Useful Direct Conversion of Tetrahydropyranyl Ethers of Fatty Alcohols into Fatty Acids

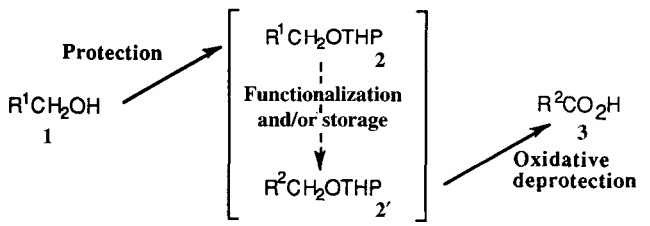
Régine Gruiec, Nicolas Noiret* and Henri Patin

Laboratoire de Chimie Organique et des Substances Naturelles, CNRS URA 1467,
Ecole Nationale Supérieure de Chimie de Rennes, 35700 Rennes-Beaulieu, France

ABSTRACT: Tetrahydro-2-pyranyl ethers from fatty primary alcohols can be converted in a one-step procedure into the corresponding carboxylic acids in high yields. This process avoids the synthesis of symmetrical esters, particularly for long-chain compounds. This reaction proved to be useful, for instance, to produce polyunsaturated fatty acids immediately before their biological testing.
JAOCS 72, 1083–1085 (1995).

KEY WORDS: Oxidation, polyunsaturated fatty acids, tetrahydropyranyl ethers.

During our studies on the desaturation of fatty acids in vegetals (1,2), we had to synthesize C_{18} acids with modified chains bearing either alkyl radicals or functional groups. In our approach, the synthetic fatty acids are used in free-acid form (V. Stefuca, and N. Noiret, unpublished work). However, it appears that long-term storage of these substrates is problematic, even under nitrogen atmosphere and at low temperature. We hypothesized that the $-CO_2H$ function was involved in the degradation process of our models, especially in polyunsaturated compounds. In this paper, we report a simple solution that allows the rapid disposal of free acids and that overcomes the instability of synthetic polyunsaturated fatty acids. Total syntheses were performed by using the corresponding tetrahydropyranyl ethers, which were readily converted into fatty acids in high yields just before their use (Scheme 1).



SCHEME 1

*To whom correspondence should be addressed at LCOSN, URA 1467, ENSCR, Avenue du Général Leclerc, 35700 Rennes-Beaulieu, France.

EXPERIMENTAL PROCEDURES

Materials. 3-Phenyl-1-propanol, azelaic acid monomethyl ester, 8-bromo-1-octanol, 3,4-dihydro-2*H*-pyran (DHP), octyl iodide, butyl lithium, *N,N'*-dimethyl propyleneurea (DMPU), ω-undecylenyl alcohol, chromium (VI) oxide, borane methyl sulfide complex, lithium acetylide ethylenediamine complex, *p*-toluenesulfonic acid (PTSA), and oleyl alcohol were obtained from Sigma-Aldrich France (St. Quentin-Fallavier, France). Jones reagent was prepared according to the standard method (3). Tetrahydrofuran (THF) was distilled from metallic sodium in the presence of benzophenone under nitrogen atmosphere. Methylene chloride (CH_2Cl_2), petroleum ether (PE), diethyl ether, and dimethylsulfoxide (DMSO) were of reagent grade and used directly. Preparative liquid chromatography was performed on silica gel GO Merck (0.040–0.063 mm; Merck, Darmstadt, Germany). Mixtures of solvents are given in volumetric ratios. Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck), and the spots were revealed by phosphomolybdic acid. All yields refer to purified compounds.

Methods. Analytical gas chromatography was conducted on a Carlo Erba (Milan, Italy) 4130 equipped with a capillary Alltech Column (25 × 0.25 mm, RSL-150, polydimethylsiloxane; Alltech Associates, Ontario, Canada). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature with a JEOL (Tokyo, Japan) FX90Q operating at 90 MHz (^1H) or 22.5 MHz (^{13}C), or a Bruker (Karlsruhe, Germany) ARX 400 spectrometer operating at 400.13 MHz (^1H) or 100.62 MHz (^{13}C). Chemical shifts are shown in ppm relative to internal tetramethylsilane as 0 ppm in $CDCl_3$. Mass spectra were recorded on a Finnigan MAT-INCOS 500 EX (Finnagan MAT, San Jose, CA) by using ammonia chemical ionization and direct introduction at ambient temperature.

