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TETRAHEDRON: *ASYMMETRY*

Resolution of (±)-2-substituted norbornadiene and hexachloronorbornadiene derivatives using CCL and PLE

Cihangir Tanyeli,* Gamze Çelikel and İdris Mecidoğlu Akhmedov

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

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Abstract—(±)-2-Hydroxymethylbicyclo[2.2.1]hepta-2,5-diene, (±)-2-acetoxymethylbicyclo[2.2.1]hepta-2,5-diene and their hexachlorinated derivatives were resolved via CCL- and PLE-catalysed hydrolysis to afford enantiomerically enriched products with e.e.s of 61–93%. The absolute configurations were determined by transforming 2-hydroxymethylbicyclo[2.2.1]hepta-2,5-diene into the 2-formylbicyclo[2.2.1]hepta-2,5-diene with known absolute configuration.

1. Introduction

The optically active norbornadienes are key intermediates for the synthesis of biologically active analogues of the prostaglandin endoperoxides PGH_2 and PGG_2 and β-santalol used by Corey[1] and Ogasawara.[2] Evans has studied the synthesis of optically active norbornadienes using chiral α,β-unsaturated *N*-acyloxazolidinones as chiral auxiliaries in Diels–Alder reactions of cyclopentadiene.[3] Yamamato achieved the first enantioselective catalytic Diels–Alder reaction of cyclopentadiene and acetylenic aldehydes.[4]

Recently, we have reported on the esterase-catalysed resolution of (±)-α′-acetoxy-α,β-unsaturated cyclic ketones,[5] 2-furyl[6] and 2-thienyl carbinols. During the course of our studies on the biotransformations of (±)-2-hydroxymethylbicyclo[2.2.1]hepta-2,5-diene (±)-**1a**, (±)-2-acetoxymethylbicyclo [2.2.1]hepta-2,5-diene (±)-**2a**, (±)-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hepta-2,5-diene (±)-**1b** and (±)-2-acetoxymethyl - 1,4,5,6,7,7 - hexachlorobicyclo[2.2.1]hepta-2,5-diene (±)-**2b**, screening reactions were first completed with various lipases (i.e. CCL, PLE, HLE, PPL and CAL) using substrate: enzyme ratios from 1:1 to 1:0.5. Among the lipases studied, CCL and PLE proved suitable for the enantioselective hydrolysis of these substrates showing some interesting enzyme- and substrate-dependant reversals of enantioselectivity, in particular with the hexachlorinated substrates (±)-**1b** and (±)-**2b**. The observed promising preliminary results directed us towards a thorough catalytic study. Thus, CCL- and PLE-catalysed reactions of non-chlorinated substrates (±)-**1a** and (±)-**2a** afforded (1*R*,4*S*)-configured alcohols with different enantioselectivities, respectively. In contrast to this, CCL yielded the (1*S*,4*R*)-configured alcohol with the hexachlorinated substrate (±)-**1b**, whereas PLE afforded the (1*R*,4*S*)-configured alcohol with (±)-**2b**. CCL in particular, exhibited higher e.e. values and showed unusual versatility and diversity in the enantioselective hydrolysis of the hexachlorinated substrate.

Herein, we describe the highly efficient resolution of the racemic substrates (±)-**1a**–**1b** with CCL and the resolution of (±)-**2a**–**2b** with PLE to afford (1*R*,4*S*)-**1a** and (1*S*,4*R*)-**1b** with the former enzyme and (1*R*,4*S*)-**1a** and (1*R*,4*S*)-**1b** with the latter enzyme (Scheme 1).

2. Results and discussion

Racemic **1a**–**1b** were obtained using slightly modified literature procedures[7] and subsequent acetylation with acetyl chloride in the presence of pyridine afforded (±)-**2a**–**2b**.[6] The first bioconversion was performed using CCL according to the following general procedure. To a stirred solution of (±)-**1a** (500 mg) in vinyl acetate (5 mL), CCL (10 mg) was added in one portion and the reaction mixture was stirred at 20°C. The conversion was monitored by TLC. After 72 h, 51% conversion was observed. The products were separated using flash column chromatography and compound (−)-**1a** was isolated with 64% e.e. in 34% yield. The

* Corresponding author.

