Synthesis of bicyclic alcohols by palladium-catalyzed Et$_2$Zn-mediated intramolecular carbonylpropargylation

Mónica Arrate and José M. Aurrecoechea*

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco UPV/EHU, Apartado 644, 48080 Bilbao, Spain
Email: jm.aurrecoechea@ehu.eus

Received 07-05-2017  Accepted 09-22-2017  Published on line 11-19-2017

Abstract

Propargylic esters derived from cyclic ketones containing a tethered aldehyde generate bicyclic homopropargyl alcohols upon treatment with Et$_2$Zn in the presence of a catalytic amount of Pd(0). The reaction is thought to involve an intramolecular carbonyl addition of intermediate allenylzinc nucleophilic species generated from the propargylic ester functionality. The resulting trisubstituted bicyclic products are obtained with high stereoselectivity. Examples are provided where the reaction is successfully applied to both cyclopentanone- and cyclohexanone-derived substrates containing either terminal or internal alkyne, thus overcoming some of the limitations previously encountered with the use of alternative methodology.

Keywords: Cyclization, palladium, propargylation, allenylpalladium, diethylzinc
Introduction

Propargylic esters are a convenient type of functionalized reagent because they are stable, readily available and easy to handle. Among other applications, propargylic esters are precursors of nucleophilic organometallic species that behave as synthetic equivalents of the propargyl anion, participating in nucleophilic addition reactions to carbonyl or imine derivatives.\(^1\)\(^-\)\(^3\) We have exploited this particular reactivity of propargylic esters (and related substrates) in SmI\(_2\)-promoted Pd-catalyzed intramolecular propargylations of carbonyl derivatives to generate alkynylcycloalkanol derivatives.\(^4\)\(^-\)\(^8\) These reactions are thought to proceed via transient allenylpalladium II intermediates that undergo transmetalation with SmI\(_2\) to generate nucleophilic allenylsamarium species IIIa capable of carbonyl nucleophilic addition (Scheme 1). A variant was also developed where acetal-type derivatives V were used as masked aldehydes to generate the same intermediates.\(^6\)\(^-\)\(^8\) Particularly interesting was the case of formation of bicyclic alkynylcyclopentanol products, compounds that have attracted attention as synthetic intermediates\(^9\)\(^-\)\(^11\) and as components of therapeutically interesting molecules related to prostaglandins.\(^12\)\(^-\)\(^19\) A high stereoselectivity was observed in that case,\(^4\)\(^,\)\(^5\) but some limitations were also found. Thus, only ketone carbonyls could be used in combination with the propargylic esters I,\(^5\) and the reactions of acetals V were limited to terminal alkynes. Furthermore, only the [3.3.0] ring fusion was accessible when forming bicyclic products from acetals V.\(^6\)

![Scheme 1. Pd(0)-Catalyzed synthesis of homopropargyl cycloalkanols.](image)

Alternatively, the use of Et\(_2\)Zn as transmetalating agent has also been reported, and in this case the method has been shown to be compatible with the use of aldehydes.\(^1\)\(^,\)\(^2\) This variant, proceeding through the corresponding allenylzinc intermediates IIIb, has been applied both inter- and intramolecularly, albeit only with linear acyclic substrates in the latter case.\(^20\)\(^,\)\(^21\) We now report the application of the Pd(0)/Et\(_2\)Zn-promoted intramolecular propargylation of carbonyl compounds to the preparation of bicyclic alkynylcyclopentanols from aldehyde-tethered propargylic ester substrates, whereupon previous limitations of the use of these substrates are overcome.
Results and Discussion

We have used aldehydes 1a-c as precursors of target bicyclic structures 2. The selected examples feature cases with both terminal and internal alkynes, as well as two different types of ring fusion.

![Scheme 2](image)

Scheme 2. Projected synthesis of bicyclic alcohols from cyclic propargylic esters.

Substrates 1 were straightforwardly prepared by alkynylmetal carbonyl addition to monoprotected 1,5-dicarbonyl derivatives 3, followed by esterification and carbonyl deprotection (Scheme 3).

![Scheme 3](image)

Scheme 3. Preparation of propargylic esters 1. Reagents: (a) (i) Ethynylmagnesium bromide, THF, -20 °C to rt; (ii) H₂O (4a and 4b); (iii) Ac₂O, Et₃N, DMAP, rt (5a). (b) (i) R¹-C≡C-M (M = Li or MgBr), THF, -20 or 78 °C to rt; (ii) BzCl, rt (5b and 5c). (c) AcOH/H₂O, reflux.

