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Formation of Non-racemic *E*- and *Z*-Olefins Based on Discrimination of Enantiotopic Carbonyl Groups in α-Diketones by a Chiral Phosphonate Reagent

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Abstract: A chiral HWE reagent reacted with an alternative carbonyl group of *meso*-α-diketones of bicyclo[2.2.1] system to give non-racemic (*Z*)- and (*E*)-olefins, respectively.

Asymmetric desymmetrization[1] of *meso*-compounds involving carbon-carbon bond formation is a versatile method for the production of chiral non-racemic organic molecules.[2] Recently, we reported asymmetric Horner-Wadsworth-Emmons (HWE) olefination[3] by utilizing a chiral phosphonate reagent (*S*)-**1**, and demonstrated that the reagent differentiated the enantiotopic carbonyl groups in *meso*-α-diketone **2** to give a (+)-(*Z*)-enone **3** in almost optically pure form concomitant with a trace amount of a (+)-(*E*)-isomer **4**, the enantiomeric excess (ee) of which was considerably low (Scheme 1).[4] The sense of absolute stereochemistry of both the (*Z*)- and (*E*)-isomers **3** and **4** was proven to be the same by the photochemical conversion of **3** into **4** without loss of optical purity. However, in our attempt to provide a rationale for such a high ee of **3**, an inexplicable aspect of the absolute stereochemistry of the minor product **4** was disclosed. This paper describes findings which support that the sense of absolute stereochemistry of the (*Z*)-isomer is inherently opposite to that of the (*E*)-isomer, and thus the low ee of **4** is due to the conversion of **3** into **4** under the reaction conditions and/or during the work-up process.

Scheme 1

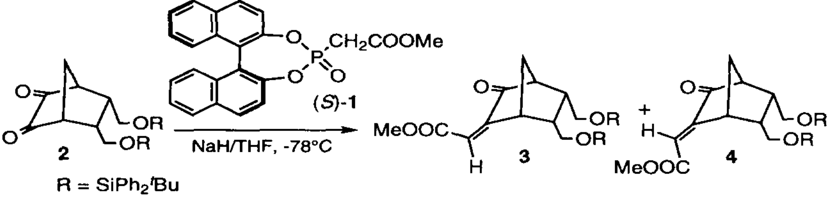
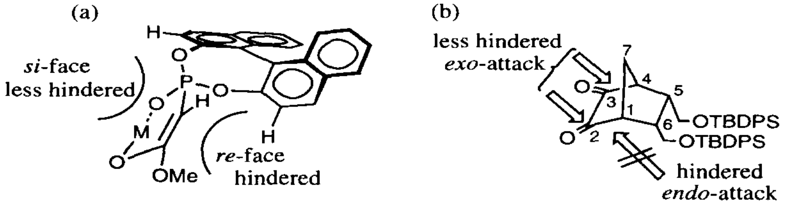


Figure 1. Schematic presentation of the steric environment for (a) the anion of HWE reagent (*S*)-**1** and (b) the substrate **2**.



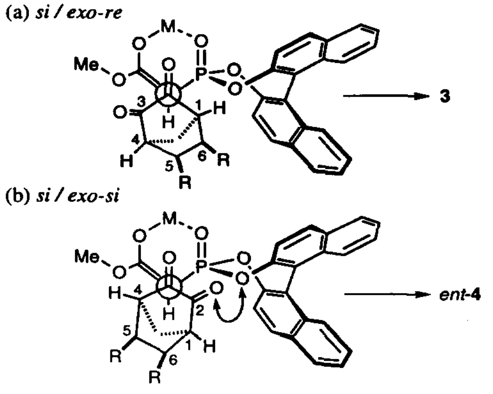
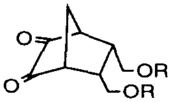


Figure 2. Possible approaches of the anion of the HWE reagent (*S*)-**1** to **2**.

