Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1163–1172

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of (*R*)-incrustoporin, an antibiotic isolated from *Incrustoporia carneola*

Renzo Rossi,[a,*] Fabio Bellina,[a] Matteo Biagetti [a] and Luisa Mannina [b]

[a] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy*
[b] *Corso di Laurea in Scienze Ambientali, Università del Molise, Via Mazzini 8, I-86170 Isernia, Italy*

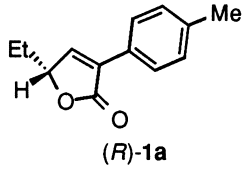
Received 16 February 1999; accepted 8 March 1999

Abstract

Highly enantiomerically enriched (*R*)-incrustoporin was enantioselectively synthesized in 43.6% overall yield starting from 4-iodotoluene. The key steps of the synthesis included the asymmetric hydrogenation of 1-(*p*-tolyl)-1-pentyn-3-one catalyzed by a non-racemic Ru(II) complex and the Pd-catalyzed cyclocarbonylation of so-obtained highly enantiomerically enriched 1-(*p*-tolyl)-1-pentyn-3-ol. This Pd-catalyzed reaction, whose stereochemical outcome was previously unknown, proceeded with retention of configuration and 2.5% or less racemization. The enantiomeric purities of (*R*)-1-(*p*-tolyl)-1-pentyn-3-ol and (*R*)-incrustoporin were evaluated by HPLC analysis on a Chiralcel OJ column as well as by performing the ^{1}H NMR spectra of these compounds in a D_2O solution which was saturated with α- or β-cyclodextrin, respectively.

1. Introduction

In connection with our ongoing projects relating to the synthesis of natural and unnatural 5*H*-furan-2-one derivatives,[1] we recently became interested in developing a convenient and efficient synthesis of (−)-incrustoporin [(−)-3-(*p*-tolyl)-5-ethyl-5*H*-furan-2-one] **1a**, an antifungal antibiotic isolated from the Basidiomycete *Incrustoporia carneola*.[2] The absolute configuration of this compound has been established as *R* by synthesis starting from (*S*)-1,2-epoxybutane and methyl *p*-tolylacetate.[3]

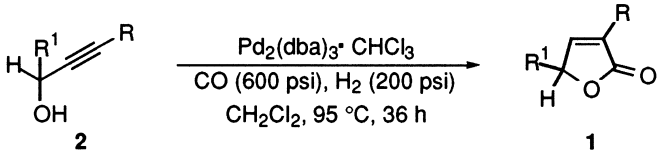


(*R*)-**1a**

* Corresponding author. E-mail: rossi@dcci.unipi.it

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00085-3

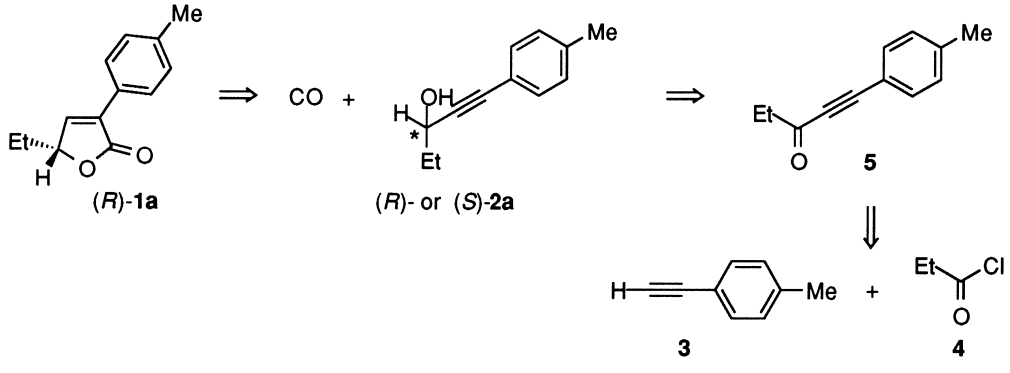
We sought a procedure for the synthesis of (*R*)-**1a** in which commercially available and inexpensive starting materials could be used and which would be more simple and efficient than the methods employed so far in the literature for the preparation of chiral non-racemic 3,5-disubstituted 5*H*-furan-2-ones **1**.[4–9] We felt that a recently reported method for the synthesis of racemic compounds **1**,[10] which is based on the Pd-catalyzed cyclocarbonylation of 1-alkynylcarbinols (Eq. 1), could be employed for the preparation of highly enantiomerically enriched (*R*)-**1a** provided that a suitable chiral non-racemic propargylic alcohol was used and the Pd-catalyzed cyclocarbonylation, whose stereochemical outcome was unknown, occurred stereospecifically.



