

A TOTAL SYNTHESIS OF (*E*)-11-HYDROXYUNDEC-2-ENOIC ACID, A NEW HOMOLOGOUS ROYAL JELLY ACID

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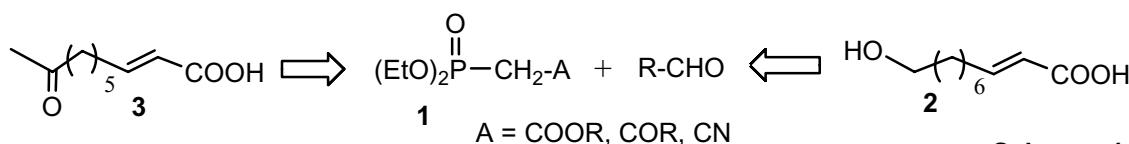
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ABSTRACT : A total synthesis of (*E*)-11-hydroxyundec-2-enoic acid **10**, an homologous of royal jelly acid and queen substance of honey bee was performed using commercially available nonan-1,9-diol. The general strategy including some key steps was based on the Wittig-Horner reaction of triethyl phosphonate in water in the presence of potassium carbonate on the protected 9-hydroxynonanal.

Key words: Wittig-Horner reaction ; (*E*)-11-Hydroxyundec-2-enoic acid ; royal jelly ; honey bee.

In conjunction with our continuing interest in the application of the Wittig-Horner reaction¹⁻⁴ we describe here a total synthesis of (*E*)-11-hydroxyundec-2-enoic acid **10**, an analogous component of royal jelly acid⁵ **2** and a bee pheromone **3**. The reaction was performed under mild conditions, using liquid-liquid media and aqueous potassium carbonate as the base in the absence of phase transfer catalyst. (Scheme 1)



Scheme 1

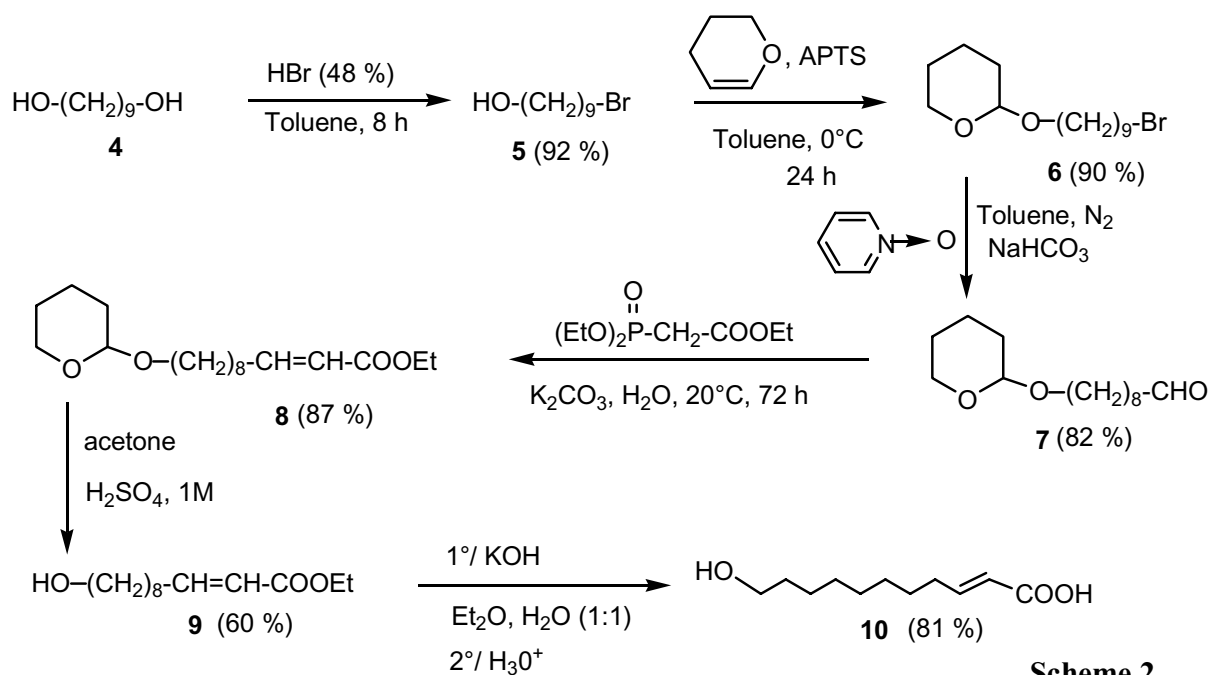
Queen's substance **3** is secreted by the queen honey bee, whereas royal jelly acid **2** is produced by the common honey bee and inhibits ovary developments in the worker bees and queen rearing within the colony⁶. Because of their biological importance, different synthetic strategies toward the synthesis of this class of compounds have been reported. All the proposed approaches require the use of expensive reagents and lengthy strategies^{7,8}. The use of the Wittig-Horner reaction offers many advantages as it reduces the sequence length whilst avoiding the use of high cost protecting groups and the difficult separations which reduce the overall yield.

