Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2001–2005

TETRAHEDRON

A new synthesis of highly functionalized 2*H*-pyran derivatives

Issa Yavari* and Mohammad Bayat

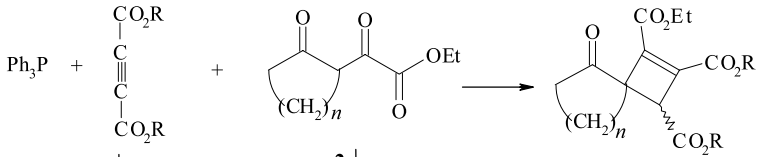
Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14115-175, Tehran, Iran

Received 7 October 2002; revised 13 December 2002; accepted 16 January 2003

Abstract—Ethyl oxo-(2-oxo-cycloalkyl)-ethanoates undergo a smooth reaction with triphenylphosphine and dialkyl acetylenedicarboxylates via intramolecular Wittig reaction to produce spiro-cyclobutene derivatives. These spiro systems undergo electrocyclic ring opening reaction to produce electron-deficient 1,3-dienes, which spontaneously cyclize to 2*H*-pyran derivatives.

Six-membered oxygen heterocyclic compounds occupy an important position in natural product chemistry, featuring in plant life, most notably as the flavonoids, and in the marine environment where they form a part of the wide range of macrocyclic molecules.[1] The presence of oxacyclic units in polyether and macrolide antibiotics, such as the avermectins,[2] swinholides[3] and milbemycins[4] has stimulated intense synthetic activity in pyran chemistry because of the significant pharmacological activity shown by these systems. We previously reported the synthesis of cyclobutene derivatives by stereoselective intramolecular Wittig reaction of a vinyltriphenylphosphonium salt.[5–7] As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems, we now report the reaction between ethyl oxo-(2-oxo-cycloalkyl)-ethanoates **2** and dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine. Thus, reaction of triphenylphosphine with electron defficient acetylenic esters **1** in the presence of a strong CH-acid such as **2** leads to spiro systems **3** in good yields. These compounds undergo electrocyclic ring opening reaction in boiling toluene to produce highly functionalized 2*H*-pyran derivatives[8,10] **4** in fairly high yields (Scheme 1). The polycarbonyl compound **2** is a readily available system, which is apparently completely enolized in solution, as indicated by NMR spectroscopy.

On the basis of the chemistry of trivalent phosphorus nucleophiles,[11,12] it is reasonable to assume that spiro-cyclobutenes



1	R
a	Me
b	Et
c	*i*Pr
d	*t*Bu

2	*n*
a	3
b	4
c	5
d	9

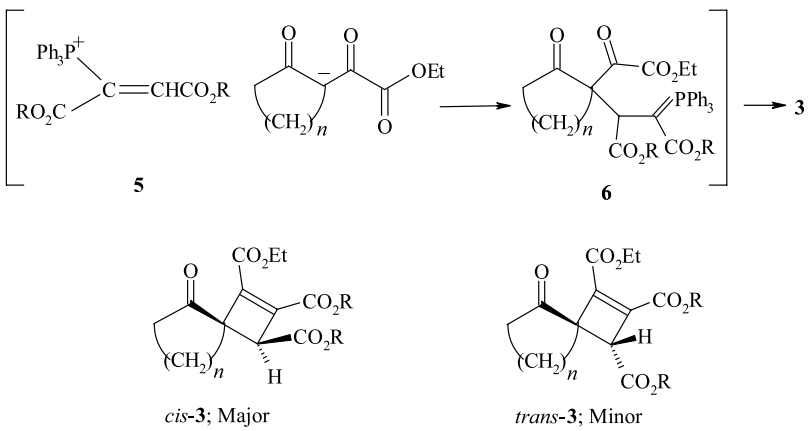
3,**4**	*n*	R	% Yield of **3**	*cis*-**3**: *trans*-**3**	%Yield of **4**
a	3	Me	96	90 : 10	98
b	3	Et	92	100	97
c	3	*i*Pr	95	100	–
d	3	*t*Bu	94	98 : 2	96
e	4	Me	89	90 : 10	86
f	5	Me	94	100	95
g	5	Et	87	100	98
h	9	Me	89	88 : 12	98

Scheme 1.

Keywords: cyclobutene; spiro systems; 2*H*-pyran; CH-acid; intramolecular Wittig reaction; acetylenic esters.

