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Synthesis of novel chiral spirodione, (6*R*,7*R*)-7-phenyl-1-oxaspiro[5.5]undec-3-ene-2,5-dione: application to the asymmetric Diels–Alder reaction with high π-facial selectivity☆

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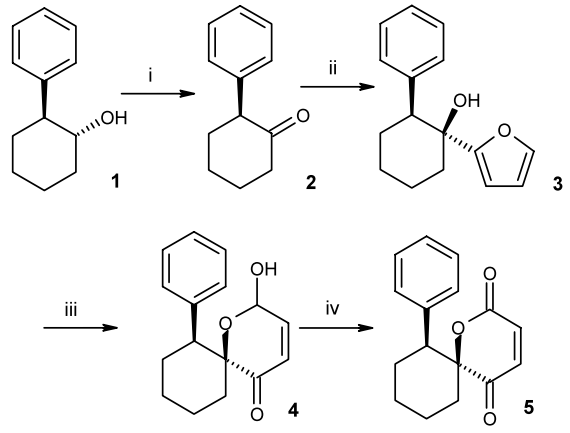
Abstract—The synthesis of the title spirodione, a new class of auxiliary based chiral synthon using (−)-*trans*-2-phenylcyclohexanol and its application to the asymmetric Diels–Alder reaction are described. Methodology for detachment of the chiral auxiliary from the cycloadduct has been developed.

Asymmetric transformations based on a chiral auxiliary are highly useful and versatile because of the reliable prediction of stereochemistry that is offered in many cases.[1] The last two decades have witnessed a tremendous upsurge of interest in asymmetric synthesis due to various emerging theories, e.g. the Cieplak effect,[2] nucleophilic and electrophilic surface theory,[3] electrostatic interactions,[4] σ–π interactions,[5] FMO theory of stereoselection,[6] theory of steric consideration[7] and steric control of diastereoselection.[8] Chiral auxiliaries such as menthol, menthone, camphor, etc., have been used extensively for asymmetric synthesis by attaching an active functional group. The attachment of a functional group to the chiral auxiliary is normally through an ester, ether or amide linkage. Herein we report the synthesis of the title auxiliary having a carbon–carbon bond derived from *trans*-2-phenylcyclohexanol and its successful application to the preparation of enantiomerically pure Diels–Alder products.

The synthesis of the chiral spirodione was achieved as shown in Scheme 1. 2-Phenylcyclohexanol **1** required for the synthesis of the chiral spirodione was prepared either by enzymatic resolution of 2-phenylcyclohexanol[9] or by the Sharpless asymmetric dihydroxylation of 2-phenylcyclohexene[10] followed by the selective hydrogenolysis of the benzylic alcohol with Raney nickel. (−)-2-Phenylcyclohexanone **2** obtained easily from **1**, was condensed with 2-furyllithium in a stereoselective manner to furnish the *trans*-1-(2-furyl)-2-phenyl-cyclohexanol **3** in 93% yield. Compound **3** was subjected to oxidative cyclisation by treatment with *m*-chloroperoxybenzoic acid, a stereospecific oxidation rearrangement sequence[11] on the furan nucleus, ultimately leading to pyranone derivative **4** which on subsequent treatment with Jones' reagent afforded the spirodione **5**[12] as a single diastereomer in excellent yield



Scheme 1. *Reagents and conditions*: (i) $Na_2Cr_2O_7$, H_2O, 30 min, 75%; (ii) Furan, *n*-BuLi, 6 h, −10°C to rt, 93%; (iii) *m*CPBA, dry DCM, 10°C, 4 h, 74%; (iv) Jones' reagent, acetone, rt, 30 min, 95%.

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(Scheme 1). The configuration of **5** was determined as (6*R*,7*R*)-7-phenyl-1-oxaspiro[5.5]undec-3-ene-2,5-dione based on single-crystal X-ray analysis[13] (Fig. 1). The phenyl group was found *syn* to the C–O bond of the oxaspirosystem.

The chiral spirodione **5** can exhibit two different facial selectivities as reported for a similar kind of skeleton.[14] Thus, reagents can approach from the 'a' side *cis* to the phenyl group or from the 'b' side opposite to the phenyl group, as shown in Figure 2.

