Asymmetric Michael Addition Reactions of Chiral Prop-2-enyl- and But-2-enylphosphonate Anions with Cyclic Enones

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Reactions of anions derived from chiral allyl- and crotylphosphonates with α,β-unsaturated cyclic ketones took place at the γ-position of the reagents and led to diastereomerically enriched products of conjugate addition, suggesting efficient enantiotopic face discrimination caused by remote asymmetric induction. Using mixtures of crotylphosphonates with different *E*/*Z* ratios, we found that the *E*/*Z* stereochemistry of the reagent was highly translated into the products. A tandem vicinal dialkylation based on Michael addition–enolate methylation was carried out to give the *trans* α,β-dialkylated product with high selectivity. Oxidative cleavage of the Michael adducts resulted in the formation of the optically active δ-keto aldehyde corresponding to the formal conjugate addition of an acetaldehyde or a propionaldehyde anion equivalent to α,β-unsaturated carbonyl compounds.

Introduction

Conjugate additions were first reported in 1883.[1,2] Among these, the 1,4-addition involving a carbon nucleophile, the so-called Michael addition, is one of the most valuable and fundamental carbon–carbon bond formations in synthetic organic transformations.[2,3] Crucial steps in natural product synthesis often involve this type of reactions.[4] Asymmetric Michael additions[5] are of particular interest, and a variety of devices have been reported to achieve this transformation, including catalytic methods with a combination of organometallics and chiral ligands,[6] chiral media,[7] and enzymes.[8] Nevertheless, a stoichiometric approach using chiral Michael donors, such as organometallics,[9] enamines,[10] imines,[11] β-keto esters,[12] sulfoxides,[13,14] and amines,[15] as well as chiral Michael acceptors,[16] is still important to achieve a high degree of asymmetric induction and accurate stereochemical prediction. Thus, a heteroatom-stabilized allyl anion is an important subset of this field, and recent advances have focused on the use of chiral, heteroatomic prosthetic groups to control diastereoselectivity. Compared with asymmetric conjugate additions with a sulfoxide-stabilized carbanion,[14] relatively few examples are known, and most involve phosphorus-stabilized allylic anions.[17] Among the limited examples, Hua and coworkers reported diastereoselective conjugate addition with an allylic chiral phosphonyl anion.[18] Chiral allylic phosphine oxides have been used for the same type of reactions and were successfully applied to the asymmetric construction of vitamin D-related compounds by

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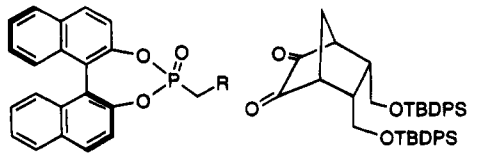
Haynes and co-workers.[14,19] Recently, Hanessian and co-workers reported successful conjugate additions using chiral allyl- and crotylphosphonyl anions, which were useful for creating vicinally substituted carbon centers.[20]



(*S*)-**1** ; R = CO_2Me **3**

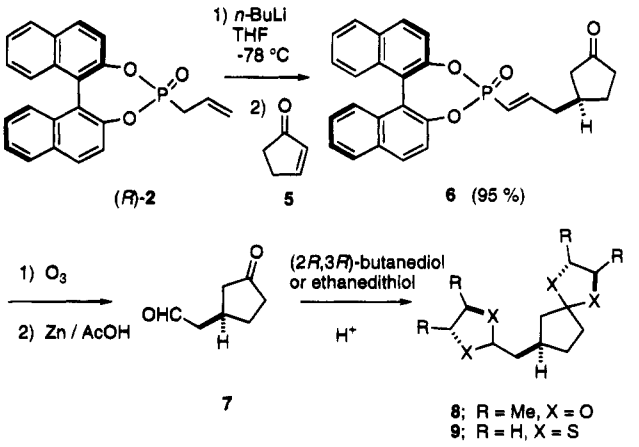
(*S*)-**2** ; R = $CH{=}CH_2$

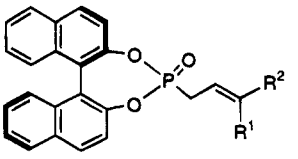
We recently reported that the anion of the chiral phosphonate (*S*)-**1**, which possesses axially chiral 1,1′-binaphthalene-2,2′-diol, exhibited an extremely high degree of differentiation for the enantiotopic carbonyls of the *meso* diketone **3** to yield enantiomerically pure enones in a Horner–Wadsworth–Emmons (H.W.E.)-type reaction.[21] In addition, the anion from a similar type of chiral reagent (*S*)-**2**, which has an allyl group in place of a (methoxycarbonyl)methylene group, showed an ambident reactivity in the reaction with **3**, yielding the γ-alkylated phosphonate together with the Wittig-type olefinic adducts caused by reaction at the α-position of the reagent.[22] The formation of the γ-alkylated phosphonate suggests the possibility that this type of chiral reagent can be applied to an asymmetric Michael addition reaction, if α,β-unsaturated carbonyls are used as substrates. Since the conjugate addition of lithiated allylic sulfoxides or phosphine oxides proceeds quite rapidly in the absence of special additives,[19] the use of a phosphonate-stabilized carbanion seems especially attractive. Furthermore, it would also be interesting to examine whether the attack of the nucleophile occurs at the Cα (C1) or Cγ (C3) position in the allylic system. We report here the highly diastereoselective asymmetric 1,4-conjugate addition to α,β-unsaturated cyclic ketones using anions of chiral allyl and crotyl binaphthylphosphonates, both enantiomers of which are readily available in enantiomerically pure form. To the best of our knowledge, this is the first example of chiral allyl- and crotylphosphonate reagents being used in an asymmetric conjugate addition reaction.