(1)

On the other hand, highly enantiomerically enriched propargylic alcohols such as those employed for the synthesis of (*R*)-**1a**, i.e. **2a**, can be easily obtained by asymmetric reduction of the corresponding α,β-acetylenic ketones.[11]

As shown from the retrosynthetic analysis reported in Scheme 1, the chiral alcohol to be employed in the synthesis of (*R*)-**1a** could be (*R*)- or (*S*)-**2a** depending on the stereochemistry of the Pd-catalyzed cyclocarbonylation reaction. On the other hand, it must be taken into account that it has been reported that the $Pd(PPh_3)_4$-catalyzed carbonylation of enantiomerically enriched propargylic mesylates in aqueous THF, which affords allenic acids, occurs with inversion of configuration and 10% or less racemization.[4]

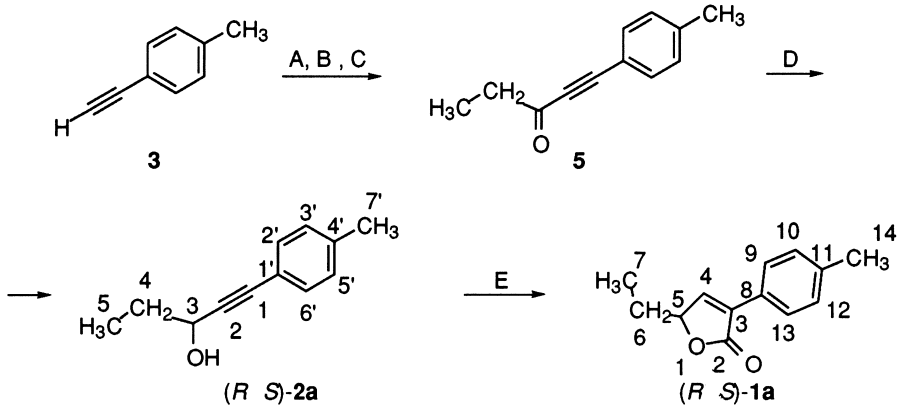


Scheme 1.

Herein we wish to report and comment on the results obtained in the study of the synthesis of (*RS*)-**1a** and (*R*)-**1a**. In fact, we commenced our study by preparing (*RS*)-**1a** since its synthesis, which was performed on the basis of a retrosynthetic analysis very similar to that shown in Scheme 1, could allow us to probe the efficiency and selectivity of the procedure. Moreover, the availability of (*RS*)-**1a** and its key precursor, i.e. (*RS*)-**2a**, could allow analytical procedures to be set up for evaluating the enantiomeric purities of the corresponding non-racemic compounds as well as to test the biological activity of (*RS*)-**1a** which is so far unknown.

2. Results and discussion

Compound (*RS*)-**1a** was synthesized according to the reaction sequence depicted in Scheme 2. In particular, 4-ethynyltoluene **3**, which was prepared in 92% yield by reaction of 4-iodotoluene with ethynylmagnesium bromide in THF at 0°C in the presence of 5 mol% $Pd(PPh_3)_4$[12], was converted into the corresponding 1-alkynylzinc bromide by treatment with a THF solution of ethylmagnesium bromide followed by transmetallation with a molar excess of dry $ZnBr_2$. Reaction between this organozinc derivative and propionyl chloride at 0°C in the presence of a catalytic amount of $Pd(PPh_3)_4$ provided compound **5** in 81% yield. This ketone was then converted in 82% yield into the corresponding α,β-acetylenic alcohol (*RS*)-**2a** by reaction with $NaBH_4$ in 2-propanol at 0°C.



Scheme 2. (a) EtMgBr, THF, Δ; (b) $ZnBr_2$, 0°C; (c) C_2H_5COCl (**4**), $Pd(PPh_3)_4$, 4 h at 0°C, 1 h at 20°C, 81%; (d) $NaBH_4$, 2-propanol, 0°C, 82%; (e) $Pd(dba)_2$, dppb, CO (600 psi), H_2 (200 psi), CH_2Cl_2, 95°C, 48 h, 68%

Finally, according to a procedure for the Pd-catalyzed cyclocarbonylation of racemic 1-alkynylcarbinols,[10] a CH_2Cl_2 solution of (*RS*)-**2a** was treated with carbon monoxide and hydrogen in the presence of catalytic quantities of $Pd(dba)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) for 48 h at 95°C. This reaction provided chemically pure (*RS*)-**1a** in 68% yield.

Analytical procedures for the separation of both enantiomers of (*RS*)-**2a** and (*RS*)-**1a** were then developed. As a result, these enantiomers were found to be easily separated by HPLC on a Chiralcel OJ column. Moreover, the enantiomers of (*RS*)-**2a** were also well differentiated by ^1H NMR analysis of this racemic alcohol in a D_2O solution containing α-cyclodextrin (α-CD). This analysis showed that the signal assigned to the H-3 proton (δ 4.605) (Fig. 1a) was shifted upfield and was resolved into two well defined triplets of equal intensity in the presence of α-CD.

The largest signal separation (Δδ=27.0 Hz) was observed when the ^1H NMR spectrum was performed using a saturated solution of α-CD in D_2O (Fig. 1b). Interestingly, either an upfield shift or an enantiomeric resolution was also observed for the H-5 resonance of (*RS*)-**2a**. However, in this case the Δδ value was 4.2 Hz. On the other hand, the enantiomers of (*RS*)-**1a** were differentiated by ^1H NMR analysis by perfoming the spectrum of this compound in a D_2O solution containing β-cyclodextrin (β-CD). Also in this case, the largest separation of the signals of the two enantiomeric forms was observed when the spectrum was performed using a saturated solution of β-CD in D_2O. Thus, the H-5 resonance (δ 5.271) was shifted downfield and resolved in two partly overlapping doublets of triplets, which were separated by 4.2 Hz. On the contrary, the doublets assigned to the H-4 proton (δ 7.909) and the H-9 and H-13 protons (δ 7.709), respectively, were shifted upfield and each of these doublets was resolved in two doublets which were separated by 6.6 and 3.6 Hz, respectively (Fig. 2).

