1, 2).^{17,21} As shown in Table II, the cis-ring fusion isomers 8predominated under all conditions. Interestingly, experiments with longer reaction time (entry 3) or higher temperature (entry 4) led to nearly exclusive formation of cis-fused isomers. Furthermore, in experiments with an internal standard (entries 5 and 6) it was shown that the cis:trans ratio was also dependent on the amount of BF₃·OEt₂. Taken together these results suggest that under more vigorous reaction conditions the cis isomers 8 are produced at the expense of trans isomers 9. To establish whether this arises from equilibration or selective destruction of the trans isomers, three GC experiments using an internal standard were run. First, it was shown (in three separate runs) that the total amount of products from cyclization of (E)-7 was unchanged by quenching at 5, 15, or 30 min. Second, a quaternary mixture of isomers 8 and 9 was treated with 1.0 equiv of BF₃·OEt₂ at -78 °C for 30 min. The ratio of the sum of the cycloadducts to the internal standard was identical before and after reaction. Finally, a mixture of 8a:8b:9a/9b (13:44:23/20), treated with BF₃·OEt₂ as above, changed to a 63:35:1/1 mixture with no loss of cyclization material. Thus, even at -78 °C, these reactions are readily reversible. Based on these observations we conclude the following: (1) cyclization of (Z)-7 does not proceed via prior isomerization and is operating under kinetic control to give cis products in high yield, (2) cyclization of (E)-7 produces both cis and trans isomers in moderate yield under kinetic control, (3) trans-fused products are extremely labile and readily isomerize via cycloreversion to cis-fused products, and (4) the ratio of anomers in 8 and 9 does not reflect the vinyl sulfide ratio in 7 indicative of a nonconcerted reaction.

These conclusions can best be unified by invoking a two-step process with significant cycloaddition character proceeding through zwitterions i and ii, Scheme III. The lower yield in the cyclization of (E)-7 compared to (Z)-7 can be understood in terms of alternate nonproductive pathways available for collapse of ii since k_5 should be less than k_2 .

Based on these experiments we have completed a stereospecific, total synthesis of (+)-nepetalactone^{20,22} (14) using a ketene dithioacetal as the dienophile²³ in Z enal (+)-12,²⁴ Scheme IV. BF3.OEt2-catalyzed cyclization produced dithioortholactone (+)-13¹¹ in 55% yield as a single diastereomer. Mercuric oxide assisted hydrolysis of 13 afforded (+)-nepetalactone (14)¹¹ in 76% yield with spectroscopic and optical properties in accord with those reported by Eisenbraun.20

Further investigation into the utility of Z enals in cycloaddition reactions to form other ring systems is planned and will be reported in due course.

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Organoboron Compounds in Organic Synthesis. 4. **Asymmetric Aldol Reactions**

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Both the anti- and syn-3-hydroxy-2-(methylcarbonyl) units (1 and 2) are frequently embedded in natural products of propionate origin such as macrolide antibiotics.¹ Since the advent of several chiral boron enolate reagents in 1981, e.g., $3a^{2a}$ and 4,^{2b} the double-asymmetric aldol methodology has been widely used for the efficient construction of the syn unit $2^{1,3}$ but the same synthetic methodology still remains to be explored for the anti unit 1.4 For this purpose we record herein a new reagent 5a which is anti selective and consistently achieves an enantioselection of more than 80:1 in reactions with typical aldehydes.⁵ A mechanistic rationale for this enantioselectivity is also presented with a brief discussion on the results obtained from 3a, 3b, 5a, and 5b. The reagents 3b and 5b are nor analogues of 3a and 5a, respectively.⁶



An initial set of experiments was aimed at the preparation of a highly E(O)-enriched boron enolate,⁷ since the anti/syn aldol product ratios are equated to the E(O)/Z(O) ratios of the boron

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(6) The recent literature (since the appearance of ref 2) concerning the constructions of 1, 2, and the 3-(hydroxycarbonyl) system via an aldol reaction or allylboration is extensively surveyed in the supplementary material. (7) For the definition of E(O) and Z(O), see ref 4.

