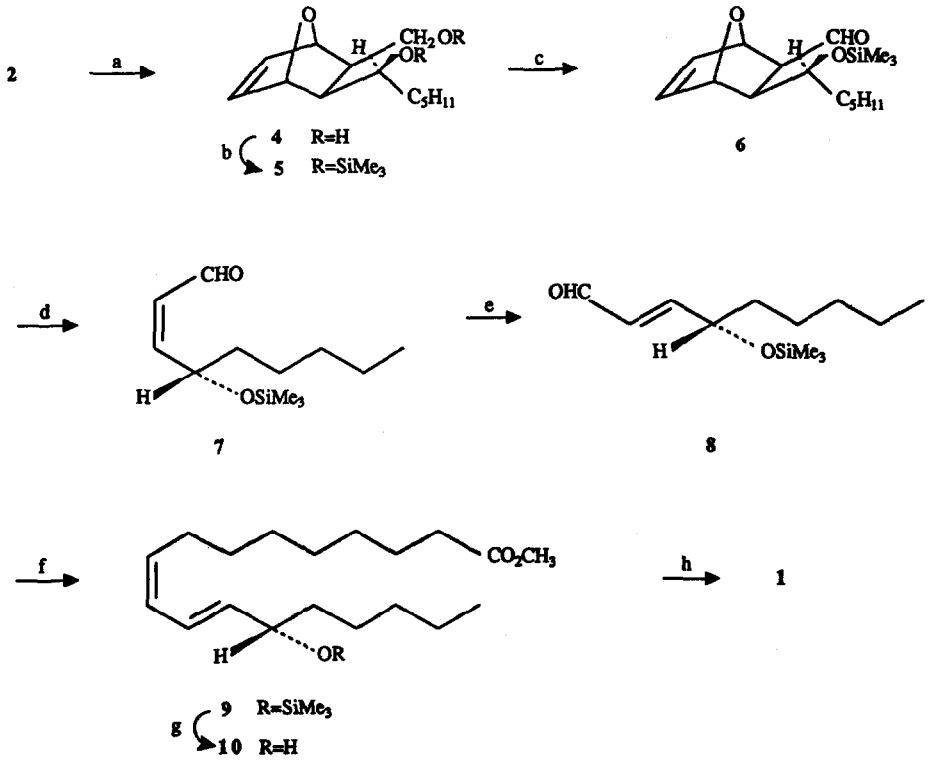
We have recently described a general route to dienols of type **3** [7], starting from the lactol **2**, but this method seems difficult to apply to compounds **3** where R is a saturated chain. We have now developed,

starting from the same material 2, a different approach to these molecules which is illustrated by the synthesis of (+)-coriolic acid. This synthesis is outlined in scheme 1.



a : $C_5H_{11}MgBr$, ZnI_2 , THF , 88% (70% after recrystallisation); b : $SiMe_3Cl$, $(SiMe_3)_2NH$, CH_2Cl_2 , 87%;

c : CrO_3 , pyridin , CH_2Cl_2 , 64% ; d : Toluene , 90°C , 30 min. , 81% ; e : I_2 / toluene (10^{-2} M) , hv , 10 min.

81% ; f : $Br^- Ph_3 P^+(CH_2)_8 COOMe$ (2 eq.) , NaN ($SiMe_3$)$_2$ (1.8 eq.) ,THF / HMPA (4/1) , -78°C to 20°C ,

79% ; g : nBu_4NF , THF , R.T. 10 min. ,83% ; h : Ref. 5f .

Scheme 1

Addition of pentylmagnesium bromide to the lactol 2 in the presence of ZnI_2 (1 equivalent) gave stereoselectively (19/1) the diol unlike 4 arising from an approach of the organometallic reagent on the Si face of the carbonyl group, corresponding to the less hindered face of a tridentate chelate [8]. The two diastereoisomers could not be well separated by liquid chromatography but fortunately the minor isomer could be easily removed by a single recrystallisation in hexane. The two hydroxy groups of the diol 4 ($[\alpha]_D^{20}$ = -13°, c = 1.05, $CHCl_3$) were then protected by reaction with trimethylsilylchloride and hexamethyldisilazane in methylene chloride [9]. The resulting bis-(trimethylsilyloxy) compound 5