Synthesis of methyl 8-hydroxynonanoate [**1a**]. Borane methyl sulfide complex (2.40 mL of 2.0 M in THF) was added dropwise in 30 min to a stirred solution of 1.01 g (4.8 mmoles) of azelaic acid monomethyl ester in 5 mL of dry THF at −20°C. The solution was then allowed to warm to room temperature and stirred overnight. Then, 10 mL of a 1:1 solution of water/THF were carefully added to the cooled

(0°C) mixture. Solvents were removed *in vacuo*, and the residue was extracted with diethyl ether. The combined organic layers were washed (diluted aqueous HCl, aqueous $NaHCO_3$ and H_2O) and dried, and the solvent was removed to dryness; 0.90 g of pure **1a** was obtained.

Methyl 8-hydroxynonanoate [**1a**]. Yield = 85%; ^{1}H NMR δ 3.7 (*s*, 3H), 3.6 (*t*, *J* = 6.3 Hz, 2H), 2.3 (*t*, *J* = 7.1, 2H), 1.8–1.3 (*m*, 12H). [CI/NH_3]: 188.30 [M^+]; 196.35 [M + NH_4]$^+$.

Synthesis of tetrahydropyranyl ethers (4) [**2**]. DHP (6.3 g, 75 mmoles) and a catalytic amount (0.05 eq.) of PTSA was added to a solution of 50 mmoles of alcohol **2** in 100 mL of CH_2Cl_2, cooled at 0°C. After stirring for 4 h at room temperature, the solvent was removed *in vacuo*, and the residue was chromatographed [diethyl ether/petroleum ether (PE), 2:8] to afford **2** in good yield.

Methyl 9-tetrahydropyranyloxynonanoate [**2a**]. Yield = 89%; ^{1}H NMR δ 4.6 (*brs*, 1H), 3.7 (*s*, 3H), 3.1–3.9 (*m*, 4H), 2.3 (*t*, *J* = 7.3, 2H), 1.8–1.4 (*m*, 10H), 1.3 (*brs*, 8H). [CI/NH_3]: 272.42 [M^+]; 290.53 [M + NH_4]$^+$.

3-Phenyl-1-tetrahydropyranyloxypropane [**2b**]. Yield = 91%; ^{1}H NMR δ 7.8 (*brs*, 5H), 4.6 (*brs*, 1H), 3.9–3.6 (*m*, 2H), 3.6–3.3 (*m*, 2H), 2.7 (*t*, *J* = 7, 2H), 2.0–1.3 (*m*, 8H). ^{13}C NMR δ 141.9, 128.3 × 2, 128.2 × 2, 125.5, 98.7, 66.6, 62.0, 32.3, 31.3, 30.6, 25.4, 19.5. [CI/NH_3]: 220.30 [M^+]; 228.35 [M + NH_4]$^+$.

11-Tetrahydropyranyloxy-1-undecylene [**2c**]. Yield = 92%; ^{1}H NMR δ 5.8 (*ddt*, *J* = 17 × 10 × 6, 1H), 5.0 (*ddt*, *J* = 17 × 2.3 × 1.4, 1H), 4.9 (*ddt*, *J* = 10 × 2.3 × 1.4, 1H), 4.6–4.5 (*m*, 1H), 3.8–3.3 (*m*, 6H), 2.2–1.9 (*m*, 4H), 1.8–1.1 (*m*, 16H). ^{13}C NMR δ 176.9, 138.8, 113.6, 33.4 × 2, 29.4 × 2, 28.6, 28.5, 28.4, 24.4 [CI/NH_3]: 254.44 [M^+]; 272.53 [M + NH_4]$^+$.