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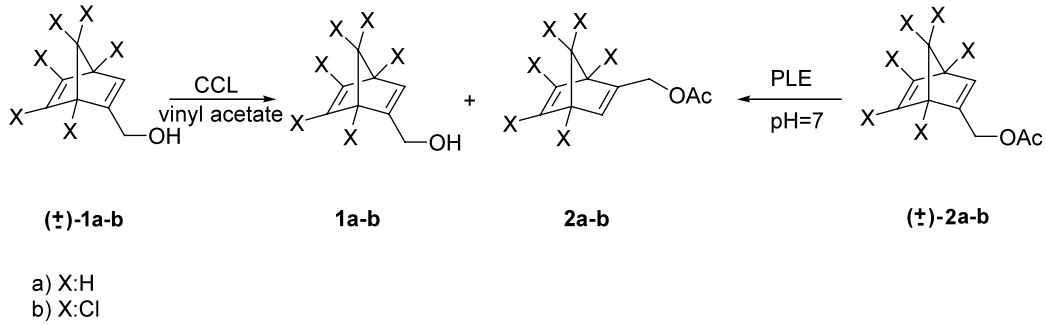
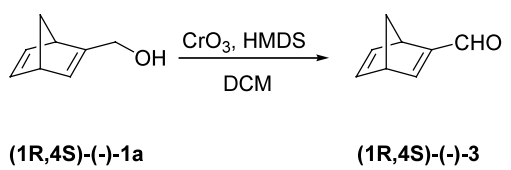


Scheme 1.

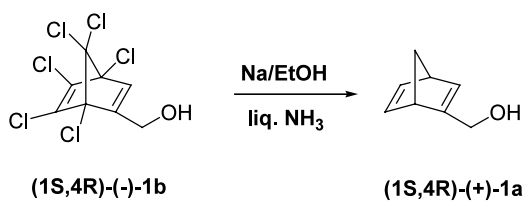
absolute configuration of (−)-**1a** was assigned as (1*R*,4*S*) by transforming it into the corresponding (1*R*,4*S*)-(−)-2-formylbicyclo[2.2.1]hepta-2,5-diene **3** via oxidation with CrO_3 and HMDSO[8] (Scheme 2).

The second attempt was completed with the (±)-2-hydroxymethyl - 1,4,5,6,7,7 - hexachlorobicyclo[2.2.1]-hepta-2,5-diene (±)-**1b** using CCL under the same conditions as above. When the hydrolysis of the above substrate catalysed by CCL was allowed to proceed to 50% conversion (6 h at 20°C), the unreacted alcohol of (1*S*,4*R*)-absolute configuration, (−)-**1b** was obtained in 45% yield and 93% e.e. The absolute configuration of the isolated product (−)-**1b** was determined by transforming it into the corresponding (+)-(1*S*,4*R*)-**1a** by reaction with Na in liquid NH_3[9] (Scheme 3).

Related to this study, the hydrolyses of (±)-**2a**–**2b** with PLE were examined. The bioconversion of (±)-**2a** was performed by PLE according to the following general procedure. To a stirred solution of (±)-**2a** (500 mg) in phosphate buffer, (pH 7.00, 50 mL) PLE (100 μL) was added in one portion and the reaction mixture was stirred at 20°C in a pH stat unit. The conversion was monitored by TLC. After 36 h, 47% conversion was observed. The products were separated using flash column chromatography and compound (−)-**1a** was isolated in 41% yield and in 61% e.e. The absolute configuration of compound (−)-**1a** was assigned as (1*R*,4*S*)-(−)-**1a** by comparison of its specific rotation with the previously determined value for (1*R*,4*S*)-(−)-**3**.



Scheme 2.



Scheme 3.

Hexachlorinated derivative (±)-**2b** was also hydrolysed by PLE under the same conditions as above and absolute configuration of the product (+)-**1b** was assessed by comparison of its specific rotation with the specific rotation of (1*S*,4*R*)-(−)-**1b**. The results are given in Table 1 and show that the enantiomeric excess (e.e.) varied from 61 to 93%.

