CHEMISTRY LETTERS, pp. 359-362, 1989.

A New Route to (+)-2,3-(Isopropylidenedioxy)-4-cyclopentenone via the Optically Active Dicyclopentadiene Intermediate

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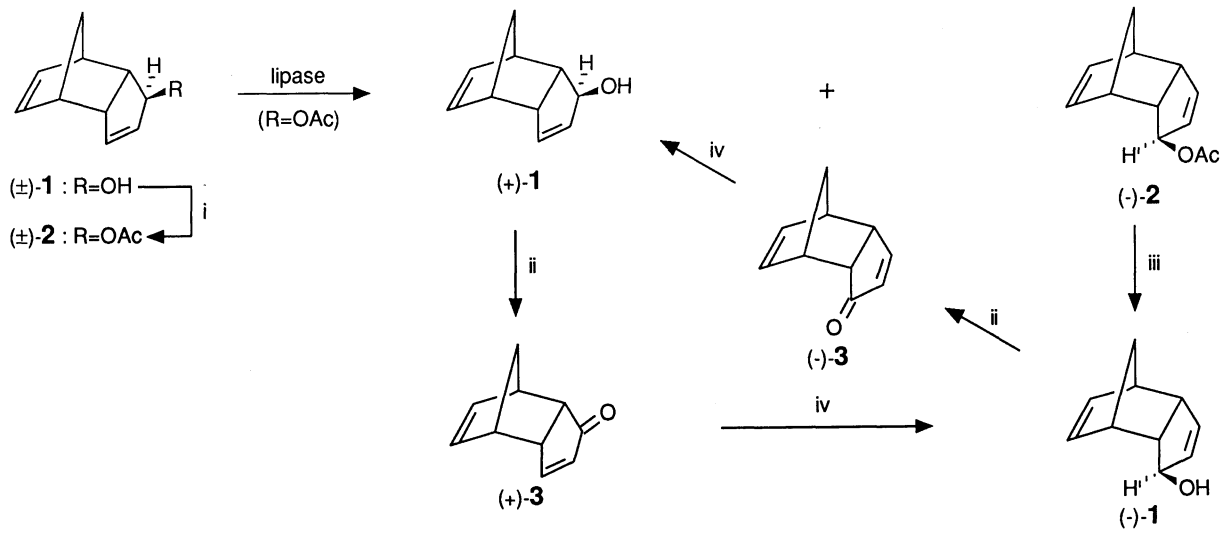
Chiral synthesis of the dicyclopentadiene derivative and its stereoselective conversion into (+)-2,3-(isopropylidenedioxy)-4-cyclopentenone, a versatile building block for the synthesis of cyclopentanoid natural products, have been described.

Recently, we succeeded[1] in resolving the racemic allylic alcohol[2] [(±)-**1**], obtainable in a large quantity from dicyclopentadiene, by employing kinetic hydrolysis of its acetate [(±)-**2**] using lipase. Since both the (+)-alcohol [(+)-**1**], obtained in 30% yield after recrystallization, and the (-)-alcohol [(-)-**1**], obtained in 22% overall yield after hydrolysis followed by recrystallization, could be interconverted one another in good yield (about 80%) via the corresponding dienone (**3**) by employing the Wharton reaction, synthesis of a single enantiomer of the alcohol (**1**) or the dienone (**3**) implies acquisition of both enantiomers (Scheme 1). We report herewith an alternative synthesis of the (+)-dienone [(+)-**3**]