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Table I.	Aldol	Reactions	of Re	presentative	Aldehvdes	with 5a ^a

		RCHO + 5a	-78 °C Pentane R	SCEt3		ОН	
				8	9a	8	
entry	RCHO	reaction time (h)	isolated ^b yield	anti/syn ^c	absolute config	% ee ^d obsd	% ee corrected for the ee of 6 used
1	СНО	12	91 (96)	33:1	2R,3R	93.0	97.9
2) —сно	18	85	30:1	2 <i>R</i> ,3 <i>R</i>	95.4	99.5
3	сно	36	95	30:1	2 <i>R</i> ,3 <i>S</i>	95.8	99.9
4	сно	21	82 (87)	32:1	2 <i>R</i> ,3 <i>R</i>	93.1	98.0
5	Сно	3	(71)	33:1	2 <i>R</i> ,3 <i>S</i>	95.7	99.8
6	~~~сно	9	93	≥30:1	2 <i>R</i> ,3 <i>R</i>	92.2	97.1

^a To a stirred solution of a propanethioate (0.17 M, 1 equiv) and $(i-Pr)_2EtN$ (0.2 M, 1.2 equiv) in pentane was added 6 (1.2 equiv) at -78 °C. After it was stirred at 0 °C for 1 h, the mixture was recooled to -78 °C and benzaldehyde (1.5 equiv) was added. After the reaction time specified above, the mixture was worked up in the usual way. The yield was calculated based on the amount of the propanethioate used. ^b The numbers in parentheses are estimated by ¹H NMR analysis using an internal standard. ^c Determined by ¹H NMR analysis. ^d Product 8 was converted to its acetate, the percent ee of which was determined by ¹H NMR with the aid of Eu(hfc)₃. ^e Percent ee of 6 was 95.0% for entries 1, 4, and 6 and 95.9% for 2, 3, and 5.

Table II. Aldol Reactions of Representative Aldehydes with 5b^a

ясно	+	5b		CEt ₃
			10	

					10			
entry	RCHO	reactn time (h)	reactn temp, °C	isolated yield, %	absolute config	% ee ^b obsd	% ee corrected for ^c the ee of 6 used	
1	СНО	6	-78	82	R	86.6	91.2	
2	∕—сно	10	-78	81	S	86.9	91.5	
3	сно	6	-78	71	S	94.4	98.4	
4	Сно	9	-78	95	S	85.6	90.1	
5	Страно	3	-82 to -85	78	S	88.4	92.2	
6	Сно	4	-100 to -105	78	S	89.0	92.8	
7	~ СНО	7	-78	93	R	84.9	89.4	

^aCarried out in the same manner as described in Table I, footnote a, except for the reaction time and temperature. ^bDetermined by ¹H NMR analysis of the corresponding acetyl derivatives with the aid of Eu(hfc)₃. ^cPercent ee's of **6** for entries 1, 2, 4, and 7 were 95.0% and 95.9% for entries 3, 5, and 6.

enolate mixtures used.³ Aldol reactions were carried out in a standard fashion using, in each case, a combination of a propanethioate and (S,S)-2,5-dimethylborolane trifluoromethane-sulfonate (6)^{8,9} to form an E,Z mixture of the corresponding boron enolates. The mixture was then allowed to react with benz-aldehyde. Upon examination of several alkane- and arenethiol esters,⁸ the trend is clearly seen: The E(O)/Z(O) ratio (or the anti-selectivity) increases with the bulk of the alkanethiol moiety, whereas the formation of the Z(O) enolates prevails with S-aryl thioates (E/Z = 7/93 and 5/95 with benzenethiol and 2-nap-thalenethiol esters, respectively). Thus, the E(O) reagent **5a** is formed almost exclusively (see below) from S-3-(3-ethyl)pentyl propanethioate (**7a**) with **6**. Despite its apparent steric demand,

5a still retains a high degree of reactivity toward aldehydes.

Table I summarizes the results obtained from aldol reactions of representative aldehydes with **5a**. All reactions proceeded smoothly at -78 °C and the major products **8** with 2,3-anti stereochemistry (anti/syn > 30/1) were reduced with LiAlH₄ to the corresponding diols **9a** which were compared with authentic samples **9b** prepared via ring opening of the epoxy alcohols with established absolute configuration.⁸ With (*S*,*S*)-**5a** the aldehydes examined provided the 2*R* aldol products **8**, most of which were of more than 98% ee. Note that the chiral auxiliary of reagent **5a**¹⁰ can be recovered as its 2-amino-2-methylpropanol complex and the product aldols **8** are equipped with a thioate functionality versatile for further synthetic transformation.

⁽⁸⁾ See the supplementary material for full experimental details and literature.