In conclusion, enzyme-dependent reversal of enantioselectivity with hexachlorinated substrates is demonstrated. Commercially available and inexpensive enzymes, CCL and PLE used in catalytic levels, renders the process very attractive for large scale preparations.

3. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. IR spectra were obtained from a Perkin–Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Optical rotations were measured in $CHCl_3$ solution in a 1 dm cell using a Bellingham & Stanley P20 polarimeter at 20°C. Elemental analyses were performed on a LECO 932. PLE and CCL were purchased from Boehringer Mannheim GmbH as a suspension in ammonium sulfate solution (3.2 mol/L) and as a powder, respectively.

3.1. Synthesis of (±)-2-hydroxymethylbicyclo[2.2.1]-hepta-2,5-diene, (±)-1a

A mixture of propargyl alcohol (5.60 g, 100 mmol) and freshly cracked cyclopentadiene (3.96 g, 60 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 170°C for 8 h. The crude product was purified by vacuum distillation to afford (±)-**1a** (6.45 g, 88%). Bp: 100–102°C at 9 mm. ^{1}H NMR: δ 1.91 (d, 1H, AB system bridge proton, $J=6$ Hz), 1.95 (d, 1H, AB system bridge proton, $J=6$ Hz), 2.20 (s, 1H, OH), 3.36 (s, 1H, CH), 3.50 (s, 1H, CH), 4.12 (dd, 1H, AB system diastereotopic H, $J=2$, and 14 Hz), 4.19 (dd, 1H, AB system diastereotopic H, $J=2$ and 14 Hz), 6.31 (d, 1H, olefinic H, $J=2$ Hz), 6.67 (dd, 1H, AB system olefinic H, $J=3$ and 5 Hz), 6.71 (dd, 1H, AB system olefinic H, $J=3$ and 5 Hz). ^{13}C NMR: δ 50.4, 51.5, 62.2, 74.0, 136.5, 142.9, 144.0, 158.2. IR (neat): 3400, 1625, 1115 cm^{-1}. Anal. calcd for $C_8H_{10}O$ (122.17): C, 78.65; H, 8.25. Found: C, 78.66; H, 8.21%.

Table 1. Results of the CCL- and PLE-catalysed hydrolysis of (±)-**1a**–**1b** and (±)-**2a**–**2b**

Substrate	Enzyme	Time (h)	Alcohol	Yield (%)[a]	$[\alpha]_D^{20}$	E.e. (%)[b]	Esters	Yield (%)	$[\alpha]_D^{20}$	E[c]
(±)-**1a**	CCL	72	(1R,4*S*)-**1a**	34	−1.5	64	(1*S*,4*R*)-**2a**	32	−2.4	24
(±)-**2a**	PLE	36	(1*R*,4*S*)-**1a**	41	−1.4	61	(1*S*,4*R*)-**2a**	45	−1.8	24
(±)-**1b**	CCL	6	(1*S*,4*R*)-**1b**	45	−7.3	93	(1*R*,4*S*)-**2b**	42	+4.1	81
(±)-**2b**	PLE	4	(1*R*,4*S*)-**1b**	39	+6.4	82	(1*S*,4*R*)-**2b**	42	−2.3	35

[a] Yields (%) are given as the isolated alcohols.
[b] Enantiomeric excess values are determined by the Chiralcel OD chiral column HPLC analysis.
[c] E, enantiomeric ratio, values are calculated by the use of equation 5 in Ref. 10.

3.2. Synthesis of (±)-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hepta-2,5-diene, (±)-1b

A mixture of propargyl alcohol (5.60 g, 100 mmol) and hexachlorocyclopentadiene (11.12 g, 40 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 170°C for 6 h. The crude product was purified by vacuum distillation to afford (±)-**1b** (11.18 g, 85% yield). Bp: 130–131°C at 1 mm, mp: 86.5–87.5°C. ^{1}H NMR: δ 2.09 (s, 1H, OH), 4.46 (AB system, 1H, CH, J=16 Hz), 4.53 (AB system, 1H, CH, J=16 Hz), 6.60 (s, 1H, olefinic H). ^{13}C NMR: δ 59.5, 83.2, 85.1, 115.4, 134.2, 137.4, 138.7, 151.7. IR (neat): 3420, 1630, 750 cm^{-1}. Anal. calcd for $C_8Cl_6H_4O$ (328.84): C, 29.22; Cl, 64.69; H, 1.23. Found: C, 29.23; Cl, 64.65; H, 1.25%.