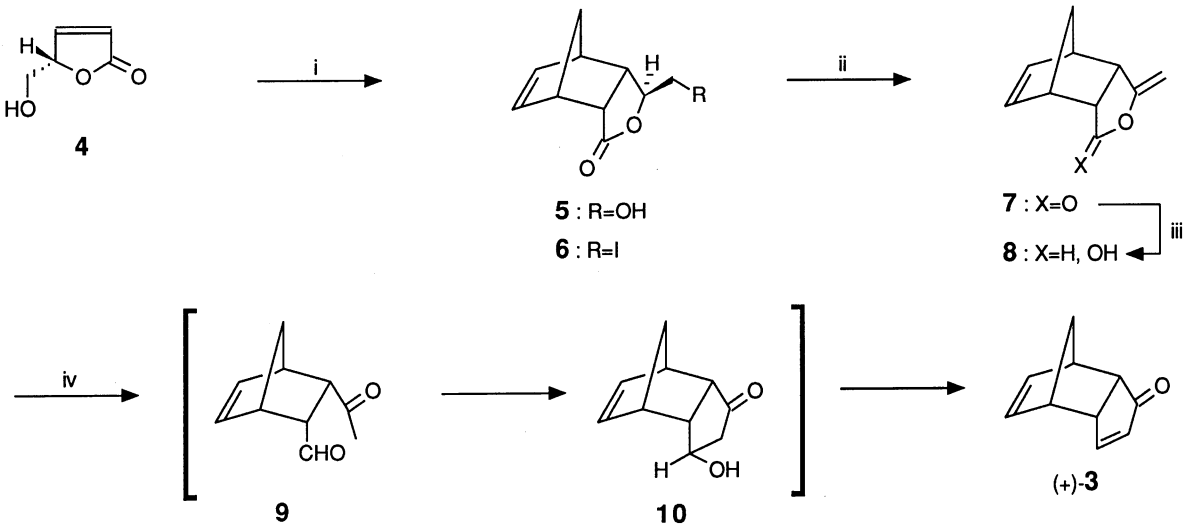


Scheme 1.
i, AcCl, pyridine, benzene; ii, PCC, CH_2Cl_2; iii, KOH, aq. dioxane; iv, (a) 30% H_2O_2, aq. NaOH, (b) $(NH_2)_2 \cdot H_2O$, AcOH.

starting from (S)-5-hydroxymethylbuten-2-olide[3] (**4**) and conversion of (+)-**3** thus obtained into (+)-2,3-(isopropylidenedioxy)-4-cyclopentenone (**17**) which is a versatile building block for the synthesis of cyclopentanoid natural products[4]

especially for prostaglandins.[4b)]

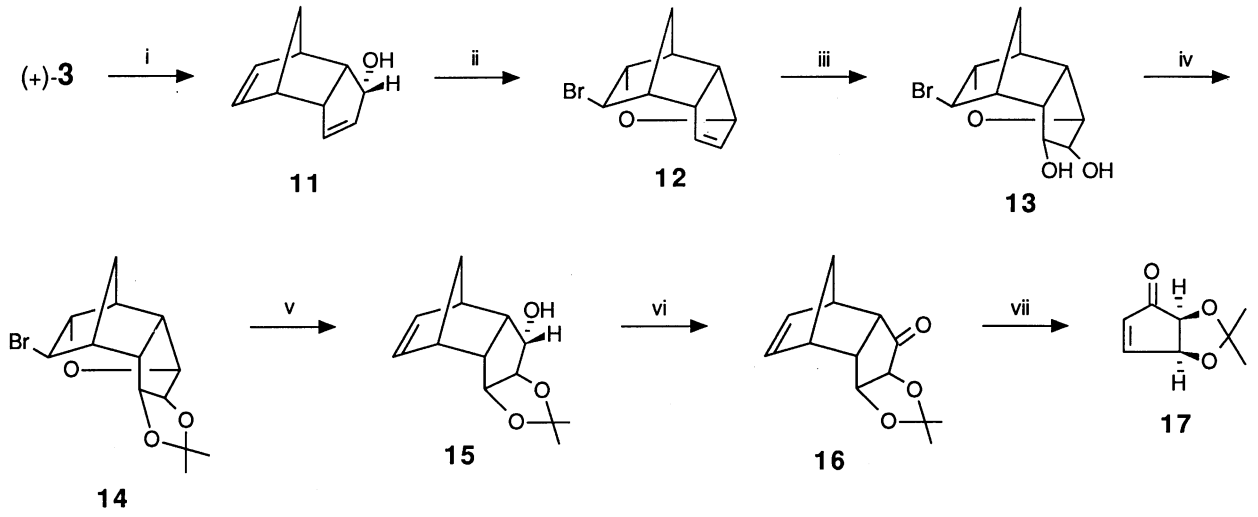
Heating **4** with an excess cyclopentadiene (6 equiv.) without solvent in a sealed tube gave a mixture of adducts which was purified by recrystallization to afford the pure endo-adduct[3)] (**5**), mp 96-97 °C, $[\alpha]_D^{26}$ -49.77° (c 1.01, $CHCl_3$), in 72% yield. Treatment of **5** with a mixture of triphenylphosphine, iodine, and imidazole[5)] gave the crude iodide (**6**) which without purification was exposed to DBU in benzene to give the enol-lactone (**7**) in 68% overall yield. Reduction of **7** with diisobutylaluminum hydride, followed by exposing the reaction mixture to aqueous sodium hydroxide (0.5 M) initiated concomitant hydrolysis and aldolization of the lactol (**8**) to furnish the (+)-dienone [(+)-**3**] (43% from **7**), mp 59-60 °C, $[\alpha]_D^{25}$ +160.7° (c 0.27, MeOH). Since physical and optical properties of (+)-**3** were identical in all respects with those of (+)-**3** [mp 59-60 °C, $[\alpha]_D^{25}$ +158.8° (c 1.01, MeOH)] obtained from the enzymatically prepared (+)-alcohol[1)] [(+)-**1**], the present transformation confirmed the absolute configuration of the enzymatic products.



