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SORBIC ACID IRON TRICARBONYL COMPLEX AS RESOLVING AGENT. CHIRAL SYNTHESES OF 4-HYDROXY NONENAL AND CORIOLIC ACID.

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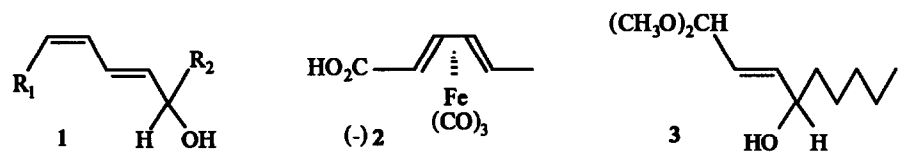
Abstract - The chiral iron tricarbonyl complex of sorbic acid 2 is an efficient resolving agent for allylic alcohol 3, which is a key intermediate in the preparation of most of the lipoxygenation products in n-6 position of polyunsaturated fatty acids. The synthesis of 4-hydroxy nonenal and methyl coriolate, in both enantiomeric forms, illustrates the potential of the method.

The E,Z dienol structure 1 is a common component of most of the lipoxygenation products of polyunsaturated fatty acids, including HETEs, leukotrienes and lipoxins [2]. Due to the potent biological properties of these derivatives, their preparation, *in both optically active forms*, is of much current interest. The commonly used strategy towards type 1 compounds involves, firstly, control of the absolute configuration at the carbon atom bearing the secondary alcohol function, starting from an appropriate molecule from the "chiral pool", and, then, introduction of the required chains [3]. Another possibility involves the preparation of type 1 compounds in racemic form followed by a resolution. This approach has not been much used [4] except for the preparation of 5-HETE [5]. It would, however, be of interest provided that a short and efficient synthesis of racemic 1 could be achieved together with effective methods for resolution. Using this route directly provides both enantiomers which are usually required for biological testing.

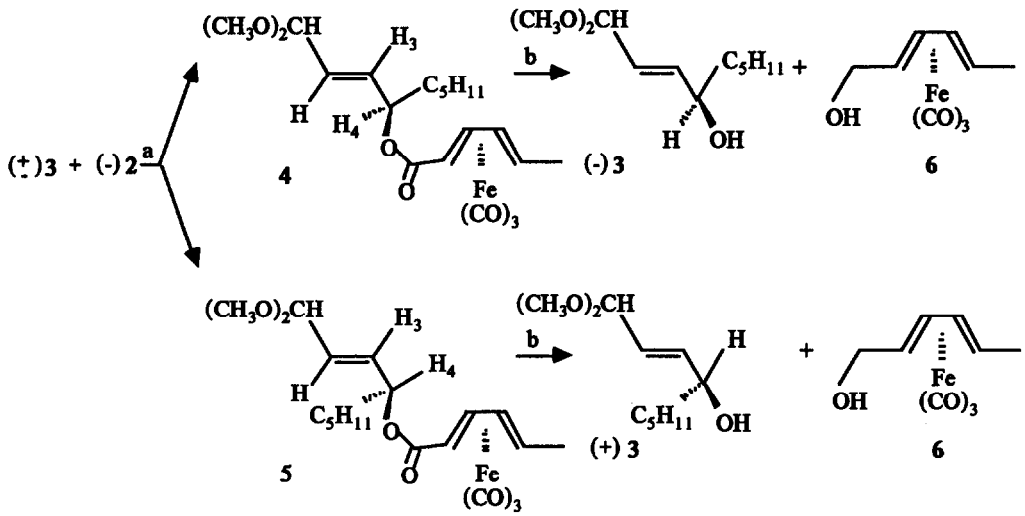


1 (-) 2 3

The purpose of this letter is to show first that the chiral complex of sorbic acid 2 is an efficient resolving agent for alcohol 3 and, second, that this compound is a key intermediate in the synthesis, in chiral form, of 4-hydroxy nonenal 7, methyl coriolate 9b and its tetranor derivative 10b.