Results and Discussion

Preparation of Chiral Michael Donors, Allyl- and Crotylphosphonates. In addition to the expected and efficient asymmetric induction, the use of optically active C_2-symmetrical binaphthyl derivatives[23] as a chiral inducer is advantageous in that no tedious separation of the diastereomers is necessary due to equivalence of the corresponding substituent on each naphthalene ring. Thus, preparation of the allyl- and crotylphosphonate reagents (*R*)-**2** and -**4** with (*R*)-1,1′-binaphthalene-2,2′-diol as a chiral auxiliary was rather straightforward. Dichloro allylphosphonate[24] was condensed with (*R*)-1,1′-binaphthalene-2,2′-diol to give (*R*)-**2** in high yield. Crotylphosphonate (*R*)-**4** was similarly prepared by reaction with dichloro crotylphosphonate,[25] which was obtained by the Arbuzov reaction of trimethyl phosphite with crotyl bromide followed by treatment with PCl_5.[26,27] No racemization occurred during these transformations, and the optical purity of (*R*)-**2** and (*R*)-**4** was verified by HPLC analysis on a chiral column.[28]

Scheme 1





(*R*)-**2** ; $R^1 = R^2 = H$

E-(*R*)-**4** ; $R^1 = H$, $R^2 = Me$

Z-(*R*)-**4** ; $R^1 = Me$, $R^2 = H$

Michael Addition Reaction of the Anion of (*R*)-2 with 2-Cyclopentenone (5). Using *n*-BuLi as a base, we first examined the Michael addition of the anion of (*R*)-**2** with 2-cyclopentenone (**5**). The reaction proceeded smoothly at −78 °C in THF for 15 min to give the γ-adduct **6** in 95% isolated yield with a considerably high degree of diastereoselectivity (Scheme 1). However, despite intensive NMR and HPLC analyses, the exact value of the diastereoselectivity could not be determined at this stage. Consequently, we relied on Wynberg's method.[29] Adduct **6** was first converted to the δ-keto aldehyde **7** by ozonolysis and successive reduction. The δ-keto aldehyde **7** was then effectively acetalized with (*R*,*R*)-2,3-butanediol to give a diastereomixture of bisdioxolane derivatives **8** of the corresponding δ-keto aldehyde, in which separated signals due to the two diastereomers were observed. Examination of the corresponding signals in the ^{13}C NMR spectrum made it possible to determine the ratio of diastereomers of

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Table 1. Michael Addition of the Lithiated (*R*)-2 with 2-Cyclopentenone (5) in Different Solvents[a]

entry	solvent	yield[b] (%)	% de[c]	recovered **2**[b] (%)
1	THF	95	91	
2	THF–HMPA	98	92	
3	THF–TMEDA	97	88	
4	DME	93	90	
5	Et_2O	36	58	31
6	toluene	30	70	27
7	toluene–HMPA	40	79	13

[a] Reactions were carried out at −78 °C for 15 min with *n*-BuLi as a base. [b] Isolated yield. [c] The ratio of diastereomers was determined by comparison of integration of signals in the ^{13}C NMR spectrum of **8**.

Table 2. Michael Addition of the Anion of (*R*)-2 Generated with Different Bases[a]

entry	base	yield[b] (%)	% de[c]	recovered **2**[b] (%)
1	LDA	98	91	
2	LHMDS	98	92	
3	$NaCH_2S(O)CH_3$	51	88	
4	KHMDS	67	77	
5	KDA	36	87	19

[a] Reactions were carried out in THF at −78 °C for 15 min using 2-cyclopentenone (**5**) as a Michael acceptor. [b] Isolated yield. [c] The ratio of diastereomers was determined by comparison of the integration of signals in the ^{13}C NMR spectrum of **8**.

diacetals and to deduce the diastereoselectivity of 91% in the Michael addition reaction. The same value of selectivity was obtained by HPLC analysis on the chiral column of the bisdithioacetals **9**, which were prepared from **7**. The absolute configurational identity of the adducts **6** was established by a comparison of the specific rotation of the δ-keto aldehyde **7** with the reported value[18a,20] and led to the conclusion that the configuration at β to the carbonyl in the major adduct **6** is *S*.

To establish optimal reaction conditions, the Michael addition of the anion of (*R*)-**2** with 2-cyclopentenone (**5**) was carried out under various conditions (Table 1). The addition of HMPA or TMEDA (each 1 equiv) caused a slight increase in chemical yield, but had little effect on either selectivity or regiochemistry. DME was found to be an equally effective solvent, whereas the use of a less polar solvent with poorer ligating ability, such as toluene or Et_2O, led to a decrease in both chemical yield and diastereoselectivity.

The reactions of the anion generated with bases other than *n*-BuLi were investigated next using THF as a solvent, and these results are summarized in Table 2. As shown, lithium was the best countercation in terms of chemical yield and diastereoselectivity, probably due to stabilization of the transition state through tight chelate formation by lithium (*vide infra*).

Mechanistic Considerations. The presence of the bulky binaphthyl group attached to the phosphorus renders the carbanions somewhat more hindered than those of sulfoxides or sulfides and may be why alkylation at C1 (Cα) is less favored. It is likely that the phosphorus carbanion is structurally similar to that of sulfoxides, which are assumed to be planar.[30] Experimentally, ^{13}C NMR and ^{1}H NMR data of lithiated benzylphosphonates have been interpreted in terms of a planar carbanion.[31] Diastereoselection arises as a consequence of enantiofacial π-face selection by the lithiated phosphonate whose

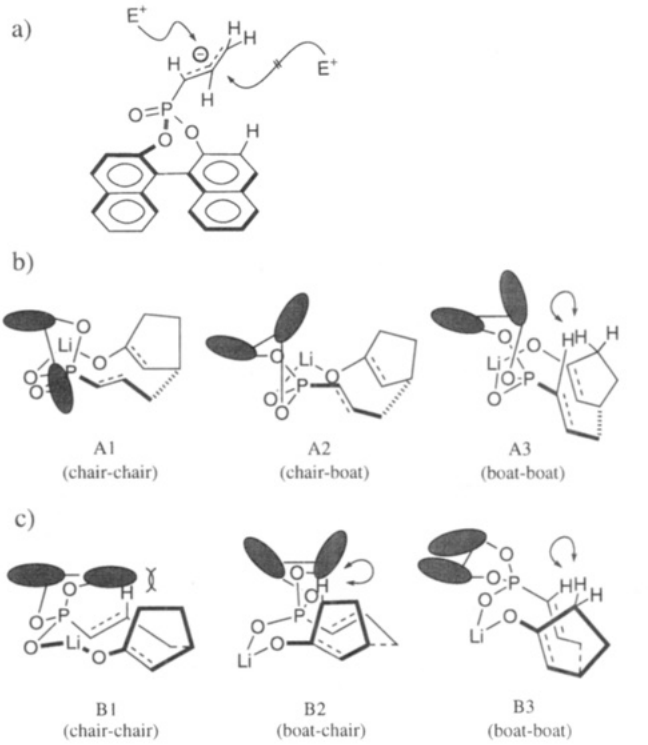

Figure 1. Approach of the electrophile to the anion of (*R*)-**2** (a) and six possible decalyl-like TSs of the reaction of the lithiated (*R*)-**2** with 2-cyclopentenone (**5**). Approach to *re*-face (b) and to *si*-face of 2-cyclopentenone (**5**) (c).