Scheme 2.

i, cyclopentadiene, 140 °C, 20 h, sealed tube; ii, (a) PPh_3, I_2, imidazole, Et_2O-CH_3CN (3:1), rt, (b) DBU, benzene, reflux; iii, DIBAL, THF, -78 °C; iv, 0.5 M NaOH, -78 °C - rt, 1 h.

We next carried out the conversion of the (+)-dienone [(+)-**3**] into (+)-2,3-(isopropylidenedioxy)-4-cyclopentenone (**17**). Reduction of (+)-**3** with sodium borohydride in the presence of cerium (III) chloride[6)] yielded the endo-alcohol (**11**), $[\alpha]_D^{24}$ -215.1° (c 0.49, $CHCl_3$) (83%), accompanied by a small amount of the exo-alcohol [(+)-**1**] (10%) which was readily separated (silica gel column) and recycled. Treatment of **11** with N-bromosuccinimide gave the bromo-ether (**12**) in 85% yield. Stirring **12** with a catalytic amount of osmium tetroxide (3% mol) and 1-methylmorpholine-1-oxide[7)] (1.5 equiv.) furnished the exo-1,2-glycol (**13**) (95% yield), $[\alpha]_D^{22}$ -123.7° (c 0.64, $CHCl_3$), selectively, which was transformed into the acetonide (**14**) (95% yield), $[\alpha]_D^{22}$ -95.4° (c 0.66, $CHCl_3$), under standard conditions. Refluxing **14** with zinc powder in ethanol containing a catalytic amount of acetic acid gave the endo-alcohol (**15**) (88% yield), $[\alpha]_D^{23}$ +55.1° (c 0.67, $CHCl_3$),



Scheme 3.

i, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; ii, NBS, CH_2Cl_2, 0 °C-rt; iii, OsO_4 (3 mol%), 1-methylmorpholine-1-oxide, aq. THF (3:1), 0 °C-rt; iv, 2,2-dimethoxypropane, p-TsOH (cat.), DMF, rt; v, Zn, AcOH (cat), EtOH, reflux; vi, PCC, CH_2Cl_2, rt; vii, o-dichlorobenzene, reflux.

which was oxidized with pyridinium chlorochromate in methylene chloride to give the ketone (**16**), $[\alpha]_D^{24}$ +266.8° (c 0.68, $CHCl_3$), in 78% yield. Finally, **16** was refluxed in o-dichlorobenzene to furnish (+)-2,3-(isopropylidenedioxy)-4-cyclopentenone (**17**), mp 36-37 °C, $[\alpha]_D^{24}$ +71.57° (c 1.01, $CHCl_3$) [lit.[4b]: mp 37.5-38.5 °C, $[\alpha]_D^{25}$ +71.8° (c 0.90, $CHCl_3$)], in 65% yield, with removal of cyclopentadiene by retrograde Diels-Alder reaction.[8] Since inversion of the (+)-dienone [(+)-**3**] into its enantiomer [(-)-**3**] could be easily carried out, the present route formally constitutes a synthesis of (-)-2,3-(isopropylidenedioxy)-4-cyclopentenone [(-)-**17**].

