Ring contraction versus β-elimination in reactions of alkynyl-substituted bicyclic lactol esters with SmI₂/Pd(0)

José M. Aurrecoechea*, Roberto Fañanás and Beatriz López

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain
E-mail: qopaufem@lg.ehu.es

(received 14 Feb 00; accepted 25 Apr 00; published on the web 03 May 00)

DOI: http://dx.doi.org/10.3998/ark.5550190.0001.204

Abstract
Selective addition of alkynyl metal reagents to either carbonyl group of 2-(2-formylethyl)cycloalkanones afforded alkynyl-substituted bicyclic lactols that were further converted into the corresponding acetate or benzoate esters. Reactions of these bicyclic esters with SmI₂/Pd(PPh₃)₄ displayed a divergent behavior which was dependent on the degree of substitution at the alkynyl terminus as well as on the bicycle ring size. Thus, 2-oxabicyclo[4.3.0]nonanes with terminal alkynes gave ring contracted bicyclic alcohols whereas the presence of substituents at the alkynyl terminus or the use of higher bicycloalkane homologues led to enol ethers, as the result of Lewis acid-promoted β-elimination.

Keywords: Lactol esters, samarium iodide, palladium(o), β-elimination

Introduction

We have recently reported on the intramolecular propargylation of carbonyl compounds using the umpolung of propargylic esters I with SmI₂/Pd(0).¹⁻² This reaction is thought to involve the initial formation of an allenylpalladium complex II that is rapidly reduced to an equilibrium mixture of allenic (V) and propargylic (VI) organosamarium intermediates that finally add to the carbonyl group (Scheme 1).³

Therefore, in this reaction the propargylic acetate acts as a synthetic equivalent of the propargyl anion synthon. As an extension of this chemistry, we have described the alternative use of acetals (III, R¹ - R³ = H) and esters (IV, R¹ - R³ = H), derived from structurally related lactols, to convert a carbohydrate to carbocycle via a ring contraction of the carbohydrate that presumably proceeds through the same intermediates.⁴⁻⁶ We aimed to apply this last reaction to bicyclic substrates 1, 2 and 4. These would presumably afford the bicyclic alcohols 3 and 5 (Scheme 2) and this paper reports on the results of that study.⁷
Scheme 1

Results and Discussion

Synthesis of starting materials. The representative substrates 1, 2, and 4 were prepared using ketoaldehydes 6 as common starting materials (Scheme 3, Table 1). The method initially selected involved in situ protection of the aldehyde carbonyl using tetrakis(diethylamino)titanium according to the procedure developed by Reetz,8 followed by addition to the ketone to give lactols 7. This procedure worked well for additions to cyclohexanone 6a (Table 1, entries 1–3) but failed when cyclopentanone 6b was used.
Scheme 2

**Table 1. Preparation of Acetates 1 from Ketoaldehydes 6**

<table>
<thead>
<tr>
<th></th>
<th>R≡-M</th>
<th>7 (%)</th>
<th>1 (%)</th>
<th>Cis/trans&lt;sup&gt;a&lt;/sup&gt; Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a&lt;sup&gt;b&lt;/sup&gt;</td>
<td>H≡-MgBr</td>
<td>7a</td>
<td>1a (71)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>6a&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TMS≡-Li</td>
<td>7b (84)</td>
<td>1b (69)</td>
</tr>
<tr>
<td>3</td>
<td>6a&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ph≡-Li</td>
<td>7c</td>
<td>1c (54)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>6b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H≡-Li</td>
<td>7d (44)</td>
<td>1d (87)</td>
</tr>
<tr>
<td>5</td>
<td>6b&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n-Hex≡-Li</td>
<td>7e (33)</td>
<td>1e (89)</td>
</tr>
</tbody>
</table>

<sup>a</sup> *Cis/trans* refers to ring fusion. Ratio determined by <sup>1</sup>H NMR integration or from isolated weights of individual isomers.  
<sup>b</sup> Protection method: Ti(NEt<sub>2</sub>)<sub>4</sub>, −78 °C, then −52−(−43) °C.  
<sup>c</sup> Yield for two steps starting from 6a.  
<sup>d</sup> Protection method: dibenzylamine, benzotriazole, 4 Å molecular sieves, 25 °C, work-up.  
<sup>e</sup> Protection method: cyclohexylamine, 25 °C, work-up.  
<sup>f</sup> An approximate 20:1 diastereoisomer ratio.

In this case the starting ketoaldehyde was recovered unchanged. Alternatively, protection of the aldehyde carbonyl of 6b as either a N-(dibenzylaminoalkyl)benzotriazole<sup>9</sup> or N-cyclohexyl imine followed by addition of appropriate alkynyl lithium or magnesium derivatives to the remaining ketone carbonyl afforded moderate yields of lactols 7<sup>d,e</sup> (Table 1, entries 4,5). Lactols 7 were obtained with moderate to high diastereoselectivity. Acetylation of the lactols using standard conditions afforded in all cases good yields of acetates 1. Alternatively, treatment of lactol 7a with HCl/MeOH led to the corresponding acetal 2 as a single diastereoisomer (Scheme 3).
Scheme 3