($[\alpha]_D^{20}$ = -53° ; c = 1.15, $CHCl_3$), derived from a diol containing a primary and a secondary hydroxy groups, was then selectively oxydized [10] by Collins reagent to the corresponding trimethylsilyloxy aldehyde **6** ($[\alpha]_D^{20}$ = -99° ; c = 0.9, $CHCl_3$). No trace of products arising from an oxidation of the secondary hydroxy group could be detected. The double bond was regenerated by a thermal cycloreversion which in this case took place in very mild conditions. The reaction was total after heating during 30 minutes a toluenic solution of **6** at 90°C and led to the (Z)-aldehyde **7** with an excellent yield. Isomerization to the key (E)-aldehyde **8** [11] was completed by a short exposure (10 minutes) of a toluenic solution of **7** containing a catalytic amount of iodine, to a "Sylvania DXX" U.V. lamp [12]. Wittig condensation of **8** with the ylide derived from 8-carboxymethyl octyltriphenylphosphonium bromide [13] gave with very high stereoselectivity the (E,Z)-diene **9** [14] (E,Z stereoisomeric purity ≥ 98% as shown by 250 MHz ^1H NMR). Desilylation of **9** using standard conditions (nBu_4NF, THF) afforded (+) methyl coriolate **10** ($[\alpha]_D^{20}$ =+7.0° ; c = 0.98, $CHCl_3$; lit. [5d] : $[\alpha]_D^{25}$ = 6.5°, c = 0.70, $CHCl_3$) of excellent enantiomeric purity (≥ 95%) as shown either by its optical rotation or by ^1H NMR in the presence of the chemical shift reagent $Eu(hfc)_3$ [15]. The saponification leading to coriolic acid **1** has already been described [5f].

In conclusion this flexible and highly selective route compares well with reported syntheses and will be applied to the syntheses of some analogs of coriolic acid.

References and notes

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11) **7** : $[\alpha]_D^{20}$ = +14.8° (c = 0.95, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ (ppm) 0.12 (9H, s, $Si(CH_3)_3$) ; 0.90 (3H, broad t, CH_3) ; 1.2 - 1.7 (8H, m, $(CH_2)_4$) ; 4.94 (1H, m, H_4) ; 5.91 (1H, dd, J = 8, 11.5 Hz, H_2) ; 6.50 (1H, dd, J = 11.5, 8 Hz, H_2) ; 10.15 (1H, d, J = 8 Hz, H_1).
8 : $[\alpha]_D^{20}$ = +7.6° (c = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ (ppm) 0.13 (9H, s, $Si(CH_3)_3$) ; 0.90 (3H, broadt,CH_3) ; 1.2 - 1.6 (8H, m, $(CH_2)_4$) ; 4.37 (1H, m, H_4) ; 6.25 (1H, dd, J = 15.5, 8 Hz, H_2) ; 6.80 (1H, dd, J = 15.5, 4 Hz, H_3) ; 9.55 (1H, d, J = 8 Hz, H_1).

12) The transformation **6** → **8** could be effected in one pot with 73% overall yield.

13) The phosphonium salt was prepared from 9-bromononanol following the scheme :

$$Br(CH_2)_9OH \xrightarrow[2\text{- } Br_2, MeOH]{1\text{- Swern}} Br(CH_2)_8COOMe \xrightarrow[CH_3CN]{PPh_3} Br^- Ph_3P^+(CH_2)_8COOMe$$

14) **9** : $[\alpha]_D^{20}$ = +1.9° (c = 0.95, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ (ppm) 0.11 (9H, s, $Si(CH_3)_3$) ; 0.90 (3H, broad t, CH_3) ; 1.2 - 1.7 (18H, m) ; 2.17 (2H, m, $\underline{CH_2}$-CH=CH) ; 2.30 (2H, t, J = 7 Hz, $\underline{CH_2}$-CO_2CH_3) ; 3.68 (3H, s, CO_2CH_3) ; 4.12 (1H, m, H_{13}) ; 5.40 (1H, dt, J = 11, 8 Hz, H_9) ; 5.61 (1H, dd, J = 15,7 Hz, H_{12}) ; 5.96 (1H, dd, J = 11, 11 Hz, H_{10}) ; 6.40 (1H, dd, J = 15, 11 Hz, H_{11}).

15) For a ratio Eu(hfc)3/**10** = 0.7, the signals due to the $\underline{OH}$ and the H_{10} protons of the racemic compound are clearly splitted. Only one set of signals is obtained for the same protons of the optically active ester **10**.

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