allyl system remains parallel to the P=O bond.[32] The high diastereoselectivity obtained with (*R*)-**2** is best understood by considering the favorable transition state (TS) for the Michael addition reaction. The axially dissymmetric binaphthyl group dictates that the orientation of the approach to the electrophile will be from the less hindered side; e.g., the *re*-face at the β-carbon of the *trans*-W (*s-trans*) conformation of the *E*-allyl anion (Figure 1a), if (*R*)-**2** reagent is employed. The planar lithiated phosphonate lies over one face of the enone such that it adopts an endo orientation with respect to the enone. Assuming that the allyl anion is oriented parallel to the P=O bond as above, the addition is likely to proceed through either TSs A1–A3 or B1–B3 obtained from the approach to the *re*-face (A) or *si*-face (B) of the enone, respectively, depending upon whether the conformation around the P–C1 bond is *s-trans* or *s-cis*. In these 10-membered cyclic models, both TSs A3 and B3 involve a boat–boat conformation and suffer from a severe transannular repulsive interaction between the C1-hydrogen and one of the δ-methylenes. Therefore, they are both unlikely. TS A1 corresponds to a *trans*-decalinoid TS, which is very similar to that previously proposed for reaction with lithiated *E*-allyl anions of allylic sulfoxides and phosphine oxides.[14] We propose that the *re*-face selectivity with (*R*)-reagent **2** is the result of a preferable TS A1 or A2, in which the cation-chelated reagent is best accommodated within the cleft of the acceptor. On the other hand, TSs B1 and B2 seem to lie at a higher energy state because of steric repulsive interaction between the C-2 hydrogen of the allylic system and the naphthalene ring or between a hydrogen of the δ-methylene of the substrate and one of the oxygen of the binaphthol. Thus, both the regiochemical and

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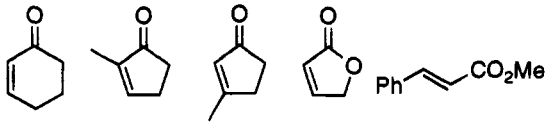
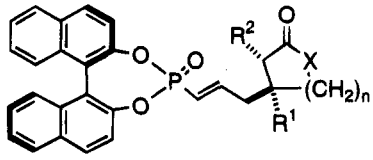
Table 3. Michael Addition of the Litiated (*R*)-2 with α,β-Unsaturated Carbonyl Compounds[a]

Electrophiles:

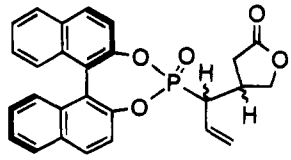


10 **11** **12** **13** **14**

Adducts:



15; n = 2, X = CH_2, $R^1 = R^2 = H$
16a; n = 1, X = CH_2, $R^1 = H$, $R^2 = Me$
17; n = 1, X = CH_2, $R^1 = Me$, $R^2 = H$
18; n = 1, X = O, $R^1 = R^2 = H$



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entry	electrophile	adduct	yield[b] (%)	% de[c]
1	**10**	**15**	43	91
2	**11**	**16**	80	*vide infra*[d]
3	**12**	**17**	17	83
4	**13**	**18, 19**	7, 50	*e, e*
5	**14**		0	

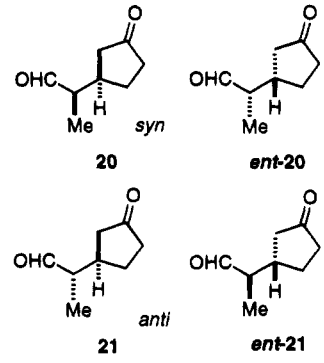
[a] Reactions were carried out in THF at −78 °C for 15 min. [b] Isolated yield. [c] De's were determined from the ^{13}C NMR spectra after derivatization to bisdioxolane derivatives. [d] See text and Table 5. [e] Not determined.

stereochemical outcomes of the reactions can be explained in terms of a 10-membered "*trans*-decalyl" TS involving a planar lithiated reagent.

Michael Addition Reaction of the Anion of (*R*)-2 with Other α,β-Unsaturated Carbonyl Compounds. Using the established reaction conditions discussed above, i.e., in THF at −78 °C for 15 min with *n*-BuLi as a base, the asymmetric Michael addition reactions of (*R*)-**2** were examined with a variety of α,β-unsaturated carbonyl compounds, **10**−**14**. The results are summarized in Table 3. Generally, the reaction using substrates with a cyclic enone structure proceeded rapidly to give the corresponding adducts with satisfactory diastereoselectivity of 83−91%. Substitution at the β-position to the carbonyl in the Michael acceptor retarded the addition, but had little effect on selectivity. In contrast to the results with cyclic enones, poor results were obtained with less reactive electrophiles, **13** and **14**. Thus, methyl cinnamate **14**, an acyclic conjugate ester, formed no 1,4-addition products, while with cyclic conjugate ester **13** regio- and stereoselection were lost, resulting in the α-adduct **19** (50%, stereochemistry was not established) rather than the expected γ-adduct **18** (7%). The diastereoselectivities of adducts **15-17** were again deduced by considering ^{13}C NMR spectra of bisdioxolane derivatives, as described for **6**. The absolute configuration of the adducts was determined by comparing the specific rotation of the keto-aldehydes with reported values.[20]

Asymmetric Michael Addition Reaction Using Different Mixtures of the *E*/*Z* Stereoisomer of (*R*)-Crotylphosphonates 4 with 2-Cyclopentenone (5). Since commercially available crotyl bromide is a mixture of *E*/*Z*-stereoisomers, the reaction using the crotylphosphonate (*R*)-**4** (*E*/*Z* ratio; 82 /18) prepared from crotyl bromide might provide a mixture of four diastereomers due to generation of vicinally aligned asymmetric carbon centers, arising from *E*/*Z* stereochemistry of the reagent. If the *E* and *Z* carbanions react in a highly diastereoselective fashion with a cyclic enone to give, respectively, *syn* and *anti* vinylic phosphonate, a clear value of these reactions would be the virtually quantitative translation of the *E*/*Z* geometry into product. Consequently, we investigated the effect of the stereochemical purity of the starting crotylphosphonates on the stereoselectivity of the reaction using crotylphosphonate (*R*)-**4** with different *E*/*Z* ratios.