In these conditions, the phosphonate **1** (A=COOR) mentioned above reacts with simple aldehydes and give rise exclusively to (*E*)-functional alkenes⁹ with a total absence of side products.

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This procedure can be extended to unprotected functional aldehydes (alcohols, phenols, ketones, nitro groups, ...) ¹⁰. In this way, the starting 9-(tetrahydro-2*H*-pyran-2-yloxy)nonanal **7** was synthesized from commercially available 1,9-nonanediol **4** easily converted into 9-bromononan-1-ol **5** in the presence of aqueous hydrobromic acid (48%) in toluene at reflux for 8 h while trapping water formed using a Dean-Stark water separator. The hydroxy group of **5** was protected by converting to the corresponding tetrahydro-2*H*-pyranyl ether **6**. The oxidation of the obtained bromide derivative **6** with pyridine oxide ¹¹ in toluene at reflux for 58 h leads to the enol ether of the fully protected 9-(tetrahydro-2*H*-pyran-2-yloxy)nonanal **7**. In order to optimize the overall yield of these strategies, the Wittig-Horner reaction was performed with 10% excess of triethyl phosphonoacetate at room temperature in water in the presence of K₂CO₃ (2 equiv) as base. The functional α,β -unsaturated ester **8** obtained as pure *E* isomer was extracted with hexane in order to remove the excess of phosphonate then purified on silicagel. The fully protected 11-hydroxy ester **8** was hydrolyzed in acetone with 2N sulfuric acid leading to the corresponding hydroxyl derivative **9** with the total absence of side products. The mixture obtained after alkaline hydrolysis of ester **9** was extracted with diethyl ether to separate any neutral and eventual side products then the aqueous layer was acidified with 2N hydrochloric acid to give yellow crystallized acid **10** in high yield. (Scheme 2)



Scheme 2

In summary, we have developed an elegant synthetic method in six steps sequences of (*E*)-11-hydroxyundec-2-enoic acid **10**, a new homologous acid of the royal jelly acid which could play an important biological role ¹².

Experimental section

Reaction progress and purity of products were monitored by TLC on silica gel plates (Fluka Kieselgel 60F₂₅₄) and Merck silica gel 60 (70-230 mesh) for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Bruker AC-300 (¹H: 300 MHz, ¹³C: 75 MHz) in CDCl₃ solution as solvent with TMS as an internal reference.

Synthesis of 9-bromononan-1-ol **5**

To a solution of nonan-1,9-diol **4** (16 g, 100 mmol) in Toluene (180 mL) were added 22 mL of aqueous hydrobromic acid 48% and the solution was stirred at reflux for 8 h in a Dean-Stark. After cooling, the reaction mixture was diluted with aqueous solution of the NaHCO₃ 10% and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over MgSO₄. After evaporation of the solvent, the residue was purified by column chromatography (petroleum ether/ether: 7/3).