For the synthesis of 4, the ketoaldehyde 6b was directly treated with the required alkynyl lithium and the resulting alkoxide intermediate was trapped with benzoyl chloride to afford moderate yields of benzoates 4. Two out of four isomers were observed at most for 1, 2 and 4. The stereochemistry of ring fusion has been determined for both isomers of 1c and the assignments were extended by analogy to 1a, 1b, 1d and 2. Thus, the major isomer of 1c, derived from cyclohexanone 6a, was assigned a cis-ring fusion based on the observed coupling constants (J) for its H-4 proton in the 1H NMR spectrum (Table 2).
Table 2. Coupling constants $J$ (in Hz) for H-4 in 1 and 2

<table>
<thead>
<tr>
<th>n (1,2)</th>
<th>R</th>
<th>X</th>
<th>Major isomer</th>
<th>Minor isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1a)</td>
<td>H</td>
<td>Ac</td>
<td>m</td>
<td>—</td>
</tr>
<tr>
<td>2 (1b)</td>
<td>TMS</td>
<td>Ac</td>
<td>m</td>
<td>dd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(10.2, 2.9)</td>
</tr>
<tr>
<td>2 (1c)</td>
<td>Ph</td>
<td>Ac</td>
<td>dd</td>
<td>dd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(7.3, 5.4)a</td>
</tr>
<tr>
<td>1 (1d)</td>
<td>H</td>
<td>Ac</td>
<td>dd</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(9.7, 2.7)</td>
</tr>
<tr>
<td>1 (1e)</td>
<td>n-Bu</td>
<td>Ac</td>
<td>dd</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(9.8, 2.6)</td>
</tr>
<tr>
<td>2 (2)</td>
<td>H</td>
<td>Me</td>
<td>m</td>
<td>—</td>
</tr>
</tbody>
</table>

These values were intermediate between those expected for axial and equatorial dispositions of that proton. This assignment was confirmed by the temperature dependence shown by the apparent $J$ values of H-4 in that isomer (see Table 2). This indicated a flexible conformation only compatible with a cis ring junction. This analysis did not allow, however, an unambiguous configurational assignment for C-4. On the other hand, H-4 in minor 1c appeared in the $^1$H NMR spectrum as doublet of doublets with $J = 10.1, 3.1$ Hz. This signal remained unchanged over a temperature interval between $-30$ and $58 \degree C$ and this was taken as an indication of a rigid trans ring fusion with an axial disposition for H-4. According to this analysis, the major isomers of cyclopentanone-derived 1d,e would present trans ring junctions as indicated by their H-4 $J$ values ($\sim 10$ and $3$ Hz). No stereochemical assignment was made for 4a,b.

Reactions with SmI$_2$/Pd(0). The major isomers of lactol esters 1 and 4 were independently treated with 2.2 equivalents of SmI$_2$ and a catalytic amount of Pd(PPh$_3$)$_4$ (5 mol%) at room temperature. The results were drastically dependent on the type of substrate employed and the presence or absence of substituents at the terminal alkynyl position (Scheme 4, Table 3).
Scheme 4

Thus, for cyclopentanone-derived substrates 1d and 4a, with a terminal alkyne, a slow reaction was observed that led to the formation of bicyclic alcohols 3d and 5a, respectively, with good yields and excellent stereoselectivities. However, the reaction took a completely different course when a terminal alkynyl substituent was present in the substrate, as in 1e and 4b. In those cases the only reaction products isolated were the enol ethers 8e and 9b, respectively. Similarly, the reactions of the cyclohexanone-derived 1a-c led predominantly to enol ethers 8a-c, accompanied occasionally by lactols 7, probably the result of hydrolysis of 8 during work-up. The formation of enol ethers 8 does not require the presence of Pd(0) in the medium, as indicated by the result of entry 3 in Table 3. The acetal 2 was inert in the presence of SmI₂/Pd(PPh₃)₄ even under refluxing conditions.

Table 3. Reactions of 1 and 4 with SmI₂/Pd(PPh₃)₄

<table>
<thead>
<tr>
<th>1a</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>8a</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>TMS</td>
<td>8b</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Ph</td>
<td>8c</td>
</tr>
</tbody>
</table>
The stereochemical assignment of 3d followed from the chemical shift differences found in the carbinolic protons of the diastereomeric mixture of alcohols 3d and 3d' obtained after NaBH₄ reduction of the ketone 10 that resulted from the PDC oxidation of 3d (Scheme 5). Thus, H-4 of 3d resonated at δ 4.37 whereas the corresponding proton in 3d’, buried in the concave face of the bicyclic structure, was found further upfield at δ 3.8−3.9. The bicycle 5a obtained from 4a was identical in all physical properties to the previously reported material prepared using the route I → VII (Scheme 1).¹

![Scheme 5](image)