* Corresponding author. Tel.: +98-21-8006631; fax: +98-21-8006544; e-mail: isayavar@yahoo.com

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00114-5



Scheme 2.

3 result from initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the reactive 1:1 adduct by **2**, followed by attack of the carbon atom of the anion of **2** to vinyltriphenylphosphonium cation **5** to generate phosphorane **6**, which is converted into strained carbocyclic spiro system **3** (Scheme 2).

Measurable amounts of *cis* and *trans* diastereoisomers are observed for **3a**, **3d**, **3e**, and **3h**, as indicated by the ^{1}H and ^{13}C NMR spectra of the reaction mixtures (see Table of Scheme 1). Since the signal of the methine proton in the major isomer appears at lower field (δ=3.8–4.1 ppm) compared to that of the minor isomer (δ=3.4–3.6 ppm), we assign the *cis*-**3** structure to the major isomer. The methine proton of the minor isomer, *trans*-**3**, is expected to be shielded as a result of the magnetic anisotropy of the C=O bond. The ^{13}C NMR spectrum of **3** exhibited distinct signals in agreement with the cyclobutene spiro systems. The methine carbon and spiro carbon of **3** shows two separate signals at about δ=49–50 and δ=59–61 ppm, respectively. Partial assignment of these signals is given in Section 1. These spiro systems undergo electrocyclic ring-opening reaction in boiling toluene to produce dienones **7**, which undergo a [3,3] sigmatropic rearrangement, giving the 2*H*-pyran derivatives **4** in fairly high yields (Scheme 3). Such a cyclization is not unprecedented.[9]

The ^{1}H and ^{13}C NMR spectra of **4** display characteristic signals at about δ=5.7 ppm and δ=70–71 ppm for the CH group and appropriate chemical shifts in the olefinic region. The structures **4a**–**h** are fully supported by NMR and other spectral data (see Section 1).

In conclusion, the present method may be considered as a practical route for the synthesis of spiro-cyclobutene systems and 2*H*-pyran derivatives using intramolecular Wittig reaction under neutral conditions. This procedure has advantages of high yields, mild reaction conditions, and simple experimental and work-up conditions.

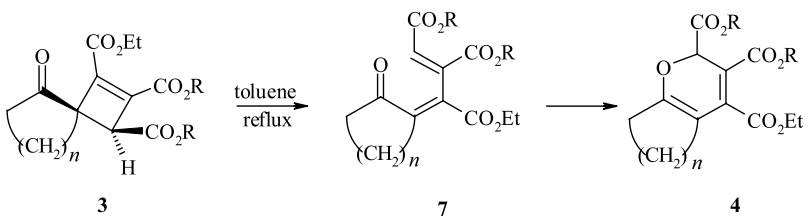
1. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR 460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a BRUKER DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.8 MHz, respectively. The mass spectra were recorded on a Shimadzu QP-1100-EX GC-Mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylates **1a**–**d**, triphenylphosphine and cyclic ketones were obtained from Fluka (Buchs, Switzerland) and used without further purification.

1.1. Preparation of ethyl oxo-(2-oxo-cycloalkyl)-ethanoates 2a–d

Compounds **2a**–**d** were prepared from diethyl oxalate and cyclic ketones in the presence of sodium ethoxide by known methods[13] and identified as follows.

1.1.1. Ethyl oxo-(2-oxo-cyclohexyl)-ethanoate (2a). Pale yellow liquid, bp 135°C/10–15 mm, (lit.[6] 105–165°C/10–15 mm). ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.42 (3H, t, $^{3}J_{HH}$=7.2 Hz, CH_3), 1.50–1.98 (4H, m, $2CH_2$), 2.21–2.75 (4H, m, $2CH_2$), 4.38 (2H, q, $^{3}J_{HH}$=7.2 Hz, OCH_2), 15.2 (1H, br s, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.84 (CH_3), 20.93, 22.23, 23.04, and 32.45 ($4CH_2$), 61.65 (OCH_2), 106.73



Scheme 3.

(C═), 163.00 (C═O ester), 179.70 (═C–OH), 190.94 (C═O).

