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A concise synthesis of (*S*)-(+)-5,6-2*H*-pyran-2-one via hydrozirconation–carbonylation–demetallation of *O*-benzyl (*S*)-(−)-4-pentyn-2-ol

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Abstract

A simple synthetic approach to α,β-unsaturated δ-lactones has been devised from the hydrozirconation of O-protected homopropargyl alcohols followed by carbonylation and quenching with iodine. The synthesis of (*S*)-(+)-5,6-2*H*-pyran-2-one (parasorbic acid) from easily available O-benzylated (*S*)-(−)-4-pentyn-2-ol was chosen to exemplify the approach.

1. Introduction

α,β-Unsaturated δ-lactones are represented in many natural products and are synthetically versatile precursors of other molecules of considerable interest, and their synthesis has attracted attention over the years.[1,2] In this respect, the naturally occurring (*S*)-(+)-5,6-2*H*-pyran-2-one (parasorbic acid) **1e** (Scheme 1) has served as a convenient starting material for the synthesis of various natural products and as a chiral building block.[3–22]

Although, the synthesis of the lactone **1e** has been reported several times in racemic and enantiomerically enriched forms, to our knowledge, no expedient method is available.[3–22] Herein, we report that **1e** and other δ-lactones can be easily prepared in essentially one-pot procedures with the key step being the hydrozirconation–carbonylation–demetallation of O-protected homopropargyl alcohols. This approach is based on previous findings that the hydrozirconation–carbonylation–demetallation of O-protected propargyl alcohols leads selectively to 3,5-disubstituted butenolides.[23] In order to extend this method to the synthesis of α,β-unsaturated δ-lactones, we have investigated the hydrozirconation–carbonylation–demetallation of a series of homopropargyl alcohols and then applied this to the synthesis of (*S*)-(+)-**1e**.

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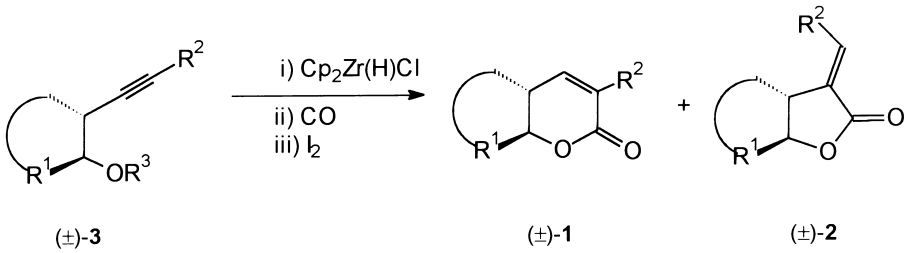


Scheme 1.

Table 1

Entry	Alkyne	R^1	R^2	R^3	Product ratio[a] (**1**:**2**)	Yield[b] (%)
1	**3a**	$(CH_2)_4$	H	Bn	1:0	60
2	**3b**	$(CH_2)_4$	Ph	Bn	1:0	65
3	**3c**	$(CH_2)_4$	*n*-Bu	Bn	1:0	55
4	**3d**	H	H	Bn	1:0	25
5	**3e**	Me	H	Bn	1:0	47
6	**3e**	Me	H	$SiMe_3$	1:0	52
7	**3e**	Me	H	$SiPh_3$	1:0	50
8	**3f**	H	Ph	Bn	15:1	56
9	**3f**	H	Ph	$SiPh_3$	15:1	60
10	**3g**	H	Me	Bn	1.2:1	55
11	**3g**[c]	H	Me	Bn	3.2:1	56
12	**3h**	Me	*t*-Bu	Bn	0:1	38

