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Journal of Organometallic Chemistry 683 (2003) 324–330
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Tetrahydrofuran-mediated radical processes: stereoselective synthesis of D,L-hexestrol

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Received 6 March 2003; received in revised form 31 May 2003; accepted 6 June 2003

Abstract

The highly stereoselective synthesis of D,L-hexestrol (**1**), an inhibitor of microtubule assembly, is developed by using, as a key step, an intermolecular coupling of $Co_2(CO)_6$-complexed propargyl radicals. The latter are generated by novel complementary processes involving an interaction of tetrahydrofuran with $Co_2(CO)_6$-complexed propargyl alcohols and cations. An isomerically pure D,L-μ-η^2-[3,4-di(4-methoxyphenyl)-1,5-hexadiyne]-bis-dicobalthexacarbonyl (D,L-**6**) is isolated in 69–91% yield with intermolecular coupling reactions exhibiting an excellent chemo- (0.5–7%) and D,L-diastereoselectivity (90–94%). The structure of D,L-**6** is determined by X-ray diffraction. The subsequent steps include BBr_3-induced demethylation of 4-methoxyaryl groups, demetalation with cerium(IV) ammonium nitrate, and hydrogenation of acetylenic termini affording D,L-hexestrol (**1**).

Keywords: Propargyl radical; Propargyl cation; Cobalt; X-ray structure; Hexestrol

1. Introduction

Last decade, the inhibitors of microtubule assembly have become a hot commodity on the pharmaceutical market. They are best represented by an antimitotic agent colchicine [1], alkaloids vinblastine [1b,2] and vincristine [3], an antitumor agent taxol [1b,2,4], and methyl [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl]carbamate, a disruptor of mitotic spindle function [5]. The current trend represents an ever increasing interest toward *small organic molecules* (MW < 800) which can interact, and structurally alter, complex biological systems, such as enzymes. D,L-Hexestrol (**1**), along with its *meso*-counterpart, belongs to a family of nonsteroidal hormones. The latter, due to its availability, has been thoroughly tested to exhibit an astonishing range of biological activities [6]. Both isomers are proven to be effective inhibitors of microtubule assembly of proteins leading to the formation of twisted ribbon structures [7]. Further studies of D,L-hexestrol (**1**) are hampered by its inaccessibility: the synthetic methods utilizing, in particular, a reduction of diethylstilbestrol or radical coupling reactions feature a low stereoselectivity, and attendant with it, a tedious isolation of target compounds [8]. Herein, we report the stereoselective synthesis of D,L-hexestrol (**1**) utilizing, as a key step, novel tetrahydrofuran (THF)-mediated dimerization of cobalt-complexed propargyl alcohols and cations [9].

2. Results and discussion

Propargyl alcohol **2**, synthesized by the condensation of sodium acetylide with anisaldehyde, was complexed with dicobaltoctacarbonyl [10] to afford a key substrate **3** in 53.1% overall yield (Scheme 1). Both electronic and steric parameters of the metal core are crucial to the subsequent radical reaction. First, the stability of the

