Acknowledgment. These investigations were supported by the NIH (GM-30738) to whom we are grateful. Additional support was provided by the NSF (Presidential Young Investigator Award), Alfred P. Sloan Foundation (1985–1987), and the Camille and Henry Dreyfus Foundation, Inc. (Teacher/Scholar Award 1984–1989). Matching funds for the NSF-PYI award were generously provided by American Cyanamid, the Upjohn Co., and Pfizer, Inc. Preliminary experiments in these studies were carried out by R. E. Claus. We thank Professor E. J. Eisenbraun (Oklahoma State University) for providing spectral data of (+)-nepetalactone and Professor Scott E. Denmark (University of Illinois at Urbana—Champaign) for many helpful and stimulating discussions.

Supplementary Material Available: Tables of 3-21G optimized geometries for **16′**, **15′**, **18′**, and **17′** and experimental section including experimental procedures and spectral data (10 pages). Ordering information is given on any current masthead page.

Intramolecular [4 + 2] Cycloadditions of (*Z*)-α,β-Unsaturated Aldehydes with Vinyl Sulfides and Ketene Dithioacetals[1a]

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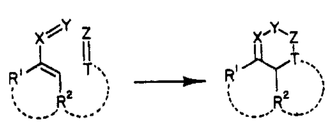
In the course of our investigations on intramolecular [4 + 2] cycloadditions of nitrosoalkenes[2] (eq 1, X=Y = N=O) we discovered that vinyl sulfides (T=Z = CH=CHSCH$_3$) were superior to enol ethers as electron-rich dienophiles. In contrast to the



(1)

extensive use of enol ethers and enamines in inverse-electron-demand heterodiene cycloadditions,[3,4] vinyl sulfides have received little attention.[5] Indeed, these activated olefins have enjoyed only sparing application in any cycloaddition process[6] despite their synthetic potential.[7] We have now extended our study to include (*Z*)-α,β-unsaturated aldehydes as the 4π-component in these intramolecular cycloadditions.[8] Our rationale for investigating the labile *Z*-geometrical isomers was based on the anticipated higher stereoselectivity of cyclization amply demonstrated in analogous Diels–Alder reactions.[9] We report herein that these reactions operate under kinetic control with Lewis acid catalysis to give exclusively cis-ring-fused products.

Scheme I

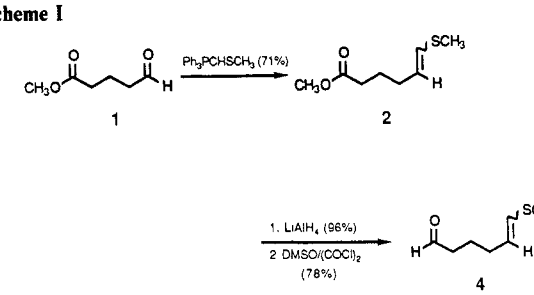
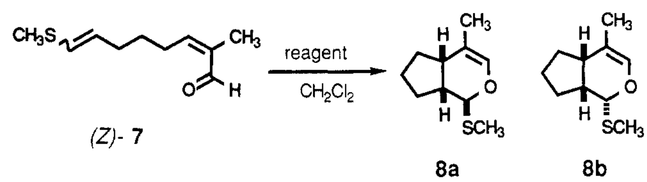


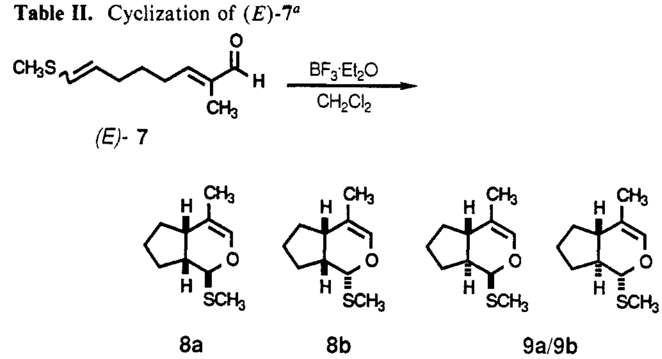
Table I. Cyclization of (*Z*)-7[a]



entry	reagent (equiv)	temp, °C	time	yield, %	8a:8b
1		50	19 h	35	96:4[b]
2	$BF_3 \cdot OEt_2$ (1.0)	−78	10 min	93	75:25[c]
3	$BF_3 \cdot OEt_2$ (1.0)	−70	15 min	91	71:29[c]

[a] The (*Z*)-7 was a 60:40 *E*:*Z* mixture of vinyl sulfides. [b] Ratio determined by ^{1}H NMR. [c] Ratio determined by capillary GC.

