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A chemoselective and regioselective catalytic way to a novel nine-membered lactone

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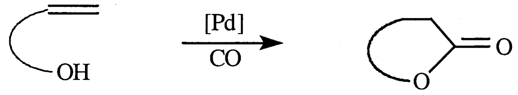
Abstract—Cyclocarbonylation of dihydromyrcenol into the corresponding lactone can be selectively performed in the presence of $PdCl_2(PPh_3)_2$/$SnCl_2 \cdot 2H_2O$ and 4 Å molecular sieves. © 2001 Elsevier Science Ltd. All rights reserved.

Lactones play an important role in organic synthesis because they give an elegant access to other functionalities and have themselves a number of biological properties.[1] They can be prepared by carbonylation of unsaturated alcohols provided the carbon chain between the alkene and OH function are not too short (Scheme 1); most of the catalysts include palladium complexes generally used under moderated to high CO pressures.[2]

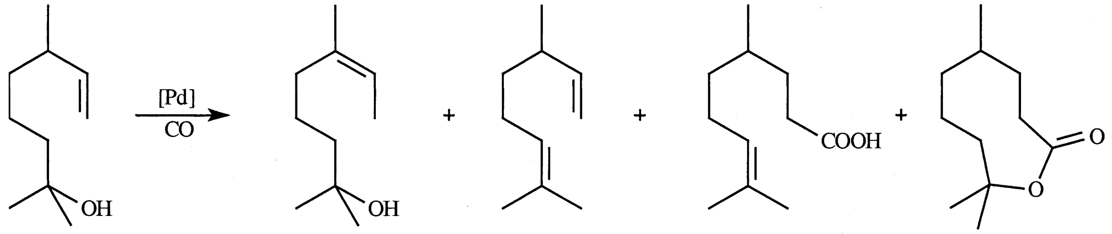
We were interested in the preparation of large ring lactones and we chose dihydromyrcenol **1** as a representative substrate for its selective carbonylation into the corresponding nine-membered lactone. In addition to this product we have summarized in Scheme 2 all the products which can be expected from the reaction either by isomerization or by carbonylation of dimethyloctadiene **3** which results from dehydration of **1**.



Scheme 1.

In a typical run we have introduced $[PdCl_2(PPh_3)_2]$ as a catalyst precursor, $SnCl_2 \cdot 2H_2O$ as a promoter, 2 equiv. of extra triphenylphosphine in order to maintain a [P]/[Pd] molar ratio of 4, 40 bar CO pressure, 75°C and a duration of 16 h.[3] Table 1 displays the main results obtained during this study.[4] In run 1, for a [substrate]/[Pd] ratio of 50, a yield of 94% was observed.

Traces of isomer **2** resulting from the migration of the terminal carbon–carbon double bond toward an inter-



1 2 3 4 5

Scheme 2.

Keywords: cyclocarbonylation; lactone; homogeneous catalysis; palladium.

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Table 1. Reactions of carbonylation of dihydromyrcenol

Run	S/C	P (bar)	Time (h)	Conversion (%)	Yield (%)			
					2	**3**	**4**	**5**
1	50	40	16	94	n.d.	33 (35)[a]	60 (64)[a]	–
2	100	40	16	43	n.d.	5 (12)[a]	25 (59)[a]	12 (28)[a]
3	50	40	40	100	–	20	80	–
4	100	40	40	100	–	20	78	2
5	50	100	16	100	n.d.	9	90	–
6	100	100	16	100	–	8	92	–
7	150	100	16	100	–	6	89	5

Conditions: catalytic precursor = 1 mmol, excess of diphosphine = 1 mmol, $SnCl_2{\cdot}2H_2O$ = 2.5 mmol, toluene = 25 mL, T = 75°C, n.d. = not determined.

[a] Selectivity (%).

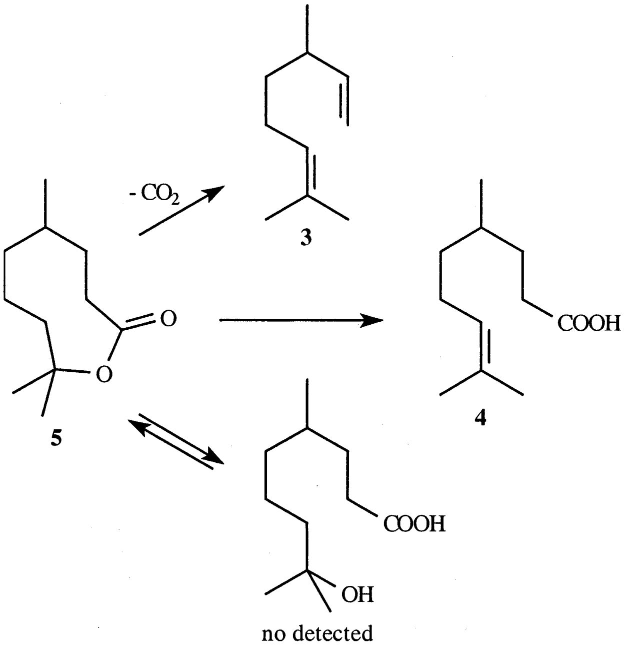
nal position (only one isomer has been represented in Scheme 4) were detected. Dehydration of **1** occurred to produce **3** containing two carbon–carbon double bonds lying in various positions. The main product is the terminal carboxylic acid **4** which corresponds exclusively to the hydroxycarbonylation of the less hindered carbon–carbon bond. As abundant quantities of **3** are obtained we suspect that **4** results directly from **3** and not from the dehydration of the carbonylated product of **1** which has been detected.

