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Differentiation of Enantiotopic Carbonyl Groups by the Horner-Wadsworth-Emmons Reaction

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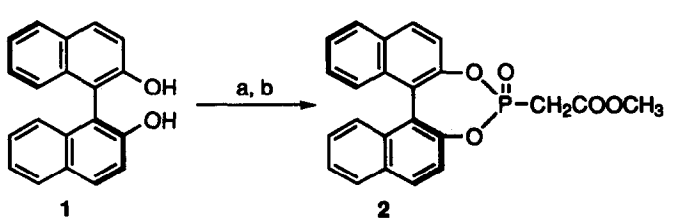
Abstract: A chiral phosphonoacetate **2** differentiates the enantiotopic carbonyl groups in an α-diketone **5** to afford the *Z*-olefin **6** in high yield and ee. The absolute stereochemistry of **6** was determined by X-ray analysis of **8** derived from **6**.

The Wittig reaction[1] is one of the most valuable synthetic transformations which introduces a new sp^2 carbon to the carbonyl group. Its importance increased with the development of several "Wittig-style" olefinations[2] as well as refinement of the reaction conditions. Consequently, the Wittig olefination can be performed chemo- and stereoselectively in a predictable manner. Since the Wittig reaction does not create a new sp^3 carbon center, efforts to develop an asymmetric version of the Wittig reaction have been focused mainly on alkylidenecycloalkanes with axial chirality.[3] If asymmetrization[4] of a dicarbonyl compound can be done by the Wittig reaction, an attractive method would become available for preparing optically active olefins with asymmetric carbon(s). Little is known about the differentiation of enantiotopic carbonyl groups,[5] though remarkable success has been reported with the asymmetrization in the transformations of various functional groups using biological systems such as microorganisms or isolated enzymes as well as under abiological conditions. Precedents for successful asymmetrization for dicarbonyl compounds include the reduction of cyclic diketones with baker's yeast[6] and intramolecular aldol condensations in the presence of an amino acid.[7] We wish to report asymmetrization of a *meso*-dicarbonyl compound by the Horner-Wadsworth-Emmons (HWE) reaction utilizing a chiral phosphonoacetate reagent bearing binaphthol as a chiral auxiliary to furnish β-alkoxycarbonyl-α,β-unsaturated ketone with nearly a 100% enantiomeric excess (ee).

Scheme I [a]

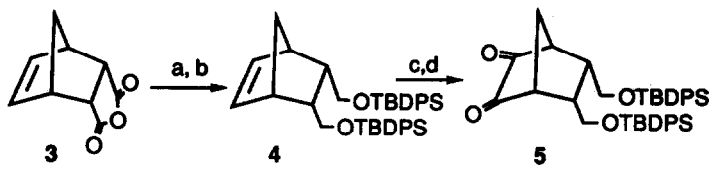


1 **2**

[a] (a) CH_3OPCl_2, $(iPr)_2NEt$, CH_2Cl_2; (b) $BrCH_2CO_2CH_3$

Cyclic phosphonate is known to react faster than its acyclic counterpart due to the pronounced release of ring strain in conversion from the tetrahedral to the pentacoordinate at phosphorus.[8] The chiral cyclic phosphonate reagent (*S*)-**2** having C_2 symmetry was prepared as an amorphous solid ($[\alpha]_D^{20}$ +307.9 ($CHCl_3$, c 1.4)), ^{31}P NMR d 28.45 ppm, M^+ 404.0827) in 67% overall yield from (*S*)-(-)-1,1'-bi-2-naphthol (**1**) *via* Arbusov reaction[9] of the phosphite intermediate without any loss of optical purity as shown in Scheme I.

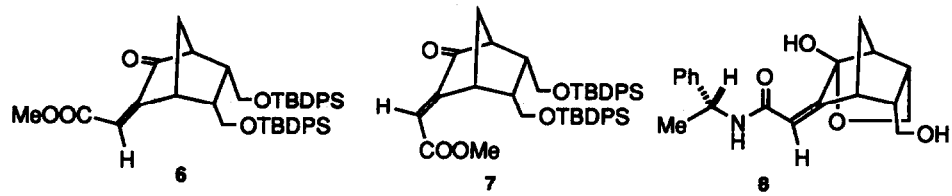
Scheme II [a]



TBDPS = *tert*-Butyldiphenylsilyl

[a](a) LAH, THF; (b) TBDPSiCl, imidazole, CH_2Cl_2,; (c) OsO_4, *N*-methylmorpholine *N*-oxide; (d) Swern oxidation.