**Results and Discussion**

Carbohydrate-derived monocyclic acetals and esters related to 1, 2 and 4 have been employed in ring reaction reactions leading to 2-alkynylcyclopentanols,⁵,⁶ a transformation that is readily understood in the mechanistic terms shown in Scheme 1. This reaction is facilitated by Lewis acidic Sm(III) species, inevitably present in the reaction medium, that activate the leaving group (OMe or OCOR) and bring about the initial oxidative addition step that begins the catalytic cycle. Always latent in these reactions is the possibility of β-elimination promoted by the same Lewis acids or even by SmI₂.¹⁰ In monocyclic systems with terminal alkynes the oxidative addition is reasonably fast and, as a result, ring opening is favored over β-elimination.⁵,⁶ This also seems to be the case with cyclopentanone-derived substrates 1d and 4a. If, on the other hand, the oxidative addition step becomes slower due to the presence of terminal alkynyl substituents, then β-elimination takes over as it is observed in the reactions of 1e and 4b. However, it is also apparent from the strikingly different results observed for 1a and 1d, that the
size of the rings containing the bridgehead propargylic position, as well as the axial or equatorial orientation of the leaving group, are also probably important to the outcome of the reaction. Thus, β-elimination from the equatorial leaving group of the conformationally rigid bicycle 1d is expected to be slower than from the much more flexible bicycle 1a where both axial and equatorial orientations of the leaving group are possible at any given time. Additionally, the hybridization change in cyclopentanone-derived 1d in going to an intermediate related to II (Scheme 1) should be more favorable than that taking place in cyclohexanone-derived 1a. Taken together, all these factors give as a result a preferred β-elimination pathway for 1a−c.

Conclusions

The SmI₂/Pd(0)-promoted ring contraction of bicyclic lactol esters leads to the expected bicyclic homopropargyl alcohols only when the oxidative addition that initiates the reaction competes efficiently with the alternative Lewis acid-promoted β-elimination. The synthetic potential of the ring contraction process for the preparation of bicyclic systems is significantly restricted by factors that adversely affect oxidative addition, namely (i) the presence of terminal alkynyl substituents and (ii) the development of torsional strain upon ring opening. At the same time, β-elimination is facilitated by axial leaving groups with an antiperiplanar β-hydrogen.

Experimental Section

General Procedures. All reactions involving air- and moisture-sensitive materials were performed using standard bench-top techniques. Diiodoethane was purified as reported. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI₂, it was deoxygenated prior to use. Other solvents were routinely purified using literature procedures. Flash column chromatography was performed on silica gel (230−400 mesh). HPLC purifications were carried out with either a LiChrosorb Si60 (7 µm, 25 x 2.5 cm, column 1) or a µ Porasil (10 µm, 19 x 1.5 cm, column 2) column using a refractive index detector. Routine ¹H and ¹³C NMR spectra were obtained at 250 MHz and 62.9 MHz, respectively, using CDCl₃ as solvent and internal reference (δ 7.26 for ¹H and δ 77.0 for ¹³C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

Ethyl 4-acetoxy-6-ethynyl-cis-5-oxabicyclo[4.4.0]decanecarboxylate (1a). To a stirred solution of 6a (543 mg, 2.40 mmol) in THF (19 mL) at −78 °C was added dropwise Ti(NEt₂)₄ (880 µL, 2.43 mmol). The mixture was allowed to reach −43 °C over a period of 1 h, and ethynylmagnesium bromide (0.5 M in THF, 9.8 mL, 4.90 mmol) was added dropwise. The resulting solution was stirred at the same temperature for 14 h and quenched with 1 M HCl (19 mL). The aqueous layer was extracted with EtOAc (3 x 45 mL) and the combined organic
extracts were washed with brine (6 mL) and dried (Na₂SO₄). The crude after evaporation of the solvent was dissolved in triethylamine (1.20 mL, 8.61 mmol) and treated with acetic anhydride (680 μL, 7.20 mmol) and then DMAP (90 mg, 0.73 mmol). The mixture was stirred at room temperature for 15 h, diluted with Et₂O (80 mL) and poured over ice-water (8 mL). The aqueous layer was extracted with Et₂O (3 x 20 mL) and the combined organic layers were successively washed with 1 M HCl (10 mL), 1 M NaOH (9 mL), H₂O (6 mL) and brine (6 mL). After drying (Na₂SO₄) and evaporation of the solvents the resulting residue was purified by flash chromatography (silica gel, 15% EtOAc in hexanes) to afford 1a (473 mg, 71%) as a colorless oil: ¹H NMR δ 1.25 (t, J = 7.1 Hz, 3H, CO₂CH₂CH₃), 1.38–2.24 (m, 13H), 2.10 (s, OCOC₂H₅, included in m at 1.38–2.24), 2.24–2.37 (m, 1H), 2.49 (td, J = 13.5, 4.8 Hz, 1H), 2.60 (s, 1H, H-2'), 4.16 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 6.21–6.26 (m, 1H, H-4); ¹³C NMR δ 14.0, 20.1, 21.7, 27.9, 28.2, 28.9, 35.8, 47.3, 60.5, 73.0, 75.0, 83.7, 93.3; IR (KBr) ν 3370, 3240, 2085, 1735 cm⁻¹. Anal. Calcd for C₁₄H₂₀O₄: C, 66.63; H, 7.99. Found: C, 66.51; H, 7.87.

