(*p*-anisyl)-3-hydroxy-2-methyl-4-hexenoyl]pyrrolidine, 97060-64-5; *syn*-*N*-[5-(*p*-anisyl)-2,3-dimethyl-5-oxopentanoyl]pyrrolidine, 97060-65-6; *anti*-*N*-[5-(*p*-anisyl)-2,3-dimethyl-5-oxopentanoyl]-pyrrolidine, 97060-66-7; 3-[1-(*p*-anisyl)-1-hydroxy-2-butenyl]-*N*-methylpyrrolidone, 97060-67-8; *syn*-3-[4-(*p*-anisyl)-4-oxo-2-butyl]-*N*-methylpyrrolidone, 97060-68-9; *anti*-3-[4-(*p*-anisyl)-4-oxo-2-butyl]-*N*-methylpyrrolidone, 97060-69-0; *N*-(3-*tert*-butyl-3-hydroxy-2-methyl-4-heptenoyl)pyrrolidine, 97060-70-3; *syn*-*N*-(3-ethyl-5-oxo-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-71-4; *anti*-*N*-(3-ethyl-5-oxo-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-72-5; 3-(6,6-dimethyl-5-hydroxy-3-hepten-5-yl)-*N*-methylpyrrolidone, 97060-73-6; *syn*-3-(6,6-dimethyl-5-oxo-3-heptyl)-*N*-methylpyrrolidone, 97060-74-7; *anti*-3-(6,6-dimethyl-5-oxo-3-heptyl)-*N*-methylpyrrolidone, 97060-75-8; *N*-(3-*tert*-butyl-2,6-dimethyl-3-hydroxy-4-heptenoyl)pyrrolidine, 97060-76-9; *syn*-*N*-(5-oxo-3-isopropyl-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-77-0; *anti*-*N*-(5-oxo-3-isopropyl-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-78-1; 3-(5-hydroxy-2,6,6-trimethyl-3-hepten-5-yl)-*N*-methylpyrrolidone, 97060-79-2; *syn*-3-(5-oxo-2,6,6-trimethyl-3-heptyl)-*N*-methylpyrrolidone, 97060-80-5; *anti*-3-(5-oxo-2,6,6-trimethyl-3-heptyl)-*N*-methylpyrrolidone, 97060-81-6; *N*-(3-*tert*-butyl-3-hydroxy-2,6,6-trimethyl-4-heptenoyl)pyrrolidine, 97060-82-7; *syn*-*N*-(3-*tert*-butyl-5-oxo-2,6,6-trimethylheptanoyl)pyrrolidine, 97071-46-0; *anti*-*N*-(3-*tert*-butyl-5-oxo-2,6,6-trimethylheptanoyl)pyrrolidine, 97071-47-1; 3-(5-hydroxy-2,2,6,6-tetramethyl-3-hepten-5-yl)-*N*-methylpyrrolidone, 97060-83-8; 3-(5-oxo-2,2,6,6-tetramethyl-3-heptyl)-*N*-methylpyrrolidone, 97060-84-9; *N*-(3-*tert*-butyl-3-hydroxy-2-methyl-5-phenyl-4-pentenoyl)pyrrolidine, 97060-85-0; *syn*-*N*-(5-oxo-3-phenyl-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-86-1; *anti*-*N*-(5-oxo-3-phenyl-2,6,6-trimethylheptanoyl)pyrrolidine, 97060-87-2; 3-(4,4-dimethyl-3-hydroxy-1-phenyl-1-penten-3-yl)-*N*-methylpyrrolidone, 97060-88-3; *syn*-3-(4,4-dimethyl-3-oxo-1-phenylpentyl)-*N*-methylpyrrolidone, 97060-89-4; *anti*-3-(4,4-dimethyl-3-oxo-1-phenylpentyl)-*N*-methylpyrrolidone, 97060-90-7.

Supplementary Material Available: A full description of the methods used to assign stereostructures to the 1,4 addition products reported in Table I and a listing of the ^{13}C NMR chemical shifts of these products (5 pages). Ordering information is given on any current masthead page.