Carbonyl addition took place in ketones 3 with very high diastereoselectivity and, as a result, products 1a-c were obtained nearly as single diastereoisomers. The stereochemical assignments of 1 were made after conversion of intermediate alcohols 4a and 4b into the known lactols 6a and 6b, respectively, by hydrolysis of the cyclic acetal unit (Scheme 4). The stereochemistry of 1c was assigned by analogy with that of 1a. In any case, the relative configuration of substrates 1 is likely to be of no consequence in their cyclization reactions since the putative intermediates, allenylzincs IIIb (Scheme 1), are expected to be of limited configurational stability at r.t.²²,²³

Starting from esters 1, the expected bicyclic products 2 were obtained in moderate to good yields upon treatment with Et₂Zn in benzene, in the presence of a catalytic amount of Pd(PPh₃)₄ (Table 1). The alternative use of THF as solvent or P(nBu₃) as ligand led to very low yielding reactions with substantial substrate degradation. Remarkably, under the conditions indicated in Table 1, the cyclization took place with high stereoselectivity, affording usually a single isomer. The yield of bicycles 2b and 2c improved when the reaction was run in the presence of ZnCl₂ (entries 3 and 5), which presumably acted as a Lewis acid to activate the carbonyl group towards nucleophilic attack. From the methodological point of view, these reactions either complement the previously reported Pd(0)/SmI₂-promoted cyclizations or provide an alternative to those cases where that methodology had failed. Thus, the preparation of 2a had only been possible through acetals of type V, and now this product becomes available also from an aldehyde substrate by using Pd(0)/Et₂Zn conditions. On the other hand, for aldehyde-type substrates, products containing an internal alkyne or a [4.3.0] ring fusion (case of 2c and 2b, respectively) had not been accessible previously using the Pd(0)/SmI₂ methodology.

Table 1. Preparation of bicyclic 2-alkynylcyclopentanols 2 from propargylic esters 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>R¹</th>
<th>R²</th>
<th>t (h)</th>
<th>2 Yieldb</th>
<th>d. r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>0.5</td>
<td>2a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>H</td>
<td>Ph</td>
<td>1.5</td>
<td>2b</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>H</td>
<td>Ph</td>
<td>0.1</td>
<td>2b</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>(CH₂)₂OBn</td>
<td>Ph</td>
<td>6</td>
<td>2c</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>(CH₂)₂OBn</td>
<td>Ph</td>
<td>0.5</td>
<td>2c</td>
<td>72</td>
</tr>
</tbody>
</table>

a Reaction conditions: Unless otherwise indicated, 1 (0.3 mmol), Pd(PPh₃)₄ (5 mol%), Et₂Zn (3 equiv) in benzene (3 mL) at room temperature. b Isolated yield (%). c ZnCl₂ (1.2 equiv) was used as additive.

The stereochemical assignments of products 2a and 2c were made based on that of 2a, which had been previously reported. Additionally, products 2a and 2c had very similar NMR characteristics, particularly...
concerning the critical $^1$H- and $^{13}$C-NMR resonances at the carbinol and ring fusion positions.$^{24}$ In the case of the major isomer $2b$, it was established that the OH and CO$_2$Et groups were trans to each other, after LAH reduction of the ethoxycarbonyl group and the observation of n.O.e. between the carbinolic methine and methylene hydrogens of the resulting diol $7$ (Scheme 5). However, the relationship between those groups and the alkynyl moiety of $2b$ remains ambiguous.

![Scheme 5. Reduction of ester $2b$ to alcohol $7$.](image)

The preparation of bicyclic products $2$ involves a ring-closure that generates a 2-alkynylcyclopentanol moiety where two new stereogenic centers are generated with high stereoselectivity. Simple monocyclic 2-alkynylcyclopentanols have been similarly prepared from the corresponding acyclic propargylic esters.$^{21}$ In that case, the cis- or trans-relationship between the alkynyl and hydroxyl functionalities was shown to depend on the choice of phosphine and solvent, and for simple aldehyde substrates, this particular combination of Pd(PPh$_3$)$_4$ as catalyst and benzene as solvent had led to low stereoselectivities.$^{21}$ It is likely that the high levels of stereocontrol observed in the present cyclizations, particularly in the case of [3.3.0] ring fusion, are due to the rigidity of the newly generated bicyclic system. Thus, a cis-ring fusion would be expected to be preferred on thermodynamic grounds.$^{25}$ Additionally, a chelate arrangement of type VI, analogous to the one typically invoked in the intermolecular reactions of allenylzincs with carbonyl compounds,$^{26}$ might be difficult to attain in this case due to its presumably strained tricyclic nature. As a result, the reaction may proceed through an “open” transition state VII leading to a trans relationship between alkynyl and hydroxyl groups.