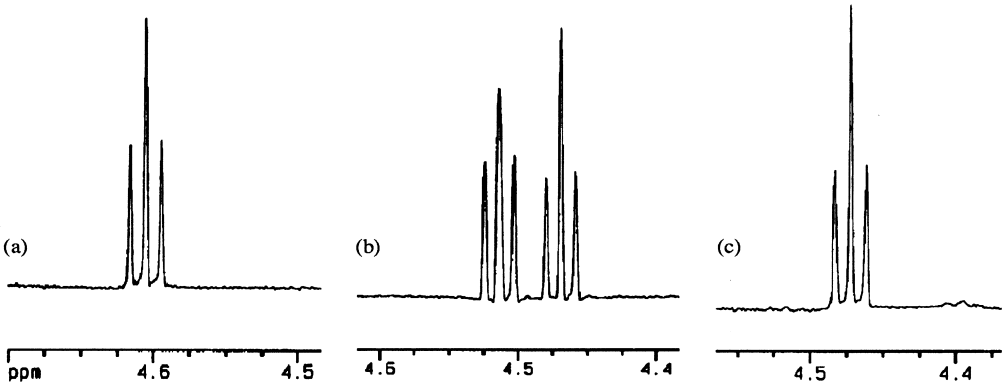


Figure 1. (a) 600.13 MHz ^{1}H NMR spectrum of (*RS*)-1-(*p*-tolyl)-1-pentyn-3-ol in D_2O. The H-3 triplet at δ 4.605 is shown. (b) 600.13 MHz ^{1}H NMR spectrum of the same compound in a saturated solution of α-cyclodextrin in D_2O. (c) 600.13 MHz ^{1}H NMR spectrum of (*R*)-(+)-1-(*p*-tolyl)-1-pentyn-3-ol, $[\alpha]_D^{22}$ +15.91 (c 0.993, Et_2O) in a saturated solution of α-cyclodextrin in D_2O

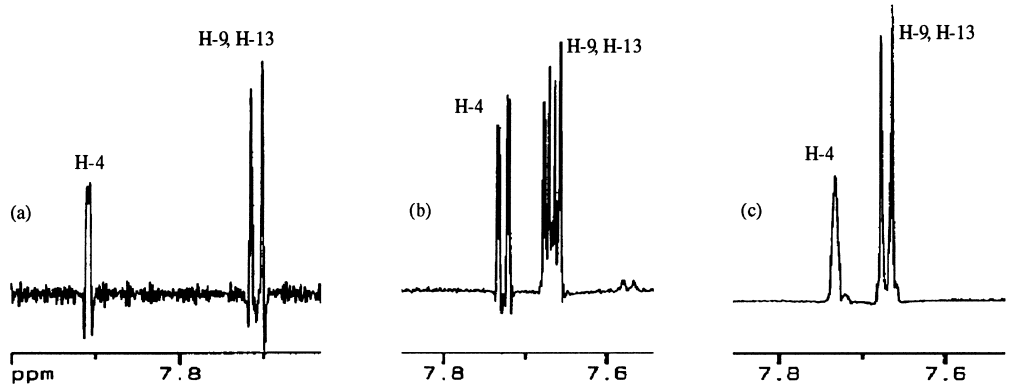
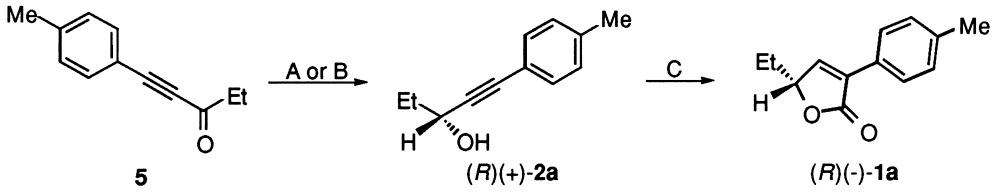


Figure 2. (a) 600.13 MHz ^{1}H NMR spectrum of (*RS*)-incrustoporin in D_2O. The H-4 doublet at δ 7.909 and the H-9, H-13 doublet at δ 7.709 are shown. (b) 600.13 MHz ^{1}H NMR spectrum of the same compound in a saturated solution of β-cyclodextrin in D_2O. (c) 600.13 MHz ^{1}H NMR spectrum of (*R*)-(−)-incrustoporinin, $[\alpha]_D^{25}$ −5.77 (c 3.156, $CHCl_3$) in a saturated solution of β-cyclodextrin in D_2O

Next we turned our attention to the synthesis of enantiomerically enriched (*R*)-**1a** and, supposing that this compound could be prepared by Pd-catalyzed cyclocarbonylation of enantiomerically enriched (*R*)-**2a**, we first synthesized this alcohol by asymmetric reduction of compound **5** with a molar excess of (*R*)-alpine-borane according to a modification[13] of the general procedure described by Midland and coworkers.[11b] This reaction (Scheme 3) gave ca. 87% yield of compound (+)-**2a**, $[\alpha]_D^{22}$ +14.54 (c 1.04, Et_2O), which on the basis of HPLC analyses on a Chiralcel OJ column was estimated to be 88.6% enantiomerically pure.