Separation of each isomer of (*R*)-**4** was carried out by preparative HPLC[33] to give (*E*)-(*R*)-**4** (>99% purity) together with a (*Z*)-(*R*)-**4** enriched mixture (*E*/*Z* ratio; 38:62). The Michael addition of the lithiated carbanion from (*E*)-(*R*)-**4** with cyclopentenone **5** gave a mixture of diastereomers in a ratio of 88:12 (*syn*/*anti*). The diastereomer ratio was determined by taking ^1H NMR of the derived δ-keto aldehydes. On the other hand, the diastereomeric ratio (*syn*/*anti*) of the Michael adducts from lithiated *Z*-enriched (*R*)-**4** was 24:76.



20 ***ent*-20** **21** ***ent*-21**

These results suggest a high diastereoselectivity in Michael addition reactions with lithiated crotyl anions. Haynes and co-workers reported the translation of the *E*/*Z* geometry of the allyl sulfoxide system bearing an alkyl group at C3 (Cγ), where diastereoselection was essentially complete within the limits of experimental error. It has also been reported that the reaction proceeds in such a way that *E*-allylic systems deliver *syn* products and *Z*-allylic systems deliver *anti* products. Enantiofacial selection at the β-position of cyclopentenone was deduced from the HPLC analysis on the chiral column of UV-active (254 nm) bis-dithioacetal derivatives **22**−***ent*-23** derived from the δ-keto aldehydes. Considering the results obtained from the reaction with racemic reagent **4**, the products using lithiated (*E*)-(*R*)-**4** can be considered *syn*-isomers, **20** and ***ent*-20**, and the two major diastereomers from the anion of *Z*-enriched (*R*)-**4** are

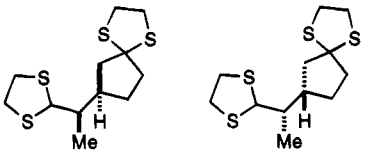
(33) The separation of the *E*/*Z* isomers by preparative HPLC was performed on a CHIRAL PAK AD column (20 × 250 mm; Daicel Chemical Industries, LTD) with 10% 2-PrOH in hexane at a flow rate of 5 mL/min.

Table 4. Michael Addition of the Anion of (*R*)-Crotylphosphonates 4 with 2-Cyclopentenone (5)

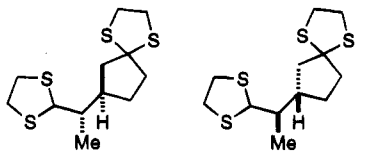
entry	crotylphosphonate 4 (*E* / *Z*)	*syn*/*anti* ratio[a] of δ-keto aldehydes **20** + *ent*-**20**:**21** + *ent*-**21**	enantiomer ratio[b] of bis-dithioacetals **22**:*ent*-**22**:**23**:*ent*-**23**	facial selectivity β-position of enone **22** + **23**:*ent*-**22** + *ent*-**23**
1	*rac*, 82:18	79:21	42:40:9:9	51:49
2	(*R*), >99:<1	88:12		
3	(*R*), 83:17		81:6:11:2	92:8
4	(*R*), 82:18	79:21		
5	(*R*), 73:27		73:3:20:4	93:7
6	(*R*), 38:62	24:76		

[a] Determined by ^{1}H NMR of δ-keto aldehyde. [b] Determined by HPLC on a chiral column (Chiralpak AD).

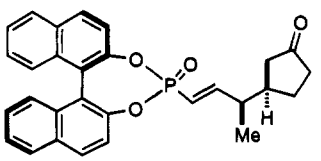
anti-isomers, **21** and *ent*-**21** (Table 4). The structure of **24**, a major diastereomer in the Michael addition with the anion of (*E*)-(*R*)-**4**, was elucidated by the transformation of **20** to the (*R*)-MTPA ester **25**, which has physical data completely identical to those previously reported.[20] According to the TS model, the configuration of the chiral auxiliary attached to phosphorus determines the face selectivity of the reaction of the lithiated carbanion with an enone. It is evident that the relative configuration at the allylic carbon atom in the products depends on the geometry of the starting allylic compound in the kinetically controlled reaction. Given the face selectivity of the reaction mentioned above (Figure 1b), the methyl group at C3 is pseudoequatorial for (*E*)-phosphonate and pseudoaxial for (*Z*)-phosphonate in the 10-membered TS. Therefore, the reaction proceeds in such a way that *E*-allylic systems deliver *syn* products and *Z*-allylic systems deliver *anti* products.



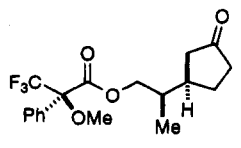
22 *ent*-**22**



23 *ent*-**23**



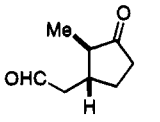
24



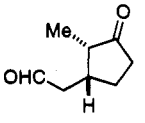
25

Tandem Michael Addition–Electrophilic Methylation of the Generated Enolate. The Michael addition reaction can be expanded to an efficient and stereoselective vicinal difunctionalization method, if the enolate anion, which is transiently produced by nucleophilic attack of the Michael donor at the position β to the carbonyl, can be trapped with an electrophile other than a proton. This procedure makes it feasible to create contiguous carbon centers at the same time, and newly introduced substituents are generally expected to be in a *trans* relationship. This strategy has received considerable attention as a synthetic tool. An intramolecular strategy is also often used to construct new ring systems.[34] It should be interesting to investigate the selectivity and the stereochemistry at the newly alkylated carbon centers in the asymmetric Michael addition reaction.

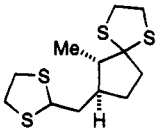
The tandem asymmetric Michael addition–alkylation starting from the lithiated anion of (*R*)-**2** and 2-cyclopentenone (**5**) was carried out to give product **16** in 56% yield using methyl iodide as a second electrophile. The stereochemistry of the major product was compared with that obtained from the Michael addition reaction with 2-methyl-2-cyclopentenone (**11**) (Table 3). The adduct **16** was similarly converted to a mixture of δ-keto aldehydes (Scheme 2), and the *trans*/*cis* ratio (**26** + *ent*-**26**:**27** + *ent*-**27**, 94:6) was determined by integrating the methyl signals in the ^{1}H NMR spectrum. The enantiomer ratio was evaluated by HPLC analysis of the derived bisdithioacetals **28**, *ent*-**28**, **29** and *ent*-**29**. The results are listed in Table 5. Although the product ratio was different between the two procedures, the major reaction product of the tandem Michael addition–alkylation sequence was identical to that obtained from the reaction with 2-methyl-2-cyclopentenone (**11**) (*vide supra*). The absolute configuration of these products was determined by comparison with reported values of specific rotation.[20]



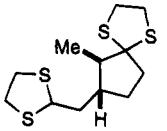
ent-**26**



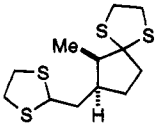
ent-**27**



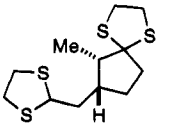
28



ent-**28**



29



ent-**29**

Thus, in both reactions, the *trans* isomer with an *S,S* configuration at positions α and β to the carbonyl, **16a**, was the predominant product. This indicates that the

(34) Hulce, M.; Chapdelaine, M. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.6.