Ethyl 4-acetoxy-6-(trimethylsilylethynyl)-5-oxabicyclo[4.4.0]decanecarboxylate (1b). The procedure described for the synthesis of 1a was followed from 6a (521 mg, 2.30 mmol) and lithium (trimethylsilyl)acetylhydride (~ 0.27 M, 2.85 mmol). Reaction time : 1.2 h at −45 °C. The intermediate lactols were purified by flash chromatography (silica gel, 20% EtOAc in hexanes, then 30% EtOAc in hexanes) and then acetylated individually as described for 1a. The acetate derived from the major lactol was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to afford cis-1b (295 mg, 35% from 6a) as a colorless oil. The acetate derived from the minor lactol was purified by flash chromatography (silica gel, 8% EtOAc in hexanes, then 10% EtOAc in hexanes) and HPLC (column 1, 10% EtOAc in hexanes, 8 mL/min, tᵣ 32 min) to yield trans-1b (173 mg, 23% from 6a). Data for cis-1b: ¹H NMR δ 0.15 (s, 9H, Si(CH₃)₃), 1.26 (t, J = 7.1 Hz, 3H, CO₂CH₂CH₃), 1.50–2.13 (m, 14H), 2.09 (s, OCOC₂H₅, included in m at 1.50–2.13), 2.24–2.51 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 6.20–6.26 (m, 1H, H-4); ¹³C NMR δ −0.2, 14.1, 20.0, 21.2, 21.5, 28.2, 28.7, 35.3, 47.3, 60.4, 74.3, 92.3, 92.6, 104.4, 169.1, 173.5; IR (neat) ν 2160, 1760, 1730 cm⁻¹. Anal. Calcd for C₁₀H₁₆O₂Si: C, 62.26; H, 8.26. Found: C, 62.32; H, 8.14. Data for trans-1b: ¹H NMR δ −0.21 (s, 9H, Si(CH₃)₃), 1.08–1.30 (m, 4H), 1.27 (t, J = 7.1 Hz, CO₂CH₂CH₃, included in m at 1.08–1.30), 1.37–2.17 (m, 13H), 2.08 (s, OCOC₂H₅, included in m at 1.37–2.17), 2.63–2.75 (m, 1H), 4.10–4.24 (m, 2H, CO₂CH₂CH₃), 6.40 (dd, J = 7.0, 2.0 Hz, 1H, H-4).
10.2, 2.9 Hz, 1H, H-4); $^{13}$C NMR δ −0.31, 14.1, 21.1, 22.0, 22.9, 27.9, 30.2, 33.0, 49.3), 60.1, 78.4, 92.4, 94.9, 103.9, 169.0, 172.3; IR (KBr) ν 2150, 1750 cm$^{-1}$. Anal. Calcd for C$\text{_{10}}$H$\text{_{30}}$O$\text{_{5}}$Si: C, 62.26; H, 8.26. Found: C, 62.07; H, 8.28.

**Ethyl 4-acetoxy-6-(phenylethynyl)-5-oxabicyclo[4.4.0]decanecarboxylate (1c).** Prepared from 6a$^{15}$ (955 mg, 4.22 mmol) and lithium phenylacetylide (~ 0.35 M, 5.08 mmol) following the procedure described for the synthesis of 1a. The addition of the lithium reagent was done at −78 °C and the reaction was allowed to proceed at −52 °C for 2.2 h. The crude product was purified by flash chromatography (silica gel, 15%, 25% and finally 35% EtOAc in hexanes) to afford cis-1c (546 mg) and trans-1c (140 mg, after additional purification by HPLC). Data for cis-1c: $^1$H NMR δ 12.7 (t, J = 7.1 Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.53−2.22 (m, 13H), 2.12 (s, OCOCH$_3$, included in m at 1.53−2.22), 2.33−2.62 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H, CO$_2$CH$_2$CH$_3$), 6.35 (dd, J = 7.3, 5.4 Hz, 1H, H-4), 7.27−7.29 (m, 3H, Ar-H), 7.41−7.45 (m, 2H, Ar-H); $^{13}$C NMR δ 14.0, 2 0.0, 21.0, 21.5, 25.3, 28.2, 28.8, 35.3, 47.5, 60.3, 74.4, 87.3, 88.2, 92.5, 122.4, 128.0, 128.1, 131.5, 168.9, 173.4; IR (neat) ν 2225, 1753, 1725 cm$^{-1}$; HRMS calcd for C$_{22}$H$_{26}$O$_{5}$ 370.1780, found 370.1778. Data for trans-1c: HPLC (column 1, 25% EtOAc in hexanes, 7 mL/min) t$\text{_{R}}$ 24 min; $^1$H NMR δ 1.19−1.31 (m, 4H), 1.28 (t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$), included in m at 1.19−1.31), 1.44−2.13 (m, 8H), 2.05−2.10 (m, 5H), 2.09 (s, OCOCH$_3$, included in m at 2.05−2.10), 2.16 (td, J = 13.6, 9.8 Hz, included in m at 2.05−2.10), 2.72−2.85 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H, CO$_2$CH$_2$CH$_3$), 6.48 (dd, J = 10.1, 3.1 Hz, 1H, H-4), 7.30−7.35 (m, 3H, Ar-H), 7.44−7.50 (m, 2H, Ar-H); $^{13}$C NMR δ 14.2, 21.2, 22.2, 23.1, 28.1, 30.5, 33.3, 49.8, 60.3, 78.7, 87.7, 89.9, 92.122.3, 128.3, 128.5, 131.6, 169.3, 172.5; IR (neat) ν 2225, 1753, 1725 cm$^{-1}$; HRMS calcd for C$_{22}$H$_{26}$O$_{5}$ 370.1780, found 370.1775.

