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SYNTHESIS OF NEW UNSATURATED ESTERS, CATALYSED BY PALLADIUM-PHOSPHINE COMPLEXES

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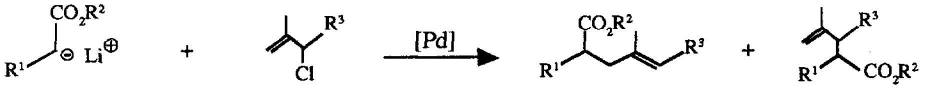
Summary : The palladium-catalysed addition of allylic chlorides to carbonucleophiles leads to the formation of new terpene derivatives. A facile and economical route of phytone is described.

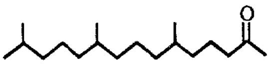
Soluble metal complexes are finding increased use in organic synthesis (1). The palladium (2), molybdenum (3), iron (4), cobalt (4) and nickel (5)-catalysed alkylations of α-dicarbonyl and related compounds with allylic chlorides, alcohols, amines, esters, sulfones, ammonium salts and ethers have been extensively described in the literature (6).

We report the synthesis of new unsaturated esters-catalysed by palladium-phosphine complexes. These esters can be used in the synthesis of phytone which is an important vitamin E intermediate (7). The key steps are the direct introduction of a C_5 unit using the anion α to an ester, and the carbon-carbon bond formation with a high regiochemical control.



The results are summarized in the following Table.

A high selectivity was observed only with the allylic chloride 1 (entries a and b) ; this problem of selectivity (entries d and e) appears to result from a competitive attack of the nucleophile at the two sites of a π-allyl intermediate (8). It would seem that the steric effect of the terpene chain allows a high selectivity for terminal attack. This result was used for the synthesis of phytone 2.



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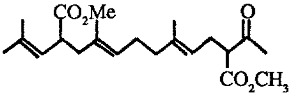
When a mixture 3 and 4 was reacted with methyl acetylacetonate in the presence of the rhodium-hydrosoluble phosphine (tris(sodium 3-sulfophenyl) phosphine) in biphasic system, $(RhCl(COD))_2$/TPPTS /H_2O/CH_3OH/ Na_2CO_3, a very high selectivity was observed. Products 5 and 6 were isolated in 94 % yield from the reaction mixture.



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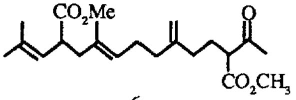

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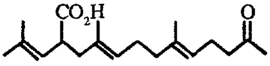
(5 / 6 = 85 / 15, GLC analysis)

This water-soluble composition (Rhodium/TPPTS) selectively catalyses the condensation of isoprene with barbituric acid to yield Isofeprazone (9) and the condensation of 2-methyl-6-methylene-1, 3E, 7-octatriene with methyl acetylacetonate to give terpenoid intermediates useful for the synthesis of pseudoionone (10).

The hydrolysis of the mixture 5 + 6 ($NaOH/H_2O$/1 h , 40°C) gave keto-acids 7 and 8 (95 % yield).



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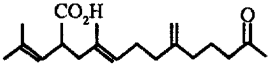

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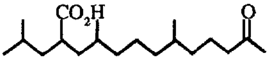
The mixture of 7 and 8 was hydrogenated (Pd – C : 10 % / pentane / hydrogen pressure 100 bar, 12 h , 25°C) ; compound 9 was isolated (98 % yield).



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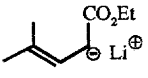
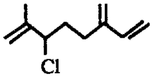
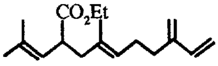
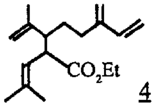
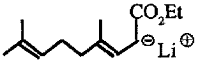
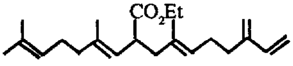
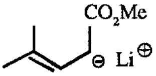
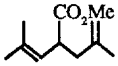
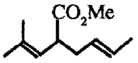
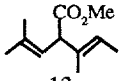
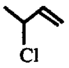
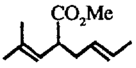
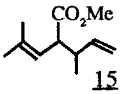
Thermolysis (150°C) of 9 yielded phytone 2 in pure form.
This synthetic methodology is useful for the synthesis of other terpenoids and natural products.

GENERAL PROCEDURE : (entry a) (13)

A mixture of 10 ml dry pentane and 2.07 g (20 mmol) diisopropylamine was cooled at 0°C, 12.5 ml of n-butyl lithium (20 mmol) in hexane (1.6 M) was added. The mixture was stirred during 20 mn at 0°C. After cooling at - 78°C, 2.78 g (20 mmol) of 10 was slowly added. The temperature was maintained at about - 78°C during 20 mn and at 20°C during 1 h.