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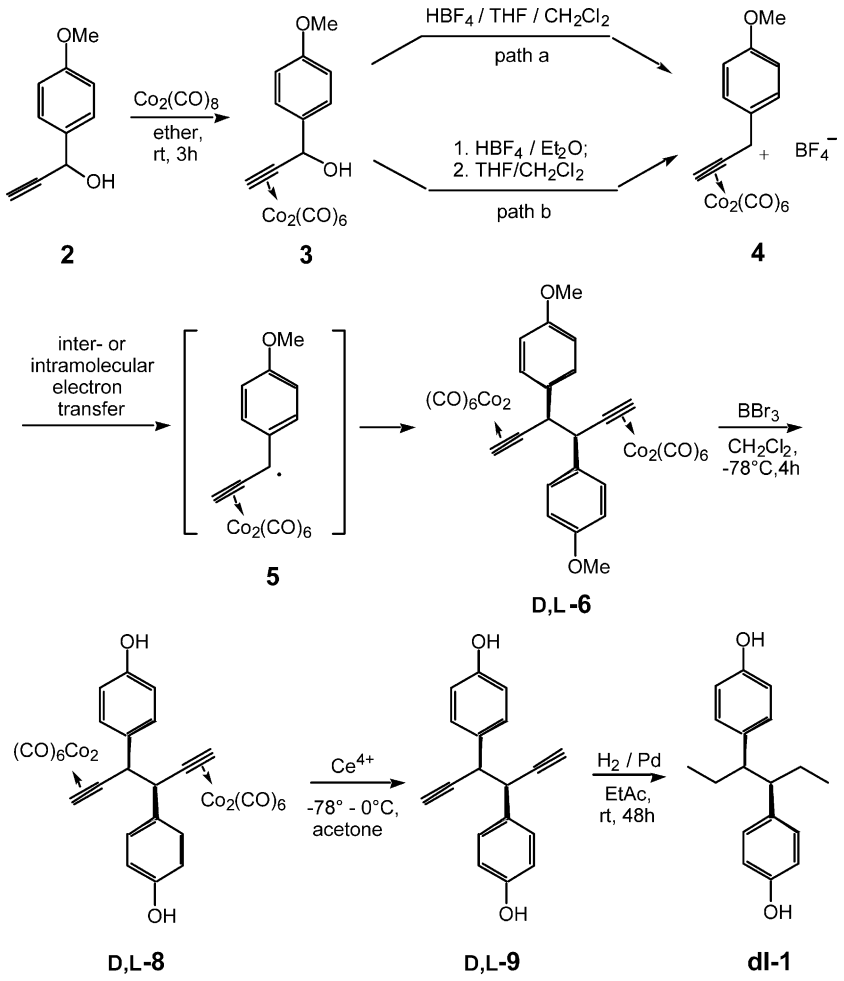
doi:10.1016/S0022-328X(03)00539-4



Scheme 1

Scheme 1. Synthesis of D,L-hexestrol (**1**) utilizing, as a key step, cobalt-templated radical coupling reactions.

cation **4** is enhanced, and isolation facilitated, due to the charge delocalization over metal cluster and structural changes attendant with it [11,12]. Second, the stereoselectivity of the dimerization step itself is favorably influenced by a bulky metal core that decreases conformational flexibility of radical **5** and creates the space constraints at the reaction site. The conversion of alcohol **3** to bis-cluster **6**, via cobalt-complexed species **4** and **5**, was effected, first, by a tandem action of HBF_4 and THF (path a) [9]. Although the mechanism of this process is still under investigation [13], a '*one-step protocol*' for dimerization of metal-complexed propargyl alcohols represents a viable synthetic method: D,L-**6**, a major product, can be easily isolated, as a pure diastereomer, from the mixture of D,L-**6**, *meso*-**6** and H-atom abstraction product, $[HC{\equiv}CCH_2C_6H_4(4\text{-}OMe)]Co_2(CO)_6$ (**7**). An alternative approach is represented by a '*two-step protocol*' that includes an isolation of cation **4** followed by its treatment with a two-fold excess of THF (Scheme 1, path b). While diastereoselectivity is comparable for both procedures (94 and 90%), the former is more feasible from the practical viewpoint: it does not require an isolation of the intermediate cation, and also the higher yield of D,L-**6** was achieved (90.6 vs. 69.0%) [13]. The chemoselectivity, represented by a ratio of dimeric and HAA products, **6**/**7**, is relatively high with only 0.5–7% of H-atom transfer taking place. Although the intimate details of '*THF magic*' remain to be understood, the formation of scarcely investigated cobalt-complexed propargyl radical, **5**, and subsequent stereoselective dimerization are implied. It is worthy to mention that coupling of organic and organometallic radicals usually occur with low, if any, diastereoselectivity [14].

The configuration of D,L-**6** was determined by X-ray crystallography. It adopts a non-imposed C_2-symmetric conformation (Fig. 1; Tables 1 and 2) with noticeably distorted gauche-orientation of phenyl groups (C7–C3–C4–C13, 44.3°) and nearly ideal disposition of Co-alkyne units (C2–C3–C4–C5, 62.0°). Atoms H3A and H4A are disposed anti to each other thus confirming the stereochemical assignment for this diastereomer (H3A–