On the other hand, the much more enantiomerically enriched (+)-**2a**, was prepared by asymmetric transfer hydrogenation of compound **5** according to a general procedure developed by Noyori and coworkers.[11a] In particular, compound **5** was asymmetrically reduced with 2-propanol in the presence of a Ru(II) catalyst, which was generated in situ by mixing $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene-diamine [(*R*,*R*)-Ts-DPEN] and KOH in a 1:2:5 molar ratio, respectively. This reaction gave in 86% yield compound (+)-**2a**, $[\alpha]_D^{22}$ +15.91 (c 0.993, Et_2O), which on the basis of HPLC analyses on a Chiralcel OJ column was 96.8% enantiomerically pure (Scheme 3).



Scheme 3. (a) (i) (*R*)-Alpine-borane, THF, 46 h, 20°C; (ii) MeCHO; (iii) −THF, −α-pinene; (iv) ethanolamine, Et_2O; (v) MPLC on silica gel, 87%; (b) $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, (*R*,*R*)-Ts-DPEN, KOH, 2-propanol, 28°C, 4 h, 86.2%; (c) $Pd(dba)_2$, dppb, CO (600 psi), H_2 (200 psi), CH_2Cl_2, 95°C, 48 h, 68–69%

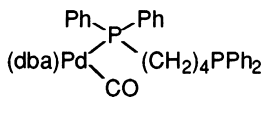
Moreover, ^{1}H NMR analysis of this sample of (+)-**2a** in a saturated solution of α-CD in D_2O allowed us to assign to this alcohol an e.e. of ca. 99%. This value was obtained by deconvolution of the H-3 resonance of (+)-**2a** (Fig. 1c).

The configuration of (+)-**2a** was expected to be *R* on the basis of either the tentative mechanism of reduction of acetylenic ketones with (*R*)-alpine-borane[14] or the configuration of known propargylic alcohols prepared by this method.[11b,d] On the other hand, this tentative configurational assignment could be confirmed by taking into account that the asymmetric transfer hydrogenation of α,β-acetylenic ketones by chiral Ru(II) complexes, which are obtained using (*S*,*S*)-TsDPEN as the chiral ligand, affords propargylic alcohols of *S* configuration.[11a]

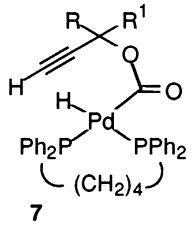
We were then pleased to observe that the Pd-catalyzed cyclocarbonylation of (*R*)-**2a** having $[\alpha]_D^{22}$ +15.91 (c 0.993, Et_2O) afforded in 68% yield compound (*R*)-**1a**, which on the basis of HPLC analyses on a Chiralcel OJ column proved to be 95.2% enantiomerically pure (Scheme 3). Unfortunately, the e.e. of this compound could not be accurately evaluated by its ^{1}H NMR analysis in a saturated solution of β-CD in D_2O. Nevertheless, on the basis of the area of the signals attributed to the H-4 proton (Fig. 2c), the enantiomeric purity of this sample was estimated to be higher than 91%.

It was also found that the Pd-catalyzed cyclocarbonylation of (*R*)-**2a** having $[\alpha]_D^{22}$ +14.54 (c 1.04, Et_2O) produced in 69% yield compound (*R*)-**1a**, which by HPLC analysis on a Chiralcel OJ column was estimated to be 86.1% enantiomerically pure. Thus, this reaction occurred with retention of configuration and 2.5% or less, of racemization.

It must be noted that these stereochemical results were not in agreement with those expected on the basis of the mechanism suggested by Yu and Alper[10] for the Pd-catalyzed cyclocarbonylation reaction of racemic 1-alkynylcarbinols. In fact, since in this mechanism the first step of the catalytic cycle involves insertion of Pd(0) into the C–O bond of the 1-alkynylcarbinol, which thus affects the stereogenic center of this compound, analogous to what has been observed for the Pd-catalyzed carbonylation of enantiomerically enriched propargylic mesylates,[5] the cyclocarbonylation reaction of (*R*)-**2a** should occur with inversion of configuration. However, our stereochemical results could be explained on the basis of a previously reported mechanism for the Pd-catalyzed carbonylation of ethynylcarbinols in 1,2-dimethoxyethane solution,[15] in which a catalytic step involves insertion of complex **6** into the O–H bond of ethynylcarbinols to afford complex **7**.



6



7

Nevertheless, this Pd-catalyzed reaction does not require the presence of hydrogen, which on the contrary seems to be necessary in order to obtain 5*H*-furan-2-ones **1** in the Pd-catalyzed reaction involving 1-alkynyl-carbinols.[5]

In conclusion, 95.2% enantiomerically pure (*R*)-incrustoporin (*R*)-**1a** has been enantioselectively synthesized in 43.6% overall yield by a procedure in which 4-iodotolune was the starting material and the key step was the Pd-catalyzed cyclocarbonylation of highly enantiomerically enriched (*R*)-1-(*p*-tolyl)-1-pentyn-3-ol (*R*)-**2a**, which was easily available by Ru(II)-catalyzed asymmetric transfer hydrogenation of the corresponding α,β-acetylenic ketone. It has also been shown that the Pd-catalyzed cyclocarbonylation of a chiral non-racemic 1-alkynylcarbinol such as (*R*)-**2a** proceeds with retention of configuration, and at least in this case, with ca. 2.5% or less, of racemization.

