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Remote Carbonylation. The Synthesis of δ-Lactones from Saturated Alcohols and Carbon Monoxide

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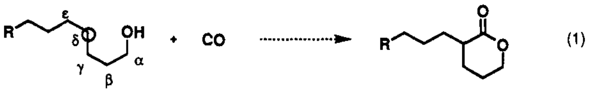
The introduction of carbon monoxide into unactivated hydrocarbons is a challenge of great synthetic importance. Nevertheless, there are very few synthetically useful processes.[1] The synthesis of δ-lactones by the transition-metal-mediated carbonylation of *unsaturated* alcohols with CO is well-known.[2] However, the corresponding synthesis of δ-lactones from *saturated* alcohols and CO has yet to be realized (eq 1). We believed that a free-radical process would be most fruitful for such a synthesis.

Our strategy is as follows: (i) the generation of an oxygen-centered radical **A**; (ii) a 1,5-hydrogen-transfer reaction[3] induced by the radical **A** to create a carbon-centered radical δ to oxygen; (iii) trapping of this radical, **B**, with CO;[4] and finally (iv) oxidation and the cyclization of the resulting radical **C** to yield δ-lactone **2** (Scheme 1). Gratifyingly, the transformation shown in eq 1 was realized by the use of lead tetraacetate (LTA), a well-established one-electron oxidant.[5]



(1)

Scheme 1

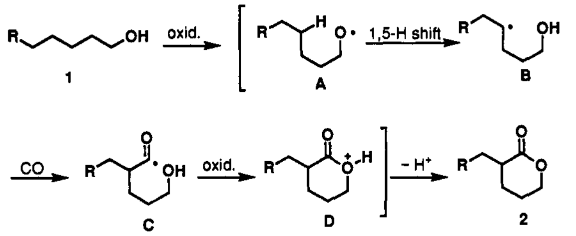
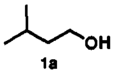
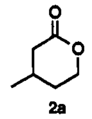
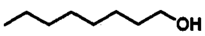
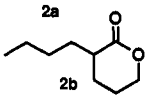
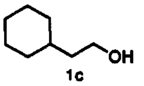
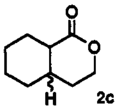
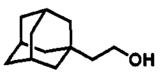
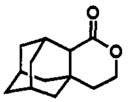
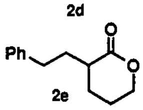
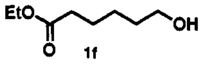
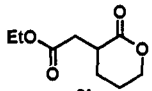
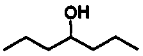
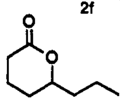
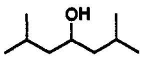
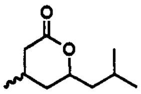
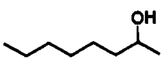
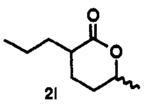
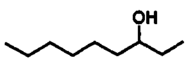
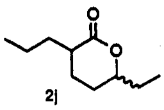


Table 1. Synthesis of δ-Lactones from Saturated Alcohols and CO

alcohol	conditions[a] (temp, time)	product	yield, %[b] (cis/trans)
 1a	60 °C, 2 d	 2a	32
 1b	40 °C, 1 d	 2b	51[c]
 1c	40 °C, 3 d	 2c	58 (44/56)[d]
 1d	40 °C, 3 d	 2d	67
 1e	40 °C, 5 d	 2e	50[c]
 1f	40 °C, 3 d	 2f	38
 1g	60 °C, 3 d	 2g	44
 1h	40 °C, 3 d	 2h	71 (59/41)[d]
 1i	40 °C, 3 d	 2i	57 (55/45)[e]
 1j	40 °C, 3 d	 2j	68 (59/41)[e]

[a] Alcohols (0.4 or 0.8 mmol) were allowed to react with LTA (1.5–2 molar equiv) in C_6H_6 (20 or 40 mL) under 80 kg/cm^2 of CO. See footnote 6. [b] Refers to yield isolated by flash chromatography on silica gel. [c] ε-Lactone was also formed (<5%). [d] Determined by ^{1}H NMR (600 MHz: Bruker AM-600). [e] Determined by GLC.