1.1.2. Ethyl oxo-(2-oxo-cycloheptyl)-ethanoate (2b). Brown gum paste, IR (KBr) (ν_{max}, cm^{-1}): 1750, and 1731 (C═O). ^1H NMR (90 MHz, $CDCl_3$): δ 1.39 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.51–2.10 (6H, m, $3CH_2$), 2.34–3.02 (4H, m, $2CH_2$), 4.39 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 15.51 (1H, br s, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.76 (CH_3), 24.55, 26.14, 28.70, 31.06, and 41.29 ($5CH_2$), 61.73 (OCH_2), 112.83 (C═), 162.96 (C═O ester), 168.01 (═C–OH), 206.37 (C═O). Anal. calcd for $C_{11}H_{16}O_4$ (212.2): C, 62.24; H, 7.60%; Found: C, 62.1; H, 7.5%.

1.1.3. Ethyl oxo-(2-oxo-cyclooctyl)-ethanoate (2c). Colorless oil, IR (KBr) (ν_{max}, cm^{-1}): 1753, 1734, and 1689 (C═O). ^1H NMR (90 MHz, $CDCl_3$): δ 1.38 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.48–2.10 (8H, m, $4CH_2$), 2.34–2.80 (4H, m, $2CH_2$), 4.38 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 15.78 (1H, br s, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.45 (CH_3), 24.16, 25.10, 25.71, 28.28, 30.43, and 35.40 ($6CH_2$), 61.26 (OCH_2), 109.47 (C═), 162.78 (C═O ester), 175.68 (═C–OH), 199.38 (C═O). Anal. calcd for $C_{12}H_{18}O_4$ (226.3): C, 63.69; H, 8.02%; Found: C, 63.7; H, 8.1%.

1.1.4. Ethyl oxo-(2-oxo-cyclododecyl)-ethanoate (2d). Yellow powder, mp 103–105°C, IR (KBr) (ν_{max}, cm^{-1}): 1729, and 1694 (C═O). ^1H NMR (90 MHz, $CDCl_3$): δ 1.12–2.80 (23H, m, CH_3 and $10CH_2$), 4.34 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 15.51 (1H, br s, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.76 (CH_3), 21.53, 22.12, 22.64, 23.33, 24.14, 24.51, 24.67, 25.45, and 25.77 ($9CH_2$), 39.13 (CH_2–C═O), 60.51 (C–H), 62.58 (OCH_2), 160.84 (C═O ester), 190.61 ($CO-CO_2Et$), 213.05 (C═O). Anal. calcd for $C_{16}H_{26}O_4$ (282.4): C, 68.05; H, 9.28%; Found: C, 68.1; H, 9.3%.

1.1.5. Preparation of 5-oxo-spiro[3.5]non-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-dimethyl ester (3a): general procedure. To a magnetically stirred solution of 0.262 g triphenylphosphine (1 mmol) and 0.198 g ethyl oxo-(2-oxo-cyclohexyl)-ethanoate (**2a**) (1 mmol) in CH_2Cl_2 (10 mL) was added, dropwise, a mixture of 0.142 g dimethyl acetylenedicarboxylate (1 mmol) in CH_2Cl_2 (1 mL) at −5°C over 10 min. The reaction mixture was then allowed to warm to room temperature and stirrer for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel 60, 70–230 mesh) column chromatography using hexane–ethyl acetate (8:2) as eluent. The solvent was removed to afford the product **3a** as white solid, the ^1H NMR spectrum of product **3a** was consistent with the presence of 90:10 mixture of *cis*/*trans* products. 0.31 g, yield 96%, mp 53–55°C, IR (KBr) (ν_{max}, cm^{-1}): 1728 and 1697 (C═O), 1644 (C═C). MS (*m*/*z*, %): 324 (M^+, 15), 266 (88), 218 (40), 190 (37), 162 (52), 131 (33), 103 (56), 77 (75), 59 (100). Anal. calcd for $C_{16}H_{20}O_7$ (324.3): C, 59.25; H, 6.21%; Found: C, 59.3; H, 6.2%.

Major isomer cis-**3a** (90%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.33 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.59–2.32 (6H, m, $3CH_2$), 2.55–2.59 (2H, m, CH_2-C═O), 3.77 and 3.79 (6H, 2s, $2OCH_3$), 3.87 (1H, s, C–H), 4.25–4.33 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.04 (CH_3), 21.58, 26.13, and 31.23 ($3CH_2$), 40.03 (CH_2–C═O), 49.61 (C–H), 52.16 and 52.28 ($2OCH_3$), 59.26 (C_{spiro}), 61.36 (OCH_2), 138.22 and 146.58 (C═C), 160.29 and 160.39 (CO_2Et and CO_2Me), 169.05 (CH–CO_2Me), 206.95 (C═O).