By taking advantage of the diastereotopic face differences in **5**, we have examined the Diels–Alder reaction with a view to preparing an optically active skeleton. The approach of the diene is based on the chiral auxiliary **5**, which is expected to undergo π-face selective cycloaddition with a variety of dienes. Thus, the Diels–Alder reaction between dienophile **5** and dienes such as cyclopentadiene **6a**; 2,3-dimethyl-1,3-butadiene **6b**; 2-methyl-1,3-pentadiene **6c**; in the presence of diethylaluminium chloride as Lewis acid gave the cycloadducts **7a**–**c**,[15] respectively, as single diastereomers in 92–94% yields (Scheme 2). Diastereoselectivity was determined on the basis of ^{13}C NMR spectroscopy.[15]

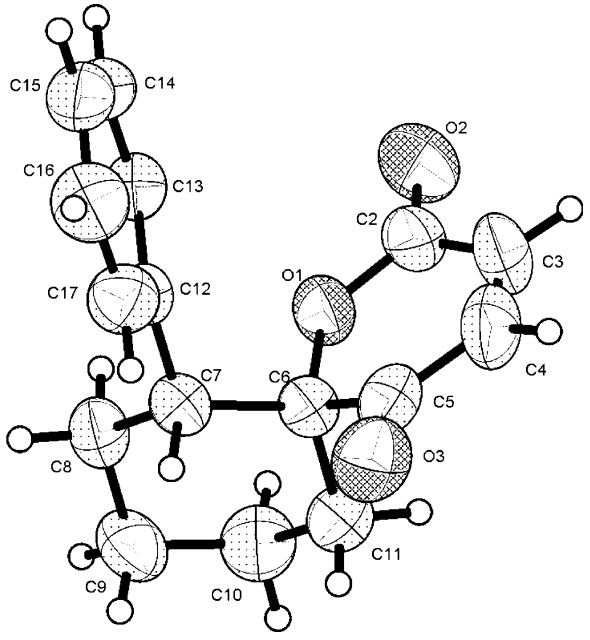


Figure 1. ORTEP diagram of **5**; thermal ellipsoids are drawn at 50% probability.

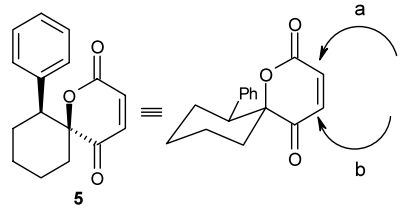
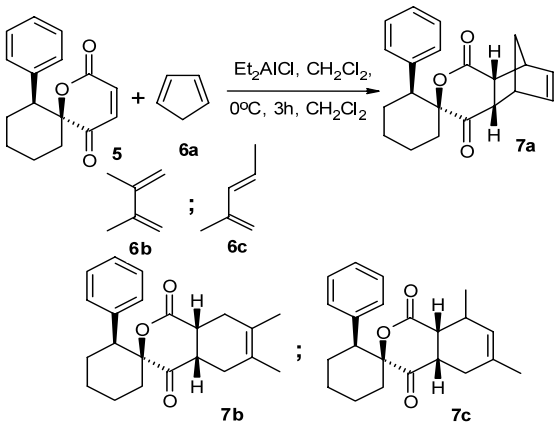


Figure 2.

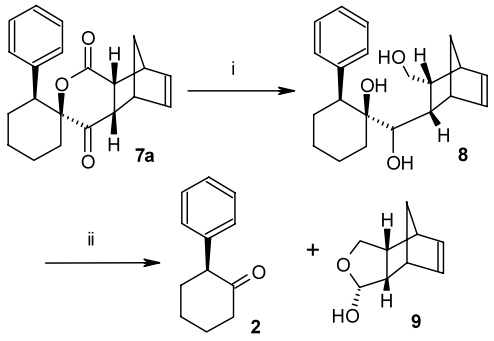


Scheme 2.

Thus, remarkable stereofacial differentiation, 100% preference for ' b' side to 'a' side as depicted in Figure 2 in the Diels–Alder reaction was observed. In contrast to the literature reports,[14c,16] the Diels–Alder reaction with new chiral spiroskeleton **5** proceeded with high stereoselectivity but with complete reverse stereofacial selectivity. The reason for this unexpected reactivity pattern may be that the approach of the reagent, i.e. diene from side 'a' would cause appreciable steric hindrance between the phenyl group and diene, hence the attack of the reagent occurs preferentially from the 'b' side.

In order to obtain the optically pure Diels–Alder product, we next attempted the detachment of the chiral auxiliary from the adduct **7a**. A variety of methods employed for the detachment of the chiral auxiliary such as Bayer–Villiger oxidation followed by hydrolysis, photochemical degradation and basic hydrolysis followed by oxidation were unsuccessful. However, when **7a** was treated with lithium aluminium hydride in refluxing THF, it gave triol, **8** which on subsequent oxidative cleavage by lead tetraacetate afforded the optically pure 2-phenyl cyclohexanone **2** and lactol **9** as a single enantiomer (Scheme 3).[17]

In conclusion, the synthesis of a new chiral spiro skeleton has been achieved. The efficient application of this



Scheme 3. *Reagents and conditions*: (i) $LiAlH_4$, THF, reflux, 3 h, 65%; (ii) $Pb(OAc)_4$, benzene, 0°C, 30 min, 64%.

chiral auxiliary to a highly versatile Diels–Alder reaction has been demonstrated. We are continuing to explore the synthetic utility of this novel chiral auxiliary for a variety of optically active compounds.