Table 5. Comparison of the Tandem Michael Addition–Methylation with Michael Addition to 2-Methylcyclopentenone (11)

entry	reagent	enone	second electrophile	*trans*/*cis* ratio[a] of keto aldehydes **26** + *ent*-**26**:**27** + *ent*-**27**	ratio[b] of bisdithioacetals **28**:*ent*-**28**:**29**:*ent*-**29**	facial selectivity at β-position of enone **28** + **29**:ent-**28** + *ent*-**29**
1	(*rac*)-**2**	**11**	proton	2:1	42:43:8:7	50:50
2	(*R*)-**2**	**11**	proton	2:1	84:7:8.5:0.5	92.5:7.5
3	(*R*)-**2**	**5**	methyl iodide	15:1	88.5:4.5:6.5:0.5	95:5

[a] Determined by ^{1}H NMR of δ-keto aldehyde. [b] Determined by HPLC on a chiral column (Chiralpak OJ).

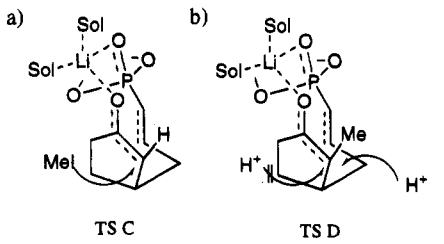
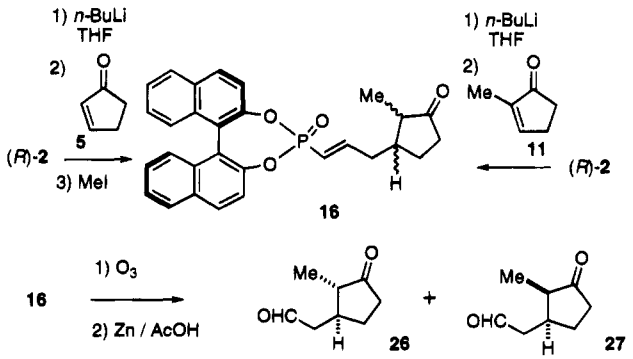


Figure 2. Proposed TSs of the coupling of the anions generated from the Michael addition reactions with methyl iodide (a) and proton (b). Binaphthyl moiety is omitted for simplification.

Scheme 2



direction of the approach of the electrophile to the generated enolate varies between protons and methyl iodide as second electrophiles. Although thermodynamically more stable *trans* products usually predominate, as predicted by both steric and product development control factors,[35] this is not always true. A complex combination of factors sometimes makes prediction difficult.[34] The stereochemistries of methylation and protonation of the enolate were well interpreted by the MM2 TS model in some cases.[36] Our results can be tentatively accounted for by considering product development control.[37] Assuming TS C (Figure 2), which follows TS A in Figure 1, it is clear that the favored approach of the electrophile is from the *si*-face, which leads to an *S,S*-product. On the other hand, if the added electrophile is a proton, which is less bulky than methyl iodide, the reverse approach occurs preferentially (TS D), since the same approach as in TS C might result in energetically unfavored movement of the built-in methyl group, i.e., retreat to a more crowded site.

Conclusion

The present study indicates the versatility of optically active phosphonate reagents with a C_2-symmetrical element. The chiral prop-2-enyl- and but-2-enyl phosphonates, which are easily prepared in optically pure forms, have been developed as useful tools for the asymmetric Michael addition reaction. Under conventional reaction conditions without the use of special additives, the lithiated phosphonate undergoes kinetically controlled conjugate addition to cyclic enones to give the vinylic phosphonate arising from reaction through C3 (Cγ) of the carbanion in good chemical yield and with high diastereoselectivity. Chelation of the lithium by the carbonyl oxygen may serve as a regiochemical "anchor" which causes the phosphorus oxygen to lie over the carbonyl group in such a way that the carbanion is constrained to react through C3. In this TS model, the binaphthyl chiral inducer has a significant effect on the stereochemical course of the reaction, and an effective remote optical induction was observed in this addition reaction. We also demonstrated that this asymmetric Michael reaction can be extended to the tandem vicinal dialkylation process with the option of trapping the produced enolates with methyl iodide to give optically active *trans* α,β-dialkylated cyclopentanone with satisfactory selectivity. Oxidative removal of the chiral auxiliary group gave δ-keto aldehydes in an optically enriched form. Although the related asymmetric transformations have been developed with optically active allylic sulfoxides, the difficulties associated with the preparation and stability of these reagents preclude their general use. In this regard, the present addition reaction offers a powerful method of stereoselective synthesis including asymmetric transformation, and the compounds prepared in this study can be used as versatile templates in the asymmetric synthesis of biologically active compounds, such as natural products.

Experimental Section

General Aspects. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 or 400 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard, and couplings are expressed in hertz. THF was distilled from sodium benzophenone, and dichloromethane was from calcium hydride. Unless otherwise noted, all reactions were run under an argon or nitrogen atmosphere. All extractive organic solutions were dried over anhydrous magnesium sulfate. Flash column chromatography was carried out with silica gel 60 spherical (150–325 mesh), and silica gel 60 F254 plates (Merck) were used for preparative TLC.

Allyl- and Crotylphosphonates, (*R*)-2 and (*R*)-4. Preparation of allyl phosphonate reagents (*R*)-**2** is typical. To a stirred solution of (*R*)-1,1′-binaphthalene-2,2′-diol (9.2 g, 32.13 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (10 mL, 71.75 mmol, 2.2 equiv) dropwise at 0 °C. After the mixture was stirred for 30 min at the same temperature, dichloro allylphosphonate (4.5 mL, 1.2 equiv) was added, and the mixture was stirred for 15 min at room temperature. The reaction mixture was poured into cold 5% HCl aqueous solution and extracted with EtOAc. The organic layer was successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and then evaporated to give a residue which was purified by flash

(35) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; p 3.
(36) (a) Yamada, H.; Shimizu, K.; Nisar, M.; Takahashi, T.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 2407. (b) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1989**, *30*, 4999.
(37) Takahashi, T.; Nisar, M.; Shimizu, K.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 5103.

column chromatography with EtOAc/hexane (1:1) to afford (*R*)-(−)-1,1′-binaphthyl allylphosphonate (**2**) in nearly quantitative yield. Racemic **2** and crotyl phosphonate (*rac*)- and (*R*)-**4** possessing different *E*/*Z* stereochemistries were similarly prepared in 94−99% yield. Dichloro crotylphosphonate was used for preparation of **4**.