**Ethyl 4-methoxy-cis-5-oxabicyclo[4.4.0]decanecarboxylate (2).** A solution of 7a (273 mg, 1.08 mmol) in MeOH/HCl (98:2, 4.3 mL) was refluxed for 3 h. Saturated K$_2$CO$_3$ (5 mL) was added until basic pH and MeOH was evaporated at reduced pressure. The aqueous layer was extracted with EtOAc (100, 25 and 25 mL) and the combined organic layers were washed with brine (10 mL) and dried (Na$_2$SO$_4$). The crude after evaporation of the solvent was purified by flash chromatography (silica gel, 7% EtOAc in hexanes) to yield 2 (230 mg, 79%, one isomer): $^1$H NMR δ 1.21 (t, J = 7.1 Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.28−2.24 (m, 11H), 2.44 (td, J = 13.3, 4.5 Hz, 1H), 2.50 (s, 1H, H-2’), 3.42 (s, 3H, OCH$_3$), 4.10 (q, J = 7.1 Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.85−4.90 (m, 1H, H-4); $^{13}$C NMR δ 14.0, 20.0, 21.6, 26.2, 28.1, 28.8, 35.5, 47.4, 55.9, 60.3, 72.5, 74.6, 83.9, 99.9, 173.8; IR (neat) ν 3255, 2101, 1733 cm$^{-1}$; Anal. Calcd for C$_{15}$H$_{22}$O$_4$: C, 67.63; H, 8.33. Found: C, 67.72; H, 8.40.

**Ethyl 6-ethynyl-4-hydroxy-5-oxabicyclo[4.3.0]nonanecarboxylate (7d).** A mixture of 6b$^{16}$ (0.223 g, 1.07 mmol), benzoic acid (0.127 g, 1.07 mmol), dibenzyamine (0.20 mL, 1.07 mmol) and 4 Å molecular sieves (4 g) in benzene (30 mL) was stirred for 12 h at 25 °C and filtered through Celite. The solvent was removed at reduced pressure and the residue was dissolved in THF (30 mL). To the well stirred solution at −78 °C was added via cannula lithium acetylide$^{17}$ (0.042 M, 1.26 mmol) and the mixture was stirred at −78 °C for 30 min. The solution was allowed to reach room temperature and stirred further 3 h. After adding 3 M HCl (15 mL) the
layers were separated, the organic layer was washed with brine (15 mL) and dried (Na₂SO₄). The crude after evaporation was purified by flash chromatography (silica gel, 35% EtOAc in hexanes) to yield 0.123 g (44%) of lactol 7e as an oil: ¹H NMR δ 0.88 (t, J = 7.1 Hz, 3H, CH₃), 1.24 (t, J = 7.2 Hz, 3H, OCH₂CH₃, major isomer, overlapped signals from the minor isomer), 1.32–1.60 (m, 4H), 1.77–2.09 (m, 8H), 2.17 (t, J = 6.8 Hz, 2H, CH₂-C), 2.27–2.48 (m, 2H), 3.33 (d, J = 6.0 Hz, 1H, OH), 4.01–4.18 (m, 2H, OCH₂CH₃), 5.10 (ddd, J = 9.6, 6.0, 1.9 Hz, 1H, H-4); ¹³C NMR (major diast.) δ 13.5, 14.0, 18.3, 21.7, 21.8, 24.8, 27.7, 30.6, 40.9, 56.1, 60.6, 77.1, 81.6, 88.0, 92.8, 174.7; IR (neat) 3420, 2230, 1730 cm⁻¹; HRMS calcd for C₁₇H₂₆O₄ 277.1804 (M-OH), found 277.1804.

Ethyl 4-acetoxy-6-ethynyl-5-oxabicyclo[4.3.0]nonanecarboxylate (1d). The acetylation procedure described for the preparation of 1a was applied to 7d (0.260 g, 1.09 mmol). The crude product was purified by flash chromatography (silica gel, 15% EtOAc in hexanes) to yield 0.265 g (87 %) of acetate 1d as an oil: ¹H NMR δ 1.20 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.54–2.12 (m, 11H), 2.03 (s, CH₃CO, included in m at 1.54–2.12), 2.28-2.49 (m, 2H), 2.56 (s, 1H, acetylenic), 4.09 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 5.97 (dd, J = 9.7, 2.7 Hz, 1H, H-4); ¹³C NMR δ 13.8, 20.9, 21.4, 24.3, 24.9, 30.6, 40.2, 55.8, 60.7, 75.9, 79.9, 81.7, 91.7, 168.8, 173.8; IR (neat) 3260, 2100, 1750, 1725 cm⁻¹; HRMS calcd for C₁₅H₂₀O₅: 280.1311, found 280.1292.

Ethyl 4-Acetoxy-6-(hex-1-ynyl)-5-oxabicyclo[4.3.0]nonanecarboxylate (1e). The acetylation procedure described for the preparation of 1a was applied to 7e (0.800 g, 2.72 mmol). The crude product was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to yield 0.814 g (89 %, ~ 20:1 diastereomeric mixture) of acetate 1e as an oil: ¹H NMR δ 0.84–0.97 (m, 3H, CH₃), 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃, major isomer, overlapped signals of the minor isomer), 1.34–2.12 (m, 15H), 2.04 (s, CH₃CO, minor diast., included in m at 1.34–2.12), 2.09 (s,
CH₃CO₂-, major diast., included in m at 1.34–2.12), 2.21 (t, J = 6.9 Hz, 2H, CH₂-C), 2.34–2.50 (m, 2H), 4.07–4.19 (m, 2H, OCH₂CH₃), 6.03 (dd, J = 9.8, 2.6 Hz, 1H, H-4); ¹³C NMR (major diast.) δ 13.4, 14.0, 18.2, 21.1, 21.6, 21.7, 24.5, 25.2, 30.5, 30.7, 40.5, 56.1, 60.6, 76.1, 82.6, 88.6, 92.1, 169.0, 174.3; IR (neat) 2230, 1730 cm⁻¹; HRMS calcd for C₁₉H₂₈O₅ 336.1937, found 336.1942.