We are currently trying to expand the scope of the strategy, which has been used for the synthesis of (*R*)-**1a**, to the preparation of other non-racemic naturally occurring 3,5-disubstituted 5*H*-furan-2-ones which are characterized by interesting biological properties and for which the absolute configuration is so far unknown.

3. Experimental

All reactions involving air- and water-sensitive materials were performed in flame dried glassware under an argon atmosphere. Air- and water-sensitive solutions were transferred with hypodermic syringes or double-ended needles. Precoated plastic silica gel sheets (Merck 60 F_{254}) were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas chromatograph. HPLC analyses were performed using a Perkin–Elmer series 410 LC pump, a 785A UV–vis detector, a 1020 Perkin–Elmer data station and a Chiralcel OJ column (25 cm×4.6 mm). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS or $CDCl_3$ as an internal standard, respectively. The structural assignments were performed by a combination of NMR techniques which included ^{1}H–^{1}H-COSY, NOESY, ^{1}H–^{13}C heteronuclear shift correlation and ^{1}H–^{13}C long range heteronuclear shift correlation. IR spectra were recorded on a Perkin–Elmer 1725-X FT-IR spectrophotometer. Measurements of optical activity were performed using a Perkin–Elmer 142 spectropolarimeter and 1 dm tubes. $Pd(PPh_3)_4$ was prepared according to the literature.[16] (*R*)-Alpine-borane [$[\alpha]_D^{20}$ −3.0 (neat)], $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] were commercially available. (1*R*,2*R*)-*N*-(*p*-Toluenesulfonyl)-1,2-diphenylethylenediamine [(*R*,*R*)-Ts-DPEN], $[\alpha]_D^{25.5}$ −30.27 (c 0.413, $CHCl_3$), was prepared from commercially available (1*R*,2*R*)-1,2-diphenylethylene-diamine, $[\alpha]_D^{20}$ +10.2 (c=1, EtOH), according to the literature.[17] 4-Ethynyltoluene **3** was prepared in 92% yield by reaction of 4-iodotoluene with ethynylmagnesium bromide in THF at 20°C in the presence of 5 mol% $Pd(PPh_3)_4$.[12]

3.1. 1-(p-Tolyl)-1-pentyn-3-one 5

A solution of compound **3** (9.05 g, 78.0 mmol) in THF (20 ml) was added dropwise to a 0.819 M THF solution of ethynylmagnesium bromide (100 ml, 81.9 mmol) and the resulting mixture was refluxed for

1 h. It was then cooled to room temperature and added to a stirred solution of dry $ZnBr_2$ (22.8 g, 101.5 mmol) in THF (100 ml) which was cooled to 0°C. The resulting suspension was stirred at 0°C for 2 h. $Pd(PPh_3)_4$ (3.46 g, 2.99 mmol) and a solution of propionyl chloride (5.55 g, 60.0 mmol) in THF (50 ml) were then sequentially added and the resulting mixture was stirred for 4 h at 0°C and for 1.5 h at 20°C. The reaction mixture was quenched with a large excess of a saturated aqueous NH_4Cl solution, extracted with Et_2O, dried over Na_2SO_4, filtered over Celite and concentrated in vacuo. The residue was diluted with a mixture of hexane and benzene (50 ml, 60:40) and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (60:40) as an eluent, to give chemically pure **5** (8.40 g, 81% yield based on propionyl chloride) as a colorless solid: m.p. 34–36°C. MS, *m/z* (%): 172 (21), 143 (96), 142 (100), 115 (27), 89 (23). IR (KBr): ν 2196, 1671, 1603, 1509, 1459, 1405, 1343, 1114, 821, 796 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.18 (2H, d, J=8.0 Hz, H-2′ and H-6′), 2.68 (2H, q, J=7.4 Hz, H-4), 2.38 (3H, s, H-7), 1.21 ppm (3H, t, J=7.4 Hz, H-5). Anal. calcd for $C_{12}H_{12}O$: C, 83.87; H, 7.02. Found: C, 84.09; H, 7.27.