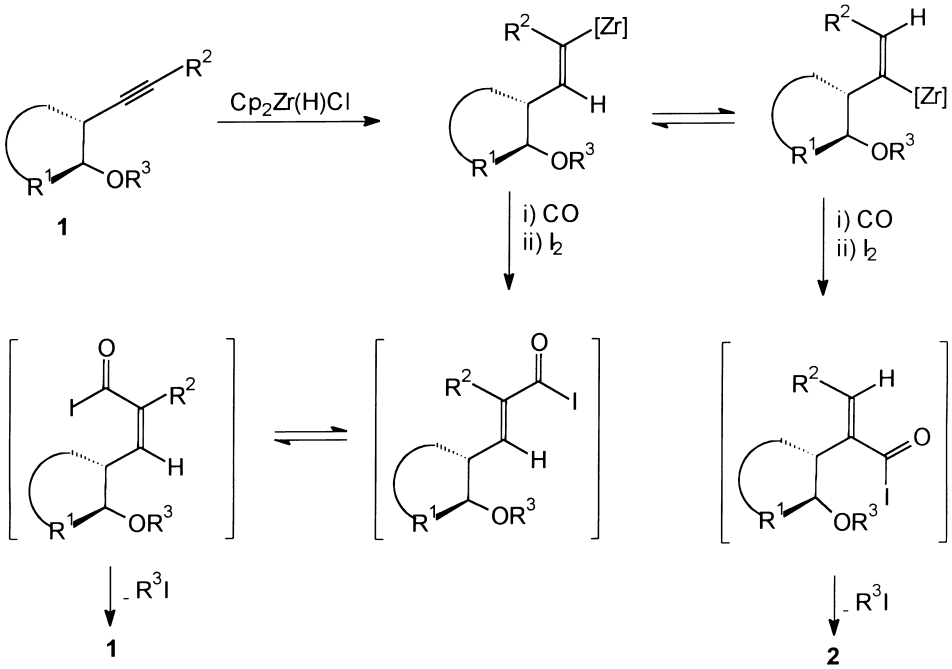
(a) The stereochemistry at the C=C bond of **2** was assigned from NOE experiments. (b) Isolated yield.
(c) Reaction performed in the presence of 1.5 equiv. of the Schwartz reagent.

2. Results and discussion

The hydrozirconation–carbonylation–demetallation procedure was first exploited with various racemic O-protected homopropargyl alcohols listed in Table 1. The addition of equimolar amounts of the O-protected homopropargyl alcohols **3a**–**3g** to a suspension of the Schwartz reagent $Cp_2Zr(H)Cl$ in benzene at room temperature yields after 12–15 h a light yellow solution. Without isolation, the carbonylation of these hydrozirconated alkynes under 1.1 atm of carbon monoxide affords after 5–6 h an orange solution, which was treated with iodine for 2–3 h. Aqueous workup and column chromatography of the reaction mixture produces the lactones **1** and/or **2** in good yields together with benzyl alcohol and trimethyl- or triphenylsilanol (Scheme 1).

The reaction scheme can be understood based on mechanisms proposed for the formation of 3,5-disubstituted butenolides.[23] In the first step, the hydrozirconation of the alkyne will lead to the vinyl–zirconium compounds. This is followed by insertion of CO into the Zr–alkenyl bond and demetallation with iodine to give the α,β acyl iodide. Intramolecular nucleophilic attack by the ether oxygen

on the electrophilic acyl iodide group leads to the γ- or δ-lactone (Scheme 2). The formed benzyl iodide and iodo trimethyl or triphenyl silane are hydrolyzed to the corresponding alcohols during the aqueous workup.



Scheme 2. [Zr]=Cp_2ZrCl

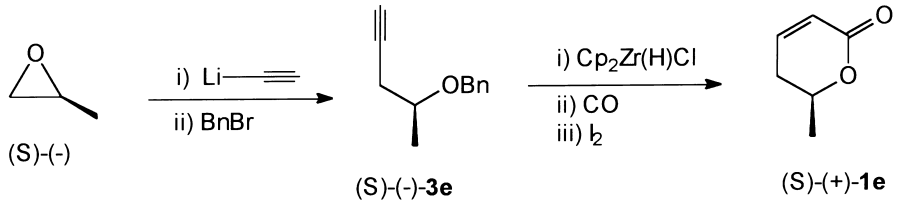
The formation of the γ- or δ-lactones is controlled during the hydrometallation step. In most of the cases, the relative steric bulkiness of the substituents at the C≡C bond (R^1 vs R^2) dictates the preferred direction of the Zr–H *cis*-β addition.[24,25] This addition of Zr–H gives mixtures of vinyl Zr complexes with the less-hindered complex predominating. Moreover, equilibration of this mixture with an excess of $Cp_2Zr(H)Cl$ should enrich less-hindered complexes.[24,25]

In the reactions with alkynes containing a 1,2-disubstituted cyclohexane moiety (**3a**–**3c**) or H (**3d** and **3e**) six-membered heterocyclic compounds were formed selectively. In contrast, the five-membered lactone is formed as the only product in the case of the alkyne **3h** (R^2=*t*-Bu). However, for the alkynes **3f** and **3g**, where the differences in the steric bulkiness of R^1 and R^2 are not so pronounced, a mixture of the γ- and δ-lactones were formed. Nevertheless, in the case of alkyne **3g**, an excess of the Schwartz reagent increased the selectivity of **1g** from 1.2:1 to 3.2:1.