**Ethyl 6-benzoyloxy-4-ethynyl-5-oxabicyclo[4.3.0]nonanecarboxylate (4a).** To a solution of 6b (2.10 g, 10.2 mmol) in THF (50 mL) at −78 °C was added via cannula over 1 h a solution of lithium acetylide (0.21 M, 10.7 mmol) in THF (50 mL). The solution was stirred at −78 °C for 90 min and benzoyl chloride (2.4 mL, 20.45 mmol) was added neat. After allowing the mixture to reach room temperature, H₂O (20 mL) was added, the aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were dried (Na₂SO₄). The crude was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to yield 1.20 g (35%) of 4a as a colorless solid: mp 163–165 °C; ¹H NMR δ 14.1, 20.4, 24.9, 26.8, 29.0, 36.5, 53.4, 61.0, 62.0, 73.3, 82.1, 109.3, 128.4, 129.8, 130.2, 133.2, 163.3, 174.1; IR (neat) 3300, 1740 cm⁻¹. Anal. Calcd for C₂₀H₂₅O₅: C, 70.16; H, 6.48. Found: C, 70.36; H, 6.62.

**Ethyl 6-benzoyloxy-4-(hex-1-ynyl)-5-oxabicyclo[4.3.0]nonanecarboxylate (4b).** The previous procedure was applied to 6b (2.30 g, 10.85 mmol) and hex-1-ynyl lithium (11.39 mmol). The crude was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to yield 1.31 g (30%, 17:1 diastereomeric mixture) of benzoate 4b as an oil: ¹H NMR δ 0.87 (t, J = 6.8 Hz, 3H, CH₃), 1.08 (t, J = 7.1 Hz, OCH₂CH₃, minor diast.) and 1.17–1.51 (m) (total 7H), 1.20 (t, J = 7.1 Hz, OCH₂CH₃, major diast., included in m at 1.17–1.51), 1.70–2.04 (m, 7H), 2.17 (t, J = 6.9 Hz, 2H, CH₂-C_), 2.43–2.60 (m, 2H), 2.71–2.87 (m, 1H), 4.05–4.24 (m, 2H, OCH₂CH₃), 4.37–4.42 (m, 1H, H-4), 7.35–7.64 (m, 3H), 8.00 (d, J = 8.0 Hz, major diast.) and 8.13 (d, J = 8.0 Hz, minor diast.) (total 2H); ¹³C NMR (major diast.) δ 13.2, 13.8, 18.2, 20.1, 21.6, 24.7, 27.1, 28.6, 30.1, 36.1, 53.0, 60.6, 62.2, 78.1, 85.4, 109.0, 128.1, 129.4, 130.0, 132.8, 163.0, 173.9; IR (neat) 2230, 1730 cm⁻¹; HRMS calcd for C₂₄H₃₀O₅ 398.2093, found 398.2068.

**General procedure for reactions of 1, 2, 4 with SmI₂/Pd(PPh₃)₄.**

In a typical experiment, a solution of the substrate (0.50 mmol) and Pd(PPh₃)₄ (0.025 mmol) in THF (4 mL) was added to a solution of SmI₂ (1.1 mmol) in THF (11 mL) at room temperature. The resulting mixture was stirred until total conversion of the substrate (as determined by TLC) and saturated K₂CO₃ (5 mL) was added. The aqueous layer was extracted with EtOAc (4 x 35 mL), the combined organic layers were washed with brine (3 mL) and dried (Na₂SO₄). The crude product obtained after evaporation was purified by flash chromatography as specified for the individual cases.

**Ethyl 6-ethynyl-cis-5-oxabicyclo[4.4.0]dec-3-ene-carboxylate (8a).** The general procedure was followed from 1a (136 mg, 0.49 mmol). Reaction time: 62 h. The crude product was purified by
flash chromatography (silica gel, 5% EtOAc in hexanes, then 40% EtOAc in hexanes) to afford 8a (75 mg, 65%) and 7a (7 mg, 6%). Data for 8a: 1H NMR δ 1.24–1.33 (m, 4H), 1.26 (t, J = 7.1 Hz, CO₂CH₂CH₃ included in m at 1.24–1.33), 1.52–1.64 (m, 4H), 1.72–1.77 (m, 2H), 1.94–2.03 (m, 2H), 2.42 (s, 1H, H-2'), 2.42–2.62 (m, 2H), 4.17 (q, J = 7.1 Hz, CO₂CH₂CH₃) and 4.18 (q, J = 7.1 Hz, CO₂CH₂CH₃) (total 2H), 4.80 (dt, J = 5.7, 2.3 Hz, 1H, H-3), 6.26 (dt, J = 5.7, 1.7 Hz, 1H, H-4); 13C NMR δ 14.1, 20.4, 21.9, 29.3, 29.7, 34.1, 47.1, 60.5, 71.5, 72.3, 84.5, 99.1, 140.1, 173.5; IR (neat) ν 3290, 1740, 1670 cm⁻¹; HRMS calcd for C₁₉H₁₈O₃Si 306.1651, found 306.1646.