Table II. Cyclization of (*E*)-7[a]



entry	equiv	temp, °C	time, min	yield, %	8a:8b:9a/9b[b]
1	1.0	−78	15	55	13:44:20/23
2	1.0	−78	15	38	41:35:24
3	1.0	−78	45	64	72:28:2
4	1.0	20	15	48	87:13:0
5	0.5	−78	30		20:40:22/18[c]
6	1.5	−78	30		36:39:14/11[c]

[a] The (*E*)-7 was a 60:40 *E*:*Z* mixture of vinyl sulfides. [b] The assignment of anomers in **9** is tentative.[21] [c] GC experiments with an internal standard; see text.

(1) (a) Presented at the 190th National Meeting of the American Chemical Society, Chicago, IL, 1985; paper ORGN 139. (b) NSF Presidential Young Investigator 1985–1990, A. P. Sloan Fellow 1985–1987.

(2) (a) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798. (b) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *Ibid.* **1984**, *49*, 4741. (c) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A.; Jacobs, R. T., manuscript in preparation.

(3) (a) For a review, see: Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) For a recent example using Lewis-acid catalysis: Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721. (c) Tietze, L. F. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 828.

(4) For examples of enamine/enal cycloadditions, see: Schreiber, S. L.; Meyers, H. V., preceding paper in this issue. We thank Professor Schreiber for generous exchange of manuscripts and information and for many stimulating discussions.

(5) (a) Takai, K.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 5246. (b) Hall, H. K.; Rasoul, H. A. A.; Gillard, M.; Abdelkader, M.; Nogues, P.; Sentman, R. C. *Tetrahedron Lett.* **1982**, *23*, 603. (c) Goerdeler, J.; Tiedt, M.-L.; Nandi, K. *Chem. Ber.* **1981**, *114*, 2713. (d) Sommer, S. *Chem. Lett.* **1977**, 583.

(6) Diels–Alder reaction: (a) Knapp, S.; Lis, R.; Michna, P. *J. Org. Chem.* **1981**, *46*, 624. (b) Stella, L.; Boucher, J. L. *Tetrahedron Lett.* **1982**, *23*, 953. (c) Boucher, J. L.; Stella, L. *Ibid.* **1985**, *26*, 5041. (d) Williams, D. R.; Gaston, R. D. *Ibid.* **1986**, *27*, 1485. [2 + 2]: (e) Gundermann, K.-D.; Röhrl, E. *Liebigs. Ann. Chem.* **1974**, 1661. (f) Okuyama, T.; Nakada, M.; Toyoshima, K.; Fueno, T. *J. Org. Chem.* **1978**, *43*, 4546. (g) Huisgen, R.; Graf, H. *Ibid.* **1979**, *44*, 2594. (h) Fries, S.; Gollnick, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 831, 832. [3 + 2]: (i) Caramella, P.; Albini, E.; Bandiera, T.; Corsico Coda, A.; Grünanger, P.; Marinone Albini, F. *Tetrahedron* **1983**, *39*, 689.

(7) (a) Field, L. *Synthesis* **1978**, 713. (b) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.

(8) For previous examples of intramolecular cycloadditions of enals as the 4π-component, see: (a) Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1980**, *45*, 3461. (b) Martin, S. F.; Benage, B. *Tetrahedron Lett.* **1984**, *25*, 4863. (c) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903.

(9) (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48. (c) Boeckman, R. K.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216. (d) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *Ibid.* **1982**, *104*, 5719. (e) Yoshioka, M.; Nakai, H.; Ohno, M. *Ibid.* **1984**, *106*, 1133.