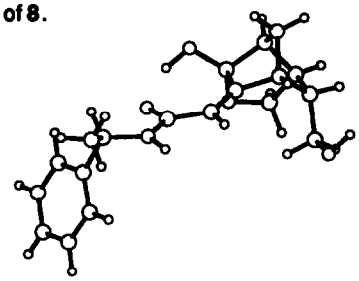
The synthesis of *meso* α-dicarbonyl compound **5** employed in the present study is shown in Scheme II. Commercially available *cis*-5-norbornene-endo-2,3-dicarboxylic anhydride (**3**) was converted into **4** in two steps in 45% overall yield. Dihydroxylation (96%) of **4** was followed by Swern oxidation to give **5** in 92% yield.



Treatment of **5** with the anion of **2** generated with NaH at -78 °C in THF for 1 h gave the *Z*-isomer **6** with 98% ee[10] (colorless oil, $[\alpha]_D^{20}$ +27.8 ($CHCl_3$, c 1.3)) in 95% yield concomitant with a small amount (2% yield) of the corresponding *E*-isomer **7** (~30% ee). It turned out that the *Z*-isomer **6** was isomerized to the *E*-isomer **7** without any loss of optical purity either on standing for 4 days without solvent at room temperature or by irradiation with uv light for 1 h in THF in 58% and 75% yield, respectively. Structures of the products **6** and **7** were deduced from comparison of the chemical shift of the olefinic protons in ^1H NMR (δ 5.92 for **6**, δ 6.40 for **7**) and confirmed by the NOE experiment (2.8%) between the olefinic proton and the methine at the bridge-head position. The absolute stereochemistry of **6** was unambiguously determined by a single X-ray diffraction analysis of the amide **8** (mp 191-192°C, $[\alpha]_D^{20}$ +24.0 ($CHCl_3$, c 0.68)), which was derived from **6** with (*R*)-(+)-α-methylbenzylamine followed by desilylation with *n*-Bu_4NF in THF. The crystal structure of **8** is shown in the Figure.[11]

Noteworthy features of this reaction include: i) almost exclusive formation of the *Z*-isomer, which is unusual for the ordinary HWE reaction,[12] and ii) attainment of nearly 100% transfer of chirality from the phosphinate **2** to the *Z*-isomer **6** in contrast to that for **7**, which was obtained in considerably lower ee. Though stepwise and reversible addition of the reagent to the carbonyl followed by decomposition of the resulting oxyanion via a transient four-membered intermediate has been generally accepted as a mechanism of the HWE reaction,[13] the details still remain to be clarified. We have no precise and definite rationale for the extremely high ee of the product **6** at the moment. It is clear, however, that both the geometry of the double bond and the absolute stereochemistry are determined by a combination of the initial *exo* attack of the reagent and the relative stability of the intermediate oxyanion or phosphetane. The high *Z*-selectivity in the HWE reaction must be attributed to an increase in the rate of elimination relative to adduct equilibration.[14]

Figure. Crystal Structure of **8**.



In conclusion, we have demonstrated, for the first time, asymmetrization of an α-dicarbonyl compound by a Wittig-type reaction. The chiral cyclic phosphonoacetate **2** was very effective for enantio group differentiation of *meso* α-diketone **5** to give *Z*-olefin **6**, in which complete transfer of chirality from the binaphthol moiety to the product was realized. Since the HWE reaction proceeds under particularly mild reaction conditions, the present approach offers a simple and efficient methodology with versatile adaptability for the enantioselective construction of the α,β-unsaturated carbonyl system for the synthesis of optically active natural and unnatural compounds.

Further studies are underway to clarify the mechanism for high stereoselectivity both in relative and absolute senses and to extend the scope of this reaction.

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(10) Determined by HPLC analysis on Bakerbond DNBPG chiral column.

(11) Compound **8** crystallized as orthorhombic, space group $P2_1$ with a = 10.473 (2), b = 24.124 (2), c 6.708 (1) Å, V = 1694.8 Å^3, Z = 4, Dx = 1.291 gcm^{-3}. The structure was refined to R = 0.0566, Rw = 0.0387 and S = 1.55. Atomic parameters and the F_O-F_C table have been deposited with the Cambridge Crystallographic Data Centre.

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