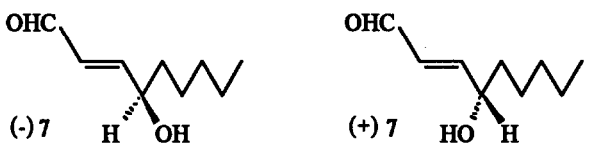
1 - Resolution of alcohol 3. Preparation of both enantiomers of 4-hydroxy nonenal.

The resolution of complex (±) 2 has already been described, [6] as well as an NMR method for checking its optical purity [7]. Racemic alcohol (±) 3 is very easily accessible in 84 % yield from fumaraldehyde monodimethyl acetal [8]. Coupling of (±) 3 with optically pure acid (-) 2 gives a 1/1 mixture of esters 4 and 5 (92 % overall yield) which are separated by chromatography [9]. Dibal reduction [10] of 4 leads to (-) 3 (92 % yield) and 6 which are separated by chromatography. The R absolute configuration of (-) 3 is established by correlation with 13(R) methyl coriolate as described later. The S enantiomer (+) 3 is obtained in a similar manner starting from 5.



a) (±) 3 (6.8 mmoles), (-) 2 (1.75 eq), DCC (2.25 eq), pyrrolidino-4 pyridine (0.5 eq), CH_2Cl_2 (110 mL), R.T., 24 hours, 92 % (overall yield) ; b) 4 (3.13 mmoles), Dibal (2 eq.), Et_2O (31 mL), - 80°C to 0°C, 2 hours, 92 %.

4(R) Hydroxy nonenal (-) 7 and its 4(S) enantiomer (+) 7 [11] have been obtained by desacetalisation (90 %) of (-) 3 and (+) 3. Their optical purity (≥ 95 %) has been established by NMR using diastereoisomeric imidazolidines formation as recently described [12] ; it establishes that the derivative previously isolated from algae [13] (with $[\alpha]_D = 0°$) was racemic. Furthermore, this will allow to study for the first time the influence of the absolute configuration at the C_4 carbon on the properties of this biologically very active compound [14].

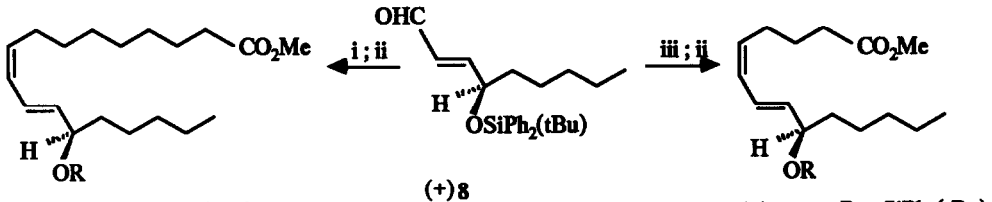


2 - Synthesis of 13(R) and 13(S) methyl coriolate and their tetranor derivatives.

The key 4(R) enal (+) 8 is prepared in two steps from (-) 3 : protection of the alcohol function followed by desacetalisation gives (+) 8 in a 83 % overall yield [15]. Wittig reaction using the phosphonium salt obtained from 9-bromo-methyl nonanoate gives (+) **9a** (78 % yield ; E,Z stereoisomeric purity ≥ 97 % by NMR). Desilylation (86 %) yields 13 (R) methyl coriolate (-) **9b**. Its optical purity (≥ 95 %) is established by NMR using $Eu(tfc)_3$ [16] and absolute configuration by comparison with literature data [17] [18].

A similar sequence of reactions is used for the preparation of the tetranor derivative (-) **10b** [19], whose acid is a known metabolite of coriolic acid [20]. The optical purity of **10b** (≥ 95 %) is also established by NMR [21].

The 13(S) methyl coriolate, as well as its tetranor derivative, have been prepared in the same way starting from (-) 8. Results of the biological tests on these molecules will be reported in due course.