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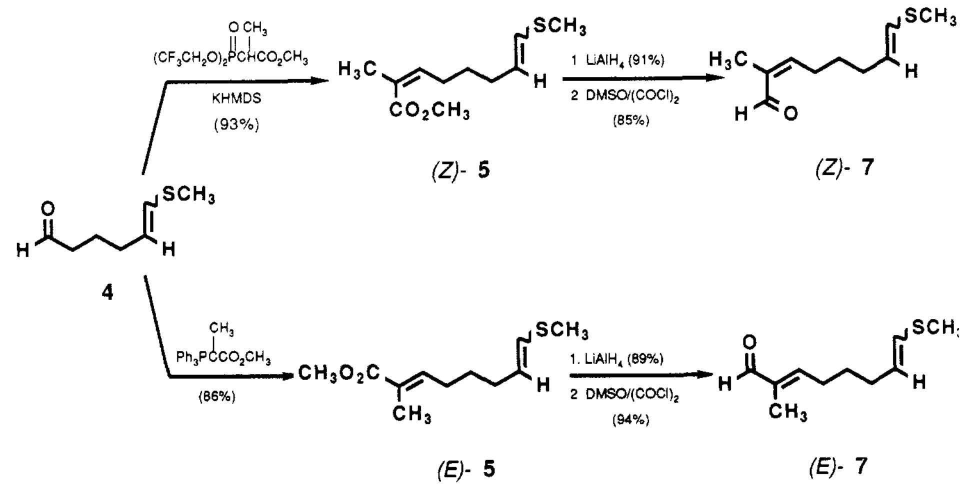
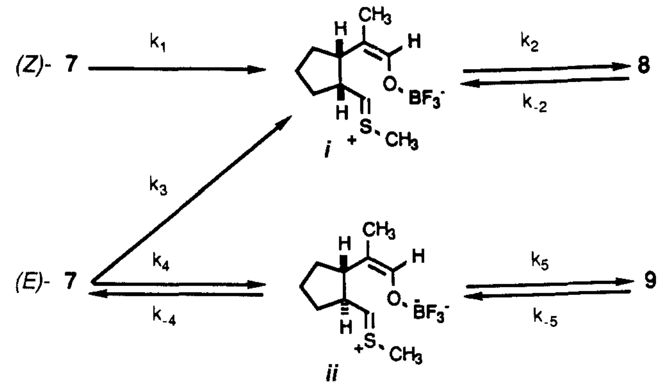
Scheme II



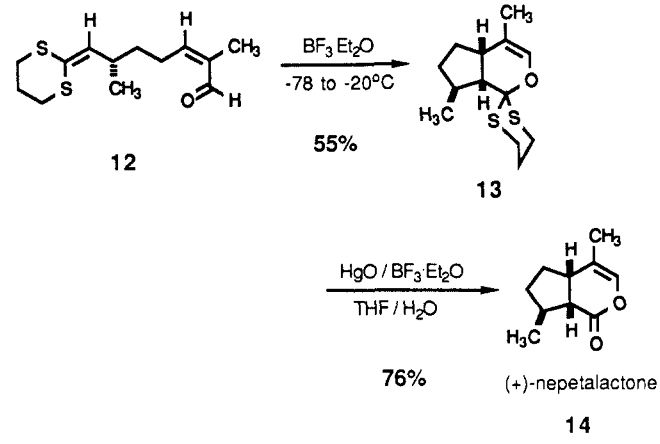
The substrates for this study were prepared in six steps from methyl 5-oxopentanoate[10] (**1**) via the common intermediate **4**,[11] Scheme I. Wittig thiomethylenation[12] of **1** afforded a 60:40 mixture of *E* and *Z* vinyl sulfides **2**,[11] which was easily transformed to aldehyde **4**, via alcohol **3**.[11] To access both *E* and *Z* enals, **4** was partitioned into (*Z*)-**5**[11] and (*E*)-**5**[11] by using stereoselective olefinations, Scheme II. Following the method of Still,[13] (*Z*)-**5**[11] was obtained in excellent yield with a 98:2 *Z*:*E* ratio at the 2,3-double bond, while reaction of **4** with the stabilized phosphorane[14] produced (*E*)-**5**[11] uncontaminated with the *Z* isomer. Rigorous assignment of stereochemistry was obtained from the ^1H and ^{13}C NMR spectra of **7** by comparison to analogous systems.[15]

