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Contra-Steric Diels-Alder Route to 3-Oxodicyclopentadiene and *Meso* 3,5-*endo*-Dihydroxy-4,5-dihydrodicyclopentadiene

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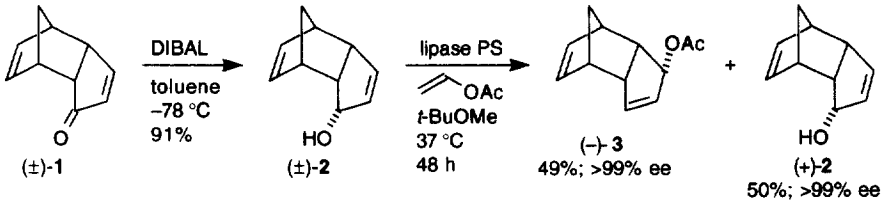
Abstract: Diels-Alder reaction between cyclopentadiene and 4-*tert*-butoxycyclopentenone occurs in a contra-steric manner to give more hindered *endo*-3-*tert*-butoxydicyclopentadiene as the major product (~15:1) in excellent yield. The product has been transformed into either (±)- and (–)-3-oxodicyclopentadiene or *meso* 3,5-*endo*-dihydroxy-4,5-dihydrodicyclopentadiene efficiently.

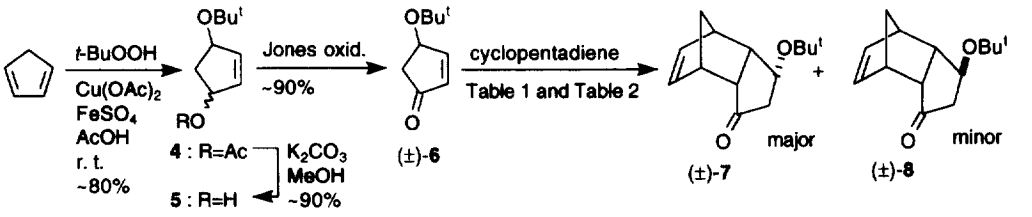
We recently reported that racemic 3-*endo*-hydroxydicyclopentadiene [(±)-**2**] is resolved to give optically pure acetate (–)-**3** in good yield in the presence of lipase PS in *tert*-butyl methyl ether containing vinyl acetate[1] leaving optically pure (+)-**2** (**Scheme 1**). Because optically pure **2** and **3** are convertible into optically pure 3-oxodicyclopentadiene[2] (**1**) which is used as a versatile chiral building block,[3] we have endeavored to establish an efficient method for the preparation of (±)-**1** as the precursor of (±)-**2** used for lipase-mediated resolution.



Scheme 1

During the investigation we encountered an interesting stereochemical outcome in the key Diels-Alder reaction between 4-*tert*-butoxycyclopentenone[4] [(±)-**6**] and cyclopentadiene which gave the contra-steric adduct **7** as the major product. We report here our finding which led to preparation of 3-oxodicyclopentadiene [(±)- and (–)-**1**] and the previously unknown *meso* 3,5-*endo*-dihydroxy-4,5-dihydrodicyclopentadiene (**11**).

Employing the established procedure,[4] cyclopentadiene was transformed into racemic 4-*tert*-butoxycyclopentenone [(±)-**6**] in a satisfactory overall yield (~65%) by hydroperoxide oxidation,[5] followed by Jones oxidation. When (±)-**6** was treated with an excess of cyclopentadiene, two isomeric adducts were formed in high yield under either catalytic or non-catalytic conditions (**Scheme 2**). However, the reaction proceeded more quickly and with greater diastereoselectivity in the presence of the catalysts as shown in **Table 1**. Titanium tetrachloride accelerated the reaction, but induced concurrent dealkylation (**Table 2**: Entry 1). Thus, the reaction was best carried out in the presence of 1.2 equivalent of zinc chloride[6] using 3.0 equivalents of cyclopentadiene to give **7** as crystals (mp 42.0-42.5 °C) and **8** as an oil in yields of 92.0 and 6.2%



Scheme 2

Table 1. Diels-Alder reaction between cyclopentadiene and 4-*tert*-butoxycyclopentenone [(±)-**6**]

