1, 2).[17,21] As shown in Table II, the cis-ring fusion isomers **8** predominated 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 $BF_3{\cdot}OEt_2$. 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 $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$ 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 dienophile[23] in *Z* enal (+)-**12**,[24] Scheme IV. $BF_3{\cdot}OEt_2$-catalyzed cyclization produced dithioortholactone (+)-**13**[11] 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.

Acknowledgment. We gratefully acknowledge financial support for this project provided by the National Institutes of Health (PHS GM-30938) and the Upjohn Co. This work was supported in part by the University of Illinois Regional Instrumentation Facility (NSF CHE 79-16100) and Mass Spectrometry Laboratory (NIH GM-27029).

(21) While this quaternary mixture could be resolved by capillary GC, we were unable to preparatively separate the trans-fused isomers. Thus, an assignment of stereochemistry was not possible even though the anomeric protons were unique at 360 MHz. Thus for H–C(1): **8a**, δ 4.60 (d, J = 6.39 Hz); **8b**, δ 4.89 (d, J = 2.32 Hz); **9a**, δ 4.93 (s); **9b**, δ 5.40 (d, J = 3.47 Hz).

(22) Isolation and structure determination: (a) McElvain, S. M.; Walters, P. M.; Bright, R. D. *J. Am. Chem. Soc.* **1942**, *64*, 1828. (b) McElvain, S. M.; Eisenbraun, E. J. *Ibid.* **1955**, *77*, 1599. (c) Eisenbraun, E. J.; McElvain, S. M. *Ibid.* **1955**, *77*, 3383. (d) Bates, R. B.; McElvain, S. M.; Eisenbraun, E. J. *Ibid.* **1958**, *80*, 3420. Syntheses: (e) Sakan, T.; Fujino, A.; Murai, F.; Suzui, A.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1737. (f) Achmad, S. A.; Cavill, G. W. K. *Proc. Chem. Soc.* **1963**, 166. (g) Trave, R.; Marchesini, A.; Garanti, L. *Gazz. Chim. Ital.* **1968**, *98*, 1132.

(23) For previous examples of ketene dithioacetals as dienophiles, see: (a) Reference 3c. (b) Dvorak, D.; Arnold, Z. *Tetrahedron Lett.* **1982**, 4401.

(24) The preparation of (+)-**12** (ca. 96% ee) was achieved in 10 steps from 5-hydroxypentanal using an asymmetric alkylation of a RAMP hydrazone[25] to install the stereodirecting methyl group. Details of the synthesis of (+)-nepetalactone will be published elsewhere.

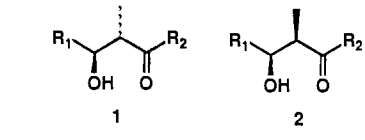
(25) For a review of these auxiliaries, see: Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 4.

Organoboron Compounds in Organic Synthesis. 4. Asymmetric Aldol Reactions

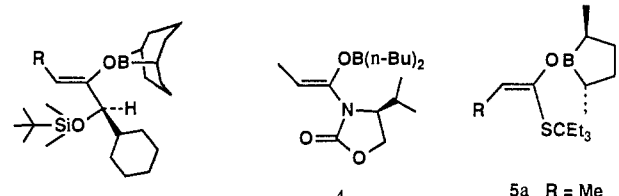
Satoru Masamune,* Tsuneo Sato, ByeongMoon Kim, and Theodor A. Wollmann

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received July 7, 1986

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]



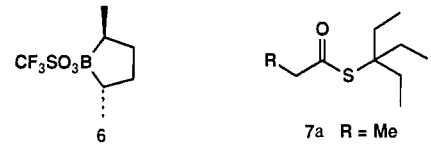
1 2



3a R = Me
3b R = H

4

5a R = Me
5b R = H



6

7a R = Me
7b R = H

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

(1) (a) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 4. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(2) (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *Ibid.* **1981**, *103*, 2127.

(3) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(4) Efforts directed toward the construction of the unit 1 have often resorted to indirect, circuitous aldol routes or different methodologies. For instance, see: Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

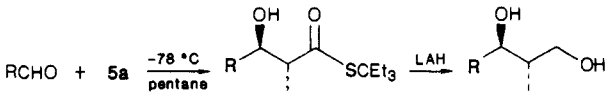
(5) Anti-selective reagents are rare. See: (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) A single example of a highly enantioselective aldol reaction is described. Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (c) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (d) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. (e) Palazzi, C.; Colombo, L.; Gennari, C. *Ibid.* **1986**, *27*, 1735. (f) Narasaka, K.; Miwa, T. *Chem. Lett.* **1985**, 1217.

(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.

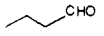
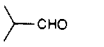
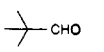
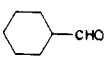
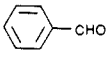
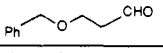
(7) For the definition of *E*(*O*) and *Z*(*O*), see ref 4.