![VI](image)

![VII](image)

**Conclusions**

The application of the Et$_2$Zn/Pd(0)-mediated intramolecular propargylation of aldehydes from carbonyl-tethered propargyl esters has been successfully extended to the stereoselective preparation of bicyclic cyclopentanols. This reaction circumvents some limitations previously encountered in the preparation of those compounds with related methodologies. Specifically, aldehydes are directly employed without resorting to masking procedures, both internal and terminal alkynes participate effectively, and the preparation of [3.3.0] as well as [4.3.0] bicyclic systems has been demonstrated.
Experimental Section

General. All reactions involving air- and moisture-sensitive materials were performed under an argon atmosphere using standard benchtop techniques. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Other solvents were routinely purified using literature procedures. Analytical thin layer chromatography (TLC) was performed on aluminum plates with Merck Kieselgel 60F254 and visualized by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolibdic acid. Flash column chromatography was performed on silica gel (230-400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 (7 μm, 25 x 2.5 cm) column using a refraction index detector. 1H NMR spectra were obtained at 250 MHz in CDCl3 at ambient temperature, with residual protic solvent as the internal reference (δH = 7.26 for CHCl3). 13C NMR spectra were recorded at 62.9 MHz in CDCl3 at ambient temperature, with the central peak of the solvent (δC = 77.0 for CDCl3) as the internal reference. The DEPT sequence was routinely used for 13C multiplicity assignment. Infrared spectra (IR) were obtained from a thin film deposited onto a NaCl glass and data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

(1R*,2S*)-Ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-ethynyl-2-hydroxycyclopentane-1-carboxylate (4a). To a solution of 3a27 (1.9 g, 7.6 mmol) in THF (50 mL) at -20 °C under Ar was added ethynylmagnesium bromide (0.5 M in THF, 16.2 mL, 8.1 mmol) dropwise. The solution was allowed to reach room temperature and stirred 1 h. Saturated NaHCO3 (50 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried (Na2SO4), the solvents were evaporated and the crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield 4a as an oil (2.1 g, 97%): 1H NMR δ 1.23 (t, J 7.1 Hz, 3H, CH3), 1.44-1.77 (m, 6H), 1.90-2.01 (m, 2H), 2.22 (m, 2H), 2.43 (s, 1H, H-2’), 3.07 (s, 1H, OH), 3.46-3.94 (m, 4H, OCH2CH2O), 4.14 (q, J 7.1 Hz, 2H, CO2CH2CH3), 4.80 (m, 1H, O-CH-O). 13C NMR δ 14.1 (CH3), 17.9 (CH2), 24.9 (CH2), 29.1 (CH2), 29.2 (CH2), 37.4 (CH2), 60.4 (C-1), 60.6 (CH2), 64.7 (CH2), 72.7 (C-2”), 77.0 (C-2), 85.9 (C-1’), 103.9 (O-CH-O), 174.5 (C=O). IR (neat) ν 3600-3400 (br, O-H), 3300-3200 (m, C=O-H). 3000-2800 (m, C-H). 2100 (m, C-H). 1744 (C=O) cm-1.

(1R*,6S*)-Ethyl 6-ethynyl-4-hydroxy-5-oxabicyclo[4.3.0]nonanecarboxylate (6a). A solution containing acetal 4a (0.32 g, 1.15 mmol) and p-TsOH (0.115 mmol) in acetone/H2O (15:1, 40 mL) was stirred at 45 °C until complete disappearance of the starting 4a (TLC). Sat. NaHCO3 (4 mL) was added and the mixture was evaporated to dryness. The residue was partitioned between H2O (4 mL) and Et2O (20 mL). After separation, the aqueous layer was extracted with Et2O (3 x 6 mL) and the combined organic layers were dried (Na2SO4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield lactol 7a as an oil (0.25 g, 92%): 1H NMR δ 1.26 (t, J 7.1 Hz, 3H, CH3), 1.44-1.59 (m, 1H), 1.72-2.14 (m, 7H), 2.19-2.45 (m, 2H), 2.49 (s, 1H, H-2”), 4.02-4.11 (q, J 7.1 Hz, 2H, CO2CH2CH3), 4.37 (br s, 1H, OH), 5.07 (d, J 9.5 Hz, H-4, major isomer) and 5.20 (m, H-4, minor isomer) (total 1H). 13C NMR δ 13.8 (CH3), 21.5 (CH2), 24.7 (CH2), 27.3 (CH2), 30.6 (CH2), 40.6 (CH2), 55.9 (C-1), 60.8 (CH2), 75.3 (C-6 or C-2’), 80.9 (C-2’ or C-6), 81.0 (C-1’), 92.8 (C-4), 174.4 (C=O). These data are consistent with those described in the literature for the same compound.6