*3.2. (*RS*)-1-(*p*-Tolyl)-1-pentyn-3-ol (*RS*)-**2a***

Sodium borohydride (2.30 g, 6.08 mmol) was added during 20 min to a solution of compound **5** (3.50 g, 20.35 mmol) in 2-propanol (100 ml) which was stirred at 0°C. After stirring the reaction mixture for 1 h at 0°C, acetone (60 ml) was added dropwise and the resulting mixture, which was maintained at 0°C, was treated with 10% aqueous HCl (170 ml) and then diluted with CH_2Cl_2 (70 ml). It was then allowed to warm up to room temperature and extracted repeatedly with CH_2Cl_2. The collected organic extracts were washed with water, diluted aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (70:30) as an eluent, to give chemically pure (*RS*)-**2a** (2.90 g, 82% yield) as a pale yellow liquid. MS, *m/z* (%): 174 (25), 156 (10), 144 (95), 115 (100), 91 (49). IR (film): ν 2232, 1510, 1463, 1456, 1099, 1049, 1020, 963, 817 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.326 (2H, d, J=8.2 Hz, H-3′ and H-5′), 7.107 (2H, d, J=8.2 Hz, H-2′ and H-5′), 4.543 (1H, t, J=6.4 Hz, H-3), 2.342 (3H, s, H-7′), 1.820 (2H, m, H-4), 1.075 ppm (3H, t, J=7.3 Hz, H-5). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.43 (C-4′), 131.55 (C-3′ and C-5′), 128.99 (C-2′ and C-6′), 119.57 (C-1′), 89.25 (C-2), 85.00 (C-1), 64.21 (C-3), 31.00 (C-2), 21.72 (C-7′), 9.47 ppm (C-5). ^1H NMR (600.13 MHz, D_2O): δ 7.438 (2H, d, J=8.4 Hz, H-3′ and H-5′), 7.270 (2H, d, J=8.4 Hz, H-2′ and H-6′), 4.605 (1H, t, J=7.1 Hz, H-3), 2.368 (3H, s, H-7′), 1.810 (2H, quint, J=7.1 Hz, H-4), 1.502 ppm (3H, t, J=7.1 Hz, H-5). ^1H NMR (600.13 MHz, saturated solution of α-CD in D_2O): δ 7.683 (2H, d, H-3′ and H-5′), 7.353 (2H, d, H-2′ and H-6′), 4.515 (0.5H, t, H-3), 4.470 (0.5H, t, H-3), 2.439 (3H, s, H-7′), 1.725 (2H, quint, H-4), 1.039 (1.5H, t, H-5) and 1.032 ppm (1.5H, t, H-5). Anal. calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.66; H, 8.23.

*3.3. Synthesis of (*R*)-1-(*p*-tolyl)-1-pentyn-3-ol (*R*)-**2a** by enantioselective reduction of **5** with (*R*)-alpine-borane*

A solution of compound **5** (3.50 g, 20.35 mmol) in deaerated dry THF (15 ml) was added dropwise to a 0.5 M THF solution of (*R*)-alpine-borane (57.0 ml, 28.50 mmol) and the resulting mixture was stirred under argon for 46 h at 20°C. It was then cooled to 0°C, acetaldehyde (1.2 ml, 21.4 mmol) was added and the solution was stirred at 0°C for 0.5 h. The solution was then allowed to warm up to 20°C and THF was removed at 20 torr. The reaction vessel was then filled with argon and the liquid residue, which was stirred at 35–40°C was maintained at 0.05 torr for 3.5 h in order to remove α-pinene liberated during

the reaction. The reaction vessel was then filled with argon, the liquid residue was diluted with dry Et_2O (60 ml) and the resulting solution was cooled to 0°C. Ethanolamine (1.73 ml, 28.47 mmol) was added and a white solid precipitated. The mixture was stirred for 1 h at 0°C and then filtered over Celite. The collected solid was washed with cold Et_2O. The collected filtrates were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (70:30) as an eluent, to give chemically pure (*R*)-**2a** (3.07 g, 86.7% yield): $[\alpha]_D^{22}$ +14.54 (c 1.04, Et_2O). The spectral properties of this compound were in good agreement with those of (*RS*)-**2a**. The enantiomeric purity of (*R*)-**2a** was estimated to be 88.7% by HPLC analysis [column: Chiralcel OJ; solvent: hexane:2-propanol (90:10); flow rate: 0.5 ml/min; detection at 254 nm]; t_R=17.3 min (>94.3%) [(*S*)-**2a**; t_R=22.6 min (<5.6%)].

*3.4. Synthesis of (*R*)-1-(*p*-tolyl)-1-pentyn-3-ol (*R*)-**2a** by asymmetric transfer hydrogenation of **5** by a chiral ruthenium(II) complex*

A flame dried reaction vessel, which was maintained under an argon atmosphere, was charged with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (40.83 mg, 0.066 mmol), (*R*,*R*)-TsDPEN (48.80 mg, 0.133 mmol) and deaerated 2-propanol (15 ml) and the mixture was stirred at room temperature. A 1.51 M solution of KOH in 2-propanol (200 μl, 0.332 mmol) and a solution of compound **5** (3.44 g, 20.0 mmol) in deaerated 2-propanol (25 ml) were sequentially added and the resulting solution, which was a deep purple color, was stirred under argon at 28°C for 4.5 h. It was then concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (70:30) as an eluent, to give chemically pure (*R*)-**2a** (3.0 g, 86.2% yield): $[\alpha]_D^{22}$ +15.91 (c 0.993, Et_2O). ^{1}H NMR (600.13 MHz, saturated solution of α-CD in D_2O): δ 7.683 (2H, d, H-3′ and H-5′), 7.353 (2H, d, H-2′ and H-6′), 4.470 (1H, t, H-3), 2.439 (3H, t, H-7′), 1.725 (2H, quint, H-4), 1.039 ppm (3H, t, H-5). A triplet at δ 4.515 and a triplet at δ 1.032, which were assigned to the H-3 and H-5 protons of (*S*)-**2a**, respectively, were also detected in this ^{1}H NMR spectrum. The spectral properties of (*R*)-**2a** were in good agreement with those of (*RS*)-**2a**. The enantiomeric purity of (*R*)-**2a** was estimated to be 96.8% by HPLC analysis [column: Chiralcel OJ; solvent: hexane:2-propanol (90:10); flow rate: 0.5 ml/min; detection at 254 nm]; t_R=17.3 min (98.4%) [(*S*)-**2a**; t_R=22.6 min (1.6%)]. On the other hand, the e.e. of (*R*)-**2a** was estimated to be ca. 99% on the basis of its ^{1}H NMR spectrum registered in a D_2O solution which was saturated with α-CD.

