An Expedient Route to Optically Pure 3-*endo*-Hydroxydicyclopentadiene

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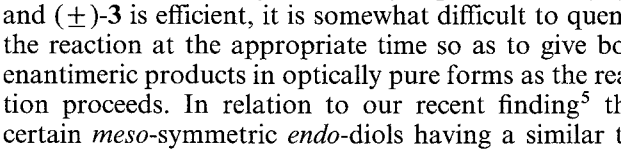
Optically pure 3-*endo*-hydroxydicyclopentadiene has been prepared expediently in both enantiomeric forms via lipase-mediated kinetic resolution. Manganese dioxide transforms the optically active 3-*endo*-alcohol into the highly versatile chiral building block 3-oxodicyclopentadiene without loss of optical purity.

We have recently established[1] an environmentally safe, non-hazardous transformation of dicyclopentadiene [(±)-**1**] into 3-oxodicyclopentadiene [(±)-**4**] via *exo*-3-acetoxydicyclopentadiene [(±)-**2**] and *exo*-3-hydroxydicyclopentadiene [(±)-**3**]. We have also established an efficient kinetic resolution of both *exo*-acetate (±)-**2** and *exo*-alcohol (±)-**3** by using lipases[2] to obtain optically pure 3-oxodicyclopentadiene[3] **(4)**, a highly versatile chiral building block, especially as a chiral cyclopentadienone synthon.[4] Although the established lipase-mediated resolution of the 3-oxygenated dicyclopentadienes (±)-**2** and (±)-**3** is efficient, it is somewhat difficult to quench the reaction at the appropriate time so as to give both enantimeric products in optically pure forms as the reaction proceeds. In relation to our recent finding[5] that certain *meso*-symmetric *endo*-diols having a similar tricyclic framework underwent clear-cut lipase-mediated asymmetrization, we examined the lipase-mediated resolution of the 3-*endo*-oxygenated dicyclopentadienes **5** and **6** in order to develop a more efficient route to optically pure 3-oxodicyclopentadiene **(4)**. We wish to report here our successful procedure which allows clear-cut resolution of the racemic *endo*-alcohol (±)-**5** and facile conversion of the optically pure *endo*-alcohol **5** into optically pure 3-oxodicyclopentadiene **(4)**.

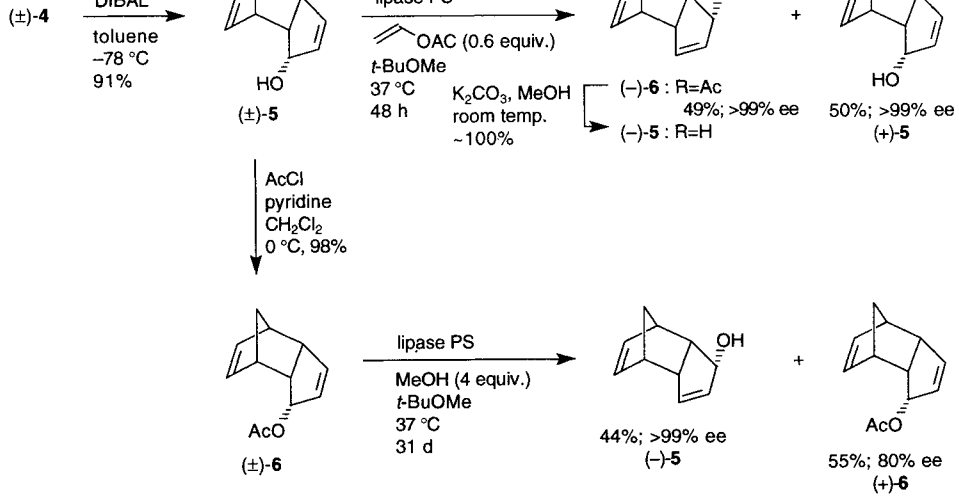


Scheme 1

We first prepared[1] racemic *endo*-3-hydroxydicyclopentadiene [(±)-**5**] by stereoselective 1,2-reduction of racemic 3-oxodicyclopentadiene [(±)-**4**], obtained in three steps from racemic dicyclopentadiene **(1)** via the 3-*exo*-acetate (±)-**2** and the 3-*exo*-alcohol (±)-**3** as shown in Scheme 1. The *endo*-alcohol (±)-**5**, obtained in an excellent yield, was next treated with acetyl chloride to give the racemic 3-*endo*-acetate (±)-**6** in nearly quantitative yield.