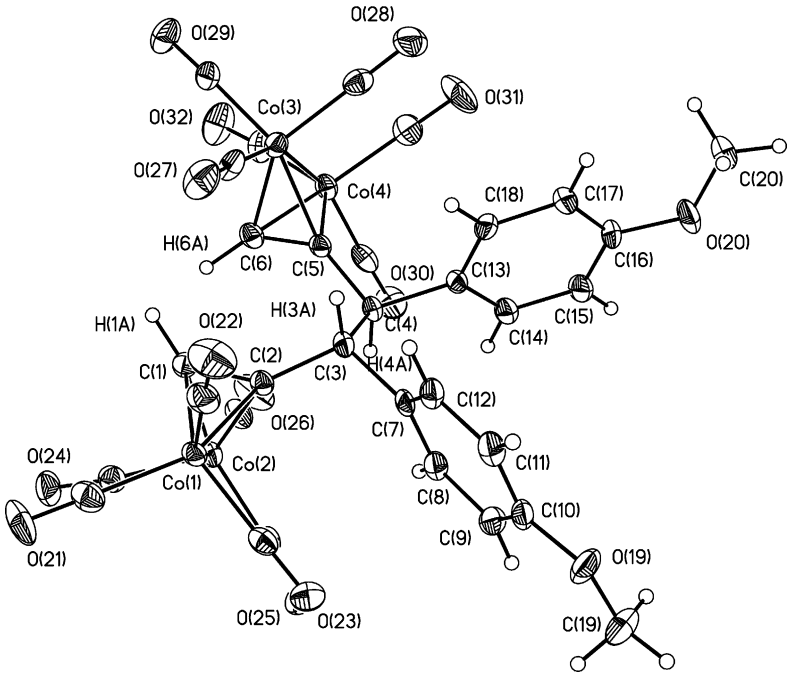


Fig. 1. X-ray determined molecular structure of complex D,L-**6** with 30% probability ellipsoids.

Table 1
Summary of the crystal structure data for complex **6**

Formula	$C_{32}H_{18}O_4Co_4$
FW	862.18
Temperature (K)	100(2)
Crystal color	Dark-red
Crystal dimension (mm)	$0.308 \times 0.300 \times 0.092$
Crystal system	Triclinic
a (Å)	11.6715(8)
b (Å)	16.9534(14)
c (Å)	19.2353(13)
α (°)	105.632(2)
β (°)	90.736(2)
γ (°)	109.416(1)
V (Å^3)	3434.8(4)
Space group	$P\bar{1}$
Z	4
D_{calc} (Mg m^{-3})	1.667
μ(Mo–K$_\alpha$) (mm^{-1})	1.965
Independent reflections	20 492 [$R_i = 0.0218$]
Absorption correction	Semi-empirical from equivalents
No. of data/restraints/params	20 492/0/901
Goodness-of-fit on F^2	1.039
Final R indices [$I > 2\sigma(I)$]	
R_1	0.0434
wR_2	0.1047
Largest difference peak, hole (e Å^{-3})	1.062, −0.489

Table 2
Selected bond lengths (Å), bond and torsion angles (°) for complex **6**

Bond lengths			
Co(1)–Co(2)	2.4642(4)	Co(3)–Co(4)	2.4707(4)
Co(1B)–Co(2B)	2.4703(4)	Co(3B)–Co(4B)	2.4641(4)
Co(1)–C(1)	1.959(2)	Co(3)–C(5)	1.9765(19)
Co(1)–C(2)	1.9664(18)	Co(3)–C(6)	1.9573(19)
C(1)–C(2)	1.334(3)	C(5)–C(6)	1.332(3)
Co(2)–C(1)	1.9640(18)	Co(4)–C(5)	1.9759(19)
Co(2)–C(2)	1.9902(19)	Co(4)–C(6)	1.9586(19)
Bond angles			
C(1)–C(2)–C(3)	142.08(18)	C(2)–C(1)–H(1A)	136.4
C(6)–C(5)–C(4)	141.67(18)	C(5)–C(6)–H(6A)	136.3
Dihedral angles			
Co(1)–Co(2)–C(1)–C(2)	73.23(11)	C(7)–C(3)–C(4)–C(13)	−44.3(2)
C(1)–C(2)–C(3)–C(7)	155.6(3)	C(13)–C(4)–C(5)–C(6)	163.1(2)
C(1)–C(2)–C(3)–C(4)	−77.3(3)	C(3)–C(4)–C(5)–C(6)	−69.9(3)
C(2)–C(3)–C(4)–C(5)	62.0(2)	H(3A)–C(3)–C(4)–H(4A)	170.7
C(7)–C(3)–C(4)–C(5)	−170.94(16)	H(1A)–C(1)–C(2)–C(3)	6.2
C(2)–C(3)–C(4)–C(13)	−171.33(15)	H(6A)–C(6)–C(5)–C(4)	7.7