1-Tetrahydropyranyloxy-Z,9-octadecene [**2d**]. Yield = 92%; ^{1}H NMR δ 5.5–5.3 (*m*, 2H), 4.6–4.5 (*m*, 1H), 4.1–3.4 (*m*, 4H), 2.2–2.0 (*m*, 6H), 1.4–1.2 (*m*, 28H), 0.9 (*t*, *J* = 7, 3H); ^{13}C NMR δ 129.4 × 2, 98.6, 67.3, 61.8, 30.6, 29.6 × 4, 29.2 × 2, 28.9 × 2, 28.6 × 2, 28.5 × 2, 25.4, 19.4, 18.6 × 2, 13.6. [CI/NH_3]: 352.77 [M^+], 370.74 [M + NH_4]$^+$.

1-Bromo-8-tetrahydropyranyloxyoctane [**2e**]. Yield = 94%; ^{1}H NMR δ 4.6–4.5 (*m*, 1H), 3.8–3.3 (*m*, 4H), 3.4 (*t*, *J* = 7, 2H), 1.8–1.3 (*m*, 18H); ^{13}C NMR δ 98.5, 67.3, 61.9, 33.5, 32.6, 30.6, 29.5, 29.0, 28.5, 27.9, 25.5, 25.3, 19.4. [CI/NH_3]: 291.97–293.99 [M^+], 309.90–311.95 [M + NH_4]$^+$.

Synthesis of 10-tetrahydropyranyloxy-1-decyne [**2f**]. Under nitrogen atmosphere, a 2M suspension of lithium acetylide ethylenediamine complex (2 eq.) in dry DMSO was well stirred. At 5°C, 5.9 g (20 mmoles) of **2e** was added slowly to maintain a constant temperature. After stirring for 2 h and 30 min at room temperature, hydrolysis, extraction (PE), and drying, the residue was chromatographed to isolate 4.1 g of **2f**.

10-Tetrahydropyranyloxy-1-decyne [**2f**]. Yield = 86%; ^{1}H NMR δ 4.6–4.5 (*m*, 1H), 3.8–3.4 (*m*, 4H), 2.2–2.1 (*m*, 2H), 1.9 (*t*, *J* = 2, 1H), 1.6–1.3 (*m*, 18H), ^{13}C NMR δ 98.6, 84.6, 68.2, 67.6, 62.2, 30.8, 29.8, 29.3, 29.0, 28.7, 28.5, 26.2, 25.6, 19.7, 18.4. [CI/NH_3]: 238.27 [M^+], 256.25 [M + NH_4]$^+$.

Synthesis of 1-tetrahydropyranyloxy-9-octadecyne [**2g**]. Butyl lithium (6.9 mL of 1.6 M in hexane) was added dropwise to a solution of 9.2 mmoles of **2f** in 10 mL of anhydrous THF at 0°C, to maintain the mixture below 5°C. Then, 11 mmoles of freshly distilled octyl iodide in 1.5 mL DMPU was added. After stirring for 30 min at room temperature, hydrolysis, extraction (diethyl ether), drying, and distillation of the solvents, the crude product was chromatographed (PE) to afford **2g**.

1-Tetrahydropyranyloxy-9-octadecyne [**2g**]. Yield = 80%; ^{1}H NMR δ 4.6–4.5 (*m*, 1H), 4.1–3.4 (*m*, 4H), 2.2–2.0 (*m*, 6H), 1.4–1.2 (*m*, 28H), 0.9 (*t*, *J* = 7, 3H); ^{13}C NMR δ 98.6, 80.1, 79.7, 67.3, 61.8, 30.6, 29.6 × 4, 29.2 × 2, 28.9 × 2, 28.6 × 2, 28.5 × 2, 25.4, 19.4, 18.6 × 2, 13.6. [CI/NH_3]: 351.02 [M^+], 369.10 [M + NH_4]$^+$.

Oxidation of O*-tetrahydropyranyl (OTHP) ethers.* Four mL of Jones reagent in several portions was added under stirring to a solution of 5 mmoles of OTHP ether in 16 mL acetone, cooled to 0°C. After a few minutes, the green suspension clarified, and small volumes of Jones reagent were added until persistence of the orange color in the supernatant. Addition of 30 mL diethyl ether and filtration were followed by extraction and conventional treatment. The crude product [**3**] was filtered through a short column of silica gel (PE). The oxidation could easily be monitored by thin-layer chromatography.