NMR ¹H (300 MHz, CDCl₃): δ 3,65 (t, 2H, CH₂O, *J* = 6,6 Hz); 3,41 (t, 2H, CH₂-Br, *J* = 6,8Hz); 2,0 (s, 1H, -OH); 1,85 (m, 2H, -CH₂CH₂O); 1,60 (m, 2H, -CH₂CH₂O); 1,30 (m, 10H, 5 CH₂). NMR ¹³C (75 MHz, CDCl₃): 25,6; 28,0; 28,5; 29,1; 29,2; 32,6; 32,7; 33,9; 62,7.

Synthesis of 2-(9-bromononyloxy) tetrahydro-2H-pyran **6**

To a stirred solution of 9-bromononal-1-ol **5** (2,52 g, 10,5 mmol) and p-toluene sulfonic acid (APTS) (0,05 g) in dry ether (25 mL) at 0°C under N₂, was slowly added dihydropyran (2 equiv, 1,91 mL, 21 mmol). The reaction mixture was quenched with saturated NaHCO₃ and extracted with ether (4 x 30 mL). The combined organic layers were washed with brine. After drying over MgSO₄, the solvent and DHP were removed under reduced pressure to give crude 2-(9-bromononyloxy)tetrahydro-2H-pyran **6** which was purified by column chromatography filled with silica gel upon elution with petroleum ether/ether: 7/3.

NMR ¹H (300 MHz, CDCl₃): δ 4,57 (m, 1H, O-CHO-); 3,77 (m, 2H, CH₂O); 3,49 (m, 2H, CH₂O-); 3,38 (m, 2H, -CH₂Br); 1,8 (m, 4H, 2 CH₂); 1,78 (m, 6H, 3 CH₂); 1,36 (m, 10H, 5 CH₂). NMR ¹³C (75 MHz, CDCl₃): δ 19,6; 25,3; 26,1; 28,0; 28,6; 29,2; 29,6; 29,6; 30,5; 30,6; 33,8; 62,2; 67,5; 98,7.



Oxidation of 2-(9-bromonyloxy)tetrahydro-2H-pyran : THP-O-(CH₂)₉-Br 6

A 100 mL two-necked round-bottomed flask, fitted with a reflux condenser, magnetic stirring bar and 50 mL pressure-equalising addition funnel, is charged under N₂ with 2-(9-bromonyloxy)tetrahydro-2H-pyran **6** (2,9 g, 9,5 mmol) and NaHCO₃ (2,57 g) in dry toluene (20,6 mL). Pyridine N-oxide (1,81 g, 19 mmol) was added *via* the pressure-equalising dropping funnel. After the addition is complete, the reaction mixture is stirred at reflux for 48 h. The mixture was cooled and quenched with saturated solution of NH₄Cl, then extracted with ether (3 x 40 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. The solvent and pyridine were removed under reduced pressure to give 9-(tetrahydro-2H-pyran-2-yloxy) nonanal **7**.

NMR ¹H (300 MHz, CDCl₃) : δ 9,73 (s, 1H, CHO) ; 4,57 (m, 1H, -O-CH-O-) ; 3,76 (m, 2H, CH₂O) ; 3,44 (m, 2H, CH₂O-) ; 2,39 (m, 2H, -CH₂CHO) ; 1,59 (m, 6H, 3 CH₂) ; 1,36 (m, 12H, 6 CH₂). NMR ¹³C (75 MHz, CDCl₃) : δ 19,7 ; 21,9 ; 25,4 ; 26,1 ; 26,2 ; 29,2 ; 29,6 ; 30,7 ; 34,0 ; 43,8 ; 62,9 ; 67,6 ; 98,8 ; 202,8.