Ethyl (1R*,2S*)-1-[2-(1,3-dioxolan-2-yl)ethyl]-2-acetoxy-2-ethynylcyclopentane-1-carboxylate (5a). To a solution of alcohol 4a (1.50 g, 5.30 mmol) and DMAP (0.200 g, 1.48 mmol) in Et3N (2.2 mL) was added Ac2O (1.14 mL, 11.9 mmol) and the mixture was stirred 2 h at r.t. After dilution with EtOAc (50 mL), H2O/ice (aprox. 50 mL) was added. The layers were separated and the organic layer was washed successively with H2O (50 mL), 1M HCl (50 mL) and NaOH 1M (50 mL), and dried (Na2SO4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield acetate 5a (1.03 g, 60%): 1H NMR δ 1.24 (t, J 7.1 Hz, 3H, CH3), 1.54-1.86 (m, 6H), 2.06 (s, 3H, CH3CO2), 2.14-2.31 (m, 3H), 2.55-2.67 (m, 2H), 2.55 (s, H-2’,
included en m at 2.55-2.67), 3.80-3.97 (m, 4H, OCH₂CH₂O), 4.14 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.84 (apparent t, J 4.3 Hz, 1H, O-CH-O).²³⁴⁶ NMR δ 14.0 (CH₃), 19.3 (CH₂), 21.6 (CH₃CO₂), 25.4 (CH₂), 29.6 (CH₂), 36.7 (CH₂), 60.7 (CH₂), 61.9 (C-1), 64.7 (CH₂), 75.0 (C-2'), 81.3 (C-1'), 81.7 (C-2), 104.2 (O-CH-O), 168.9 (C=O), 172.9 (C=O). IR (neat) ν (c-H) 3270 (m, C=H), 3000-2800 (m, C-H), 2110 (w, C=C), 1750 (s, C=O), 1270 (m, C-O-C) cm⁻¹.

(1R*,2S*)-Ethyl 2-acetoxy-2-ethylphenyl-1-(3-oxopropyl)cyclopentene-1-carboxylate (1a). A stirred solution of acetal 5a (0.93 g, 2.87 mmol) in AcOH:H₂O (1/1.2, 2.1 mL) was refluxed for 1 h. After cooling to r. t., the solution was made neutral with sat. K₂CO₃ and extracted with EtOAc (4 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried (Na₂SO₄). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield aldehyde 1a (0.68 g, 85%): ¹³C NMR δ 1.25 (t, J 7.1 Hz, 3H, CH₃), 1.62-1.74 (m, 2H), 1.77-1.95 (m, 2H), 2.07 (s, 3H, CH₃CO₂), 2.23-2.58 (m, 5H), 2.59 (s, 1H, H-2'), 2.60-2.70 (m, 1H), 4.16 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 9.77 (t, J 1.2 Hz, 1H, CHO).²³⁴⁶ NMR δ 13.9 (CO₂CH₂CH₃), 19.6 (CH₂), 21.5 (CH₃CO₂), 23.4 (CH₂), 30.5 (CH₂), 36.8 (CH₂), 40.0 (CH₂), 60.9 (CH₂), 61.6 (C-1), 75.4 (C-2'), 80.9 (C-1'), 81.7 (C-2), 168.8 (O=C=O), 172.7 (O=C=O), 201.3 (HC=O). IR (neat) ν (c-H) 3270 (m, C=H), 3000-2800 (m, C-H), 2100 (w, C=C), 1750 (s, C=O), 1730 (s, C=O) cm⁻¹. Anal. calcd for C₁₅H₂₀O₅: C, 64.26; H, 7.19. Found: C, 63.89; H, 7.32.