Azelaic acid monomethyl ester [**3a**]. F = 22°C; ^{1}H NMR δ 10.2 (*brs*, 1H) 3.6 (*brs*, 3H), 2.4–2.2 (*m*, 2H), 1.6–1.5 (*m*, 4H), 1.3 (*s*, 8H). ^{13}C NMR δ 178.4, 174.4, 51.4, 33.8 × 2, 32.7, 28.6 × 2, 24.6, 24.4. [CI/NH_3]: 202.27 [M^+], 230.30 [M + NH_4]$^+$.

3-Phenyl-propanoic acid [**3b**]. F = 48°C; ^{1}H NMR δ 11.3 (*s*, 1H), 7.2 (*s*, 5H), 2.9 (*d*, 2H), 2.7 (*d*, 2H). ^{13}C NMR δ 178.3, 141.8, 128.3 × 2, 128.2 × 2, 125.6, 33.8, 31.3. [CI/NH_3]: 150.10 [M^+], 168.15 [M + NH_4]$^+$.

ω-Undecylenic acid [**3c**]. ^{1}H NMR δ 9,7 (*brs*, 1H), 5.8 (*ddt*, *J* = 17 × 10 × 6, 1H), 5.0 (*ddt*, *J* = 17 × 2.3 × 1.6, 1H), 4.9 (*ddt*, *J* = 10 × 2.3 × 1.6), 2.3 (*t*, *J* = 7, 2H), 1.8–1.1 (*m*, 2H). ^{13}C NMR δ 176.9, 138.8, 113.6, 33.4 × 2, 29.4 × 2, 28.6, 28.5, 28.4, 24.4 [CI/NH_3]: 184.29 [M^+], 202.34 [M + NH_4]$^+$.

Oleic acid [**3d**]. ^{1}H NMR δ 9,4 (*brs*, 1H) 5.4 (*t*, *J* = 5, 2H), 2.4 (*t*, *J* = 7, 2H), 2.1–1.9 (*m*, 4H), 1.8–1.1 (*m*, 22H), 0.9 (*t*, 3H). ^{13}C NMR δ 180.2, 129.7 × 2, 34.3, 31.5, 29.6, 29.5 × 6, 29.4, 27.3 × 2, 24.7, 22.7, 14.0. [CI/NH_3]: 282.50 [M^+], 300.41 [M + NH_4]$^+$.

8-Bromooctanoic acid [**3e**]. F = 40°C; ^{1}H NMR δ 10.2 (*brs*, 1H), 3.4 (*t*, *J* = 7, 2H), 2.3 (*t*, *J* = 7.5, 2H), 1.8 (*q*, *J* = 7, 2H), 1.6 (*q*, *J* = 7.5, 2H), 1.4 (*q*, *J* = 7, 2H), 1.3 (*brs*, 4H). ^{13}C NMR δ 178.2, 34.2, 32.9, 29.5, 29.2, 28.8, 28.3, 25.0. [CI/NH_3]: 221.12–222.14 [M^+].

9-Decynoic acid [**3f**]. ^{1}H NMR δ 10.4 (*brs*, 1H), 2.3–2.0 (*m*, 4H), 1.9 (*t*, *J* = 2, 1H), 1.5–1.1 (*m*, 12H). ^{13}C NMR δ 178.5, 84.0, 64.0, 33.6, 28.7, 28.4, 28.2, 28.1, 24.6, 18.0. [CI/NH_3]: 168.06 [M^+].

9,10-Octadecynoic acid [**3g**]. ^{1}H NMR: δ 10.2 (*brs*, 1H); 2.3–2.2 (*m*, 2H); 2.1–2.0 (*m*, 4H); 1.3–1.1 (*m*, 22H); 0.9 (*t*, *J* = 7, 3H). ^{13}C NMR δ 180.2, 80.2 × 2, 34.0, 31.0, 29.4 × 3, 29.3, 29.1, 28.8, 28.7, 28.1, 24.8, 22.7, 18.2 × 2, 14.0. [CI/NH_3]: 279.91 [M^+], 298.00 [M + NH_4]$^+$.