Ethyl 6-(trimethylsilylethynyl)-cis-5-oxabicyclo[4.4.0]dec-3-ene-carboxylate (8b). The general procedure was followed from 1b(110 mg, 0.30 mmol) for 16 h. The crude product was purified by flash chromatography (silica gel, 2.5% EtOAc in hexanes) to yield 8b (58 mg, 63%) as an oil: 1H NMR δ 0.12 (s, 9H, Si(CH₃)₃), 1.25 (t, J = 7.1 Hz, 3H, CO₂CH₂CH₃), 1.34–1.73 (m, 6H), 1.90–2.00 (m, 2H), 2.40–2.56 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.69–4.75 (m, 1H, H-3), 6.21 (apparent d, J = 6.0 Hz, 1H, H-4); 13C NMR δ -0.1, 14.1, 20.5, 21.7, 29.0, 29.9, 34.0, 47.2, 60.4, 72.6, 88.2, 98.7, 106.1, 140.0, 173.5; IR (neat) ν 3065, 2169, 1736, 1663 cm⁻¹; HRMS calcd for C₁₉H₂₂O₂Si 306.1651, found 306.1646.

Ethyl 6-(phenylethynyl)-cis-5-oxabicyclo[4.4.0]dec-3-ene-carboxylate (8c). A solution of 1c (115 mg, 0.38 mmol) in THF (4 mL) was added to a solution of SmI₂ (0.1 M in THF, 9.5 mL, 0.95 mmol) at room temperature. The mixture was stirred for 22 h at the same temperature and was elaborated as specified in the general procedure. The crude product was purified by flash chromatography (silica gel, 8% EtOAc in hexanes) to yield 8c (72 mg, 78%) as an oil: 1H NMR δ 1.24–2.00 (m, 7H), 1.26 (t, J = 7.1 Hz, CO₂CH₂CH₃ included in m at 1.24–2.00), 2.05–2.11 (m, 2H), 2.47–2.69 (m, 2H), 4.19 (q, J = 7.0 Hz, CO₂CH₂CH₃) and 4.20 (q, J = 7.1 Hz, CO₂CH₂CH₃) (total 2H), 4.79 (td, J = 5.9, 2.2 Hz, 1H, H-3), 6.29 (d, J = 5.9 Hz, 1H, H-4), 7.26–7.27 (m, 3H, Ar-H), 7.38–7.42 (m, 2H, Ar-H); 13C NMR δ 14.1, 20.6, 21.8, 29.3, 29.9, 47.5, 60.4, 72.8, 83.6, 90.0, 98.9, 122.9, 128.0, 131.7, 140.2, 173.5; IR (neat) ν 3063, 2230, 1733, 1662 cm⁻¹; HRMS calcd for C₂₀H₂₂O₃Si 310.1569, found 310.1574.

(1R*,4R*,5R*)-Ethyl 5-ethynyl-4-hydroxybicyclo[3.3.0]octanecarboxylate (3d). Prepared from acetate 1d (0.714 mmol) and Pd(PPh₃)₄ (0.036 mmol) in THF (8 mL) using the general procedure. Reaction time: 64 h. The crude was purified by flash chromatography (silica gel, 35% EtOAc in hexanes) to yield the alcohol 3d (0.134 g, 84%) as a colorless oil. The spectral sample was obtained after HPLC (column 2, 15% EtOAc in hexanes, 6 mL/min): tᵣ 15 min; 1H NMR δ 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.41–2.20 (m, 9H), 2.18 (s, acetylenic, included in m at 1.41–2.20), 2.26–2.55 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.37 (dd, J = 10.3, 6.3 Hz, 1H, H-4); 13C NMR δ 14.1, 26.2, 31.6, 32.0, 35.3, 38.3, 56.4, 60.8, 63.9, 70.3, 80.2, 88.5, 175.4; IR (neat) 3450, 2100, 1725 cm⁻¹; HRMS calcd for C₁₃H₁₉O₃ (M+1) 223.1334, found 223.1357.

Ethyl 5-ethynyl-4-oxobicyclo[3.3.0]octanecarboxylate (10). To a solution of alcohol 1d (0.053 g, 0.238 mmol) in CH₂Cl₂ (6 mL) was added PDC (0.30 g, 0.79 mmol) and the mixture was stirred at room temperature for 60 h, diluted with ether (25 mL), filtered through silica gel (70–230 mesh) and evaporated to dryness. The crude after evaporation was purified by flash...
chromatography (silica gel, 20% EtOAc in hexanes) to yield the ketone 10 (0.049 g, 94%) as a colorless oil: $^1$H NMR $\delta$ 1.28 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.57−2.05 (m, 3H), 2.12−2.33 (m, 4H), 2.29 (s, acetylenic, included in m at 2.12−2.33), 2.37−2.58 (m, 3H), 2.67−2.82 (m, 1H), 4.20 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$); $^{13}$C NMR $\delta$ 14.1, 24.1, 28.2, 35.4, 35.8, 37.6, 58.8, 61.1, 62.4, 73.1, 81.1, 173.9, 213.1; IR (neat) 3060, 2210, 1730 cm$^{-1}$.