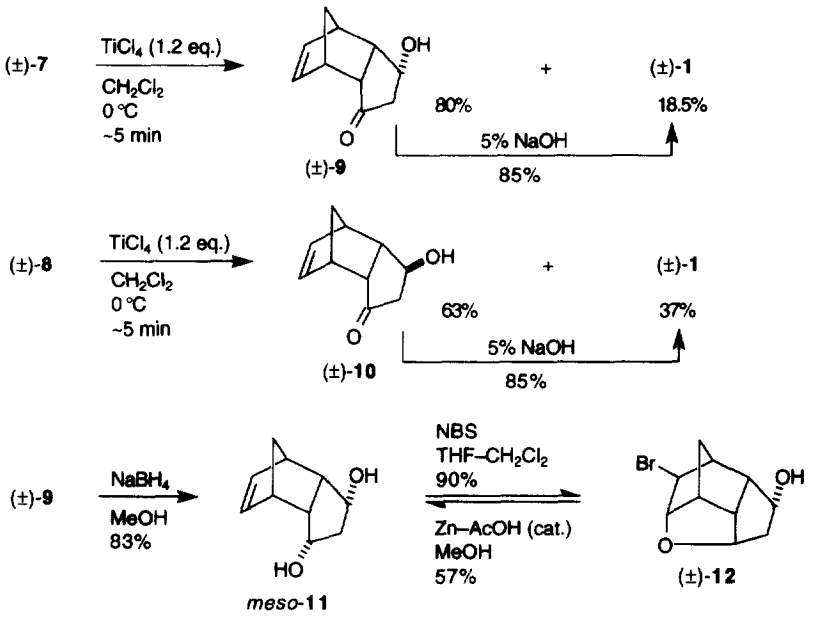
Entry	Cyclopentadiene (equiv.)	Additive (equiv.)	Solvent	Temperature (h)	Product[a] (%) (±)-**7**	(±)-**8**
1	10	none	benzene	reflux (24)	48.0[b]	30.8
2	10	ZnI_2 (0.5)	CH_2Cl_2	r. t. (18)	72.4[b]	17.6
3	3	ZnI_2 (1.0)	benzene	r. t. (10)	81.4	16.8
4	3	$ZnCl_2$ (1.2)	benzene	r. t. (3)	92.0	6.2
5	3	$ZnCl_2$ (3.0)	benzene	r. t. (6)	80.0	13.4

a. isolated yield after silica gel column chromatography
b. **6** was not completely consumed

respectively, after separation by silica gel column chromatography (**Table 1**: Entry 4). On brief exposure to 1.2 equivalent of titanium(IV) chloride,[7] **7** and **8** were dealkylated to give the corresponding secondary alcohols, **9** (mp 154-155 °C) and **10**, in yields of 80 and 63% respectively, accompanied by (±)-**1** in yields of 18.5% from **7** and 37.0% from **8**. Since both **9** and **10** gave (±)-**1** (mp 52-55 °C) under basic conditions, the adducts **7** and **8** were determined to be epimeric at the alkoxy stereogenic center. At this point we believed that the major adduct must be the steric product having an *exo*-alkoxy group. To verify the stereochemistry, **9** was reduced with sodium borohydride to give stereoselectively **11** (mp 152-155 °C). This compound was then treated with *N*-bromosuccinimide[2e] (NBS) to give **12** (mp 127-128 °C). On exposure to zinc powder in methanol containing acetic acid, **12** regenerated **11** indicating that rearrangement did not occur during these transformations (**Scheme 3**). However, the X-ray analysis[8] revealed the unexpected *endo*-hydroxy structure of **12** (**Fig. 1**) and unambiguously confirms the contra-steric structure of the major adduct **7**.

The stereochemical outcome of the Diels-Alder reaction of **6** may be explained in terms of the dominance of the electronic effects (Cieplak effect[9]) over steric factors. The same contra-steric mechanism has been proposed by Zwanenburg and coworkers[10] to rationalize their observation that the Diels-Alder reaction between optically active 4-*tert*-butyldimethylsiloxycyclopentenone and cyclopentadiene gives **1**. In this instance, optically active **1** was generated in a moderate optical yield having the opposite configuration to that expected based on steric control. However, they failed to prove their speculation as the intermediate *endo*-siloxy adduct underwent facile elimination to give **1** directly under the reaction conditions.