*3.5. (*RS*)-Incrustoporin (*RS*)-**1a***

A mixture of compound (*RS*)-**2a** (2.56 g, 14.71 mmol), $Pd(dba)_2$ (0.677 g, 1.18 mmol), dppb (0.502 g, 1.18 mmol) and deaerated anhydrous CH_2Cl_2 (100 ml) was reacted with carbon monoxide (600 psi) and hydrogen (200 psi) at 95°C in a stainless steel autoclave for 48 h. After the autoclave was cooled to room temperature, the gases were released and the crude rection mixture was filtered over Celite. The filtrate was concentrated in vacuo, the residue was diluted with a mixture of hexane and THF (50 ml, 90:10) and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel using a mixture of hexane and THF (90:10) as an eluent, to give chemically pure (*RS*)-**1a** (2.01 g, 67.6% yield) as a colorless solid: m.p. 53–55°C. MS, *m/z* (%): 202 (15), 145 (19), 117 (100), 91 (14), 57 (11). IR (KBr): ν 1752, 1514, 1337, 1117, 966, 825, 733 cm^{-1}. ^{1}H NMR (600.13 MHz, $CDCl_3$): δ 7.756 (2H, d, J=8.2 Hz, H-9 and H-13), 7.488 (1H, d, J=1.9 Hz, H-4), 7.219 (2H, d, J=8.2 Hz, H-9 and H-13), 7.488 (1H, dt, J=1.9 and 6.2 Hz, H-5), 2.376 (3H, s, H-14), 1.876 (1H, m, H-6), 1.796 (1H, m, H-6), 1.061 ppm (3H, t, J=7.5 Hz, H-7). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.90 (C-2), 146.56 (C-4), 139.40 (C-11), 131.76 (C-3), 129.33 (C-10 and C-12), 127.19 (C-9 and C-13), 126.42 (C-8), 81.42 (C-

5), 24.78 (C-6), 21.36 (C-14), 9.184 ppm (C-7). These spectral data were in satisfactory agreement with those reported for the natural product.[2] ^{1}H NMR (600.13 MHz, D_2O): δ 7.909 (1H, d, J=1.5 Hz, H-4), 7.709 (2H, d, J=8.8 Hz, H-9 and H-13), 7.365 (2H, d, J=8.2 Hz, H-10 and H-12), 5.271 (1H, dt, J=1.5 and 5.5 Hz, H-5), 2.398 (3H, s, H-14), 1.957–1.864 (2H, m, H-6), 1.000 ppm (3H, t, J=7.5 Hz, H-7). ^{1}H NMR (600.13 MHz, saturated solution of β-CD in D_2O): δ 7.732 (0.5H, d, H-4), 7.721 (0.5H, d, H-4), 7.670 (1H, d, H-9 and H-13), 7.664 (1H, d, H-9 and H-13), 7.331 (2H, d, H-10 and H-12), 5.347 (0.5H, dt, H-5), 5.340 (0.5H, dt, H-5), 2.430 (3H, s, H-14), 2.055 (1H, m, H-6), 1.893 (1H, m, H-6), 0.983 ppm (3H, t, H-7).

*3.6. (*R*)-Incrustoporin (*R*)-**1a***

The Pd-catalyzed cyclocarbonylation of 96.8% enantiomerically pure (*R*)-**2a**, $[\alpha]_D^{22}$ +15.91 (c 0.993 Et_2O), which was performed according to the same procedure used for the synthesis of (*RS*)-**1a**, provided chemically pure (*R*)-**1a** in 68% yield. Compound (*R*)-**1a** had: m.p. 32–34°C (lit.[3] m.p. 43°C); $[\alpha]_D^{25}$ −5.77 (c 3.156, $CHCl_3$) [lit.[2] $[\alpha]_D$ −4 (c 0.3, $CDCl_3$); lit.[3] $[\alpha]_D^{23}$ −6.8 (c 0.3, $CHCl_3$)]. ^{1}H NMR (600.13 MHz, saturated solution of β-CD in D_2O): δ 7.732 (1H, d, H-4), 7.670 (2H, d, H-9 and H-13), 7.331 (2H, d, H-10 and H-12), 5.340 (1H, dt, H-5), 2.430 (3H, s, H-14), 2.055 (1H, m, H-6), 1.893 (1H, m, H-6), 0.893 ppm (3H, t, H-7). A doublet at δ 7.721, a doublet at δ 7.664 and a doublet of triplets at δ 5.347, which were assigned to the H-4, H-13 and H-5 protons of (*S*)-**1a**, respectively, were also observed in this ^{1}H NMR spectrum. The enantiomeric purity of (*R*)-**1a** was estimated to be 95.2% by HPLC analysis [Chiralcel OJ column; solvent: hexane:2-propanol (75:25); flow rate: 0.7 ml/min; detection at 254 nm]; t_R 24.4 min (97.6%) [(*S*)-**1a**; t_R=17.2 min (2.4%)]. On the other hand, the e.e. of (*R*)-**1a** was estimated to be higher than 91% on the basis of its ^{1}H NMR spectrum registered in a D_2O solution which was saturated with β-CD.