Synthesis de of (E)-ethyl 11-(tetrahydro-2H-pyran-2-yloxy) undec-2-enoate 8

In a 50 mL flask equipped with a magnetic stirrer, was added a solution of potassium carbonate (3,7 g, 27,4 mmol) in water (5 mL) to triethyl phosphonoacetate (2,04 g, 9,11 mmol). After homogenisation, 9-(tetrahydro-2H-pyran-2-yloxy)nonanal **7** (2,8 g, 11,6 mmol) was added and the heterogeneous reaction mixture was stirred for 48 h at room temperature. The mixture was treated with water then extracted with hexane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ether: 8/2).

NMR ¹H (300 MHz, CDCl₃) : δ 6,95 (dt, 1H, CH₂-CH=CH-) ; 5,81 (d, 1H, CH=CH-CO₂Et) ; 4,57 (m, 1H, -O-CH-O-) ; 4,15 (q, 2H, -O-CH₂CH₃) ; 3,76 (m, 2H, CH₂O) ; 3,44 (m, 2H, CH₂O-) ; 1,59 (m, 6H, 3 CH₂) ; 1,36 (m, 17H, 7 CH₂, 1CH₃). NMR ¹³C (75 MHz, CDCl₃) : δ 19,8 ; 25,6 ; 25,9 ; 26,0 ; 26,2 ; 26,3 ; 28,1 ; 28,2 ; 29,1 ; 29,4 ; 29,8 ; 51,5 ; 62,4 ; 67,7 ; 99,0 ; 120,3 ; 129,1 ; 167,3.

Synthesis de of (*E*)-ethyl 11-hydroxyundec-2-enoate 9

In a 50 mL flask equipped with a magnetic stirrer were placed (*E*)-ethyl 11-(tetrahydro-2*H*-pyran-2-yloxy) undec-2-enoate **8** (1,63 g, 5,22 mmol), sulfuric acid 2N (3,9 mL) and acetone (9 mL). The solution was stirred at reflux for 24 h, the mixture was cooled and treated with water then extracted with ether (3 x 30 mL). The organic layer was dried over MgSO₄ then concentrated, the crude product was purified by column chromatography on silica gel (petroleum ether/ether: 7/3).

NMR ¹H (300 MHz, CDCl₃) : δ 6,96 (dt, 1H, CH₂-CH=CH-, *J* = 7,0) ; 5,81 (d, 1H, CH=CH-CO₂Et, *J* = 14,4) ; 3,67 (t, 2H, CH₂-O-) ; 2,20 (q, 2H, -O-CH₂CH₃) ; 1,88 (m, 1H, -O-H) ; 1,55 (m, 2H, -CH₂CH₂-CH=CH-) ; 1,43 (m, 2H, -CH₂-CH₂-CH₂OH) ; 1,36 (m, 15H, 5 CH₂, 1CH₃).

Saponification of ester 7 : preparation of (*E*)-11-hydroxyundec-2-enoic acid 10

To a stirred solution of ethyl 11-hydroxyundec-2-enoic acid (0,7 g, 3,07 mmol) in ethanol (2,3 mL) was added slowly at 0°C a solution of potassium hydroxide (0,31 g) in water (2,3 mL). The reaction was complete as monitored by TLC. The aqueous layer was acidified with concentrated hydrochloric to precipitate the acid **10** and the solid obtained is solubilized in ether then extracted with the same solvent. The removal of solvent under reduced pressure, gave a solid which on purification by column chromatography on silica gel (acetone /hexane: 1/1).