We also examined the direct formation of (±)-**1** without isolation of the adducts **7** and **8**. Thus, **6** was treated with 3 equivalents of cyclopentadiene in benzene containing 0.5 equivalent of titanium(IV) chloride at 0 °C for 1 h. The reactant was exposed to an additional 1.0 equivalent of titanium(IV) chloride in dichloromethane, followed by 7.0 equivalents of 5% aqueous sodium hydroxide to afford (±)-**1** in 83.4% yield (**Table**



Scheme 3

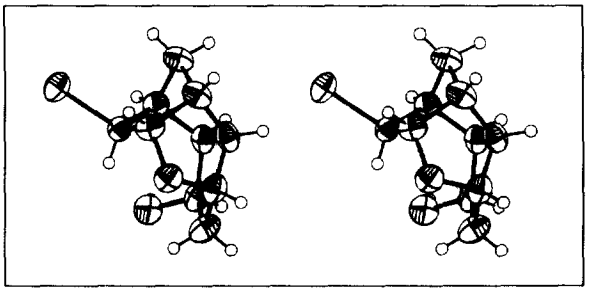


Fig. 1 X-ray structure of the bromo-ether (±)-**12**

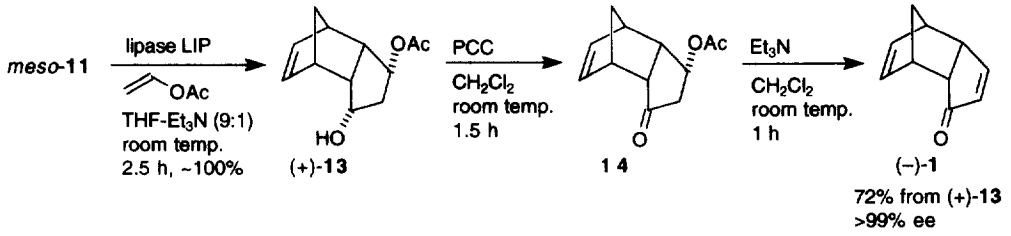
Table 2. One-pot formation of 3-oxodicyclopentadiene [(±)-**1**] from cyclopentadiene and (±)-**6**

Entry	Cyclopentadiene (equiv.)	(i) 1st additive (equiv., temp., time)[a] (ii) 2nd additive (equiv., temp., time)[b]	Solvent	5% NaOH (equiv.)[c]	(±)-1[d] (%)
1	10	(i) $TiCl_4$ (0.25, –63 °C, 1 h)	CH_2Cl_2	none	
		(ii) $TiCl_4$ (1.0, 0 °C, 5 min)	CH_2Cl_2		24.0[e]
2	3	(i) $TiCl_4$ (0.5, 0 °C, 40 min)	benzene		
		(ii) $TiCl_4$ (1.0, 0 °C, 5 min)	CH_2Cl_2	7	83.4
3	3	(i) $ZnCl_2$ (1.2, r. t., 12 h)	benzene		
		(ii) $TiCl_4$ (1.1, 0 °C, 5 min)	CH_2Cl_2	8	80.6

a. Diels-Alder stage. b. elimination stage. c. added after stage (ii). d. isolated yield after silica gel column chromatography. e. 40% yield of the *endo*-alcohol [(±)-**10**] was isolated.

2: Entry 2).

The serendipitous acquisition of *meso* diol **11** prompted us to examine the lipase-mediated asymmetrization.[11] Thus, treatment of **11** with 6 equivalents of vinyl acetate in THF containing triethylamine (9:1) in the presence of lipase LIP[12] at room temperature for 2.5 h afforded the optically active (+)-**13**, $[\alpha]_D^{28}$ +90.8 (*c* 0.99, $CHCl_3$), in quantitative yield. Interestingly, the enzymatic reaction did not proceed completely in the absence of triethylamine. Sequential treatment of (+)-**13** with pyridinium chlorochromate (PCC) and triethylamine gave optically pure (−)-**1**, $[\alpha]_D^{28}$ −135.7 (*c* 0.73, MeOH) [lit.[2c]: $[\alpha]_D^{25}$ −139.4 (MeOH)] (>99% ee by HPLC: CHIRALCEL OB, *i*-PrOH/hexane, 1:9) in 72% overall yield. Since the enantiomerization of optically pure 3-oxodicyclopentadiene (**1**) has already been established,[2g] the present synthesis of (−)-**1** constitutes a formal synthesis of (+)-**1** (**Scheme 4**).



Scheme 4

In conclusion, we have developed an expedient route to racemic and chiral 3-oxodicyclopentadiene (**1**) and *meso* 3,5-*endo*-dihydroxy-4,5-dihydrodicyclopentadiene (**11**) employing a Diels-Alder reaction which occurs in a contra-steric manner.

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12. We thank Mr. Shinji Tarama, Toyobo Co., Osaka, Japan, for a donation of lipase LIP.

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