It is generally accepted that the addition step is rate-determining in the HWE reaction, when the (*Z*)-isomer is the major product.[3b,5] Since the reaction of (*S*)-**1** with **2** gave the (*Z*)-isomer **3** predominantly, energetically favorable approach of the reagent (*S*)-**1** to the substrate **2** should govern the stereochemistries of the products. It is also accepted that the anion derived from the phosphoryl-stabilized HWE reagent exists in a chelated form as shown in Figure 1a.[3a] Since the *re*-face of the planar nucleophilic carbon derived from (*S*)-**1** is sterically hindered due to the hydrogen atom at C-3 of the naphthyl ring, an electrophile should approach from the *si*-face of the reagent. Figure 1b illustrates the approach of the anion of (*S*)-**1** to the *meso*-diketone **2**, in which *endo*-attack is severely impeded due to the substituents at C-5 and C-6. Note that the *exo*-faces of C-2 and C-3 carbonyls are the *re*- and the *si*-face, respectively. Thus, only two possible combinations of the anion and the substrate **2** can be considered as a transition state (Figure 2a and b). The former involving the *si/exo-re* combination does not have the severe steric and electronic interactions such as exist in the latter combination. Thus, the (*Z*)-isomer was obtained as a major product. The (*E*)-isomer obtained from the latter combination should be not **4** but *ent*-**4**. The conclusion drawn from this consid-



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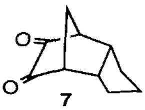
6 : R = Bn



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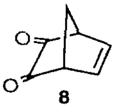

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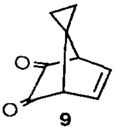

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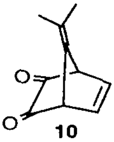

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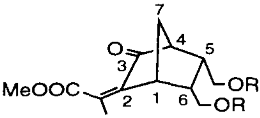

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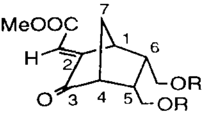

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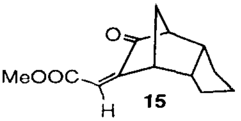

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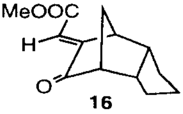

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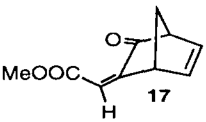

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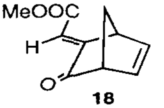

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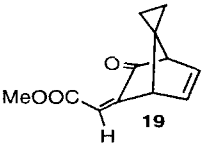

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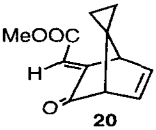

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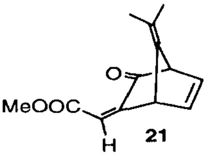

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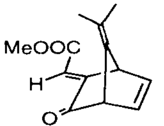

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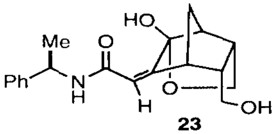

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eration is that a different carbonyl group is selected for the production of the (*Z*)- and the (*E*)-isomer, respectively, so that the sense of chirality of the (*Z*)-product is opposite to that of the (*E*)-product.

We studied the asymmetric HWE reaction of (*S*)-**1** with compounds **5**-**10**[6,7] to obtain the substantiative evidence for the above conclusion. Results are summarized in Table 1. The observed *Z*/*E* ratio[8] varied with the structure of α-diketones. The (*Z*)-isomers were formed in preference to (*E*)-isomers for **5**-**7** having *endo*-substituents at C-5 and C-6 and *vice versa* for **8**-**10** having an olefinic linkage between C-5 and C-6. A higher degree of asymmetric induction was observed with (*Z*)-adducts in every case.

Table 1. The Asymmetric HWE Reaction of **5** - **10** with (*S*)-**1**.

α-diketone	product						
	(*Z*)-isomer	yield, %[a]	% ee	(*E*)-isomer	yield, %[a]	% ee	*Z*/*E* ratio
5	**11**	58	90	**12**	23	23[b]	72 : 28
6	**13**	68	89	**14**	23	8[b]	75 : 25
7	**15**	57	93	**16**	15	<1[b]	79 : 21
8	**17**	25	97	**18**	58	79	30 : 70
9	**19**	35	97	**20**	62	45	36 : 64
10	**21**	30	99	**22**	53	28	36 : 64

[a]Isolated yield. [b]Varied within ±10%.