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12. Spectral data: **5**: Yield: 95%, mp: 97°C $[\alpha]_D^{25}$: +74.9 (*c* 10, $CHCl_3$), IR (neat), cm^{-1}: 2910, 2860, 1735, 1690, 1625, 1470, 1385, 1330, 1310. ^1H NMR ($CDCl_3$, 200 MHz): 1.45–1.65 (m, 1H), 1.68–1.80 (m, 2H), 1.85–2.10 (m, 4H), 2.12–2.22 (dd, $J=16$, 4 Hz, 1H), 3.10–3.20 (dd, $J=16$, 4 Hz, 1H), 6.20–6.27 (d, $J=16$ Hz, 1H), 6.35–6.45 (d, $J=16$ Hz, 1H), 7.05–7.15 (m, 2H), 7.17–7.29 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 196.31, 160.57, 139.46, 137.20, 134.39, 128.96, 128.79, 127.73, 91.28, 51.46, 35.80, 26.82, 25.51, 20.02. MS *m*/*z*: 256 (M^+, 14%), 212, 165, 139, 131, 126, 117, 104, 91, 82. Anal. calcd for $C_{16}H_{16}O_3$ (256.29): C, 74.98; H, 6.29. Found: C, 75.13; H, 6.25%.
13. (a) Single crystals were grown by slow evaporation of a solution in ethyl acetate/pet. ether. Colourless thin needles of approximate size 0.425×0.210×0.085 mm, were used for data collection on Bruker SMART APEX CCD (CCDC Ref. No. 197048) diffractometer using Mo Kα radiation. $C_{16}H_{16}O_3$; M.wt = 256.29. Crystals belong to monoclinic space group $P21/c$, a = 10.637 (1), $b=7.922$ (1), $c=15.781$ (2) Å, $\beta=97.200$ (2)°, $V=1319.4(3)$ Å^3, $Z=4$, $D_{calcd}=1.290$ mg m^{-3}, μ(Mo Kα) = 0.088 mm^{-1}, $T=293(2)$ K, 7552 reflections measured, 2994 unique [$I>2\sigma(I)$], *R* value 0.0593, $wR_2=0.1564$. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (SHELXTL)[13b] was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model; (b) Sheldrick, G. M., SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.
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15. Spectral data: **7a**: Yield: 90%; $[\alpha]_D^{25}$ +16.6 (*c* 11, $CHCl_3$); IR (neat), cm^{-1}: 1750, 1710, 1455, 1250. ^1H NMR (200 MHz) δ: 0.98–1.08 (m, 1H), 1.22–1.47 (m, 2H), 1.55–1.73 (m, 4H), 1.75–2.05 (m, 4H), 2.12–2.25 (m, 1H), 2.82–2.95 (dd, $J=16$, 4 Hz, 1H), 3.26–3.40 (m, 2H), 6.00–6.10 (m, 1H), 6.14–6.22 (m, 1H), 7.07–7.18 (m, 2H), 7.21–7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): 208.83, 169.81, 139.22, 136.48, 129.52, 128.82, 127.91, 91.51, 52.01, 48.90, 48.37, 42.27, 33.91, 26.76, 25.38, 19.78. MS *m*/*z* 322 (M^+, 5%), 256 (29), 212 (85), 165 (20), 148 (33), 139 (71), 130 (100), 120 (71), 91 (98). Anal. calcd for $C_{21}H_{22}O_3$ (322.39): C, 78.23; H, 6.88. Found: C, 78.31; H, 6.78%.
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17. Spectral data: **9**: Yield: 64%, $[\alpha]_D^{25}$: −23.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$), cm^{-1}: 3390, 2900, 2870, 1251, 1085, 1045, 995. ^1H NMR ($CDCl_3$, 200 MHz): 1.30–1.45 (m, 2H), 2.80–3.02 (m, 4H), 3.38–3.45 (dd, $J=8$, 4 Hz, 2H), 3.90–4.00 (m, 1H), 4.95 (s, 1H), 6.02–6.09 (m, 1H), 6.14–6.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 136.29, 135.51, 88.23, 65.06, 55.45, 46.91, 44.30, 44.20, 43.71. MS *m*/*z*: 152 (M^+, 2%), 135, 122, 105, 91, 66.