C3–C4–H4A, 170.7°). As molecular modeling shows, the repulsion between CO-ligands pushes the metal clusters away from each other, which in turn brings the C–C triple bonds in close-to-parallel locations (C1C2–C5C6, 19.7°). Acetylenic hydrogens (H1A, H6A) are remarkably proximate to each other with a separation distance of 2.46 Å, close to the sum of the van der Waals radii (about 2.5 Å). Other noteworthy structural features of D,L-**6** include: (a) an essentially undistorted planarity of alkyne moieties (H1A–C1–C2–C3, 6.2°, H6A–C6–C5–C4, 7.7°); (b) a bent geometry [11] for coordinated alkyne unit (C6–C5–

C4, 141.7°, C1–C2–C3, 142.1°) with substantially smaller angles for acetylenic termini (C2–C1–H1A, 136.4°, C5–C6–H6A, 136.3°); and (c) a lengthened coordinated C–C triple bond (1.33 vs. 1.21 Å for free ligand) attendant with complexation to the transition metal.

The subsequent steps in total synthesis include BBr_3-induced demethylation [15] of D,L-**6**, followed by demetalation of D,L-**8** with cerium(IV) ammonium nitrate and hydrogenation of acetylenic termini in D,L-**9**. An empirical ratio of D,L-**6**:BBr_3, 1:13, suggests that, prior to deprotection of hydroxy groups, a donor–acceptor coordination between CO-ligands and Lewis acid takes place [15]. A moderate yield of decomplexation reaction (46.6%) reflects a relative lability of bis-alkyne **9** in the presence of the oxidizing agents, such as tetravalent cerium.

The synthetic strategy utilizing, as a key step, the highly stereoselective, THF-mediated dimerization of cobalt-complexed propargyl alcohols and cations, was developed for D,L-hexestrol (**1**), an inhibitor of microtubule assembly. Gram-quantities of the target compound, as well as its structural and functional analogs, will become available for an extensive biological probe.

3. Experimental

3.1. Materials and methods

All manipulations of air-sensitive materials were carried out in flame-dried Schlenk-type glassware on a dual-manifold Schlenk line interfaced to a vacuum line. Argon and nitrogen (Airgas, ultra high purity) were dried by passing through a Drierite tube (Hammond). All solvents were distilled before use under dry nitrogen over appropriate drying agents (ether, THF, from sodium benzophenone ketyl; CH_2Cl_2, from CaH_2). The reagents—$HBF_4 \cdot Me_2O$, anisaldehyde, BBr_3, Ce$(NH_4)_2(NO_3)_6$, Pd/C—were purchased from Aldrich and used as received. $Co_2(CO)_8$ was received from Strem.

3.2. Physical and analytical measurements

NMR spectra were recorded on Bruker ACF-200 (^{1}H, 200 MHz). Chemical shifts were referenced to internal solvent resonances and are reported relative to tetramethylsilane. Elemental analyses were performed by Desert Analytics (Tucson, AZ). Melting temperatures (uncorrected) were measured on Mel-Temp II (Laboratory Devices) apparatus. Thin-layer and column chromatography were conducted on Silica gel 60 F_{254} (EM Science) and Silica Gel S733-1 (200–425 mesh; Fisher), respectively. Mass spectra were run at the Regional Center on Mass-Spectroscopy, UC Riverside, Riverside, CA (FAB, ZAB-SE; CI-NH_3, 7070EHF; Micromass).