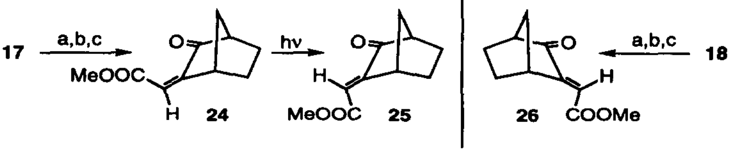
Table 2. Selected CD Spectral Data of Adducts and Related Compounds.[a]

compound	λ_{max} ([θ])		
11	290 (-700)	241 (5,800)	205 (-15,100)
ent-**12**	293 (-1,000)	244 (33,400)	206 (-21,300)
17	353 (-5,300)	265 (17,900)	230 (-8,800)
18	361 (6,400)	262 (-38,200)	231 (53,300)
19	353 (-5,600)	271 (14,800)	238 (-23,300)
20	345 (2,600)	265 (-13,800)	238 (37,300)
24	266 (-1,900)	230 (14,400)	206 (-11,900)
26	278 (2,100)	237 (-30,000)	206 (24,800)

[a]Measured in MeOH at 24 °C.

CD data shown in Table 2 indicate that the absolute configurations at C-1 and C-4 of (*Z*)-adducts are opposite to those of the (*E*)-series. The (*Z*)-adduct **11** was converted into the known compound **23**[4] by the reaction with (*R*)-1-phenylethylamine followed by the hydrolysis. Photoisomerization of **11** afforded *ent*-**12** to confirm that the sense of absolute stereochemistry of (*Z*)-isomer **11** is opposite to that of *E*-isomer **12**. Other (*Z*)-isomers **13** and **15** were readily converted to the corresponding (*E*)-isomers on

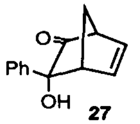
Scheme 2[a]



[a]Reagents: (a) $HOCH_2CH_2OH$/TsOH; (b) KOOCN=NCOOK/AcOH/CH_2Cl_2; (c) H_3O^+

standing at room temperature or by the irradiation of uv light, which might be the reason why the low and inconstant ee values were observed for (*E*)-products **12**, **14**, and **16**. On the other hand, **17**, **19**, and **21** bearing the sp^2-carbons at C-5 and C-6 resisted the photoisomerization. Thus, ketalization of **17** followed by the reduction of the double bond across C-5 and C-6 with diimide gave **24** after deprotection. Isomerization of **24** took place easily by the irradiation with a Xe lamp to afford the corresponding (*E*)-isomer **25**, which turned out to be enantiomeric to **26** derived from **18** by a sequence of reactions similar to that for **17** (Scheme 2).

These findings strongly support our mechanistic picture proposed in Figure 2, in which the reagent (*S*)-**1** differentiates the enantiotopic carbonyl groups of α-diketones in the bicyclo[2.2.1] system to give the (*Z*)- and the (*E*)-isomer, respectively. An intriguing feature of the mechanism in Figure 2 is that the HWE reagent approaches a carbonyl group from the *exo*-face exclusively even for **8** - **10**, although the *endo*-face seems to be less hindered. The exclusive *exo*-approach of a nucleophile was supported experimentally. Thus, the reaction of **8** with phenylmagnesium bromide gave **27**^{9} in 87% yield. Theoretical calculations are currently underway to clarify the face selectivity of a nucleophilic attack to **8**.



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References and Notes

(1) For the terminology of desymmetrization, see Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566.

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(6) Compounds **5** - **7** were prepared in a similar way to that reported for **2**.[4] Diketones **8** - **10** were synthesized according to the reported methods.[7]

(7) (a) Scharf, H.-D.; Küsters, W. *Chem. Ber.* **1972**, *105*, 564. (b) Blankespoor, R. L.; Gollehon, D. J. *J. Org. Chem.* **1977**, *42*, 63.

(8) Easily determined by the ^{1}H NMR chemical shifts of the olefinic protons.

(9) Relative stereochemistry was determined by COSY and NOESY spectra.

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