In the demetallation step, *E* α,β-unsaturated acyl iodides are formed and an equilibrium with their *Z* isomers in the presence of an excess of iodide (Scheme 2) can be assumed. This isomerization process is essential in the case of δ-lactone formation. However, only γ-lactones with *trans*-stereochemistry at the C=C bond (with respect to R^2 and the acyl group) have been obtained. This clearly indicates that the reaction leading to the five-membered lactones is faster than the *E*–*Z* isomerization process. The nature of the alcohol protecting group (CH_2Ph, $SiMe_3$ and $SiPh_3$) has no significant influence on the selectivity or yield of the lactone formation (compare entries 5–7 and 8–9 of Table 1).

On the basis of the above results, the methodology has been applied to the synthesis of (*S*)-(+)-**1e**. The addition of the lithium acetylide ethylene diamine complex to a solution of (*S*)-(−)-propylene oxide affords (*S*)-(−)-4-pentyn-2-ol that has been transformed without isolation into (*S*)-(−)-**3e** ($[\alpha]^{25}_{589}$=−9.8

(c=2.85, Et_2O)) in 60% overall yield by reaction with benzylbromide. Using the same protocol described for the preparation of racemic **1e**, the (*S*)-(+)-5,6-2*H*-pyran-2-one was prepared in 62% yield (Scheme 3).



Scheme 3.

In summary, a simple and efficient route to non-racemic α,β-unsaturated δ-lactones has been developed. The availability of both enantiomers of homopropargyl alcohols from chiral epoxides should allow the concise and enantiospecific synthetic route to various substituted α,β-unsaturated δ-lactones.

3. Experimental

3.1. General considerations

All manipulations were performed under dry, oxygen-free argon using standard techniques. All solvents were dried and distilled under argon prior to use. Infrared spectra (Nujol mulls or KBr pellets) were recorded in the region 4000–400 cm^{-1} using a Mattson 3020 FT-IR spectrometer. The ^1H and $^{13}C–\{^1H\}$ NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively, using Varian VXR-200 or Varian 300 Inova instruments. Proton and carbon shifts (δ/ppm, *J*/Hz), are positive downfield relative to external $SiMe_4$. Elemental analyses were carried out by the Central Analítica IQ/UFRGS (Porto Alegre, Brazil). Mass spectra were obtained with a GC–MS HP 5988A (EI, 70 eV). Optical rotations were measured using a Perkin–Elmer 341 polarimeter with a 1.0 dm tube (1.0 mL). The racemic homopropargyl alcohols **3a**–**3f** were obtained from the reaction of the acetylide anions with the corresponding epoxides[26] and protected according to the procedure described for *O*-benzyl-(*S*)-(−)-4-pentyn-2-ol (**3e**). All other reagents were obtained from Aldrich and used as purchased.

3.2. General procedure for the preparation of the lactones

A solution of the O-protected homopropargyl alcohol (3 mmol) in benzene (10 mL) was added to a white suspension of $Cp_2Zr(H)Cl$ (0.8 g, 3.1 mmol) in benzene (25 mL) at room temperature. The reaction mixture was stirred at room temperature for 12–16 h. The resulting yellow solution was treated with carbon monoxide (1.1 atm) for 6–8 h at room temperature to produce an orange–red solution. A solution of iodide (0.78 g, 3.1 mmol) in benzene (20 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of a suspension of sodium disulfide (2–3 g) in water (2 mL) and the organic phase was immediately extracted with diethyl ether (3×50 mL). The organic phase was dried over magnesium sulfate and the volatiles were removed under reduced pressure (15 mmHg). Column chromatography (hexane/diethyl ether) affords the lactone.