3.3. [1-(4-Methoxyphenyl)-prop-2-yn-1-ol]dicobalthexacarbonyl (3)

Under an atmosphere of nitrogen, a solution of *p*-anisaldehyde (1.36 g, 10 mmol) in dry THF (10 ml) was added dropwise (10 min) to a suspension of sodium acetylide (0.72 g, 15 mmol; 4 g, 18% suspension in xylene) in THF (30 ml) at −50 °C. The reaction mixture was stirred for 5 h at 20 °C, diluted with saturated aqueous ammonium chloride (40 ml) at 0 °C, extracted with ether (4 × 25 ml), and the combined ethereal extracts were dried over Na_2SO_4. The filtrate was evaporated to dryness, crude alcohol **2** was dissolved in dry ether (50 ml), and a solution, under an atmosphere of nitrogen, was added dropwise (60 min) to a solution of $Co_2(CO)_8$ (3.76 g, 11 mmol) in degassed ether (100 ml) at 20 °C. Upon stirring for 3 h (TLC control), a solvent was stripped under reduced pressure, and residue was fractionated on a Florisil column (60–100 mesh, 200 g, PE, PE:E, 5:1, 2:1) to afford **3** (2.38 g, 53.1%) as dark-red crystals. M.p. 59.5 °C (sealed capillary). TLC (PE:E, 2:1): R_f 0.42. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 2.30 (1H, d, OH, $J = 3.5$), 3.80 (3H, s, CH_3), 5.86 (1H, d unresolved, OCH), 6.06 (1H, d, HC≡, $J = 0.8$), 6.83–6.94 (2H, m, aromatic H), 7.30–7.42 (2H, m, aromatic H). MS FAB+: *m/z* [M^+] 448, 431 [M^+ − OH], 420 [M^+ − CO], 403 [M^+ − OH–CO], 392 [M^+ − 2CO), 364 [M^+ − 3CO], 347 [M^+ − OH–3CO], 336 [M^+ − 4CO], 319 [M^+ − OH–4CO], 308 [M^+ − 5CO], 291 [M^+ − OH–5CO], 280 [M^+ − 6CO], 145 [M^+ − OH–6CO–2Co]. Microanalysis: Found: C, 43.02; H, 2.20. $C_{16}H_{10}O_8Co_2$ requires: C, 42.88; H, 2.25%.

3.4. D,L-, meso-μ-η²-[3,4-Di(4-methoxyphenyl)-1,5-hexadiyne]-bis-dicobalthexacarbonyl (D,L-6, meso-6) and [3-(4-methoxyphenyl)-1-propyne]dicobalthexacarbonyl (7)

3.4.1. One-step protocol (path a)

Under an atmosphere of nitrogen, $HBF_4 \cdot Me_2O$ (335 mg, 2.50 mmol) was added dropwise to a solution of alcohol **3** (560 mg, 1.25 mmol) and THF (180 mg, 2.50 mmol) in dry CH_2Cl_2 (12.5 ml) at −5 °C. The reaction mixture was stirred for 5 h at 20 °C (TLC control), diluted with Et_2O (25 ml), then, at 0 °C, with water (20 ml). The organic layer was washed with water (4 × 5 ml), dried ($MgSO_4$), and solvents were stripped off under reduced pressure. By NMR, the crude mixture contained D,L-**6**, *meso*-**6** and **7** in the ratio of 96.7:2.8:0.5 (de 94%). Fractionation on a silica gel column (250 g, degassed, +5 °C, PE:E, 15:1) afforded D,L-**6** (244 mg, 90.6% [13]) along with *meso*-**6** and HAA-7.

D,L-**6**: dark-brown crystals. M.p. 136 °C (sealed capillary). TLC (PE:E, 7:1): R_f 0.36. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 3.71 (6H, s, CH_3), 4.28 (2H, s, CH), 6.28 (2H, s, HC≡), 6.69 (4H, d, aromatic H, J = 8.0), 7.00 (4H, d, aromatic H). MS FAB+: *m/z* 863 [MH^+], 778 [M^+-3CO], 750 [M^+-4CO], 722 [M^+-5CO], 694 [M^+-6CO], 666 [M^+-7CO], 638 [M^+-8CO], 610 [M^+-9CO], 582 [M^+-10CO], 554 [M^+-11CO], 526 [M^+-12CO], 436 [$M^+-11CO-2Co$]. Anal. Found: C, 44.64; H, 2.34. $C_{32}H_{18}O_{14}Co_4$ requires: C, 44.59; H, 2.10%. X-ray quality crystals were obtained by ethanol vapor diffusion into heptane solution of D,L-**6** (Fig. 1).