When twice the quantity of dihydromyrcenol was introduced (run 2) to reach a molar substrate/catalyst ratio, the reaction proceeded faster at the beginning so that 12% of lactone **5** was obtained, thus with a selectivity of 28%, beside **3** and **4** (12 and 59% selectivity, respectively). Increasing the duration of the experiments to 40 h, as in runs 3 and 4, shows that compound **4** is significantly more abundant, and should also be perhaps formed from the lactone **5**.

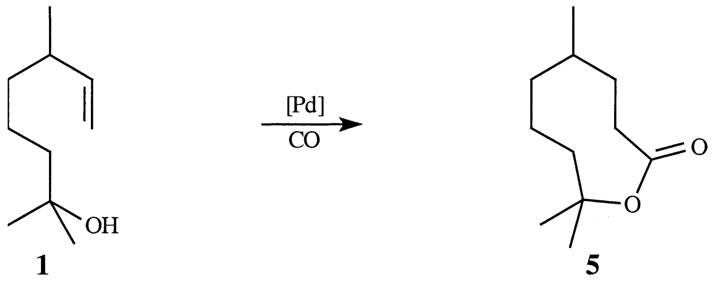
Scheme 3 shows that opening the lactone provides directly the unsaturated carboxylic acid **4** and can, by decarboxylation, restore the dehydrated product **3**. These observations were confirmed by working at 100 bar (runs 5–7), where the reaction proceeds faster since the substrate is fully transformed in 16 h; for a ratio [S]/[C] = 150 a low yield of lactone was obtained, whereas in a lower lactone **5**/acid **4** ratio. Thus, we consider that lactone **5** is formed by carbonylation of dihydromyrcenol in the early stages of the reaction, and that in a competitive way dehydration occurs directly from the substrate and can be hydroxycarbonylated ($\mathbf{3}+CO/H_2O \rightarrow \mathbf{4}$). A kinetic study in the conditions of run 1 shows clearly that during the first 3 h **3**, **4** and **5** are coproduced in parallel ways, after which time the quantities of lactone begin to decrease.

We have explored various operating conditions to drive the selectivity toward the formation of lactone **5** (Scheme 4).

Addition of trimethylorthoformate to the medium in order to remove water induced 10% selectivity in **5**, but



Scheme 3.



Scheme 4.

Table 2. Reactions of cyclocarbonylation of dihydromyrcenol

Run	Additive	Time (h)	Conversion (%)	Yield (selectivity)			
				2	**3**	**4**	**5**
1	H_2O^a	40	48	–	n.d.	42 (90)	5 (10)
2	$HC(OMe)_3$	40	21	19 (90)	–	–	2 (10)
3	Zeolites	23	56	–	2	n.d.	53 (95)
4	Zeolites	40	60	–	n.d.	–	59 (98)
5^b	Zeolites	16	42	–	n.d.	2	39 (93)

Conditions: catalytic precursor = 1 mmol, excess of diphosphine = 1 mmol, $SnCl_2{\cdot}2H_2O = 2.5$ mmol, toluene = 25 mL, 4 Å molecular sieves = 3 g, $T = 75°C$.

[a] $H_2O = 50$ mmol.

[b] $P = 100$ bar, S/C = 100.

with a low conversion (21%) and 90% of isomerisation (**2**). In contrast, addition of water in order to shift the equilibrium of dehydration of **1** to give **3** still provided 10% of **5** besides 90% of the expected acid **4** (48% of conversion). In addition, to improve the selectivity into lactone **5**, we introduced 4 Å molecular sieves. Anhydrous zeolites added in an excess with regard to the quantities of water which could result from the full dehydration of **1**, led to a moderate conversion of the substrate, but to a quite complete selectivity in lactone (Table 2). For shorter reactions times or at higher pressure (runs 3 and 5, respectively) this selectivity is maintained and only traces of the other products are detected. We interpret these high yields in lactone as being due mainly to the trapping of HCl generated from $PdCl_2L_2/SnCl_2$ when the active hydride species is formed. Simultaneously, the system is completely anhydrous so that in the absence of wet HCl, no dehydration of the tertiary alcohol occurs.[5]

It should be underlined that this carbonylation reaction presents a high level of chemoselectivity to introduce a CO building block in the carbon framework. From a structural point of view, the CO insertion occurs exclusively on the terminal carbon atom of the starting material **1** to give **4** and the lactone **5**. In addition, the presence of a molecular sieve permits an almost full selectivity in the expected lactone.