Compound **1a**: Calculated for $C_9H_{12}O_2$: C, 71.03; H, 7.95; found: C, 71.29; H, 7.89. IR (KBr pellets): 1707 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$, 300 MHz, RT), δ 6.68 (dd, 1H, HC=CH); 6.01 (dd, 1H, CH=CH); 4.01 (m, 1H, CH–O); 2.32–1.24 (4m, 9H, CH+CH_2). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 75 MHz, RT), δ 164.5 (C=O); 150.6 (H**C**=C); 120.9 (HC=**C**H); 81.9 (CH–O); 39.5 (**C**H–C); 31.1, 28.8, 25.2 and 23.9 (CH_2).

Compound **1b**: M.p. (DSC): 140°C. Calculated for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; found: C, 78.79; H, 6.89. IR (KBr pellets): 1709 cm^{-1} (ν C=O); 1599 cm^{-1} (ν C=C). ^1H NMR ($CDCl_3$, 300 MHz, RT), δ 7.47–7.31 (m, 5H, aromatic H); 6.71 (d, 1H, $^3J_{HH}$=1.47 Hz, HC=C); 4.07 (m, 1H, CH–O); 2.41 (m, 1H, CH–C); 2.20–1.20 (4m, 8H, CH_2). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 75 MHz, RT), δ 165.2 (C=O); 146.5 (H**C**=C); 135.7 (HC=**C**); 133.1 (C_{ipso}); 128.0–129.1 (CH aromatic); 81.8 (CH–O); 40.4 (**C**H–C); 31.5, 29.5, 25.5 and 24.3 (CH_2). GC–MS (EI, 70 eV): 228 (46, M^+); 200 (91); 129 (97); 105 (100).

Compound **1c**: Calculated for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; found: C, 74.78; H, 9.81. IR (KBr pellets): 1717 cm^{-1} (ν C=O); 1599 cm^{-1} (ν C=C). ^1H NMR ($CDCl_3$, 200 MHz, RT), δ 6.32 (s br, 1H, HC=C); 3.90 (m, 1H, CH–O); 2.33–1.20 (m, 15H, CH+CH_2); 0.93 (t, 3H, $^3J_{HH}$=1.47 Hz, 7.8 Hz, CH_3). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 165.7 (C=O); 143.7 (H**C**=C); 132.5 (HC=**C**); 81.6 (CH–O); 39.6 (**C**H–C); 31.0, 30.3, 30.2, 29.1, 25.1, 23.9, and 22.2 (CH_2), 13.8 (CH_3).

Compound **1d**: IR and NMR data identical to literature values.[27]

Compound **1e**: $[\alpha]^{25}_{589}$=+219.2 (c=0.96, $CHCl_3$) compared to the literature values ($[\alpha]^{25}_{589}$=+224.2 (c=0.98, $CHCl_3$)[3] and $[\alpha]^{25}_{589}$=+213.4 (c=1.0, $CHCl_3$)[6], also IR and NMR data are identical to literature values.[6]

Compound **1f**: Calculated for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; found: C, 75.64; H, 6.01. IR (KBr pellets): 1715 cm^{-1} (ν C=O); 1625 cm^{-1} (ν C=C). ^1H NMR ($CDCl_3$, 200 MHz, RT), δ 7.50–7.31 (m, 5H, aromatic H); 7.02 (t, 1H, $^3J_{HH}$=4.50 Hz, HC=C); 4.50 (t, 2H, $^3J_{HH}$=4.5 Hz, CH_2O); 2.64 (m, 2H, CH_2). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 164.0 (C=O); 141.6 (H**C**=C); 135.8 (**C**=CH); 134.0 (C_{ipso} aromatic); 128.6 and 128.5 (CH aromatic); 66.7 (CH_2O); 25.2 (CH_2). GC–MS (EI, 70 eV): 174 (100, M^+); 144 (65); 129 (12); 115 (99). Compound **2f** was observed only by gas chromatography. GC–MS (EI, 70 eV): 174 (M^+, 96); 173 (100, M^+-1); 129 (45).