We next examined the kinetic resolution[6] of the racemic substrates using lipase PS-on-Celite (Amano: *Pseudomonas* sp.) which exhibited excellent enantioselectivity in the asymmetrization of certain *meso*-symmetric tricyclic *endo*-diols.[3] After several attempts, we found that clear-cut kinetic acylation did occur when the racemic *endo*-alcohol (±)-**5** was treated with vinyl acetate in an organic solvent. Thus, the reaction of (±)-**5** with 0.6 equiv of vinyl acetate in *tert*-butyl methyl ether in the presence of lipase PS-on-Celite (10% w/w of the substrate) furnished the *endo*-acetate (−)-**6** in 49% yield in >99% ee leaving the *endo*-alcohol (+)-**5** in 50% recovery in >99% ee after 48 h at 37 °C.

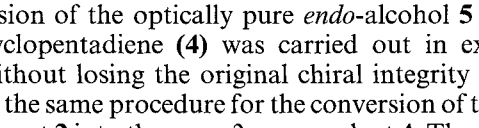
On the other hand, the hydrolytic reaction of the *endo*-acetate (±)-**6** was found to proceed at an uncontrollable rate under hydrolytic conditions in a phosphate buffer solution in the presence of the same lipase. However, a promising alternative for the hydrolytic procedure was discovered by carrying out the lipase-mediated reaction in an organic solvent in the presence of methanol. Al-



Scheme 2

though the lipase-mediated methanolysis was found to be sluggish, it proceeded in an enantiocomplementary way to the acylation method to give rise to the optically pure (−)-*endo*-alcohol (−)-**5** leaving the optically enriched (+)-*endo*-acetate **6**. Thus, the reaction of the racemic *endo*-acetate (±)-**6** with four equiv of methanol in *tert*-butyl methyl ether in the presence of lipase PS-on-Celite (100% w/w of the substrate) furnished the *endo*-alcohol (−)-**5** in 44% yield in >99% ee leaving the *endo*-acetate (+)-**6** in 55% recovery in ca. 80% ee after 31 d at 37°C. The alcohol (−)-**5** generated was found to be enantiomeric with the alcohol (+)-**5** left in the acylation method and identical with the alcohol (−)-**5** generated by the methanolysis of the acetate (−)-**6** obtained by the acylation method. These results indicated that the enzymatic reactions occurred at the oxygen functionalities on the same stereogenic center in both substrates **5** and **6**. Moreover, they also confirm that the 3-*endo*-oxygenated compounds are more suitable substrates than the 3-*exo*-counterparts[2] in the lipase-mediated kinetic resolution (Scheme 2).

Conversion of the optically pure *endo*-alcohol **5** into 3-oxodicyclopentadiene **(4)** was carried out in excellent yield without losing the original chiral integrity by employing the same procedure for the conversion of the *exo*-counterpart **3** into the same 3-oxo product **4**. Thus, treatment of the optically pure *endo*-alcohol (−)-**5** with manganese(IV) oxide in dichloromethane at room temperature afforded optically pure 3-oxodicyclopentadiene [(+)-**4**] in excellent yield without difficulty (Scheme 3).



Scheme 3

In conclusion, we have developed an expedient alternative route to optically pure 3-oxodicyclopentadiene **(4)** by establishing a clear-cut kinetic resolution of racemic *endo*-3-hydroxydicyclopentadiene [(±)-**5**] and its acetate (±)-**6** using lipase PS-on-Celite as a catalyst.