Minor isomer trans-**3a** (10%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.92 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.59–2.32 (6H, m, $3CH_2$), 2.55–2.59 (2H, m, CH_2–C═O), 3.69 (1H, s, C–H), 3.77 and 3.79 (6H, 2s, $2OCH_3$), 4.25–4.33 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 11.11 (CH_3), 22.76, 26.52, and 36.86 ($3CH_2$), 40.29 (CH_2–C═O), 52.16 and 52.28 ($2OCH_3$), 54.78 (C–H), 61.32 (C_{spiro}), 61.60 (OCH_2), 137.55 and 146.91 (C═C), 160.30 and 160.40 (CO_2Et and CO_2Me), 167.65 (CH–CO_2Me), 206.84 (C═O).

1.1.6. Triethyl 5-oxo-spiro[3.5]non-1-ene-1,2,3-tricarboxylate (3b). Colorless crystals, 0.32 g, yield 92%, mp 40–42°C, IR (KBr) (ν_{max}, cm^{-1}): 1719 (C═O), 1643 (C═C). MS (*m*/*z*, %): 352 (M^+, 29), 306 (64), 279 (64), 261 (35), 232 (56), 204 (100), 176 (62), 149 (25), 131 (25), 105 (29), 55 (21). Anal. calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86%; Found: C, 61.2; H, 6.7%. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.26–1.35 (9H, 3 t, $^3J_{HH}$=7.2 Hz, $3CH_3$), 1.64–2.40 (6H, m, $3CH_2$), 2.53–2.61 (2H, m, CH_2–C═O), 3.83 (1H, s, C–H), 4.18–4.30 (6H, m, $3OCH_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.08, 14.12, and 14.25 ($3CH_3$), 21.69, 26.15, and 31.24 ($3CH_2$), 40.09 (CH_2–C═O), 49.86 (C–H), 59.20 (C_{spiro}), 61.27, 61.30, and 61.37 ($3OCH_2$), 138.87 and 146.03 (C═C), 159.91 and 160.54 (2 CO_2Et), 168.61 (CH–CO_2Et), 207.07 (C═O).

1.1.7. 5-Oxo-spiro[3.5]non-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-diisopropyl ester (3c). Pale yellow powder, 0.36 g, yield 95%, mp 53–55°C, IR (KBr) (ν_{max}, cm^{-1}): 1718 (C═O), 1640 (C═C). MS (*m*/*z*, %): 381 (M^++1, 11), 311 (54), 294 (100), 283 (57), 207 (85), 185 (67), 69 (53), 43 (62). Anal. calcd for $C_{20}H_{28}O_7$ (380.4): C, 63.14; H, 7.42%; Found: C, 63.1; H, 7.3%. ^1H NMR (80 MHz, $CDCl_3$): δ 0.86 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.10–1.51 (12H, d, $^3J_{HH}$=5.0 Hz, $2Me_2CH$), 1.52–2.41 (6H, m, $3CH_2$), 2.41–2.84 (2H, m, CH_2–C═O), 3.79 (1H, s, C–H), 4.30 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 5.18 (2H, sept., $^3J_{HH}$=6.2 Hz, 2CH–Me_2). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.15 (CH_3), 21.69, (CH_2), 21.72 and 21.93 (CH–Me_2), 26.16 and 31.17, ($2CH_2$), 40.09 (CH_2–C═O), 50.10 (C–H), 59.11 (C_{spiro}), 61.26 (OCH_2), 69.20 and 69.80 ($2OCH-Me_2$), 139.40 and 145.55 (C═C), 159.44 and 160.57 (CO_2Et and CO_2CHMe_2), 168.15 (CH–CO_2CHMe_2), 207.24 (C═O).

1.1.8. 5-Oxo-spiro[3.5]non-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-di-*tert*-butyl ester (3d). Pale yellow powder, 0.38 g, yield 94%, mp 56–58°C, IR (KBr) (ν_{max}, cm^{-1}): 1705 (C═O), 1645 (C═C). MS (*m*/*z*, %): 410 (M^++2, 12), 409 (M^++1, 2); 353 (58), 297 (100), 278 (60), 250 (58), 222 (46), 204 (100), 176 (8), 57 (100), 41 (50). Anal. calcd for $C_{22}H_{32}O_7$ (408.5): C, 64.69; H, 7.89%; Found: C, 64.8; H, 7.9%.