(+) 8

(+) **9a** : R = $SiPh_2(tBu)$
(-) **9b** : R = H

(+) **10a** : R = $SiPh_2(tBu)$
(-) **10b** : R = H

i) (+) **8** (0.45 mmole), Br⁻, $Ph_3P^+(CH_2)_8CO_2Me$ (1.4 eq.), $LiN(TMS)_2$ (1.3 eq), THF/HMPA (8/1, 18 mL), - 80°C 1 hour then -15°C 1 hour, 86 % ; ii) $nBu_4NF, 3H_2O$ (2 eq.), THF (7 mL), R.T, 8 hours, 86 % ; iii) (+) **8** (0.48 mmole), Br⁻, $Ph_3P^+(CH_2)_4CO_2H$ (2 eq.), $LiN(TMS)_2$ (4 eq.), THF/HMPA (8/1, 16 mL), -80°C 1 hour then -15°C 1 hour, then addition of Me_2SO_4 (5 eq.) and Na_2CO_3 (3 eq.), 86 %.

It is interesting to point out that **8** is a key intermediate, not only for the preparation of **9** and **10**, but also for most of the lipoxygenation products in the n-6 position of polyunsaturated fatty acids and such syntheses are under study in the laboratory. Other uses of (-) **2** as a resolving agent are also currently being investigated.

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(9) **4** : ^1H NMR (300 MHz ; $CDCl_3$; δ) : 5.82 (ddd ; J = 15.8, 5.8, 1.1 ; H_3) ; 5.78 (dd ; J = 8.1, 4.7 ; H_{11}) ; 5.64 (ddd ; J = 15.8, 4.4, 1.1 ; H_2) ; 5.25 (broad q ; J ~ 6 ; H_4) ; 5.25 to 5.18 (m ; H_{12}) ; 4.81 (d ; J = 4.4 ; H_1) ; 3.32 (s ; 3H ; OCH_3) ; 3.31 (s ; 3H ; OCH_3) ; 1.65 to 1.20 (m ; 9H ; H_5 ; H_6 ; H_7 ; H_8 ; H_{13}) ; 1.46 (s ; 3H ; H_{14}) ; 1.01 (dd ; J = 8.1, 1.0 ; H_{10}) ; 0.86 (t ; 3H ; J = 6.9 ; H_9).

IR (film ; ν cm^{-1}) : 2960, 2940 and 2860 (CH) ; 2050 and 1985 (C = O) ; 1710 (C = O).

TLC : SiO_2 ; ether-petroleum ether (1 : 1) Rf = 0.77. $[\alpha]^{25}_D$ = -104° (c = 0.22 ; acetone).

5 : ^{1}H NMR (300 MHz ; $CDCl_3$; δ) : 5.81 (ddd ; J = 15.8, 6.2, 1.1 ; H_3) ; 5.76 (dd ; J = 8.1, 5.0 ; H_{11}) ; 5.61 (ddd ; J = 15.8, 4.4, 1.1 ; H_2) ; 5.28 (broad q ; J ~ 6 ; H_4) ; 5.25 to 5.18 (m ; H_{12}) ; 4.78 (d ; J = 4.4 ; H_1) ; 3.30 (s ; 3H ; OCH_3) ; 3.29 (s ; 3H ; OCH_3) ; 1.70 to 1.25 (m ; 9H ; H_5 ; H_6 ; H_7 ; H_8 ; H_{13}) ; 1.46 (s ; 3H ; H_{14}) ; 1.00 (dd ; J = 8.1, 1.0 ; H_{10}) ; 0.90 (t ; 3H ; J = 6.9 ; H_9).

IR (film ; ν cm^{-1}) : 2960, 2940 and 2860 (CH) ; 2050 and 1985 (C = O) ; 1710 (C = O).

TLC : SiO_2 ; ether-petroleum ether (1 : 1) Rf = 0.66. $[\alpha]^{25}_D$ = -98° (c = 0.17 ; acetone).

(10) Saponification of **4** or **5** was unsuccessful : either recovery of the starting material or its decomposition were observed.

(11) (-) **7** : $[\alpha]^{25}_D$ = - 46° (c = 0.45, $CHCl_3$) ; (+) **7** : $[\alpha]^{25}_D$ = + 48° (c = 0.69, $CHCl_3$).