The first reaction examined was the carbonylation of a linear saturated alcohol, 1-octanol (**1b**). When the reaction of **1b** with CO was carried out in the presence of LTA (1.5 molar equiv) at 40 °C for 24 h ([**1b**] = 0.02 M in benzene, 80 kg/cm^2), the expected δ-lactone, 2-butyl-5-pentanolide (**2b**), was obtained in reasonable yield (63% GC yield, 51% isolated yield) (eq 2). The major byproduct was uncarbonylated 2-butyltetrahydrofuran (13%). Higher concentrations and higher temperatures gave

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(1) Leading references: (a) Sakakura, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1987**, 758. (b) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. (c) Barton, D. H. R.; Csuhai, E.; Doller, D. *Tetrahedron Lett.* **1992**, *33*, 4389. (d) Fujiwara, Y.; Takaki, K.; Watanabe, J.; Uchida, Y.; Taniguchi, H. *Chem. Lett.* **1989**, 1687. (e) Sato, K.; Watanabe, J.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1991**, 1433. (f) Nakata, K.; Watanabe, J.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1991**, 1437. (g) Ferguson, R. R.; Crabtree, R. H. *J. Org. Chem.* **1991**, *56*, 5503. (h) Lin, M.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1992**, 892. (i) Sen, A.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1992**, 508. (j) Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1992**, *114*, 350. (k) Boese, W. T.; Goldman, A. S. *Tetrahedron Lett.* **1992**, *33*, 2119. (l) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; Labounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. Cf.: (m) Souma, Y.; Sano, H. *J. Org. Chem.* **1973**, *38*, 3633.

(2) For selected examples of metal-mediated carbonylation of *unsaturated* alcohols to lead to δ-lactones, see: (a) Murray, T. F.; Varma, V.; Norton, J. R. *J. Org. Chem.* **1978**, *43*, 353. (b) Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun.* **1985**, 511. (c) Chenal, T.; Naigre, R.; Ciprés, I.; Kalck, P.; Daran, J.-C.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1993**, 747.

(3) For leading reviews of 1,5-H shift from C–H to O•, see: (a) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1. (b) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501. (c) Walling, C. *Pure Appl. Chem.* **1967**, *15*, 69. (d) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168. (e) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525. An excellent survey of 1,5-H shifts has been made in a recent paper from Curran's group; see: (f) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

(4) For our recent report on free-radical carbonylation, see: Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187.

(5) For pioneering work on THF formation by oxidative cyclization of alcohols with LTA, see: (a) Cainelli, G.; Mihailović, M. L.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 1124. (b) Mihailović, M. L.; Čeković, Ž.; Maksimović, Z.; Jeremić, D.; Lorenc, L.; Mamuzić, R. I. *Tetrahedron* **1965**, *21*, 2799. Also see leading reviews: (c) Mihailović, M. L.; Čeković, Ž.; Lorenc, L. *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Eds.; Plenum Press: New York, 1986; p 758. (d) Mihailović, M. L.; Čeković, Ž. *Synthesis* **1970**, 209. (e) Rubottom, G. M. *Oxidation in Organic Chemistry*; Academic Press: New York, 1982; Part D, p 2. (f) Rotermund, G. W. *Methoden der Organischen Chemie* (*Houben-Weyl*); Müller, E., Ed.; Georg Thieme: Stuttgart, 1975; Band 4, Teil 1b, Oxidation II, p 204. (g) Reference 3e.

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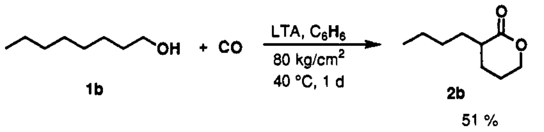
inferior results, with increased amounts of uncarbonylated product observed.

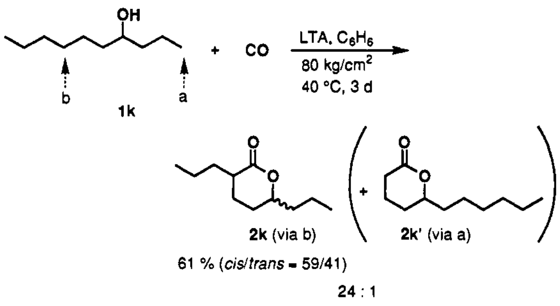


(2)