(1R*,2R*)-Ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-ethyl-2-hydroxycyclohexane-1-carboxylate (4b). The procedure described above for the preparation of 4a was followed starting from 3b (2.0 g, 7.4 mmol). The residue after evaporation was purified by flash chromatography (silica gel, 75:25 hexanes/EtOAc) to yield 4b (2.1 g, 96%, 30:1 diast. mixture) as an oil: ¹³C NMR δ 1.18-1.32 (m, 5H), 1.22 (t, J 7.1 Hz, CO₂CH₂CH₃, included in m at 1.18-1.32), 1.43-2.03 (m, 10H), 2.40 (s, 1H, C=C-H), 3.73-3.90 (m, 4H, OCH₂CH₂O), 4.15 (qd, J 7.1, 2.6 Hz, 2H, CO₂CH₂CH₃), 4.40 (s, 1H, OH), 4.75 (m, 1H, O-CH-O).²³⁴⁶ NMR δ 13.9 (CH₃), 19.6 (CH₂), 21.6 (CH₂), 22.4 (CH₂), 26.6 (CH₂), 28.5 (CH₂), 33.1 (CH₂), 53.0 (C-1), 60.7 (CH₂), 64.5 (CH₂), 71.4 (C-2 or C-2''), 72.9 (C-2'' or C-2), 85.5 (C-1''), 103.7 (O=CH-O), 176.3 (C=O). IR (neat) ν (b, O-H) 3000-3400, 3300-3200 (m, C=O), 3000-2800 (m, C-H), 2100 (w, C=C), 1740 (s, C=O), 1270 (m, C-O-C) cm⁻¹.

(1R*,8R*)-Ethyl 6-ethynyl-4-hydroxy-5-oxabicyclo[4.4.0]decane-2-carboxylate (6b). The procedure described above for the preparation of 6a was followed starting from 4b (0.20 g, 0.67 mmol). The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield 6b (0.14 g, 82%): ¹³C NMR δ 1.22-1.95 (m, 12H), 1.25 (t, J 7.1 Hz, CO₂CH₂CH₃, included in m at 1.22-1.95), 2.03-2.31 (m, 2H), 2.43-2.56 (m, 2H), 2.53 (s, H-2'), included in m at 2.43-2.56), 4.15 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.37 (d, J 5.7 Hz, 1H, OH), 5.35 (ddd, J 9.7, 5.7, 3.0 Hz, 1H, H-4).²³⁴⁶ NMR δ 14.0 (CH₃), 20.1 (CH₃), 21.7 (CH₂), 27.9 (CH₂), 28.2 (CH₃), 28.9 (CH₃), 35.8 (CH₂), 47.3 (C-1), 60.5 (CH₂), 73.0 (C-6 or C-2'), 75.0 (C-2' or C-6), 83.7 (C-1'), 93.3 (C-4), 173.7 (C=O). These data are consistent with those described in the literature for the same compound.⁶

(1R*,2R*)-2-[2-(1,3-dioxolan-2-yl)ethyl]-2-(ethoxycarbonyl)-1-ethylnylcyclohexyl benzoate (5b). The procedure described above for the preparation of 4a was followed starting from 3b (1.00 g, 3.7 mmol). When the reaction mixture reached r. t., benzyl chloride (0.47 mmol, 4.05 mmol) was added, the mixture was stirred at r. t. for 1 h and then at 50 °C for a further 1 h. After cooling to r. t., sat. NH₄Cl (30 mL) was added, the layers were separated, the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried (Na₂SO₄). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield benzoate 5b (1.37 g, 92%): ¹³C NMR δ 1.20 (t, J 7.1 Hz, 3H, CO₂CH₂CH₃), 1.26-1.74 (m, 6H), 1.83-2.18 (m, 4H), 2.41 (td, J 12.8, 4.4 Hz, 1H), 2.69-2.78 (m, 2H), 2.69 (s, H-2', included in m at 2.69-2.78), 3.78-3.98 (m, 4H, OCH₂CH₂O), 4.16 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.88 (t, J 4.5 Hz, 1H, O-CH-O), 7.43 (apparent t, 2H, Ar-H), 7.54 (apparent t, 1H, Ar-H), 8.07 (d, J 7.7 Hz, 2H, Ar-H_fortho).²³⁴⁶ NMR δ 14.2 (CH₃), 20.1 (CH₂), 22.0 (CH₂), 23.7 (CH₂), 27.9 (CH₂), 28.9 (CH₂), 31.5 (CH₂), 54.3 (C-2), 60.8 (CH₂), 64.9 (CH₂), 77.1 (C-2'), 78.3 (C-1), 80.8 (C-1'), 104.3 (O-CH-O), 128.3 (Ar-CH), 129.8 (Ar-CH), 130.9 (Ar-C), 132.9 (Ar-CH), 164.1