Meso-**6**: dark-red oil. TLC (PE:E, 7:1): R_f 0.53. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): only signals different from those of D,L-**6** are shown, δ 4.31 (2H, s, CH), 5.06 (2H, s, HC≡). MS FAB+: *m/z* 778 [M^+-3CO], 750 [M^+-4CO], 694 [M^+-6CO], 666 [M^+-7CO], 638 [M^+-8CO], 610 [M^+-9CO], 582 [M^+-10CO], 554 [M^+-11CO], 526 [M^+-12CO], 436 [$M^+-11CO-2Co$].

HAA-**7**: dark-red oil. TLC (PE:E, 7:1): R_f 0.59. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 3.79 (3H, s, CH_3), 4.04 (2H, d, CH_2), 6.07 (1H, t, HC≡, J = 1.1) 6.87 (2H, dt, aromatic H, J = 8.6, 2.1), 7.18 (2H, dt, aromatic H). An authentic sample of **7** was synthesized in a high yield (86.1%) by quenching cation **4** with tributyltinhydride.

3.4.2. Two-step protocol (path b)

Under an atmosphere of nitrogen, complex **3** (112 mg, 0.25 mmol) was placed in a flame-dried flask and dissolved in dry diethyl ether (20 ml). The solution was cooled (−20 °C) and treated with $HBF_4 \cdot Me_2O$ (122 μl, 134 mg, 1.00 mmol). After stirring for 1 h at −20 °C, an ethereal layer was removed, and cation **4** was washed with dry ether (3 × 15 ml) at −20 °C. Residual amount of ether was stripped under reduced pressure, dry methylene chloride (2.5 ml) was added, followed by THF (36 mg, 0.5 mmol). The reaction mixture was stirred 2 h, at +20 °C (TLC control). By NMR, the crude mixture contained D,L-**6**, *meso*-**6** and **7** in the ratio of 88:5:7 (de 90%). Fractionation of the crude mixture on the preparative TLC plate (silica gel, PE:E, 7:1) afforded D,L-**6** (37 mg, 69.0% [13]), as a pure stereoisomer (by NMR).

3.5. X-ray crystallography of D,L-6

A total of 30 362 reflections were measured on a Bruker D8 diffractometer with APEX CCD detector and graphite monochromator by φ and ω scans; unit cell determination using 3288 reflections. Data collection, data reduction, Lorentz and polarization corrections carried out using SMART [16a] and SAINT [16b]; a multi-scan absorption correction was applied using SADABS [16c]. Structure solution by direct methods and LS-ΔF syntheses, refinement against F^2 (SHELXTL [16d]) with all H atoms included in idealized positions. All non-H atoms refined anisotropically with hydrogens as riding atoms; final residual electron density of 1.054 and −0.490 e $Å^{-1}$. Structure solution, refinements, graphics and tables calculations performed with SHELXTL. Further details of the structural refinement are given in Tables 1 and 2. The Crystallographic Information File (CIF, no. 185838) can be obtained from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK: Fax: +44-1223-336033, World Wide Web: http://www.ccdc.cam.ac.uk).

3.6. D,L-μ-η^2-[3,4-Di(4-hydroxyphenyl)-1,5-hexadiyne]-bis-dicobalthexacarbonyl (D,L-8)

Under an atmosphere of nitrogen, a solution of BBr_3 (8.81 g, 35.10 mmol) in CH_2Cl_2 (35.10 ml, 1 M) was slowly added to a solution of D,L-**6** (2.33 g, 2.70 mmol) in dry CH_2Cl_2 (250 ml) at −78 °C (45 min). The cold bath was removed and the mixture was stirred for 4 h (TLC control), poured into the mixture of ice water (250 ml), CH_2Cl_2 (50 ml) and ether (50 ml), stirred an hour, and saturated with NaCl. Aqueous layer was extracted with CH_2Cl_2 (50 ml), and combined organic extracts were dried over Na_2SO_4. The solvents were stripped off under reduced pressure, and the residue was fractionated on Florisil (125 g, degassed, +5 °C, PE:E, 2:1) affording D,L-**8** (980 mg, 43.5%) as dark-red crystals. $T_{dec.}$ 80–92 °C (sealed capillary). TLC (PE:E, 1:3): R_f 0.68. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 4.25 (2H, s, CH), 4.58 (2H, s, OH), 6.29 (2H, s, HC≡), 6.63 (4H, d, aromatic H, J = 8.4), 6.97 (4H, d, aromatic H). MS FAB+: *m/z* 806 [M^+-CO], 750 [M^+-3CO], 722 [M^+-4CO], 694 [M^+-5CO], 666 [M^+-6CO], 638 [M^+-7CO], 610 [M^+-8CO], 582 [M^+-9CO], 554 [M^+-10CO]. Anal. Found: C, 43.73; H, 1.76. $C_{30}H_{14}O_{14}Co_4$ requires: C, 43.17; H, 1.68%.