It must also be noted that the Pd-catalyzed cyclocarbonylation reaction of (*R*)-**2a** having $[\alpha]_D^{22}$ +14.54 (c 1.04 Et_2O) provided in 69% yield chemically pure (*R*)-**1a** which had: m.p. 32–35°C; $[\alpha]_D^{25}$ −5.10 (c 3.126, $CHCl_3$). The enantiomeric purity of this sample of (*R*)-**1a** was estimated to be 86.1% by HPLC on a Chiralcel OJ column using the same experimental conditions employed for the HPLC analysis of (*R*)-**1a** having $[\alpha]_D^{25}$ −5.77 (c 3.156, $CHCl_3$).

Finally, it is worth mentioning that although it has been reported that recrystallization of 94.5% enantiomerically pure (*R*)-**1a** from hexane/ethyl acetate affords (*R*)-**1a** with an enantiomeric purity higher than 99%,[3] we made no attempt to increase, by recrystallization, the enantiomeric purity of (*R*)-**1a** which had a value of 95.2% e.e.

Acknowledgements

We gratefully acknowledge the financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Progetto Finallizzato Beni Culturali (CNR, Roma). We wish also to thank Prof. Annalaura Segre for the use of NMR facilities at the Servizio NMR dell'Area della Ricerca di Roma (CNR, Roma).

References

1. (a) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 3017; (b) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7599; (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7799; (d) Rossi, R.; Bellina, F.; Biagetti, M. *Synth. Commun.* in press.

2. Zapf, S.; Anke, T.; Sterner, O. *Acta Chem. Scand*. **1995**, *49*, 233.
3. Yajima, A.; Mori, K. *Liebigs Ann. Chem*. **1996**, 1091.
4. For the synthesis of enantiomerically enriched 3,5-disubstituted 5*H*-furan-2-ones starting from enantiomerically enriched propargylic mesylates, see: Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem*. **1997**, *62*, 367.
5. For the synthesis of (*R*)-3-alkyl-5-methyl-5*H*-furan-2-ones by retro-Diels–Alder reaction of the adducts from cyclopentadiene and (*R*)-angelica lactone, see: Corber, J.; Font, J.; Monsalvatje, M.; Ortuno, R. M.; Sanchez-Ferrando, F. *J. Org. Chem*. **1988**, *53*, 4393.
6. For the synthesis of the chiral non-racemic 3-substituted 5-methyl-5*H*-furan-2-one moiety of annonaceous acetogenins by a CpRu(COD)Cl-catalyzed annulation on a monosubstituted carbon–carbon double bond with enantiomerically pure ethyl (*S*)-4-hydroxypentynoate, see: (a) Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc*. **1995**, *117*, 1888; (b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc*. **1994**, *116*, 7459.
7. For the synthesis of the chiral non-racemic 3-substituted 5-methyl-5*H*-furan-2-one moiety and annonaceous acetogenins starting from L-lactic acid derivatives, see: (a) Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem*. **1995**, *60*, 1170; (b) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975; (c) Yao, Z.-J.; Yu, Q.; Wu, Y.-L. *Synth. Commun*. **1996**, *26*, 3613; (d) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc*. **1993**, *115*, 4891.
8. For the synthesis of the chiral non-racemic 3-substituted 5-methyl-5*H*-furan-2-one moiety of annonaceous acetogenins starting from (*S*)-1,2-epoxybutane, see: (a) Thi, T. V.; Chaboche, C.; Figadère, B.; Chappe, B.; Chi, H. B.; Cavé, A. *Tetrahedron Lett*. **1994**, *35*, 883; (b) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett*. **1993**, *34*, 5043; (c) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc*. **1996**, *118*, 1801; (d) Franck, X.; Figadère, B.; Cavé, A. *Tetrahedron Lett*. **1996**, *37*, 1593.
9. For the synthesis of naturally occurring (+)-1,11-dodecadien-1-yl-5-methyl-5*H*-furan-2-one (hamabiwa-lactone B) from (2*RS*,4*S*)-4-methyl-2-phenylsulfanyl-γ-butyrolactone, see: Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron Lett*. **1998**, *39*, 8901.
10. Yu, W-Y.; Alper, H. *J. Org. Chem*. **1997**, *62*, 5684.
11. (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1997**, *119*, 8738 and references cited therein; (b) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc*. **1980**, *102*, 867; (c) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Villarosa, J. *J. Org. Chem*. **1996**, *61*, 9021; (d) Singh, V. K. *Synthesis* **1992**, 605 and references cited therein.
12. Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem*. **1997**, *62*, 8957.
13. Ramachandran, P. V.; Teodorovic', A. V.; Rangaishenvi, M. L.; Brown, H. C. *J. Org. Chem*. **1992**, *57*, 2379.
14. (a) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc*. **1982**, *104*, 525; (b) Tramontano, A.; Zderic, S. A. *J. Organomet. Chem*. **1978**, *156*, 203.
15. El-Ali, B.; Alper, H. *J. Org. Chem*. **1991**, *56*, 5357.
16. Coulson, D. R. *Inorg. Synth*. **1971**, *13*, 121.
17. Halle, R.; Bréherét, A.; Schulz, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2101.