The selection of reaction conditions for cyclization of (*Z*)-**7** was guided by the known thermal instability of (*Z*)-2-methyl-2-pentenal.[16] Indeed, prolonged heating of (*Z*)-**7** in CH_2Cl_2 (entry 1, Table I) produced only a 35% yield of cycloadducts along with recovered **7** which had isomerized to a 70:30 *Z*:*E* mixture. However, treatment of (*Z*)-**7** with 1.0 equiv of $BF_3 \cdot OEt_2$ at −78 °C produced a 91% yield of the cycloadducts **8a**[11] and **8b**[11] as a 71:29 mixture.[17] We tentatively assigned a cis ring fusion to both **8a** and **8b** and assumed that they differed only in the anomeric configuration. These assumptions were verified by transformation of a mixture of **8a** and **8b** to the single lactone **11**[18] which displayed a 9.08-Hz ^3J coupling across the ring fusion indicative of cis stereochemistry.[19,20] The major anomer was assigned the β-configuration based on the larger $^3J_{1,7a}$ (6.40 vs. 2.22 Hz for the minor isomer) since only in this isomer can the protons achieve a large dihedral angle.[2b]

Scheme III



Scheme IV



The possibility that the observed products were arising from either (1) prior isomerization of the enal followed by stereoselective cyclization or (2) post-facto isomerization of kinetically formed trans isomers was addressed by cyclization of (*E*)-**7**. These results are compiled in Table II. Under identical conditions with those employed for the *Z* enal we observed the formation of *all four isomeric cycloadducts* **8a**, **8b**, **9a**, and **9b** in 38–65% yield (entries

(10) Huckstep, M.; Taylor, R. J. K. *Synthesis* **1982**, 881.

(11) All new compounds have been thoroughly characterized by ^1H NMR (200 or 360 MHz), IR, mass spectrometry, and combustion analysis (±0.4%).

(12) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373.

(13) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 4405.

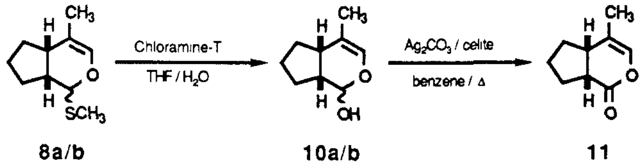
(14) Bestmann, H.-J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198.

(15) Rapoport[16] reports a 0.73 ppm downfield shift of the aldehydic proton in (*Z*)-2-methyl-2-pentenal. H–C(1): (*Z*)-**7**, δ 10.14; (*E*)-**7** δ 9.41.

(16) Chan, K. D.; Jewell, R. A.; Nutting, W. H.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 3382.

(17) These components could only be resolved by capillary GC (OV-17 50m) and gave a correct microanalysis for the mixture proving isomeric composition.

(18) The transformation was performed as follows:



(19) Vicinal coupling constants are less diagnostic in these ring systems than in the decalin type. The range of ^3J for cis-ring fusion is 7–9 Hz and for trans-ring fusion 11–14 Hz. For related systems, see: (a) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. (b) Cicero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914. (c) Brettle, R.; Jafri, I. A. *J. Chem. Soc., Perkin Trans 1* **1983**, 387.

(20) Additional evidence for the cis ring fusion comes from the similarity of ^{13}C resonances for C(1), C(3), C(4), C(4a), and C(5) to two known cis-fused nepetalactone isomers compared to those of the trans-fused diastereomer. Eisenbraun, E. J.; Browne, C. E.; Irvin-Willis, R. L.; McGurk, D. J.; Eliel, E. L.; Harris, D. L. *J. Org. Chem.* **1980**, *45*, 3811.

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

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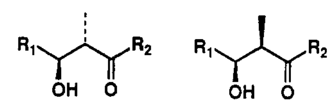
Both the *anti*- and *syn*-3-hydroxy-2-(methylcarbonyl) units (**1** and **2**) are frequently embedded in natural products of propionate origin such as macrolide antibiotics.[1] Since the advent of several chiral boron enolate reagents in 1981, e.g., **3a**[2a] and **4**,[2b] the double-asymmetric aldol 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]



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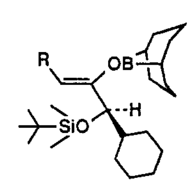
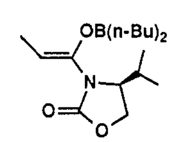
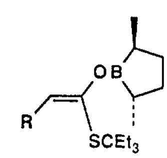


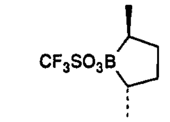
3a R = Me
3b R = H



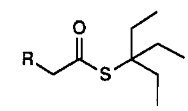
4



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.

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