Page 263
Zn/Pd(0)-mediated Cyclizations

To a solution of 4-benzyloxybut-1-yne (1.90 g, 12.0 mmol) in THF (20 mL) at -78 °C under Ar, was added n-BuLi (1.6 M in hexanes, 6.9 mL, 11.0 mmol) and the solution was stirred for 30 min at the same temperature. A solution of ketone 3a (2.50 g, 9.90 mmol) in THF (10 mL) was added, and the solution was allowed to reach r. t. Benzoyl chloride (11.0 mmol) was added and the mixture was stirred for 3h. Sat. NH₄Cl (20 mL) was added, the layers were separated, the aqueous layer was extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried (Na₂SO₄). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield benzoate 5c (4.0 g, 80 %, a 31:1 diastereomeric mixture) as an oil. Data for the major isomer: ¹H NMR δ 1.23 (t, J 7.1 Hz, 3H, CH₃), 1.59-1.91 (m, 6H), 2.23-2.42 (m, 3H), 2.50 (t, J 7.3 Hz, 2H, H-3'), 2.53-2.87 (m, 1H), 3.53 (t, J 7.3 Hz, 2H, H-4'), 3.80-3.98 (m, 4H, OC₂H₅), 7.44-7.53 (m, 5H, Ar-H), 7.44 (apparent t, J 7.4 Hz, 2H, Ar-H), 7.55 (apparent t, J 7.3 Hz, 1H, Ar-H), 8.05 (d, J 7.7 Hz, 2H, Ar-H). ¹³C NMR δ 14.1 (CH₃), 19.1 (CH₃), 20.1 (CH₃), 25.4 (CH₂), 29.0 (CH₂), 29.6 (CH₂), 36.7 (CH₂), 60.6 (CH₂), 62.3 (C-2), 64.8 (CH₂), 68.2 (CH₂), 72.8 (CH₂), 79.0 (C), 82.4 (C), 84.1 (C), 104.2 (O-CH-O), 127.4 (Ar-CH), 127.5 (Ar-CH), 128.2 (Ar-CH), 129.6 (Ar-CH), 130.0 (Ar-C), 132.8 (O=C-CH₂), 137.9 (Ar-C), 164.4 (C=O), 173.1 (C=O). IR (neat) ν 3000-2800 (s, C-H), 2248 (w, C=O).

The procedure described above for the preparation of 1a was followed starting from acetal 5b (2.6 g, 5.2 mmol, 31:1 isomer mixture). The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield benzoate 5c (1.50 g, 63 %, 28:1 isomer mixture) as an oil. Data for the major isomer: ¹H NMR δ 1.24 (t, J 7.1 Hz, 3H, CH₃), 1.69-2.08 (m, 5H), 2.28-2.60 (m, 6H), 2.74-2.85 (m, 1H), 3.54 (t, J 7.3 Hz, 2H, H-4'), 4.15 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.50 (s, 2H, PhCH₂O), 7.26-7.33 (m, 5H, Ar-H), 7.44 (apparent t, J 7.1 Hz, 2H, Ar-H), 7.57 (apparent t, 1H, Ar-H), 8.05 (d, J 8.3 Hz, 2H, Ar-H), 9.78 (s, 1H, CHO). ¹³C NMR δ 14.1 (CH₃), 19.5 (CH₂), 20.1 (CH₃), 23.7 (CH₃), 30.2 (CH₂), 37.0 (CH₂), 40.2 (CH₂), 60.9 (CH₂), 62.2 (C-2), 68.2 (CH₂), 72.9 (CH₂), 78.7 (C), 82.7 (C), 84.7 (C), 127.6 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 129.6 (Ar-CH), 130.7 (Ar-C), 133.0 (Ar-CH), 137.9 (Ar-C), 164.4 (C=O), 172.9 (C=O), 201.4 (HC=O). IR (neat) ν 3000-2800 (m, C=O), 2248 (w, C=O). MS (El) m/z (%) 476 (M), 325 (19), 105 (base), 91 (45), 84 (30). HRMS calcd for C₂₉H₃₂O₆ 476.2199, found 476.2196.