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8) The endo-alcohol (**15**) was found to be stable under the same or more forcing retrograde Diels-Alder conditions.
9) All the new products obtained gave satisfactory spectral data as follows:
5: mp 96-97 °C; $[\alpha]_D^{26}$ -49.8° (c 1.01, $CHCl_3$); IR (Nujol) ν 3350, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (d, 1H, J=9.0 Hz), 1.63 (dt, 1H, J=9.0, 1.0 Hz), 2.16 (br.t, 1H, J=7.0 Hz, exchangeable with D_2O), 2.85-3.22 (m, 2H), 3.27-3.34 (m, 2H), 3.45-3.75 (m, 2H), 3.80-4.08 (m, 1H), 6.29 (s, 2H); MS (m/z) 180, 149, 66 (100%).
6: $[\alpha]_D^{22}$ -34.9° (c 1.07, $CHCl_3$); IR (film) ν 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.48 (d, 1H, J=10.0 Hz), 1.65 (d, 1H, J=10.0 Hz), 2.70-2.99 (m, 1H), 3.05-3.22 (m, 1H), 3.22-3.48 (m, 4H), 3.82-4.01 (m, 1H), 6.15-6.40 (m, 2H); MS (m/z) 290, 66 (100%).
7: $[\alpha]_D^{22}$ +41.8° (c 0.34, $CHCl_3$); IR (film) ν 1795, 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.37-1.55 (m, 1H), 1.55-1.73 (m, 1H), 3.15-3.70 (m, 4H), 4.27 (dd, 1H, J=2.4, 1.5 Hz), 4.62 (dd, 1H, J=2.4, 1.5 Hz), 6.15-6.31 (2H, m); MS (m/z) 162, 66 (100%).
11: $[\alpha]_D^{24}$ -215.1° (c 0.49, $CHCl_3$); IR (Nujol) ν 3200 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18-1.67 (m, 3H, 1H, exchangeable with D_2O), 2.29-3.10 (m, 2H), 3.20-3.41 (m, 1H), 4.65 (br.t, 1H, J=8.6 Hz), 5.10 (s, 2H), 5.81 (dd, 1H, J=7.1, 3.1 Hz); MS (m/z) 148, 68 (100%).
12: $[\alpha]_D^{23}$ -148.8° (c 0.70, $CHCl_3$); IR (film) ν 1460, 1025, 1035 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.89-2.15 (m, 1H), 2.35-2.60 (m, 2H), 2.60-2.85 (m, 1H), 2.95-3.20 (m, 2H), 4.0-4.15 (m, 1H), 4.55-4.80 (m, 2H), 5.75 (m, 1H), 6.05 (dd, 1H, J=5.7, 2.6 Hz); MS (m/z) 227, 117, 63 (100%).
13: mp 131-132 °C; $[\alpha]_D^{22}$ -123.7° (c 0.64, $CHCl_3$); IR (Nujol) ν 3400, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.70-2.00 (m, 2H), 2.35-2.70 (m, 2H), 2.70-2.95 (m, 2H, 1H exchangeable with D_2O), 2.95-3.29 (m, 2H, 1H exchangeable with D_2O), 3.85 (d, 1H, J=2.9 Hz), 4.10-4.45 (m, 3H), 4.53 (d, 1H, J=5.7 Hz); MS (m/z) 229, 163 (100%).
14: $[\alpha]_D^{22}$ -95.4° (c 0.67, $CHCl_3$); IR (film) ν 2950 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.45 (s, 3H), 1.62-1.88 (m, 1H), 2.12-2.38 (m, 1H), 2.48-2.60 (m, 1H), 2.60-2.90 (m, 2H), 2.95-3.25 (m, 1H), 3.55 (d, 1H, J=2.9 Hz), 4.40 (d, 1H, J=5.7 Hz), 4.60 (dd, 1H, J=11.4, 5.7 Hz), 4.60-4.65 (m, 2H); MS (m/z) 301, 286 (100%).
15: mp 116-118 °C; $[\alpha]_D^{23}$ +55.07° (c 0.67, $CHCl_3$); IR (Nujol) ν 3200 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.45 (s, 3H), 1.18-1.55 (m, 2H), 2.50-2.70 (m, 1H exchangeable with D_2O), 2.75-3.20 (m, 4H), 4.05 (d, 1H, J=2.1 Hz), 4.09 (d, 1H, J=2.1 Hz), 4.05-4.30 (m, 1H), 6.1 (dd, 1H, J=5.4, 3.0 Hz), 6.27 (dd, 1H, J=5.4, 3.0 Hz); MS (m/z) 222, 207, 66 (100%).
16: $[\alpha]_D^{24}$ +266.8° (c 0.68, $CHCl_3$); IR (film) ν 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.48 (s, 3H), 1.48-1.75 (m, 2H), 3.0-3.15 (m, 2H), 3.15-3.35 (m, 2H), 3.95 (d, 1H, J=5.8 Hz), 4.30 (d, 1H, J=5.8 Hz), 6.05-6.30 (m, 2H); MS (m/z) 220, 205, 66 (100%).

(Received December 3, 1988)