0002-7863/86/1508-8279$01.50/0

Table I. Aldol Reactions of Representative Aldehydes with **5a**[a]



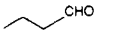
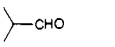
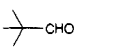
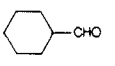
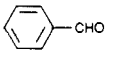
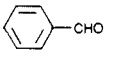
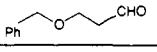
8 **9a**

					8		
entry	RCHO	reaction time (h)	isolated[b] yield	anti/syn[c]	absolute config	% ee[d] obsd	% ee corrected for[e] the ee of **6** used
1		12	91 (96)	33:1	2*R*,3*R*	93.0	97.9
2		18	85	30:1	2*R*,3*R*	95.4	99.5
3		36	95	30:1	2*R*,3*S*	95.8	99.9
4		21	82 (87)	32:1	2*R*,3*R*	93.1	98.0
5		3	(71)	33:1	2*R*,3*S*	95.7	99.8
6		9	93	≥30:1	2*R*,3*R*	92.2	97.1

[a] To a stirred solution of a propanethioate (0.17 M, 1 equiv) and (*i*-Pr)$_2$EtN (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 ^{1}H NMR analysis using an internal standard. [c] Determined by ^{1}H NMR analysis. [d] Product **8** was converted to its acetate, the percent ee of which was determined by ^{1}H 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]

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		6	−78	82	*R*	86.6	91.2
2		10	−78	81	*S*	86.9	91.5
3		6	−78	71	*S*	94.4	98.4
4		9	−78	95	*S*	85.6	90.1
5		3	−82 to −85	78	*S*	88.4	92.2
6		4	−100 to −105	78	*S*	89.0	92.8
7		7	−78	93	*R*	84.9	89.4

[a] Carried out in the same manner as described in Table I, footnote *a*, except for the reaction time and temperature. [b] Determined by ^{1}H NMR analysis of the corresponding acetyl derivatives with the aid of Eu(hfc)$_3$. [c] Percent 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 trifluoromethanesulfonate (**6**)[8,9] to form an *E*,*Z* mixture of the corresponding boron enolates. The mixture was then allowed to react with benzaldehyde. 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-naphthalenethiol 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 LiAlH$_4$ 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.

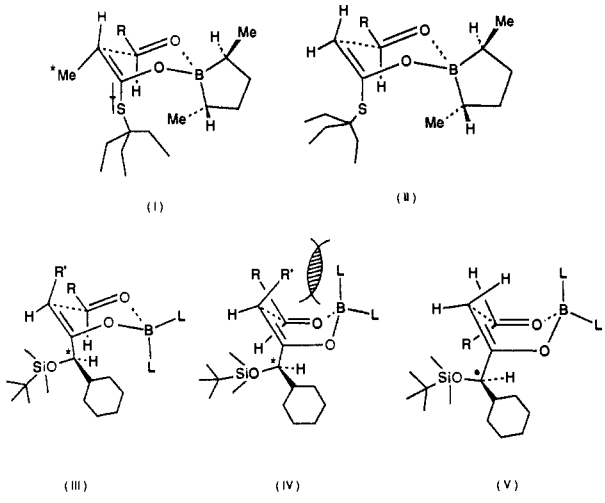
(8) See the supplementary material for full experimental details and literature.

(9) Masamune, S.; Kim, B.; Petersen, J. S.; Sato, T.; Veenstra, J.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

(10) A reaction involving a chiral reagent provides the product which either does or does not contain the chiral moiety of the reagent. We propose that if it does, the reagent is called "internal" and if not, "external". We find this classification of chiral reagents to be convenient.

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 severe[11]), 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.

Acknowledgment. We thank the National Institutes of Health (GM 33039 and GM 35879) for financial support. T.A.W. is a recipient of a Deutschen Forschungsgemeinshaft postdoctoral fellowship.

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.

(11) Thus the presence of the methyl group (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′ exhibit excellent selection.

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

Masahito Ochiai,*[1a] Munetaka Kunishima,[1a] Yoshimitsu Nagao,[1a] Kaoru Fuji,[1a] Motoo Shiro,[1b] and Eiichi Fujita*[1c]

Institute for Chemical Research, Kyoto University Uji, Kyoto 611, Japan
Shionogi Research Laboratories, Shionogi & Co. Ltd. Fukushima-ku, Osaka 553, Japan
Osaka University of Pharmaceutical Sciences 10-65 Kawai 2-Chome, Matsubara 580, Japan

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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** ($X^- = BF_4^-$)[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]

(1) (a) Kyoto University. (b) Shionogi & Co. Ltd. (c) Osaka University of Pharmaceutical Sciences.

(2) For reviews, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971. (c) Jones, M., Jr.; Moss, R. A., Eds. *Carbenes*; Wiley-Interscience: New York, 1973; Vol. I, II.

(3) For general synthesis of alkynyliodonium salts **1**, see: (a) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4700. (b) Ochiai, M.; Kunishima, M.; Sumi, K.; Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1985**, *26*, 4501.

(4) (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930. (b) Merkushev, E. B.; Karpitskaya, L. G.; Novosel'tseva, G. I. *Dokl. Akad. Nauk SSSR* **1979**, *245*, 607. (c) Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324.

(5) Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.

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