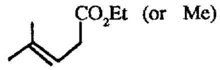
In a second flask under argon, 40 mg (0.1 mmol) of $(C_3H_5PdCl)_2$, 2.30 mg (0.87 mmol) of TPP, 5 ml of dry toluene and 3.5 g (20 mmol) of 1 were added. The first mixture was added slowly (20 mn) to the second flask. The mixture was stirred at 20°C during 2 h. After hydrolysis (HCl, 10 %), the mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo and yielded a yellow oil (5.08 g). Distillation under reduced pressure gives 4.5 g of a mixture 3 and 4 $Eb_{1.4}$ = 111-118°C.

TABLE : Reaction of allylic chlorides and bromides with carbonucleophiles (a).

ENTRY	Nucleophiles (b)	Allylic compounds (c)	Results	Yield (d)	Selectivity (e)
a		 1	 3  4	81,5	3/3 + 4 = 98 %
b		"	 (f)	28	100
c				62	—
d	"		 12  13	61	12/12 + 13 = 67 %
e	"		 14  15	37,5	14/14 + 15 = 64 %

(a) Reactions were carried out using the catalyst system : $(C_3H_5PdCl)_2$ and TPP (triphenylphosphine) in dry toluene at room temperature under argon.

(b) Nucleophiles were prepared by treatment of unsaturated esters 10 and 11 with LDA (lithium diisopropylamide). These esters were prepared in good yield by alcoxycarbonylation of isoprene and myrcene (11).



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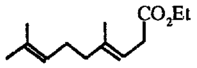

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(c) The allylic chloride 1 was prepared by direct chlorination of myrcene (12).

(d) Isolated yield.
Satisfactory analytical and spectroscopic data were obtained for all new derivatives.

(e) Selectivity : GC

(f) Isolated by preparative HPLC (SiO_2 columm, cyclohexane/dichloromethane).

REFERENCES

(1) S. DAVIES, Organotransition Metal Chemistry : Applications to organic synthesis, Pergamon Press, 1982.
L. HEGEDUS, Applications of organometallic reagents in organic synthesis. Journal of organometallic chemistry library 1,
Edited by D. SEYFERTH, ELSEVIER, 1, (1976), 329.

(2) J. TSUJI, Acc. Chem. Res., 2 (1969) 144 ;
J. TSUJI, M. TAKAHASHI, M. MORIKAWA, Tetrahedron Lett., (1965), 4387.
B. M. TROST, Acc. Chem. Res., 13 (1980) 385.

(3) B. M. TROST, M. LAUTENS, J. Am. Chem. Soc., 104 (1982) 5543.

(4) J. L. ROUSTANT, J. Y. MEROUR, F. HOULIHAN, Tetrahedron Lett., (1979) 3721.

(5) G. CONSIGLIO, F. MORANDINI, O. PICCOLO, J. Am. Chem. Soc., 103 (1981) 1846.

(6) K. E. ATKINS, W. E. WALKER, R. M. MANYIK, Tetrahedron Lett., (1970) 3821.
B. M. TROST, N. R. SCHMUFF, M. J. MILLER, J. Am. Chem. Soc., 102 (1980) 5979.
T. HIRAO, N. YAMADA, Y. OHSHIRO, T. AGAWA, J. Organomet. Chem., 236 (1982) 409.

(7) P. KARRER, H. FRITZCHE, B. RINGIER, H. SALOMON, Helv. Chim. Acta., 21 (1938) 520 and 820.

(8) B. M. TROST, Tetrahedron, 33 (1977) 2615,
B. M. TROST, T. R. VERHOEVEN, J. Org. Chem., 41 (1976) 3215.
B. M. TROST, P. STREGE, L. WEBER, T. FULLERTON, J. Am. Chem. Soc., 100 (1978) 3426.

(9) G. MIGNANI, D. MOREL, Y. COLLEUILLE, Tetrahedron Lett., 26 (1985) 6337.

(10) G. MIGNANI, D. MOREL, Y. COLLEUILLE, Tetrahedron Lett., 27 (1986) 2591.

(11) RHONE-POULENC CHIMIE DE BASE, European patent, 60, 734 (09-22-82).

(12) G. MIGNANI, D. MOREL, P. CHABARDES, RHONE-POULENC SANTE. European patent 145, 554 (06-19-85).

(13) G. MIGNANI, D. MOREL, RHONE-POULENC SANTE. European patent 145, 555 (06-19-85).

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