3.3. Acetylation of (±)-2-hydroxymethylbicyclo[2.2.1]-hepta-2,5-diene, (±)-1a

To a stirred solution of (±)-**1a** (5.00 g, 41 mmol) in CH_2Cl_2 (100 mL), dry pyridine (4.75 g, 60 mmol) was added at 0°C and the mixture was stirred for 30 min. Acetyl chloride (4.71 g, 60 mmol) was added dropwise. The resultant mixture was stirred for 12 h at rt. The organic phase was extracted with 0.1N HCl (3×50 mL), saturated $NaHCO_3$ (3×50 mL) and brine (2×50 mL), dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford (±)-**2a** (EtOAc:hexane, 1:5). (6.58 g, 98% yield). ^{1}H NMR: δ 1.98 (AB system, 2H, bridge protons, J=6 Hz), 1.99 (s, 3H, CH_3), 3.36 (s, 1H, CH), 3.49 (s, 1H, CH), 4.62 (d, 2H, CH_2, J=2 Hz), 6.43 (d, 1H, olefinic H, J=2 Hz), 6.67 (AB system, 1H, olefinic H, J=3 and 5 Hz), 6.70 (AB system, 1H, olefinic H, J=3 and 5 Hz). ^{13}C NMR: δ 21.2, 50.6, 51.8, 63.8, 74.1, 139.3, 142.8, 143.8, 153.1, 170.7. IR (neat): 1715, 1610, 738 cm^{-1}. Anal. calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.36. Found: C, 73.13; H, 7.38%.

3.4. Acetylation of (±)-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hepta-2,5-diene, (±)-1b

To a stirred solution of (±)-**1b** (5.00 g, 15 mmol) in CH_2Cl_2 (100 mL), dry pyridine (1.78 g, 22.5 mmol) was added at 0°C and the mixture was stirred for 30 min. Acetyl chloride (1.77 g, 22.5 mmol) was added dropwise. The resultant mixture was stirred for 12 h at rt. The organic phase was extracted with aqueous HCl (0.1N, 3×50 mL), saturated $NaHCO_3$ (3×50 mL) and brine (2×50 mL), dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford (±)-**2b** (EtOAc:hexane, 1:6). (5.34 g, 96% yield). ^{1}H NMR: δ 2.10 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 6.55 (s, 1H, olefinic H). ^{13}C NMR: δ 21.0, 59.4, 83.1, 85.2, 115.5, 137.0, 137.5, 138.4, 147.5, 169.8. IR (neat): 1728, 1680, 750 cm^{-1}. Anal. calcd for $C_{10}Cl_6H_6O_2$ (370.88): C, 32.39; Cl, 57.36; H, 1.63. Found: C, 32.40; Cl, 57.33; H, 1.61%.

3.5. CCL hydrolysis of (±)-2-hydroxymethylbicyclo-[2.2.1]hepta-2,5-diene, (±)-1a

To a stirred solution of (±)-**1a** (500 mg) in vinyl acetate (5 mL), CCL (10 mg) was added in one portion and the reaction mixture was stirred at 20°C (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated under reduced pressure. The products (1*S*,4*R*)-(−)-**1a** and (1*R*,4*S*)-(+)-**2a** were purified by flash column chromatography (EtOAc:hexane, 1:5). (1*R*,4*S*)-(−)-**1a**: (0.17 g, 34% yield). $[\alpha]_D^{20}$=−1.5 (*c*, 0.83). (1*S*,4*R*)-(−)-**2a**: (0.22 g, 32% yield). $[\alpha]_D^{20}$=−2.4 (*c*, 0.66).

3.6. CCL hydrolysis of (±)-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hepta-2,5-diene, (±)-1b

To a stirred solution of 500 mg (±)-**1b** in 5 mL vinyl acetate, 10 mg of CCL was added in one portion and the reaction mixture was stirred at 20°C (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated under reduced pressure. The products (1*S*,4*R*)-(−)-**1b** and (1*R*,4*S*)-(+)-**2b** were purified by flash column chromatography (EtOAc:hexane, 1:6). (1*S*,4*R*)-(−)-**1b**: (0.23 g, 45% yield). $[\alpha]_D^{20}$=−7.3 (*c*, 1.66). (1*R*,4*S*)-(+)-**2b**: (0.24 g, 42% yield). $[\alpha]_D^{20}$=+4.1 (*c*, 1.33).