2: mp 202.5−203.5 °C (from *n*-hexane and CH_2Cl_2); $[\alpha]^{20}_D$ −454.9 (c 1.16, $CHCl_3$, ~100% ee); ^1H NMR δ 2.83 (d, 1H, *J* = 7.4), 2.93 (d, 1H, *J* = 7.4), 5.36 (m, 2H), 5.93 (m, 1H), 7.27−7.63 (m, 8H), 7.94−8.07 (m, 4H); ^{13}C NMR δ 148.2, 148.0, 146.6, 146.4, 133.2, 133.0, 132.5, 132.2, 132.0, 131.8, 129.2, 129.1, 127.9, 127.5, 127.3, 126.5, 126.3, 126.2, 126.0, 122.5, 122.4, 122.3, 122.2, 121.7, 120.9, 120.8, 31.3, 28.7; ^{31}P NMR δ 37.19 (from 85% H_3PO_4); IR ($CHCl_3$) 1590, 1505, 1280 cm^{-1}; MS (*m*/*z*) 372 (M^+); HRMS *m*/*z* calcd for $C_{23}H_{17}O_3P$ (M^+) 372.0916, found 372.0922. Anal. Calcd for $C_{23}H_{17}O_3P$: C, 74.19; H, 4.60. Found: C, 74.02; H, 4.53.

***(R)-E*-4**: amorphous solid; $[\alpha]^{20}_D$ −404.6 (*c* 1.19, $CHCl_3$, *E*:*Z* = >99:<1 (~100% ee)); ^1H NMR δ 1.73 (t, 3H, *J* = 6.0), 2.80 (dd, 2H, *J* = 20.9, 7.0), 5.53 (m, 1H), 5.76 (m, 1H), 7.23−7.64 (m, 8H), 7.90−8.04 (m, 4H); ^{13}C NMR δ 147.6, 147.4, 145.9, 145.7, 132.6, 132.4, 132.2, 132.3, 131.7, 131.4, 131.2, 131.0, 128.5, 128.3, 127.1, 126.8, 126.7, 126.6, 125.7, 125.6, 121.7, 121.1, 121.0, 120.3, 120.2, 117.6, 117.4, 29.4, 26.7, 17.8; ^{31}P NMR δ 38.35 (from 85% H_3PO_4); IR ($CHCl_3$) 1590, 1280, 1230 cm^{-1}; MS *m*/*z* 386 (M^+); HRMS *m*/*z* calcd for $C_{24}H_{19}O_3P$ (M^+) 386.1072, found 386.1086. Anal. Calcd for $C_{24}H_{19}O_3P$: C, 74.61; H, 4.96. Found: C, 74.25; H, 4.84.

(R)-(Z)-enriched-4: amorphous solid; $[\alpha]^{20}_D$ −442.4 (c 1.43, $CHCl_3$, *E*:*Z* = 38:62 ~100% ee); ^1H NMR δ 1.68 (dt, 3H, *J* = 6.1, 1.8), 2.86 (dd, 2H, *J* = 22.0, 7.0), 5.53 (m, 1H), 5.76 (m, 1H), 7.23−7.64 (m, 8H), 7.90−8.04 (m, 4H).

General Procedure for Michael Addition with Anion of (*R*)-2. The Michael reaction of the anion of (*R*)-**2** with cyclopentenone **5** is typical. To a stirred solution of (*R*)-**2** (493 mg, 1.32 mmol, 1.3 equiv) in THF (15 mL) was added *n*-BuLi (860 μL, 1.54 M solution in hexane, 1.3 equiv dropwise) at −78 °C. After the mixture was stirred for 15 min at the same temperature, a solution of cyclopentenone **5** (850 μL, 1.19 M solution in THF) was added, and the mixture was stirred for 15 min at -78 °C. The reaction mixture was poured into cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue which was purified by flash column chromatography with EtOAc/hexane (4:1) to afford **6** (438 mg) in 95% yield.

6: amorphous solid; ^1H NMR δ 1.51 (m, 1H), 1.78 (m, 1H), 2.03−2.38 (m, 7H), 5.69 (dd, 1H, *J* = 24.0, 17.1), 5.81 (d, 1H, *J* = 17.1), 6.98 (ddt, 1H, *J* = 22.8, 17.2, 6.8), 7.25−7.61 (m, 8H), 7.92−8.05 (m, 4H); ^{13}C NMR δ 155.7, 155.6, 147.6, 147.4, 146.4, 146.2, 132.9, 132.8, 132.7, 132.2, 132.0, 131.8, 131.5, 129.0, 128.9, 127.6, 127.3, 127.2, 126.3, 126.2, 122.4, 122.1, 121.5, 120.8, 117.3, 113.6, 44.6, 39.9, 38.3, 35.7, 29.1; ^{31}P NMR δ 37.71 (from 85% H_3PO_4); IR (KBr) 1740, 1620, 1590, 1280, 1220 cm^{-1}; MS *m*/*z* 454 (M^+); HRMS *m*/*z* calcd for $C_{28}H_{23}O_4P$ (M^+) 454.1334, found 454.1353. Anal. Calcd for $C_{28}H_{23}O_4P$: C, 74.00; H, 5.10. Found: C, 73.89; H, 5.19.

15: amorphous solid; ^1H NMR δ 1.34 (m, 1H), 1.62 (m, 1H), 1.76−2.10 (m, 3H), 2.15−2.43 (m, 6H), 5.75 (dd, 1H, *J* = 24.1, 17.1), 6.93 (ddt, 1H, *J* = 22.6, 17.1, 7.2), 7.27−7.64 (m, 8H), 7.93−8.06 (m, 4H); ^{13}C NMR δ 154.9, 154.8, 147.2, 147.0, 146.0, 145.8, 132.5, 132.4, 131.9, 131.7, 131.4, 131.2, 128.6, 127.3, 127.1, 127.0, 126.8, 125.9, 125.8, 121.8, 121.7, 121.2, 120.6, 120.5, 117.4, 113.7, 47.3, 41.2, 41.0, 40.7, 37.5, 30.4, 24.6; IR (KBr) 1750, 1660, 1620, 1320, 1260 cm^{-1}; MS *m*/*z* 468 (M^+); HRMS *m*/*z* calcd for $C_{29}H_{25}O_4P$ (M^+) 468.1491, found 468.1525. Anal. Calcd for $C_{29}H_{25}O_4P \cdot 1/8H_2O$: C, 73.63; H, 5.43. Found: C, 73.30; H, 5.38.