Major isomer cis-**3d** (98%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.32 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.50 (18H, s, $2CMe_3$), 1.78–2.40 (6H, m, $3CH_2$), 2.50–2.55 (2H, m, CH_2–C═O),

3.63 (1H, s, C–H), 4.23–4.28 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.98 (CH_3), 21.62 and 26.06 ($2CH_2$), 27.79 and 27.84 ($2CMe_3$), 31.03 (CH_2), 39.93 (CH_2–C=O), 50.94 (C–H), 58.62 (C_{spiro}), 60.80 (OCH_2), 81.71 and 81.80 (2 CMe_3), 140.58 and 144.43 (C=C), 158.83 and 160.44 (CO_2Et and CO_2CMe_3), 167.62 (CH–CO_2CMe_3), 206.99 (C=O).

Minor isomer trans-**3d** (2%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.88 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.46 (9H, s, CMe_3), 1.54 (9H, s, CMe_3), 1.56–2.56 (8H, m, $4CH_2$), 3.47 (1H, s, C–H), 4.09 (2H, q, $^3J_{HH}$=7.2 Hz OCH_2).

1.1.9. 5-Oxo-spiro[3.6]dec-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-dimethyl ester (3e). Pale yellow oil, 0.31 g, yield 89%, IR (KBr) (ν_{max}, cm^{-1}): 1725 (C=O), 1644 (C=C). MS (*m/z*, %): 338 (M^+, 8), 280 (64), 262 (19), 232 (39), 204 (57), 176 (54), 117 (60), 91 (58), 59 (100), 41 (75). Anal. calcd for $C_{17}H_{22}O_7$ (338.4): C, 60.34; H, 6.55%; Found: C, 60.2; H, 6.4%.

Major isomer cis-**3e** (90%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.32 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.40–2.26 (8H, m, $4CH_2$), 2.63–2.88 (2H, m, CH_2–C=O), 3.74 and 3.80 (6H, 2s, $2OCH_3$), 4.07 (1H, s, C–H), 4.25–4.28 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.02 (CH_3), 24.96, 26.15, 29.10, and 30.53 ($4CH_2$), 42.26 (CH_2–C=O), 49.52 (C–H), 52.16 and 52.23 ($2OCH_3$), 61.67 (C_{spiro}), 61.46 (OCH_2), 139.24 and 147.01 (C=C), 160.13 and 160.37 (CO_2Et and CO_2Me), 169.42 (CH–CO_2Me), 209.72 (C=O).

Minor isomer trans-**3e** (10%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.30 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.31–2.40 (8H, m, $4CH_2$), 2.53–2.82 (2H, m, CH_2–C=O), 3.56 (1H, s, C–H), 3.69 and 3.83 (6H, 2s, $2OCH_3$), 4.20–4.25 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.02 (CH_3), 24.82, 26.55, 30.58, and 33.62 ($4CH_2$), 43.52 (CH_2–C=O), 44.66 (C–H), 49.52 and 53.31 ($2OCH_3$), 63.23 (C_{spiro}), 61.41 (OCH_2), 139.44 and 146.19 (C=C), 159.78 and 160.94 (CO_2Et and CO_2Me), 168.85 (CH–CO_2Me), 211.74 (C=O).

1.1.10. 5-Oxo-spiro[3.7]undec-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-dimethyl ester (3f). Pale yellow powder, 0.33 g, yield 94%, mp 48–50°C, IR (KBr) (ν_{max}, cm^{-1}): 1720 (C=O), 1644 (C=C). MS (*m/z*, %): 353 (M^++1, 10), 293 (29), 246 (27), 218 (46), 131 (44), 84 (100), 59 (60), 41 (69). Anal. calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86%; Found: C, 61.3; H, 6.7%. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.33 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.45–2.37 (10H, m, $5CH_2$), 2.58–2.72 (2H, m, CH_2–C=O), 3.77 and 3.80 (6H, 2s, $2OCH_3$), 3.86 (1H, s, C–H), 4.24–4.33 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.64 (CH_3), 24.43, 24.45, 25.48, 27.52, and 29.07 ($5CH_2$), 37.94 (CH_2–C=O), 48.74 (C–H), 51.75 and 51.96 ($2OCH_3$), 60.96 (C_{spiro}), 61.81 (OCH_2), 137.71 and 146.39 (C=C), 160.15 and 160.16 (CO_2Et and CO_2Me), 168.74 (CH–CO_2Me), 211.74 (C=O).