General Procedure for Et₂Zn/Pd(0)-mediated Cyclizations. In a typical experiment, to a solution of propargyl ester 1 (0.300 mmol) and Pd(PPh₃)₄ (0.015 mmol, 5 mol%) in benzene (3 mL) was added ZnCl₂ (where appropriate, see Table 1, (1.0 M in Et₂O, 0.360 mmol), followed by Et₂Zn (1.0 M in hexanes, 900 μL, 0.90 mmol) at room temperature under Ar, and the reaction mixture was stirred for the time indicated in Table 1. After...
diluting with EtOAc (10 mL), the solution was successively washed with 1 M HCl (5 mL), sat. NaHCO₃ (5 mL) and brine (5 mL), and dried (Na₂SO₄). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield bicyclic products 2. Characterization data for the individual compounds is given below.

**{(1R*,4R*,5R*)}-Ethyl 5-ethyl-4-hydroxybicyclo[3.3.0]octanecarboxylate (2a).** Obtained from 1a. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc). ¹H NMR δ 1.26 (t, J 7.1 Hz, CH₃), 1.41-2.18 (m, 9H, that includes s at δ 2.18, H-2'), 2.27-2.52 (m, 3H), 4.12 (q, J 7.1 Hz, 2H, CH₂CH₂CH₃), 4.37 (m, 1H, H-4). ¹³C NMR δ 14.1 (CH₃), 26.2 (CH₂), 31.5 (CH₃), 31.9 (CH₂), 35.2 (CH₂), 38.2 (CH₂), 56.4 (C), 60.7 (C), 63.9 (CH₂), 70.3 (C-2'), 80.1 (C-4), 88.5 (C-1'), 175.4 (C=O). These data are consistent with those described in the literature for the same compound.⁶

**{(1R*,7R*)}-Ethyl 6-ethynyl-7-hydroxybicyclo[4.3.0]nonanecarboxylate (2b).** Obtained from 1b. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) and the isomers were separated by HPLC (65:35 hexanes/EtOAc, 8 mL/min), to yield 2b and a minor diastereoisomer (2b'). Data for 2b: tₑ = 27 min. ¹H NMR δ 1.24 (t, J 7.1 Hz, 3H, CH₃), 1.30-2.16 (m, 13H, that includes a s at δ 2.16, H-2'), 2.23-2.36 (m, 1H), 4.11 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.75 (apparent t, J H-H, 2H, CH₃-2'). ¹³C NMR δ 14.1 (CH₃), 21.0 (CH₂), 21.4 (CH₂), 27.0 (CH₂), 27.8 (CH₂), 28.5 (CH₂), 29.3 (CH₂), 46.5 (C), 55.3 (C), 60.6 (CH₂), 71.0 (C-2'), 79.8 (C-7), 86.8 (C-1'), 176.1 (C=O). IR (neat) ν̇ 3500-3400 (br, O-H), 3301 (m, =C-H), 3000-2800 (m, C-H), 2106 (w, =C=C), 1714 (s, C=O) cm⁻¹. MS (EI) m/z (%) 236 (M), 179 (base), 151 (59), 91 (30). HRMS calc'd for C₁₄H₂₀O₃ 236.1412, found 236.1409. Data for the minor isomer 2b': tₑ = 15 min. ¹H NMR δ 0.97-1.15 (m, 1H), 1.23 (t, J 7.1 Hz, 3H, CH₃), 1.46-2.19 (m, 12H), 2.45 (s, 1H, H-2'), 4.10 (q, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.63-4.74 (m, 1H, H-H), ¹³C NMR δ 14.1 (CH₃), 22.2 (CH₂), 22.9 (CH₂), 28.4 (CH₂), 30.8 (CH₂), 32.2 (CH₂), 32.6 (CH₂), 54.5 (C), 55.8 (C), 60.4 (CH₂), 74.7 (C-7), 76.9 (C-2'), 84.5 (C-1'), 174.9 (C=O). IR (neat) ν̇ 3500-3400 (br, O-H), 3295 (m, =C-H), 3000-2800 (m, C-H), 2100 (w, =C=C), 1714 (s, C=O) cm⁻¹. MS (EI) m/z (%) 236 (M), 179 (97), 163 (40), 151 (base), 91 (38). HRMS calc'd for C₁₄H₂₀O₃ 236.1412, found 236.1411.