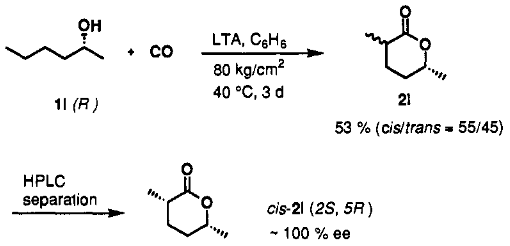
To survey the reaction generality, we examined four classes of saturated alcohols: primary alcohol with primary δ-carbon (**1a**), primary alcohols with secondary δ-carbons (**1b–f**), secondary alcohols with primary δ-carbons (**1g,h**), and secondary alcohols with secondary δ-carbons (**1i,j**). As shown in Table 1, this new method for the construction of δ-lactones from saturated alcohols and CO is quite general for primary alcohols and secondary alcohols, affording the corresponding δ-lactones in good yields.[6] On the other hand, tertiary alcohols were virtually inert under the aforementioned reaction conditions.[7]

Substrate **1k** is unique in that it contains both primary and secondary δ-carbons, a and b (eq 3). We were pleased to observe that CO was incorporated at methylene carbon b with excellent selectivity. Thus, 2-propyl-5-octanolide (**2k**) was formed predominantly over 5-undecanolide (**2k′**) in a ratio of 24:1. Purification of **2k** by flash chromatography on silica gel was sufficient to eliminate the minor product **2k′**. The preferential formation of **2k** is reasonable in light of the weaker C–H bond strength of methylene relative to that of methyl (ΔE = ca. 3 kcal/mol).[8]

We applied the reaction sequence to a one-step synthesis of carpenter bee pheromone[9] from commercially available, optically pure (*R*)-(–)-2-hexanol (**1l**). Thus, treatment of **1l** with CO in the presence of LTA yielded a cis/trans mixture of 2-methyl-5-hexanolide (**2l**) (eq 4). Separation of the mixture by preparative HPLC afforded pure *cis*-(2*S*,5*R*)-2-methyl-5-hexanolide (~100% ee),[10,11] a sex pheromone of the carpenter bee *Xylocopa hirutissima*. The observed quantitative optical yield confirmed that the absolute configuration of the hydroxy carbon was completely retained.



(3)



(4)

In conclusion, we have shown that *saturated* alcohols are suitable building blocks for δ-lactones. Obviously modern chemistry still faces many challenges with regard to functionalization of unactivated C–H bonds. The present findings demonstrate the great potential of free-radical methodology in this area. Efforts to expand the generality of this new preparation of δ-lactones as well as to elucidate the reaction mechanisms are currently in progress.

Supplementary Material Available: Detailed experimental procedure and compound characterization data for all products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(6) Representative experimental procedure: to a solution of 1-adamantaneethanol (**1d**) (72 mg, 0.4 mmol) in benzene (40 mL) placed in a stainless steel autoclave lined with a glass liner was added LTA (90%, 295 mg, 0.6 mmol). After the autoclave was sealed and filled with CO (80 kg/cm^2), it was heated to 40 °C for 3 days. The residual CO was ventilated, and the mixture was poured into 0.4 N aqueous hydrogen chloride, extracted with ether (3 × 20 mL), and dried ($MgSO_4$). Rotary evaporation of solvents followed by flash chromatography on silica gel (C_6H_{14}, then 10% AcOEt–C_6H_{14} eluent) afforded the δ-lactone **2d** (55 mg, 67% yield).

(7) We have also examined alcohols having tertiary δ-carbons. Unfortunately, CO trapping was unsuccessful due to rapid oxidation of the generated tertiary radical to lead to an olefin. It should be noted that the key steps of the present reaction appear to involve a free-radical mechanism (Scheme 1), but interaction between key radical species and lead salts is not clear at this stage. Cf.: Čeković, Ž.; Ilijev, D. *Tetrahedron Lett.* **1988**, *29*, 1441.

(8) (a) Sanderson, R. T. *Chemical Bonds and Bond Energy*; Loebl, E. M., Ed.; Academic Press: New York, 1976; p 165. For examples of competitive 1,5-H abstraction, see: (b) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1597. (c) Reference 5b.

(9) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron* Lett. **1976**, 4029.

(10) Optical purity was estimated by GC (column: Chiraldex G-TA, 20 m × 0.25 mm i.d.).

(11) (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978**, *43*, 378. (b) Bacardit, R.; Moreno-Mañas, M. *J. Chem. Ecol.* **1983**, *9*, 703. (c) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (d) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81. (e) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726. (f) Ikuba, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (g) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 651. (h) Bernardi, R.; Ghiringhelli, D. *Synthesis* **1989**, 938. (i) Schink, H. E.; Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 1588. (j) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991. (k) Jacobs, H. K.; Mueller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, *48*, 8891.