**Reduction of ketone 10.** To a solution of 10 (22 mg, 0.10 mmol) in ethanol (5 mL) at 0 °C was added NaBH$_4$ (5 mg, 0.13 mmol). The mixture was stirred for 30 min and water (2 mL) was added. The mixture was extracted with ether (3 x 20 mL) and the organic extracts were dried (Na$_2$SO$_4$). The crude after evaporation was purified by flash chromatography (silica gel, 5% EtOAc in hexanes and then 40% EtOAc in hexanes) to yield the alcohols 3d, 3d’ (15 mg, 69%, 1:1 diastereomeric mixture) as a colorless oil. The spectral sample was obtained after HPLC (column 2, 20% EtOAc in hexanes, 6 mL/min): $t_R$ 9 (3d) and 10 (3d’) min; $^1$H NMR (mixture of isomers) $\delta$ 1.28 and 1.29 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.39−2.17 (m, 8H), 2.31−2.68 (m, 2H), 2.20 and 2.37 (s, 1H, acetylenic), 2.83 (d, $J = 8.2$ Hz, OCH, one isomer). 3.81-3.88 (m, H-4, 3d’), 4.11−4.22 (m, 2H, OCH$_2$CH$_3$), 4.40 (br t, H-4, 3d); $^{13}$C NMR (mixture of isomers) $\delta$ 14. (3d), 25.3 (3d’), 26.2 (3d), 31.6 (3d’), 32.1 (3d), 33.6 (3d’), 34.0 (3d’), 35.3 (3d), 37.9 (3d’), 38.3 (3d), 39.8 (3d’), 56.5 (3d), 59.4 (3d’), 60.8 (3d), 61.1 (3d’), 63.9 (3d), 64.3 (3d’), 70.4 (3d), 74.1 (3d’), 79.2 (3d’), 80.3 (3d), 84.7 (3d’), 88.5 (3d), 175.3 (3d), 176.0 (3d’); GC-MS $t_R$ 8.65 (3d) and 8.82 (3d’) min.

**Ethyl 6-(hex-1-ynyl)-5-oxabicyclo[4.3.0]non-3-enecarboxylate (8e).** Prepared from 1e (0.625 mmol) and Pd(PPh$_3$)$_4$ (0.031 mmol) in THF (8 mL) following the general procedure. Reaction time: 77 h. The crude was purified by flash chromatography (silica gel, hexanes) to yield the ether 8e (0.152 g, 88 %) as a colorless oil: $^1$H NMR $\delta$ 0.85 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.23 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.29−1.48 (m, 4H), 1.66−2.10 (m, 6H), 2.15 (t, $J = 6.8$ Hz, 2H, CH$_2$C$_3$), 2.26−2.38 (m, 1H), 2.64 (ddd, $J = 17.9$, 2.6, 2.5 Hz, 1H, H-2), 4.12 (q, $J = 7.1$ Hz, 1H, OCHCH$_3$), 4.13 (q, $J = 7.1$ Hz, 1H, OCHCH$_3$), 4.69 (ddd, $J = 6.2$, 5.0, 2.6 Hz, 1H, H-3), 6.21 (ddd, $J = 6.2$, 2.5, 2.5 Hz, 1H, H-4); $^{13}$C NMR $\delta$ 13.4, 14.0, 18.3, 20.4, 21.7, 23.7, 30.5, 31.7, 38.8, 54.9, 60.6, 77.9, 78.8, 85.8, 95.3, 139.7, 173.9; IR (neat) 2230, 1730 (C=C), 1700, 1650 cm$^{-1}$; HRMS calcd for C$_{17}$H$_{26}$O$_3$ 276.1735, found 276.1732.

**Ethyl 4-(hex-1-ynyl)-5-oxabicyclo[4.3.0]non-6-enecarboxylate (9b).** Prepared from 4b (0.606 mmol) and Pd(PPh$_3$)$_4$ (0.031 mmol) in THF (8 mL) following the general procedure. Reaction time: 19 h. The crude after evaporation was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to yield in order of elution the ether 9b (0.063 g, 37%) and recovered starting material 4b (0.077 g, 32%) as colorless oils. Data for 9b: $^1$H NMR $\delta$ 0.88 (t, $J = 7.0$ Hz,3H, CH$_3$), 1.23 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.26−1.52 (m, 4H), 1.60−2.44 (m, 10H), 4.03−4.29 (m, 2H, OCH$_2$CH$_3$), 4.84 (m, 1H, H-4), 5.17 (br s, $W_{1/2}$ = 8.0 Hz, 1H, H-7); $^{13}$C NMR $\delta$ 13.5, 14.1, 18.2, 21.7, 25.8, 27.9, 29.9, 30.6, 36.8, 51.5, 60.8, 67.8, 77.5, 87.6, 109.4, 152.7, 175.0; IR (neat) 3060, 2210, 1730 cm$^{-1}$; HRMS calcd for C$_{17}$H$_{26}$O$_3$ 277.1804 (M+1), found
Acknowledgments

Financial support by the Dirección General de Investigación Científica y Técnica (DGICYT PB89-0412, PB92-0449 and PB95-0344) and by the Universidad del País Vasco (UPV 170.310-0133/89, UPV 170.310-EC021/92 and UPV 170.310-EC216/97) is gratefully acknowledged. We also thank the Departamento de Educación, Universidades e Investigación (Gobierno Vasco, Spain) for Fellowships to R.F. and B. L.

References

7. A portion of this work has been communicated: Aurrecoechea, J. M.; Fañanás-San Antón, R. J. Org. Chem. 1994, 59, 702.
10. See, for example, the discussion in: Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. Tetrahedron 1997, 53, 9023.
16. Prepared following the procedure described in ref 15 for 6a.