3.7. D,L-3,4-Di(4-hydroxyphenyl)-1,5-hexadiyne (D,L-9)

Under a N_2 atmosphere, a solution of $Ce(NH_4)_2(NO_3)_6$ (1.21 g, 2.20 mmol) in dry acetone (15 ml; degassed) was slowly added to a solution of D,L-**8** (183 mg, 0.22 mmol) in dry acetone (10 ml; degassed) at −78 °C (25 min). Upon addition, the reaction mixture was warmed up to −40 °C, stirred for 25 min, then warmed up to 0 °C, and poured into saturated NaCl solution (20 ml). Aqueous-acetone layer was extracted with ether (6 × 7 ml) and dried (mol. sieves, 4 Å). The solvents were evaporated, and the residue was chromatographed on Florisil (15 g, +5 °C, degassed, P:E, 2:1) affording D,L-**9** (27 mg, 46.6%) as a white solid (benzene dried, 2 × 2 ml). $T_{dec.}$ 170–175 °C (melting observed at 178–179 °C;

sealed capillary); lit. data: [8e] m.p. 178–179 °C dec. TLC (PE:E, 1:2): R_f 0.39. ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 2.37 (2H, d, HC≡, $J = 1.0$), 3.91 (2H, d, CH), 6.74 (4H, d, aromatic H, $J = 6.6$), 7.13 (4H, d, aromatic H). MS DIP: *m/z* 262 (9%), 131 (100%). HR-MS/CI-NH_3: Calc. for $C_{18}H_{15}O_2$ MH^+ 263.107 205. Found: 263.107 290. Anal. Found: C, 82.78; H, 5.21. $C_{18}H_{14}O_2$ requires: C, 82.44; H, 5.34%.

3.8. D,L-3,4-Di(4-hydroxyphenyl)hexane (D,L-1)

Under an atmosphere of hydrogen, a solution of D,L-**9** (42 mg, 0.16 mmol) in ethyl acetate (8 ml) was stirred over 5% Pd/C (28 mg) for 48 h at 20 °C. The reaction mixture was filtered off on a short bed of celite, evaporated to dryness, then fractionated on a Florisil column (P, P:E, 2:1, 1:1) to yield D,L-**1** (37 mg, 86.0%) as a white solid. M.p. 124–124.5 °C (sealed capillary); lit. data: m.p. 126–128 °C [8a]; 123–124 °C [8c]. TLC (PE:E, 1:2): R_f 0.52. ^{1}H-NMR (200 MHz, [d_6]acetone, TMS): δ 0.69 (6H, t, CH_3, $J = 7.3$), 1.38–1.58 (2H, m, CH_2), 1.73–1.92 (2H, m, CH_2), 2.63 (2H, m, CH), 6.57–6.75 (8H, m, aromatic H), 7.93 (2H, s, OH). MS DIP: *m/z* 270 (3%), 135 (100%). HR-MS/CI-NH_3: Calc. for $C_{18}H_{26}NO_2$ MNH_4^+ 288.196 354. Found: 288.195 968.

4. Supplementary material

Tables of crystallographic details, bond distances and angles, atomic coordinates and equivalent isotropic displacement parameters, as well as torsion angles for D,L-**6**; data are also available as files in CIF format.

Acknowledgements

Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for support of this research (Grant #39104–B1). The authors are greatly indebted to Hewlett Packard and Office of Graduate Studies, Research and International Programs, College of Science and Mathematics and University Corporation, California State University Northridge for generous support.

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