16 (Inseparable mixture of *anti*- and *syn*-**16**): amorphous solid;

***anti*-16:** ^1H NMR δ 1.05 (d, 3H, *J* = 6.5), 1.43 (m, 1H), 1.61−2.46 (m, 6H), 2.59 (m, 1H), 5.82 (dd, 1H, *J* = 24.1, 17.1), 7.06 (ddt, 1H, *J* = 24.1, 17.1, 7.2), 7.28−7.65 (m, 8H), 7.96−8.09 (m, 4H); ^{13}C NMR δ 155.2, 155.0, 146.8, 146.6, 145.6, 145.4, 131.9, 131.8, 131.6, 131.3, 131.2, 131.0, 130.8, 128.6, 128.2, 127.9, 127.8, 127.7, 127.6, 127.0, 126.6, 126.5, 126.1, 125.9, 125.5, 125.4, 125.1, 121.5, 121.4, 120.7, 120.1, 116.5, 112.9, 48.9, 42.6, 38.4, 37.9, 36.3, 26.0, 11.7; ^{31}P NMR δ 26.95 (from 85% H_3PO_4); IR ($CHCl_3$) 1740, 1620, 1590, 1505, 1280 cm^{-1}; MS *m*/*z* 468 (M^+); HRMS *m*/*z* calcd for $C_{29}H_{25}O_4P$ (M^+) 468.1489, found 468.1503. Anal. Calcd for $C_{29}H_{25}O_4P$: C, 74.35; H, 5.38. Found: C, 74.05; H, 5.53.

***syn*-16:** ^1H NMR δ 0.97 (d, 3H, *J* = 7.0), 1.43 (m, 1H), 1.61−2.46 (m, 6H), 2.59 (m, 1H), 5.82 (dd, 1H, *J* = 24.1, 17.1), 7.06 (ddt, 1H, *J* = 24.1, 17.1, 7.2), 7.28−7.65 (m, 8H), 7.96−8.09 (m, 4H); ^{13}C NMR δ 155.8, 155.7, 146.8, 146.6, 145.6, 145.4, 131.9, 131.8, 131.6, 131.3, 131.2, 131.0, 130.8, 128.6, 128.2, 127.9, 127.8, 127.7, 127.6, 127.0, 126.6, 126.5, 126.1, 125.9, 125.5, 125.4, 125.1, 121.3, 121.2, 121.0, 120.4, 116.2, 112.5, 45.7, 37.8, 35.0, 33.9, 33.5, 24.4, 9.1.

17: amorphous solid; ^1H NMR δ 1.03 (s, 3H), 1.68−1.86 (m, 2H), 2.03 (s, 2H), 2.18−2.37 (m, 4H), 5.76 (dd, 1H, *J* = 24.3, 17.0), 7.01 (ddt, 1H, *J* = 24.3, 17.0, 7.4), 7.26−7.63 (m, 8H), 7.92−8.06 (m, 4H); ^{13}C NMR δ 153.8, 153.7, 147.1, 146.9, 145.9, 145.7, 132.5, 132.3, 131.8, 131.6, 131.3, 131.1, 128.5, 128.4, 127.2, 126.9, 126.8, 125.9, 125.7, 122.0, 121.9, 121.7, 121.6, 121.0, 120.4, 118.5, 114.8, 51.2, 46.1, 45.7, 39.3, 36.3, 34.4, 25.1; IR ($CHCl_3$) 1740, 1620, 1590, 1510, 1280, 1220 cm^{-1}; MS *m*/*z* 468 (M^+); HRMS *m*/*z* calcd for $C_{29}H_{25}O_4P$ (M^+) 468.1489, found 468.1483. Anal. Calcd for $C_{29}H_{25}O_4P \cdot 1/8H_2O$: C, 73.64; H, 5.43. Found: C, 73.35; H, 5.45.

18: amorphous solid; ^1H NMR δ 2.07−2.28 (m, 1H), 2.41 (brs, 2H), 2.51−2.77 (m, 2H), 3.94 (brs, 1H), 4.37 (brs, 1H), 5.80 (dd, 1H, *J* = 22.4, 17.5), 6.91 (m, 1H), 7.28−7.63 (m, 8H), 7.96−8.08 (m, 4H); ^{13}C NMR δ 176.3, 153.1, 147.0, 146.8, 145.8, 145.6, 132.3, 131.9, 131.7, 131.5, 131.2, 128.7, 128.6, 127.2, 127.1, 126.9, 126.0, 125.9, 122.0, 121.6, 121.0, 120.3, 118.3, 114.6, 72.1, 37.5, 37.1, 33.6, 33.5; IR ($CHCl_3$) 1775, 1510, 1275, 1230 cm^{-1}; MS *m*/*z* 456 (M^+); HRMS *m*/*z* calcd for $C_{27}H_{21}O_5P$ (M^+) 456.1126, found 456.1138.

19: amorphous solid; ^1H NMR δ 2.38 (dd, 1H, *J* = 17.6, 8.8 Hz), 2.74 (t, 1H, *J* = 17.3), 2.76 (dd, 1H, *J* = 17.6, 9.0), 3.24 (quin, 1H, *J* = 8.1), 4.28 (dd, 1H, *J* = 9.6, 7.7), 4.50 (dd, 1H, *J* = 9.6, 7.7), 5.47 (dd, 1H, *J* = 16.8, 4.0), 5.64 (d, 1H, *J* = 10.0), 6.00 (m, 1H), 7.24−7.58 (m, 8H), 7.94−8.07 (m, 4H); ^{13}C NMR δ 176.1, 147.4, 147.2, 145.2, 132.7, 132.5, 132.1, 131.7, 131.3, 128.8, 128.6, 128.1, 127.9, 127.5, 127.3, 127.1, 127.0, 126.3, 126.1, 124.7, 124.4, 121.8, 120.9, 120.1, 70.5, 70.3, 44.9, 42.2, 34.6, 34.5, 33.1, 33.0; ^{31}P NMR δ 35.56 (from 85% H_3PO_4); IR ($CHCl_3$) 1780, 1590, 1220, 1210 cm^{-1}; MS *m*/*z* 456 (M^+); HRMS *m*/*z* calcd for $C_{27}H_{21}O_5P$ (M^+) 456.1126, found 456.1117. Anal. Calcd for $C_{27}H_{21}O_5P \cdot 1/4H_2O$: C, 70.36; H, 4.70. Found: C, 70.27; H, 4.79.