RESULTS AND DISCUSSION

Protection of the hydroxy function is generally required in the synthesis of polyfunctional molecules. For this purpose, DHP is widely used because of its low cost, availability, and moderate toxicity. The corresponding tetrahydro-2-pyranyl ethers are stable in various conditions. Moreover, their direct conversion into bromides (5), aldehydes (6), or acetates (7) can be effected in good yields. However, two-step sequences always involve deprotection and oxidation of the alcohols to convert them into carboxylic acids. Consequently, it was of interest to find a method that allows the direct transformation of the $-CH_2OTHP$ group into the $-CO_2H$ function. The transformation of primary and secondary alcohols into the corresponding aldehydes, carboxylic acids, or ketones is often carried out with chromium (VI) oxidants (8,9). However, in acidic conditions, competitive esterification may occur, probably *via* oxidation of an intermediate hemiacetal (10–12). This occurs especially in the case of long-chain alcohols (Scheme 2).

SCHEME 2

We have found that careful control of oxidation conditions with Jones reagent allowed nearly quantitative and rapid direct transformation of tetrahydropyranyl ethers into the desired carboxylic acids. This method is compatible with different functional groups (Table 1).

The oxidation process takes advantage of the OTHP group because, in similar conditions, the corresponding alcohols gave mixtures of products [e.g., entry **1b**: 53% yield of symmetrical ester (13)] or much lower yields (two steps required). Moreover, the OTHP group is suitable in all common reactions used in lipids chemistry, such as Wittig condensation, Grignard reaction, acetylenic coupling, and in catalytic hydrogenation processes.

TABLE 1
Synthesis of Carboxylic Acids 3 from OTHP Ethers 2

Entry	Entry	Isolated yields (%)
3a	$MeO_2C(CH_2)_7CO_2H$	79
3b	$Ph(CH_2)_2CO_2H$	95
3c	$CH_2{=}CH(CH_2)_8CO_2H$	77
3d	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	82
3e	$Br(CH_2)_7CO_2H$	85
3f	$HC{\equiv}C(CH_2)_7CO_2H$	80
3g	$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$	95

REFERENCES

1. Génard, S., and H. Patin, *Bull. Soc. Chim. Fr. 128*:397 (1991).
2. Gruiec, R., N. Noiret and H. Patin, *Ibid. 131*:699 (1994).
3. Bowers, A., T.G. Halsall, E.R.H. Jones and A.J. Lemin, *J. Chem. Soc.*:2548 (1953).
4. Fieser, L.F., and M. Fieser, *Reagents for Organic Synthesis*, J. Wiley and Sons, New York, Vol. 1 (1967), p. 256; Vol. 3 (1972), p. 99; Vol. 5 (1974), p. 220; Vol. 7 (1979), p. 109; Vol. 10 (1982), p. 147.
5. Wagner, A., M-P. Heitz and C. Mioskowski, *Tetrahedron Lett. 30*:557 (1989).
6. Sonnet, P.E., *Org. Prep. Proced. Int. 10*:91 (1978).
7. Bakos, T., and I. Vincze, *Synth. Commun. 19*:523 (1989).
8. Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers Inc., New York, 1989, pp. 834–836.
9. Cainelli, G., and G. Cardillo, *Chromium Oxidation in Organic Chemistry*; Springer-Verlag, 1984.
10. Cymerman-Craig, J., and E.C. Horning, *J. Org. Chem. 25*:2098 (1960).
11. Pierre, J., and E. Puchot, *Liebigs Ann. Chem. 163*:193 (1872).
12. Robertson, G.R., *Org. Synth. Coll. 1*:138 (1941).
13. Cymerman-Craig, J., E.G. Davis and J.S. Lake, *J. Chem. Soc.* 2098 (1954).

[Received November 28, 1994; accepted June 3, 1995]