NMR ¹H (300 MHz, CDCl₃) : δ 10,2 (s br, 1H, -CO₂H) ; 7,06 (dt, 1H, CH₂CH=CH-, *J* = 7,0) ; 5,81 (d, 1H, -CH=CH-CO₂H, *J* = 15,1) ; 3,65 (t, 2H, CH₂-O-, *J* = 6, 6) ; 1,88 (m, 1H, -OH) ; 1,55 (m, 2H, -CH₂-CH₂-CH=CH-) ; 1,43 (m, 2H, -CH₂-CH₂-CH₂OH) ; 1,36 (m, 10H, 5 CH₂). NMR ¹³C (75 MHz, CDCl₃) : δ 25,4 ; 29,0 ; 29,1 ; 29,2 ; 29,6 ; 32,2 ; 32,6 ; 62,9 ; 120,7 ; 151,9 ; 171,3.

REFERENCES

1. Rambaud, M. ; Del Vecchio, A. ; Villieras, J. *Synth. Commun.* **1984**, 14833.
2. Villieras, J. ; Rambaud, M. *Synthesis* **1982**, 924 ; **1983**, 300 ; **1984**, 405.
3. Villieras, J. ; Rambaud, M. *C. R. Acad. Sc. Paris, Série II* **1983**, 296, 1175.



4. Villiéras, J. ; Rambaud, M. ; Kirschleger, B. *Phosphorus and Sulfur* **1983**, 14, 385.
5. Bulter, G. G.; *The world of the honey bee* (Collins, London) 1954; *Bee World*, **1950**, 40, 2269.
6. Sannasi, A. ; George, C. J. *Nature* **1972**, 337, 457.
7. a-Hase, T. A. ; Kivikar, R. *Acta Chem. Scand* **1979**, B33, 589.
b-Yokoi, K ; Matsubara, Y. *Nippon Kagaku Kaishi* **1978**, 1415.
c-Tsuji, J. ; Yasuda, H. *J. Organomet. Chem.* **1977**, 131, 133 and references cited therein.
8. a-Trost, B. M. ; Hiroi, K. ; Junheim, L. N. *J. Org. Chem.* **1980**, 45, 1839.
b-Subramaniam, C. S. ; Thomas, P. J. ; Mamdapur, U. R. ; Chadha, M. S. *Indian J. Chem.* **1978**, 16B, 318.
c-Tamaru, Y. ; Yamada, Y. ; Yoshida, Z. *Tetrahedron* **1979**, 35, 329.
d-Trehan, I. R. ; Vig, R. ; Singh, V. ; Sharma, S. ; Kad, G. L. *Indian J. Chem.* **1992**, 31B, 2257.
9. a-Kadogan, J. I. *Organophosphorous reagent in organic synthesis, academic press, New york* **1979**.
b-Bergelson, L. D. ; Vaver, V. A. ; Barsukov, L. L. ; Shemyakin, M. M. *Izv. Akad. Nauk.. SSSR, otd. Khim. Nauk.* **1963**, 1053, C. A. 59, 8783.
c- Bissing, D. E. ; *J. Org. Chem.* **1965**, 30, 1296.
d-Wadsworth, W. S. ; Emmons, D. W. *J. Am. Chem. Soc.* **1961**, 83, 1733.
e-Chiron, R. *J. Chem. Ecology* **1982**, 88, 709 and references cited therein.
f-Bestmann, J. ; kunstmann, R. ; Schulz, H. *Liebigs. Ann. Chem.* **1966**, 33, 699.
g-Tolochko, A. F. ; Dombroskü, A. V. *Ukr. Khim. Zh.* **1965**, 31, 220 ; C.A. **1965**, 63 17227e.
h-Larsen, R. O. ; Aksnes, G. *Phosphorus and Sulfur* **1983**, 15, 229.
10. a-Villiéras, J. ; Rambaud, M. ; Graff, M. *Tetrahedron Lett.* **1985**, 26, 53.
b-Villiéras, J. ; Rambaud, M. ; Graff, M. *Synth. Commun.* **1985**, 15, 569.
11. Kilenyi, S. N. *Comprehensive Organic Synthesis*, Vol. 7, 661.
12. Masato, S. ; Shizuo, N. *Hoshi Yakka Daigaku Kiyo* **1984**, 26, 19.