Melting points are uncorrected. IR spectra were recorded on a JASCO-IR-700 spectrometer, ^{1}H NMR spectra on a HITACHI R-3000 (300 MHz), mass spectra on a JEOL JMS-DX303 instrument. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

Racemic *endo*-3-Hydroxydicyclopentadiene [(±)-5]:
To a stirred solution of (±)-**4** (503 mg, 3.45 mmol) in toluene (10 mL) was added dropwise *i*-Bu_2AlH (1.5 M in toluene, 3.0 mL, 4.5 mmol) at −78°C. After 20 min at the same temperature, the mixture was diluted with Et_2O (40 mL) and treated with 30% aq NH_4OH (1 mL) at 0°C. After 2 h at r.t., the mixture was filtered through a Celite pad and the filtrate was extracted with CH_2Cl_2 (200 mL × 2). The extract was washed with brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 100 g; EtOAc/hexane, 1:6) to give the *endo*-alcohol[7] (±)-**5** as a colorless solid, mp 82.0–83.0°C; yield: 463 mg (91%). Spectral data are given under optically active **5**.

Racemic *endo*-3-Acetoxydicyclopentadiene [(±)-6]:
To a stirred solution of (±)-**5** (1.73 g, 11.7 mmol) in CH_2Cl_2 (30 mL) containing pyridine (1.73 mL, 17.5 mmol) was added dropwise acetyl chloride (0.99 mL, 14 mmol) at 0°C. After 2 h, the mixture was diluted with CH_2Cl_2 (200 mL) and the solution was washed with brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed (silica gel, 110 g; EtOAc/hexane, 1:20) to give the *endo*-acetate (±)-**6** as a colorless solid, mp 31.5–32.5°C; yield: 2.16 g (98%). Spectral data are given under optically active **6**.

Kinetic Acetylation of Racemic *endo*-3-Hydroxydicyclopentadiene:
A suspension of (±)-**5** (971 mg, 6.56 mmol), vinyl acetate (30 µL, 3.94 mmol), and lipase PS-on-Celite (Amano) [97 mg, 10% w/w of (±)-**5**] in *tert*-BuOMe (20 mL) was stirred at 37°C for 48 h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed (silica gel, 100 g; EtOAc/hexane, 1:20) to give the optically active acetate (−)-**6** as colorless crystals and the optically active alcohol (+)-**5** as colorless crystals (eluent: EtOAc/hexane, 1:6).

(−)-endo-3-Acetoxydicyclopentadiene [(−)-6]:
Yield: 620 mg (49.8%), mp 58.5–59.5°C, $[\alpha]_D^{27}$ −5.3° (c = 1.03, $CHCl_3$). Optical purity was estimated to be >99% ee by HPLC using a chiral column (CHIRALCEL OB; *i*-PrOH/hexane, 1:9) after transformation into the 3-oxo-derivative (+)-**4**.

IR (Nujol): ν = 1725 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.98 (dd, 1H, J = 5.7, 2.7 Hz), 7.56 (dd, 1H, J = 5.7, 3.1 Hz), 5.69–5.72 (m, 1H), 5.43–5.46 (m, 1H), 5.44 (dd, 1H, J = 8.8, 1.5 Hz), 3.26–3.31 (m, 1H), 3.08 (ddd, 1H, J = 8.8, 7.7, 4.0 Hz), 2.89 (br s, 1H), 2.76 (br s, 1H), 2.07 (s, 3H), 1.50–1.53 (m, 1H), 1.40–1.43 (m, 1H).

MS: m/z = 190 (M^+), 82 (100%).

HRMS: m/z calc. for $C_{12}H_{14}O_2$, 190.0994; found, 190.1003.

Anal. ($C_{12}H_{14}O_2$): Calc. C, 75.76; H, 7.42. Found C, 75.60; H, 7.40.

(+)-endo-3-Hydroxydicyclopentadiene [(+)-5]:
Yield: 480 mg (49.4%), mp 81–82.5°C, $[\alpha]_D^{28}$ +151.1° (c = 0.95, $CHCl_3$). Optical purity was estimated to be >99% ee by HPLC using a chiral column (CHIRALCEL OB; *i*-PrOH/hexane, 1:9) after transformation into the 3-oxo-derivative (−)-**4**.