3.7. PLE hydrolysis of (±)-2-Acetoxymethylbicyclo-[2.2.1]hepta-2,5-diene, (±)-2a

To a stirred solution of (±)-**2a** (500 mg) in phosphate buffer (pH 7.00, 50 mL), PLE (100 μL) was added in one portion and the reaction mixture was stirred at 20°C in a pH stat unit. The conversion was monitored by TLC. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The products (1*R*,4*S*)-(−)-**1a** and (1*S*,4*R*)-(−)-**2a** were purified by flash column chromatography (EtOAc:hexane, 1:5). (1*R*,4*S*)-(−)-**1a**: (0.15 g, 41% yield). $[\alpha]_D^{20}$=−1.4 (*c*, 4.17). (1*S*,4*R*)-(−)-**2a**: (0.23 g, 45% yield). $[\alpha]_D^{20}$=−1.8 (*c*, 3.33).

3.8. PLE hydrolysis of (±)-2-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hepta-2,5-diene, (±)-2b

To a stirred solution of (±)-**2b** (500 mg) in phosphate buffer (pH 7.00, 50 mL), PLE (100 μL) was added in one portion and the reaction mixture was stirred at 20°C in a pH stat unit. The conversion was monitored by TLC. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The products (1*R*,4*S*)-(+)-**1b** and (1*S*,4*R*)-(−)-**2b** were purified by flash column chromatography (EtOAc:hexane, 1:6). (1*R*,4*S*)-(+)-**1b**: (0.17 g, 39% yield). $[\alpha]_D^{20} = +6.4$ (*c*, 2.12). (1*S*,4*R*)-(−)-**2b**: (0.21 g, 42% yield). $[\alpha]_D^{20} = -2.3$ (*c*, 2.53).

3.9. Oxidation of (1*R*,4*S*)-(−)-2-hydroxymethylbicyclo-[2.2.1]hepta-2,5-diene, (1*R*,4*S*)-(−)-1a

A mixture of CrO_3 (2.00 g, 20 mmol) and hexamethyldisiloxane (3.24 g, 20 mmol) was stirred for 1 h at 60°C under an argon atmosphere. The reaction vessel was cooled down to 25°C and CH_2Cl_2 (10 mL) was added to the reaction mixture. (1*R*,4*S*)-(−)-**1a** (1.22 g, 10 mmol) was diluted with CH_2Cl_2 (5 mL) and added dropwise to the mixture at 0°C. The final mixture was stirred for 25 min at 0°C and diluted with ether (50 mL), extracted with HCl (0.1N, 3×50 mL), saturated $NaHCO_3$ (3×50 mL) and brine (2×50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford (1*R*,4*S*)-(−)-**3**. (EtOAc:hexane, 1:5). (0.67 g, 56%). All spectroscopic data and optical rotation sign are in accordance with the literature values.[4]

3.10. Dechlorination of (1*S*,4*R*)-(−)-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hepta-2,5-diene (1*S*,4*R*)-(−)-1b

To a stirred solution of metallic sodium (2.05 g, 89.5 mmol) in liquid NH_3 (80 mL), (1*S*,4*R*)-(−)-**1b** (1.46 g, 4.45 mmol) in absolute EtOH/ether (24 mL, 1:1 ratio) was added dropwise under argon atmosphere over 20 min. The resultant mixture was stirred for additional 20 min and then solid NH_4Cl was added in small portions until the solution became colorless. NH_3 was removed by passing N_2 through the mixture and ice-water was added. The resultant mixture was acidified with 2N HCl and extracted with ether (3×50 mL). Organic phase was washed with saturated $NaHCO_3$ (3×50 mL), brine (2×50 mL) and dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford (1*S*,4*R*)-(+)-**1a**. (EtOAc:hexane, 1:5). (0.40 g, 72%).

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