1.1.11. Triethyl 5-oxo-spiro[3.7]undec-1-ene-1,2,3-tricarboxylate (3g). Pale yellow oil, 0.33 g, yield 87%, IR (KBr) (ν_{max}, cm^{-1}): 1724 (C=O), 1642 (C=C). MS (*m/z*, %): 380 (M^+, 19), 333 (55), 306 (58), 288 (40), 277 (45), 259 (58), 232 (100), 203 (53), 105 (25), 55 (20). Anal. calcd for $C_{20}H_{28}O_7$ (380.4): C, 63.14; H, 7.42%; Found: C, 63.1; H, 7.3%. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.26–1.37 (9H, 3 t, $^3J_{HH}$=7.2 Hz, $3CH_3$), 1.34–2.79 (10H, m, $5CH_2$), 2.65–2.80 (2H, m, CH_2–C=O), 3.81 (1H, s, C–H), 4.20–4.33 (6H, m, $3OCH_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.01, 14.11, and 14.26 ($3CH_3$), 24.74, 24.99, 25.83, 27.89, and 29.47 ($5CH_2$), 38.31 (CH_2–C=O), 49.32 (C–H), 61.96 (C_{spiro}), 61.25, 61.30, and 61.37 ($3OCH_2$), 138.65 and 146.12 (C=C), 160.15 and 160.63 (2 CO_2Et), 168.60 (CH–CO_2Et), 212.36 (C=O).

1.1.12. 5-Oxo-spiro[3.11]pentadec-1-ene-1,2,3-tricarboxylic acid 1-ethyl ester 2,3-dimethyl ester (3h). Pale yellow oil, 0.36 g, yield 89%, IR (KBr) (ν_{max}, cm^{-1}): 1723, and 1712 (C=O), 1640 (C=C). MS (*m/z*, %): 408 (M^+, 2), 363 (10), 349 (83), 321 (21), 91 (21), 59 (48), 55 (85), 41 (100). Anal. calcd for $C_{22}H_{32}O_7$ (408.5): C, 64.68; H, 7.89%; Found: C, 64.8; H, 8.0%.

Major isomer cis-**3h** (88%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.12–2.30 (21H, m, CH_3 and $9CH_2$), 2.45–2.90 (2H, m, CH_2–C=O), 3.76 (6H, s, $2OCH_3$), 4.11 (1H, s, C–H), 4.27–4.37 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.96 (CH_3), 20.87, 21.48, 22.42 22.47, 22.80, 23.66, 26.33, 26.88, and 29.95 ($9CH_2$), 34.48 (CH_2–C=O), 48.93 (C–H), 51.90 and 52.08 ($2OCH_3$), 61.30 (C_{spiro}), 64.46 (OCH_2), 137.67 and 147.11 (C=C), 160.30 and 161.06 (CO_2Et and CO_2Me), 169.44 (CH–CO_2Me), 207.29 (C=O).

Minor isomer trans-**3h** (12%), ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.12–2.50 (21H, m, CH_3 and $9CH_2$), 2.65–3.25 (2H, m, CH_2–C=O), 3.56 (1H, s, C–H), 3.72, and 3.73 (6H, 2s, $2OCH_3$), 4.27–4.37 (2H, m, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.99 (CH_3), 21.31, 21.67, 22.17, 22.33, 22.53, 22.59, 24.98, 26.48, and 28.11 ($9CH_2$), 34.27 (CH_2–C=O), 52.26 (C–H), 51.93 and 52.03 ($2OCH_3$), 61.43 (C_{spiro}), 66.57 (OCH_2), 138.80 and 146.28 (C=C), 160.10 and 161.04 (CO_2Et and CO_2Me), 169.62 (CH–CO_2Me), 205.87 (C=O).