24: amorphous solid; ^1H NMR δ 1.03 (d, 3H, *J* = 6.6), 1.48 (m, 1H), 1.76−2.43 (m, 7H), 5.72 (dd, 1H, *J* = 23.8, 17.2), 6.92 (ddd, 1H, *J* = 23.0, 17.2, 8.0), 7.27−7.65 (m, 8H), 7.94−8.08 (m, 4H); ^{13}C NMR δ 160.5, 160.4, 147.3, 147.1, 146.2, 146.0, 132.6, 132.5, 132.0, 131.7, 131.5, 131.1, 131.0, 128.7, 128.6, 127.4, 127.2, 127.1, 126.9, 126.8, 126.0, 125.9, 122.3, 122.2, 121.8, 121.3, 121.2, 120.6, 115.1, 111.4, 44.1, 43.7, 43.0, 41.8, 38.6, 27.7, 17.5; IR ($CHCl_3$) 1740, 1620, 1590, 1510, 1280 cm^{-1}; MS *m*/*z* 468 (M^+); HRMS *m*/*z* calcd for $C_{29}H_{25}O_4P$ (M^+) 468.1491, found 468.1498. Anal. Calcd for $C_{29}H_{25}O_4P$: C, 74.35; H, 5.38. Found: C, 74.01; H, 5.43.

General Procedure for Ozonolysis of Michael Adducts to δ-Keto Aldehydes. Ozonolysis of the Michael adducts **6** to δ-keto aldehyde **7** is typical. Oxygen-containing ozone was passed through a stirred solution of **6** (710 mg, 1.56 mmol) in CH_2Cl_2−MeOH (30 mL−5 mL) at −78 °C for 1 h. Glacial acetic acid (50%, 500 μL) and Zn powder (500 mg) were added, and the mixture was warmed to room temperature with stirring for 1 h. The reaction mixture was neutralized with $NaHCO_3$ (aq), filtered with a celite pad, and washed three times with EtOAc. The filtrate and washings were combined, washed with brine, dried, and evaporated to give a residue which was purified by flush column chromatography with EtOAc/hexane (1:2) to afford **7** (112 mg) in 57% yield.

Acetalization of δ-Keto Aldehydes with (2*R*,3*R*)-Butanediol. Acetalization of the δ-keto aldehyde **7** with (2*R*,3*R*)-butanediol to **8** is typical. A mixture of **7** (78 mg, 0.62 mmol), (2*R*, 3*R*)-butanediol (250 μL, 2.74 mmol, 4.4 equiv), *p*-TsOH (15 mg, 10% mol), and C_6H_6 (30 mL) was refluxed with stirring

for 2 h. The reaction mixture was poured into $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue which was subjected to flash column chromatography with EtOAc/hexane (1:5) to afford **8** (156 mg) in 93% yield.

Acetalization of δ-Keto Aldehydes with ethanedithiol. Thioacetalization of the δ-keto aldehyde **7** with ethanedithiol to **9** is typical. A solution of **7** (70 mg, 0.56 mmol), ethanedithiol (115 μL, 1.37 mmol, 2.5 equiv), and one drop of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (3 mL) was stirred for 2 h at room temperature. The reaction mixture was poured into cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue which was purified by flash column chromatography with EtOAc/hexane (1:5) to afforded **9** (90 mg) in 95% yield.

9: colorless oil; ^1H NMR δ 1.43 (m, 1H), 1.79–2.49 (m, 8H), 3.16–3.28 (m, 4H), 3.32 (s, 4H), 4.46 (t, 1H); ^{13}C NMR δ 69.9, 52.2, 50.1, 45.3, 43.6, 39.4, 39.3, 38.6, 38.1, 31.3; IR (neat) 2960, 2920, 1435, 1280, 1240 cm^{-1}; MS *m/z* 278 (M^+); HRMS *m/z* calcd for $C_{11}H_{18}S_4$ (M^+) 278.0291, found 278.0283.

22 and 23 (inseparable mixture): colorless oil.

22: ^1H NMR δ 1,05 (d, 3H, *J* = 6.6), 1.53 (m, 1H), 1.76–2.40 (m, 7H), 3.18 (brs, 4H), 3.32 (s, 4H), 4.72 (d, 1H, *J* = 4.8); IR ($CHCl_3$) 2960, 2940, 1460, 1440, 1430, 1380, 1280 cm^{-1}; MS *m/z* 292 (M^+); HRMS *m/z* calcd for $C_{12}H_{20}S_4$ (M^+) 292.0447, found 292.0443.

23: ^1H NMR δ 1.07 (d, 3H, *J* = 6.5), 1.53 (m, 1H), 1.76–2.40 (m, 7H), 3.18 (brs, 4H), 3.32 (s, 4H), 4.67 (d, 1H, *J* = 5.0).

28 and 29 (inseparable mixture): colorless oil;

28: ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.2), 1.24–1.45 (m, 2H), 1.65–1.81 (m, 2H), 1.92–2.06 (m, 2H), 2.13–2.30 (m, 2H), 3.26 (brs, 8H), 4.51 (dd, 1H, *J* = 9.2, 3.7); IR ($CHCl_3$) 2960, 2920, 2870, 1455, 1430, 1375, 1275 cm^{-1}; MS *m/z* 292 (M^+); HRMS *m/z* calcd for $C_{12}H_{20}S_4$ (M^+) 292.0447, found 292.0429.

29: ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 (d, 3H, *J* = 7.0), 1.24–1.45 (m, 2H), 1.65–1.81 (m, 2H), 1.92–2.06 (m, 2H), 2.13–2.30 (m, 2H), 3.26 (brs, 8H), 4.51 (m, 1H).

Tandem Michael Addition with the Anion of (*R*)-2 and Enolate Methylation to 16. To a stirred solution of (*R*)-**2** (1.0 g, 2.69 mmol) in THF (30 mL) was added dropwise *n*-BuLi (1.7 mL of 1.59 M solution in hexane, 1.3 equiv) at −78 °C. After being stirred for 15 min at the same temperature, a solution of cyclopentenone **5** (1.75 mL of 1.19 M solution in THF) was added, the mixture was stirred for 15 min at −78 °C, and then MeI (500 μL) was added. The reaction mixture was stirred for 1 day at an ambient temperature and then poured into cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue which was purified by flash column chromatography with EtOAc/hexane (4:1) to afford **16** (545 mg) in 56% yield, together with **6** (211 mg) in 22% yield.

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