**{(1R*,4R*,5R*)}-Ethyl 5-(4-benzyloxybut-1-ynil)-4-hydroxybicyclo[3.3.0]octanecarboxylate (2c).** Obtained from 1c. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc). ¹H NMR δ 1.22 (t, J 7.1 Hz, 3H, CH₃), 1.37-2.15 (m, 8H), 2.26-2.53 (m, 4H), 2.42 (t, J 7.1 Hz, H-3'), included in m at 2.26-2.53, 2.69 (br s, 1H, OH), 3.48 (t, J 7.1 Hz, 2H, H-4'), 4.07 (quint, J 7.1 Hz, 2H, CO₂CH₂CH₃), 4.29 (dd, J 10.1, 6.1 Hz, 1H, H-4), 4.50 (s, 2H, PhCH₂O), 7.26-7.33 (m, 5H, Ar-H). ¹³C NMR δ 14.1 (CH₃), 20.0 (CH₂), 26.1 (CH₂), 31.4 (CH₂), 31.9 (CH₃), 38.2 (CH₂), 56.7 (C), 60.5 (CH₂), 63.7 (C), 68.6 (CH₂), 72.7 (CH₂), 78.6 (C-1' or C-2'), 80.2 (C-4), 85.4 (C-2' or C-1'), 127.6 (Ar-CH), 128.3 (Ar-CH), 137.9 (Ar-C), 175.5 (C=O). IR (neat) ν̇ 3500-3400 (br, O-H), 3000-2800 (m, C-H), 1722 (s, C=O) cm⁻¹. MS (EI) m/z (%) 356 (M), 265 (21), 191 (33), 91 (base). HRMS calc'd for C₂₂H₂₆O₃ 356.1988, found 356.1992.

**{(1R*,7R*)}-1-(Hydroxymethyl)-6-ethynylbicyclo[4.3.0]nonanecarboxylate (7).** A solution of ester 2b (53.0 mg, 0.220 mmol) in Et₂O (4 mL) was added to a suspension of LiAlH₄ (36.0 mg, 1.32 mmol) in Et₂O (6 mL) at 0 °C under Ar. The reaction mixture was allowed to reach r.t., and stirred for 4 days. After addition of EtOAc (4 mL), the mixture was filtered and the solid residue was washed with EtOAc (20 mL). The combined solution and washings was evaporated and the crude product was purified by was purified by flash chromatography (silica gel, 60:40 hexanes/EtOAc) to yield diol 7 (18 mg, 42%). The characterized sample was obtained after HPLC (10 mL/min, 50:50 hexanes/EtOAc). tₑ = 44 min. ¹H NMR δ 1.33-1.93 (m, 13H), 2.04-2.24 (m, 1H), 2.27 (s, 1H, H-2'), 3.41 (d, J 11.3 Hz, 1H, CHOH), 3.64 (d, J 11.3 Hz, 1H, CHOH), 4.58 (t, J 8.6 Hz, 1H, H-7). ¹³C NMR δ 21.2 (CH₂), 21.8 (CH₂), 26.0 (CH₂), 28.1 (CH₂), 28.4 (CH₂), 28.7 (CH₂), 46.2 (C), 47.9 (C), 70.5 (CH₂O), 72.1 (C-2'), 80.1 (C-7), 87.9 (C-1'). IR (neat) ν̇ 3600-3400 (br, O-H), 3300 (s, =C-H), 3000-2800 (m, C-H), 2100 (w, C=O) cm⁻¹. MS (EI) m/z (%) 194 (M), 137 (base), 91 (24), 79 (17). HRMS calc'd for C₁₂H₁₈O₂ 194.1307, found 194.1302.
Acknowledgements

Financial support by the Universidad del País Vasco (170.310-EB001/99) and Ministerio de Ciencia y Tecnología (DGI BQU2000-01354 and fellowship to M. A.) is gratefully acknowledged. We also thank SGiker UPV/EHU for technical support (NMR and analytical facilities).

Supplementary Material

Copies of $^1$H and $^{13}$C NMR spectra of new compounds.

References

   https://doi.org/10.1021/cr000003u
   https://doi.org/10.1021/jo070787c
   https://doi.org/10.1021/cr100284m
   https://doi.org/10.1021/jo00083a003
   https://doi.org/10.1021/jo9819133
   https://doi.org/10.1021/jo0005619
   https://doi.org/10.1016/S0040-4020(03)01103-7
   https://doi.org/10.1021/ja962162u
    https://doi.org/10.1021/jo0005619
    https://doi.org/10.1021/acs.orglett.7b01154
    https://doi.org/10.1021/pr00402a007
    https://doi.org/10.1016/S0040-4020(97)01803-0
    https://doi.org/10.1021/ja030200l