1.1.13. 5,6,7,8-Tetrahydro-2*H*-cyclohexa[*b*]pyran-2,3,4-tricarboxylic acid 4-ethyl ester 2,3-dimethyl ester (4a). Compound **3a** was refluxed in toluene for 24 h. The solvent was removed under reduced pressure and **4a** was obtained as pale yellow oil, 0.32 g, yield 98%, IR (KBr) (ν_{max}, cm^{-1}): 1725 (C=O), 1645 (C=C). Anal. calcd for $C_{16}H_{20}O_7$ (324.3): C, 59.25; H, 6.21%; Found: C, 59.2; H, 6.1%. ^1H NMR (80 MHz, $CDCl_3$): δ 1.34 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.51–2.60 (8H, m, $4CH_2$), 3.74 and 3.79 (6H, 2s, $2OCH_3$), 4.40 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 5.72 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.16 (CH_3), 21.74, 22.00, 22.67, and 27.65 ($4CH_2$), 52.09 and 52.67 ($2OCH_3$), 61.64 (OCH_2), 70.86 (C–H), 106.07, 108.84, 140.48, and 158.95 (olefinic carbons), 163.97 and 166.62 (CO_2Et and CO_2Me),169.95 (CH–CO_2Me).

1.1.14. Triethyl 5,6,7,8-tetrahydro-2*H*-cyclohexa[*b*]-pyran-2,3,4-tricarboxylate (4b). Pale yellow oil, 0.35 g, yield 97%, IR (KBr) (ν_{max}, cm^{-1}): 1724 (C=O), 1640 (C=C). Anal. calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H,

6.86%; Found: C, 61.3; H, 6.8%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.12–1.29 (9H, 3 t, $^3J_{HH}$=7.0 Hz, $3CH_3$), 1.35–2.68 (8H, m, $4CH_2$), 4.04–4.28 (6H, m, $3OCH_2$), 5.70 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.03, 13.07, and 13.14 ($3CH_3$), 20.77, 21.05, 21.65, and 26.67 ($4CH_2$), 59.95, 60.45, and 60.54 ($3OCH_2$), 69.94 (C–H), 104.94, 108.60, 139.00, 157.56 (olefinic carbons), 162.51 and 165.66 ($2CO_2Et$), 168.49 (CH–CO_2Et).

1.1.15. 5,6,7,8-Tetrahydro-2*H*-cyclohexa[*b*]pyran-2,3,4-tricarboxylic acid 4-ethyl ester 2,3-di-*tert*-butyl ester (4d). Pale yellow solid, 0.39 g, yield 96%, IR (KBr) (ν_{max}, cm^{-1}): 1728 (C=O), 1644 (C=C). Anal. calcd for $C_{22}H_{32}O_7$ (408.5): C, 64.69; H, 7.89%; Found: C, 64.7; H, 7.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.26 (3H, t, $^3J_{HH}$= 7.1 Hz, CH_3), 1.36 and 1.40 (18H, 2s, $2CMe_3$), 1.60–2.21 (8H, m, $4CH_2$), 4.14–4.30 (2H, m, OCH_2), 5.45 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.07 (CH_3), 20.85, 21.17, 21.96, and 26.70 ($4CH_2$), 26.92 and 27.02 ($2CMe_3$), 60.17 (OCH_2), 70.31 (C–H), 80.43 and 81.32 ($2CMe_3$), 104.61, 111.03, 137.15, and 156.71 (olefinic carbons), 161.90 and 165.74 (CO_2Et and CO_2CMe_3), 167.76 (CH–CO_2CMe_3).

1.1.16. 5,6,7,8,9-Pentahydro-2*H*-cyclohexa[*b*]pyran-2,3,4-tricarboxylic acid 4-ethyl ester 2,3-dimethyl ester (4e). Yellow oil, 0.29 g, yield 86%, IR (KBr) (ν_{max}, cm^{-1}): 1728 (C=O), 1640 (C=C). Anal. calcd for $C_{17}H_{22}O_7$ (338.4): C, 60.34; H, 6.55%; Found: C, 60.3; H, 6.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.35 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.50–2.90 (10H, m, $5CH_2$), 3.73 and 3.77 (6H, 2s, $2OCH_3$), 4.28–4.35 (2H, m, OCH_2) 5.71 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.15 (CH_3), 23.18, 24.26, 26.83, 27.61, and 30.75 ($5CH_2$), 52.04 and 52.20 ($2OCH_3$), 61.72 (OCH_2), 71.11 (C–H), 106.60, 110.80, 139.29, and 158.31 (olefinic carbons), 163.87 and 164.18 (CO_2Et and CO_2Me), 170.04 (CH–CO_2Me).