Compound **1g**: IR (KBr pellets): 1718 cm^{-1} (ν C=O); 1681 cm^{-1} (ν C=C). ^1H NMR ($CDCl_3$, 200 MHz, RT), δ 6.61 (m, 1H, HC=C); 4.36 (t, 2H, $^3J_{HH}$=7.7 Hz, CH_2O); 2.45 (m, 2H, CH_2); 1.94 (d, 3H, $^3J_{HH}$=1.9 Hz). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 165.8 (C=O); 139.9 (H**C**=C); 128.9 (**C**=CH); 67.0 (CH_2O); 24.7 (CH_2); 17.6 (CH_3). GC–MS (EI, 70 eV): 112 (100, M^+); 82 (56); 67 (15); 54 (77).

Compound **2g**: IR (KBr pellets): 1756 cm^{-1} (ν C=O); ^1H NMR ($CDCl_3$, 200 MHz, RT), δ 6.80 (m, 1H, HC=C); 4.35 (t, 2H, $^3J_{HH}$=6.2 Hz, CH_2O); 2.86 (m, 2H, CH_2); 1.91 (d, 3H, $^3J_{HH}$=2.7 Hz, CH_3). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 172.0 (C=O); 136.0 (H**C**=C); 126.0 (**C**=CH); 65.7 (CH_2O); 25.2 (CH_2); 16.1 (CH_3). GC–MS (EI, 70 eV): 112 (100, M^+); 97 (9); 94 (12); 82 (63); 67 (32).

Compound **2h**: Calculated for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; found: C, 71.21; H, 9.45. IR (KBr pellets): 1756 cm^{-1} (ν C=O); ^1H NMR ($CDCl_3$, 300 MHz, RT), δ 6.74 (t, 1H, $^3J_{HH}$=2.8 Hz, HC=C); 4.64 (m, 1H, CHO); 3.15 and 2.60 (2m, 2H, CH_2); 1.41 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3); 1.17 (s, 9H, CH_3). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 172.5 (C=O); 150.6 (H**C**=C); 123.0 (**C**=CH); 74.1 (CHO); 33.7 (CH_2); 29.6 and 22.6 (CH_3).

3.3. Synthesis of O*-benzyl (*S*)-(−)-4-pentyn-2-ol **3e***

To a suspension of solid lithium acetylide ethylenediamine complex (3.17 g, 34.5 mmol) in DMSO (15 mL), a solution of (*S*)-(−)-propylene oxide (1.0 g, 17.2 mmol) in DMSO (3 mL) was added dropwise at 0°C. After stirring at room temperature for 30 h the brown solution was diluted with a saturated aqueous solution of NH_4Cl (30 mL). The organic phase was extracted with diethyl ether (3×30 mL) and dried over magnesium sulfate. Evaporation of the volatiles at atmospheric pressure afforded an orange oil (1.11 g). The alkyne thus obtained was dissolved in THF (30mL) and sodium hydride (0.8 g, 20 mmol) was added at room temperature. After stirring at room temperature for 0.2 h, benzyl bromide (2.4 mL, 20 mmol) was added and the reaction mixture was stirred for 2 h. Addition of water (200 mL), extraction

of the organic phase with MTBE (3×40 mL) that was dried over magnesium sulfate and removing the volatiles under reduced pressure afforded a yellow oil. Column chromatography (hexane/diethyl ether 3%) gave **3e** as a colourless oil (1.79 g, 60% overall yield).

Compound **3e**: Calculated for $C_{12}H_{14}O$: C, 82.72; H, 8.10; found: C, 82.59; H, 8.45. $[\alpha]^{25}_{589}=-9.8$ (c=2.85, Et_2O). IR (KBr pellets): 3298 cm^{-1} (ν C–H); 2119 cm^{-1} (ν C≡C); ^1H NMR ($CDCl_3$, 200 MHz, RT), δ 7.37–7.24 (m, 5H, CH aromatic); 4.56 (s, 2H, CH_2O); 3.70 (m, 1H, CH); 2.45 (m, 2H, CH_2); 2.01 (m, 1H, CH); 1.31 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3). $^{13}C–\{^1H\}$ NMR ($CDCl_3$, 50 MHz, RT), δ 138.3 (C_{ipso}); 129.5, 1128.2 and 127.5 (CH aromatic); 81.5 and 69.1 (C≡C); 73.1 (CH); 70.6 (CH_2O); 25.9 (CH_2); 19.4 (CH_3).

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