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References

1. (a) Maurer, B.; Hauser, A. *Chem. Ind. (London)* **1988**, *18*, 587; (b) Tateba, H.; Mihara, S. *Agric. Biol. Chem.* **1990**, *54*, 2271; (c) McNaughton-Smith, G. A.; Taylor, R. J. K. *Tetrahedron* **1996**, *52*, 2113.
2. (a) Alper, H.; Leonard, D. *Tetrahedron Lett.* **1985**, *26*, 5639; (b) Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun.* **1985**, 511; (c) Tamaru, Y.; Mojo, M.; Yoshida, Z. I. *Tetrahedron Lett.* **1987**, *28*, 325; (d) Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135; (e) El Ali, B.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357; (f) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 7471; (g) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1997**, *62*, 4665; (h) Rönn, M.; Andersson, P. G.; Bäckwall, J. E. *Acta Chem. Scand.* **1998**, *52*, 524; (i) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708; (j) El Ali, B.; Alper, H. *Synlett* **2000**, *2*, 161.
3. General procedure: a mixture of 0.702 g (1 mmol) of dichlorobis(triphenylphosphine) palladium(II), 0.474 g (2.5 mmol) of hydrated tin(II) chloride and 0.524 g (2 mmol) of triphenylphosphine was introduced into a 250 mL stainless steel autoclave with mechanical stirring. A dinitrogen-saturated mixture of 15.627 g of dihydromyrcenol (100 mmol) in 25 mL toluene was introduced into the evacuated autoclave by aspiration. It was heated to 70°C under 40 bar of carbon monoxide at constant pressure. After 16 h, the autoclave was cooled and then slowly depressurized. The yellow–orange reaction mixture was analyzed by gas chromatography.
4. GC analyses, performed on a Carlo Erba MFC 500 apparatus equipped with a Econo-Cap FFAP (30 m; 0.53 mm; 1.2 μm) capillary column and a flame ionization detector. Products were identified by GC/MS on a Perkin Elmer QMass 910, with a Crompack CP WAX 52 CB (50 m; 0.32 mm; 0.2 μm) polar column. After the catalytic reaction, organometallic compounds and phosphine excess were separated from the crude solution by adding CCl_4. The deeply colored oily layer was decanted. After concentration by rotary evaporation, the oily residue was purified by column chromatography on silica gel (*n*-heptane:dichloromethane:ethyl acetate, 75:15:10 for **5** and *n*-heptane:dichloromethane:ethyl acetate, 90:5:5 for **4**).
   Spectral data for **4**: IR (KBr): $\nu = 1709$ cm^{-1} (C=O). ^1H NMR (250 MHz, $CDCl_3$): $\delta = 10.79$ (m, 1H, OH), 5.05 (t, $J = 6$ Hz, 1H), 2.31 (m, 2H), 1.95 (m, 1H), 1.64 (s, 3H), 1.57 (s, 3H), 1.5 and 1.1 (m, 6H), 0.86 (d, $J = 6.1$ Hz, 3H). $^{13}C\{^1H\}$ NMR (250 MHz, $CDCl_3$): $\delta = 180.8$, 131.1, 124.4, 36.5, 31.7, 31.2, 25.5, 25.2, 19.0, 14.5. MS (CI) *m*/*z* (rel. int.): 69 ($(CH_3)_2C{=}C{-}CH_2^+$, 1000), 41 ($C_3H_5^+$, 998), 124 (MacLafferty, 29), 185 (M+1, 14). Microanalyses (exp. %; cald %): C (71.9; 71.7), H (11.4; 10.9), O (16.6; 17.4).
   Spectral data for **5**: IR (KBr): $\nu = 1729$ cm^{-1} (C=O). ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.16$ (m, 2H), 1.91 (m, 1H),

1.63–1.49 (m, 6H), 1.35 (s, 6H), 1.16 (m, 2H), 0.80 (d, $J=5.8$ Hz, 3H). $^{13}C\{^1H\}$ NMR (250 MHz, $CDCl_3$): $\delta=173.5$, 82.3, 41.1, 37.0, 33.4, 32.3, 26.1, 21.3, 19.3. MS (CI) m/z (rel. int.): 41 ($C_3H_5^+$, 1000), 43 ($C_3H_7^+$, 335), 97 (M–$C_3H_7^+$, 188), 184 (M, 62), 185 (M+1, 27). Microanalyses (exp. %; cald %): C (70.8; 71.7), H (11.7; 10.9), O (16.5; 17.4).

5. (a) Chenal, T.; Naigre, R.; Ciprés, I.; Kalck, Ph.; Daran, J.-C.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1993**, 747; (b) Kudo, K.; Mitsuhashi, K.; Mori, S.; Komatsu, K.; Sugita, N. *Chem. Lett.* **1993**, 1615; (c) Naigre, R.; Chenal, T.; Ciprés, I.; Kalck, Ph.; Daran, J.-C.; Vaissermann, J. *J. Organomet. Chem.* **1994**, *480*, 91.