IR (Nujol): ν = 3228 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.15 (dd, 1H, J = 5.7, 2.4 Hz), 5.81 (dd, 1H, J = 5.7, 3.1 Hz), 5.59 (s, 2H), 4.64–4.69 (m, 1H), 3.30 (dd, 1H, J = 7.3, 4.0 Hz), 2.91–2.99 (m, 3H), 1.57 (br, d, 1H, J = 8.1 Hz), 1.45 (br d, 1H, J = 8.1 Hz), 1.25 (br d, 1H, J = 8.8 Hz).

MS: m/z = 148 (M^+), 129 (100%).

HRMS: m/z calc. for $C_{10}H_{12}O$, 148.0888; found, 148.0893.

Anal. ($C_{10}H_{12}O$): Calc. C, 81.04; H, 8.16. Found C, 80.88; H, 8.15.

Methanolysis of (−)-*endo*-4-Acetoxydicyclopentadiene [(−)-6]:
A mixture of (−)-**6** (1.13 g, 5.93 mmol) and K_2CO_3 (0.82 g, 5.93 mmol) in MeOH (20 mL) was stirred at r.t. for 20 h. After evaporation of the solvent under reduced pressure, the residue was extracted with Et_2O (100 mL × 2) and the extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed (silica gel, 100 g; EtOAc/hexane, 1:6) to give the *endo*-alcohol (−)-**5** as colorless crystals, mp 81–82.5°C, $[\alpha]_D^{28}$ −151.7° (c = 0.97, $CHCl_3$); yield: 875 mg (100%). Spectral data and chromatographed behavior were identical with those of (+)-**5**.

Kinetic Methanolysis of Racemic *endo*-3-Acetoxydicyclopentadiene [(±)-6]:
A suspension of (±)-**6** (1.45 g, 7.61 mmol) and lipase PS-on-Celite (Amano) [1.50 g, 100% v/v of (±)-**6**] in *t*-BuOMe (13 mL) containing MeOH (1.28 mL, 31.6 mmol) was stirred at 37°C for 31 d. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed (silica gel, 100 g; EtOAc/hexane, 1:20) to give the optically active acetate (+)-**6** as colorless crystals and the optically active alcohol (−)-**5** as colorless crystals (eluent: EtOAc/hexane, 1:6).

(+)-endo-3-Acetoxydicyclopentadiene [*(+)*-6]:

Yield: 800 mg (55%). Optical purity was estimated to be 80% ee by HPLC using a chiral column (CHIRALCEL OB; *i*-PrOH/hexane, 1:9) after transformation into the 3-*exo*-derivative (−)-**4**. Spectral data and chromatographic behavior were identical with those of the above obtained (+)-**6**.

(−)-endo-3-Hydroxydicyclopentadiene [*(−)*-**5**]:

Yield: 493 mg (44%). Optical purity was estimated to be > 99% ee by HPLC using a chiral column (CHIRALCEL OB; *i*-PrOH/hexane, 1:9) after transformation into the 3-*oxo*-derivative (+)-**4**. Spectral data and chromatographic behavior were identical with those of the above obtained (−)-**5**.

Transformation of Optically Active *endo*-3-Hydroxydicyclopentadiene (5) into 3-Oxodicyclopentadiene; Typical Procedure:

To a stirred solution of (−)-**5** (56 mg, 0.38 mmol) in CH_2Cl_2 (1.5 mL) was added portionwise MnO_2 (150 mg, 1.73 mmol) at r.t. After stirring for 24 h, the mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed (silica gel, 5 g; EtOAc/hexane, 1:8) to give (+)-**4** as colorless crystals, mp 76–76.5°C, $[\alpha]_D^{28}$ + 138.4° (*c* = 0.81, MeOH) {Lit.[1] mp 76.5–77°C, $[\alpha]_D^{25}$ + 140.3° (*c* = 0.94, MeOH)}. > 99% ee by HPLC (CHIRALCEL OB; *i*-PrOH/hexane, 1:9); yield: 51.0 mg (92%). Spectral data and chromatographed behavior were identical with those of an authentic sample.[1]

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