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(14) See for instance "Aldehydes in biological systems" E. SCHAUENSTEIN, H. ESTERBAUER, H. ZOLLNER Ed., Pion Ltd, London, 1977, p. 35-102 and references therein.

(15) **8** : ^{1}H NMR (90 MHz ; $CDCl_3$; δ) : 9.44 (d ; J = 7.8 ; H_1) ; 7.95 to 7.30 (m ; 10H ; C_6H_5) ; 6.70 (dd ; J = 15.5, 5.0 ; H_3) ; 6.15 (ddd ; J = 15.5, 7.8, 1.2 ; H_2) ; 4.50 (broad q ; J = 6.4 ; H_4) ; 2.00 to 1.30 (m ; 8H ; H_5 ; H_6 ; H_7 ; H_8) ; 1.09 [s ; 9H ; $C(CH_3)_3$] ; 0.82 (t ; 3H ; J = 6.8 ; H_9).

IR (film ; ν cm^{-1}) : 3060 and 3040 (aromatic CH) ; 2960, 2940 and 2860 (CH) ; 1675 (C = O) ; 1630 (C = C). TLC : SiO_2 ; ether-petroleum ether (1 : 1) Rf = 0.73.

(+) **8** : $[\alpha]^{25}_D$ = + 20.1° (c = 1.47 ; $CHCl_3$). (-) **8** : $[\alpha]^{25}_D$ = - 18.9° (c = 1.67 ; $CHCl_3$).

(16) Racemic (±) **9b** exhibits a clear splitting of the proton H_{11} (at 6.83 and 6.90 ppm) in the presence of 0.7 eq. of Eu(tfc)$_3$. No splitting is observed, under the same conditions, with (+) **9b** or (-) **9b**.

(17) (-) **9b** : $[\alpha]^{25}_D$ = - 6.7° (c = 0.56, $CHCl_3$) ; (+) **9b** : $[\alpha]^{25}_D$ = + 6.5° (c = 0.70, $CHCl_3$) ; Litt. [18] : $[\alpha]^{25}_D$ = + 6.1° (c = 0.98, $CHCl_3$).

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(19) **10b** : ^{1}H NMR (300 MHz ; $CDCl_3$; δ) : 6.46 (ddd ; J = 15.2, 11.1, 1.1 ; H_7) ; 6.02 (dd ; J = 11.1, 10.7 ; H_6) ; 5.69 (dd ; J = 15.2, 6.8 ; H_8) ; 5.41 (dt ; J = 10.7, 7.6 ; H_5) ; 4.16 (broad q ; J = 6.4 ; H_9) ; 3.67 (s ; 3H ; CO_2CH_3) ; 2.33 (t ; 2H ; J = 7.5 ; H_2) ; 2.22 (broad q ; 2H ; J = 7.6 ; H_4) ; 1.73 (broad p ; 2H ; J = 7.4 ; H_3) ; 1.68 to 1.20 (m ; 8H ; H_{10} ; H_{11} ; H_{12} ; H_{13}) ; 0.89 (t ; 3H ; J = 6.8 ; H_{14}).

IR (film ; ν cm^{-1}) : 3420 (broad ; OH) ; 2960, 2940 and 2860 (CH) ; 1735 (C = O).

TLC : SiO_2 ; ether-petroleum ether (1 : 1) Rf = 0.43.

(-) **10b** : $[\alpha]^{25}_D$ = - 13.9° (c = 0.98 ; $CHCl_3$). (+) **10b** : $[\alpha]^{25}_D$ = + 13.6° (c = 0.75 ; $CHCl_3$).

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(21) Racemic (±) **10b** shows splittings of the proton H_7 (at 7.11 and 7.06 ppm) and of the OCH_3 signals (at 3.96 and 3.95 ppm) in the presence of 0.7 eq. of Eu(tfc)$_3$. No splitting is observed, under the same conditions, with (+) **10b** and (-) **10b**.

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