1.1.17. 5,6,7,8,9,10-Hexahydro-2*H*-cycloocta[*b*]pyran-2,3,4-tricarboxylic acid 4-ethyl ester 2,3-dimethyl ester (4f). Pale yellow oil, 0.33 g, yield 95%, IR (KBr) (ν_{max}, cm^{-1}): 1725 (C=O), 1645 (C=C). Anal. calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86%; Found: C, 61.3; H, 6.8%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.35 (3H, t, $^3J_{HH}$= 7.0 Hz, CH_3), 1.40–2.48 (12H, m, $6CH_2$), 3.74 and 3.77 (6H, 2s, $2OCH_3$), 4.27–4.41 (2H, m, OCH_2), 5.73 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.11 (CH_3), 24.76, 25.15, 26.53, 27.78, 29.85, and 31.19 ($6CH_2$), 52.06 and 52.63 ($2OCH_3$), 61.62 (OCH_2), 71.04 (C–H), 107.81, 108.52, 141.17, and 161.72 (olefinic carbons), 167.06 and 169.14 (CO_2Et and CO_2Me), 170.48 (CH–CO_2Me).

1.1.18. Triethyl 5,6,7,8,9,10-hexahydro-2*H*-cycloocta[*b*]-pyran-2,3,4-tricarboxylate (4g). Pale yellow oil, 0.37 g, yield 98%, IR (KBr) (ν_{max}, cm^{-1}): 1726 (C=O), 1645 (C=C). Anal. calcd for $C_{20}H_{28}O_7$ (380.4): C, 63.14; H, 7.42%; Found: C, 63.1; H, 7.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.26–1.37 (9H, 3 t, $^3J_{HH}$=7.2 Hz, $3CH_3$), 1.34–2.79 (12H, m, $6CH_2$), 4.20–4.33 (6H, m, $3OCH_2$), 5.71 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.01, 14.11, and 14.26 ($3CH_3$), 24.74, 24.99, 25.83, 27.89, 29.47, and 38.30 ($6CH_2$), 49.32 (C–H), 61.25, 61.30, and 61.37 ($3OCH_2$), 105.10, 107.89, 139.20, and 158.20 (olefinic carbons), 160.15 and 160.63 ($2CO_2Et$), 168.60 (CH–CO_2Et).

1.1.19. 5,6,7,8,9,10,11,12,13,14-Decahydro-2*H*-cyclododeca[*b*]pyran-2,3,4-tricarboxylic acid 4-ethyl ester 2,3-dimethyl ester (4h). Pale yellow oil, 0.40 g, yield 98%, IR (KBr) (ν_{max}, cm^{-1}): 1725 (C=O), 1640 (C=C). Anal. calcd for $C_{22}H_{32}O_7$ (408.5): C, 64.68; H, 7.89%; Found: C, 64.7; H, 7.9%. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.01–3.10 (23H, m, CH_3 and $10CH_2$), 3.71 and 3.78 (6H, s, $2OCH_3$), 4.31–4.50 (2H, m, OCH_2), 5.74 (1H, s, C–H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.08 (CH_3), 21.71, 22.60, 23.77, 24.75, 24.87, 24.91, 25.01, 25.04, 27.59, and 28.19 ($10CH_2$), 52.10 and 52.47 ($2OCH_3$), 61.63 (OCH_2), 70.82 (C–H), 109.52, 111.27, 141.81, and 160.34 (olefinic carbons), 163.79 and 167.16 (CO_2Et and CO_2Me), 169.95 (CH–CO_2Me).

References

1. Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
2. Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967.
3. Blizzard, T. A. *Org. Prep. Proced. Int.* **1994**, *26*, 159.
4. Paterson, I.; Cumming, J. G.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413.
5. Yavari, I.; Asghari, S. *Tetrahedron* **1999**, *55*, 11853.
6. Yavari, I.; Nourmohammadian, F. *Tetrahedron* **2000**, *56*, 5221.
7. Yavari, I.; Samzadeh-Kermani, A. R. *Tetrahedron Lett.* **1998**, *39*, 6343.
8. Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821.
9. Parker, K. A.; Midt, T. L. *Org. Lett.* **2001**, *3*, 3875.
10. Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry*, 2nd ed. Pergamon: Oxford, 1996; Vol. 5. pp 324–350.
11. Zbiral, E. *Synthesis* **1974**, 775.
12. Becker, K. B. *Tetrahedron* **1987**, *36*, 1717.
13. Ingersoll, A. W.; Babcock, S. H. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2 p 531.