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We have also examined whether reagent 5b, prepared from S-3-(3-ethyl)pentyl ethanethioate (7b) in a similar manner as that for 5a, achieves equally high enantioselection in the aldol reaction with achiral aldehydes.⁶ As outlined in Table II, the ee's of the aldol products obtained from primary and secondary alkylcarboxaldehydes and aromatic aldehydes are found in a narrow region of 89-93% (entries 1, 2, and 4-7), and thus there is still room for further improvement. It is noted, however, that the selectivity increases with pivalaldehyde.

As has been the case for many aldol reactions,³ a Zimmerman-Traxler model is again most conveniently used to rationalize the higher enantioselectivity exhibited by 5a than by 5b. In the transition state I for reaction of an aldehyde with reagent 5a, the asterisked methyl group steers the 3-ethyl-3-pentanethiol group toward the borolane moiety, the chirality of which is thus transferred effectively. In the absence of this "steering effect",



as may be the case in transition state II for the reaction with reagent 5b, the enantioselection of the reaction decreases. This supposition that both reactions proceed through a chair-form transition state is of great interest in that both 5a and 5b have no Z(O)-methyl substituent (see below). It has been known for some time that the reaction with 3a proceeds with near-perfect enantioselection but that with 3b provides a roughly 1/1 mixture of two diastereomeric aldols,³ a puzzling fact for which no reasonable explanation has been offered. While the preferred transition state of the reaction with 3a is III^{2a} (rather than IV where the steric hindrance between the Z(O)-methyl group (R' = Me) and the ligand (L) attached to the borane atom is prohibitively severe¹¹), the reaction with **3b** may in all likelihood proceed through the boat-form transition state IV (R' = H) or V. Both transition states would then be expected to be of approximately equal energy, differing only in the orientation of the reacting aldehyde with respect to 3b as shown. The reaction thus proceeds stereorandomly. In contrast, the triethylcarbinyl group in I and II, despite its large steric bulk, apparently can be accommodated within the chair-form framework as the conformation of the group is flexible due to its rotation along the axis of the sulfur and carbon atoms indicated by the dagger.

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Supplementary Material Available: Tables containing survey of the recent literature on the enantioselective aldol reaction and allylboration and experimental methods and spectral data (27 pages). Ordering information is given on any current masthead page.

Tandem Michael-Carbene Insertion Reactions of Alkynyliodonium Salts. Extremely Efficient **Cyclopentene Annulations**

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Intramolecular carbon-hydrogen insertion reactions of carbenes have proven to be powerful and invaluable tools in the synthesis of highly functionalized, five-membered ring systems.² We report herein a novel and potentially highly versatile cyclopentene annulation utilizing hypervalent organoiodine(III) compounds, alkynyliodonium salts, via the tandem Michael-carbene insertion (MCI) reaction (Scheme I).

Michael-type addition of "soft" carbanions generated from 1,3-diketones or 1,3-diesters by base abstraction of a methine hydrogen to the carbon-carbon triple bond of alkynyliodonium tetrafluoroborates 1 (X⁻ = BF₄⁻)^{3,4} constitutes a key step of the facile cyclopetene annulation reaction. On the other hand, reaction of alkynyliodonium tosylate 1 (R = t-Bu, $X^- = OTs^-$) with "hard" carbanions like 2-lithiofuran has been shown to occur at the hypervalent iodine atom of 1 to give diaryliodonium tosylates with a concomitant loss of the *tert*-butylethynyl group.⁵ Thus, the reaction described here is the first to show the effectiveness of alkynyliodonium salts 1 as a good Michael acceptor toward carbanions.4a,6

When 1-decynyl(phenyl)iodonium tetrafluoroborate (1a) dissolved in tert-butyl alcohol or THF was treated with stable enolate anions generated from 1,3-diketones or 1,3-diesters, 3-pentylcyclopentenes 6-9 were obtained directly in reasonable yields (Table I, entries 1-4). Similarly, [1-(3-cyclopentyl)propynyl]phenyl- and [1-(4-cyclohexyl)butynyl]phenyliodonium tetrafluoroborates (1b and 1c) afforded fused bicyclic and spiro products, respectively (entries 5-7). (4-Methylhexynyl)iodonium salt 1d showed some 1,2-diastereoselection in the annulation and produced trans-3,4 diastereomer 13 as the major product (entry 8). The reaction process, shown in Scheme I, may account for the formation of these cyclopentenes. Michael addition of an enolate anion (Nu⁻) to 1 produces unstable iodonium ylide 2,8.9

⁽¹¹⁾ Thus the presence of the methyl group (\mathbf{R}') is essential for reagent 3a to be enantioselective, and for that matter, all other known reagents of the same or a similar type having a group other than hydrogen for R^\prime exhibit excellent selection.

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