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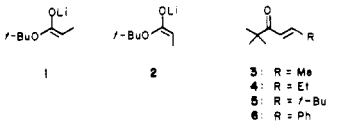
Stereoselection in the Michael Addition Reaction. 3. Relationship between Ester Enolate Geometry and Adduct Stereochemistry in the Kinetic Michael Reaction of Lithium Enolates with Enones[1]

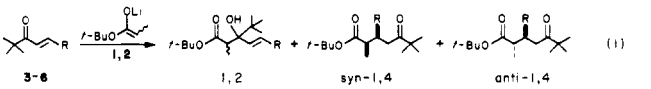
Summary: A systematic study of the stereochemistry of the kinetic Michael addition of the *Z* and *E* lithium enolates of *tert*-butyl propionate has provided conclusive evidence that the stereostructure of a lithium enolate determines the stereostructure of the resulting Michael adduct.

Sir: In the previous paper in this series we reported an investigation of the kinetic Michael reaction of amide lithium enolates with enones and rationalized the observed diastereoselectivity in terms of an open transition state.[1] In this communication, we report a parallel investigation of the stereochemistry of the reaction of the *Z* and *E* lithium enolates of *tert*-butyl propionate (**1** and **2**, respectively).[2] The results obtained in this study clearly show that there is a correlation between enolate geometry and Michael adduct stereostructure, provide additional evidence in favor of the open transition state hypothesis, and establish a synthetically useful, stereoselective synthesis of δ-keto acids having two stereocenters.

The *E* enolate **2** was prepared in the normal manner,[3] by addition of *tert*-butyl propionate to a THF solution of lithium diisopropylamide (LDA) at −78 °C. For preparation of *Z* enolate **1**, the method of Ireland, wherein a 23% (volume/volume) mixture of hexamethylphosphoric triamide (HMPT) and THF is used as solvent, was employed.[4] The enolate *E*/*Z* ratio was determined by withdrawing an aliquot, which was treated with *tert*-butyldimethylsilyl chloride. The resulting silyl ketene acetal was analyzed by capillary GLPC. The enones investigated were compounds **3**–**6**. Michael reactions were normally



carried out by adding the enone to a solution of the enolate at −78 °C; reaction was either quenched after 15 min at this temperature or after the reaction mixture had been warmed to 25 °C for 90 min (eq 1). Diastereomer ratios



were determined by ^{13}C NMR spectroscopy or capillary GLPC. The products were identified by conversion to keto acids of previously determined stereostructure.[1,5] Results are summarized in Table I.

Examination of Table I reveals several interesting features. First, as we found in the reactions of amide enolates with enones,[1] the 1,2/1,4 ratio depends on the steric demand of the group at the β-position of the enone (R in **3**–**6**). With enones **3** and **4**, only the 1,4 adduct is seen, even at −78 °C. With enone **6**, mixtures of 1,2 and 1,4 adducts are observed, *E* enolate **2** showing a greater propensity for 1,2 addition. With enone **5** and *Z* enolate **1**, no reaction is observed at −78 °C; the same enone reacts with *E* enolate **2** at −78 °C to give only the 1,2 adduct. Both with enones **5** and **6**, reaction for 90 min at 25 °C results in 1,2 to 1,4 equilibration. Relative to the reactions of enones **3**–**6** with amide enolates,[1] the following generalizations may be made. First, the ester enolates generally show a greater intrinsic preference for 1,4 addition than do the amide enolates at −78 °C. Second, 1,2 addition is more freely reversible with the ester enolates than with the amide enolates. Third, with both types of enolates, *E* enolates show a greater preference for 1,2 addition than *Z* enolates.[6] Fourth, isolated yields of 1,4 adducts are

(1) Part 31 in the series "Acyclic Stereoselection". For part 30, see: Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.*, previous communication in this issue.

(2) The stereochemical descriptors *E* and *Z* are employed in the manner recommended by Evans: Evans, D. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 11.

(3) See inter alia: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(4) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(5) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

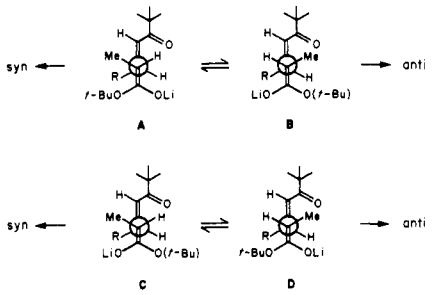
0022-3263/85/1950-3022$01.50/0

Table I. Stereochemistry of Addition of Enolates 1 and 2 to Enones (Eq 1)[a]

entry	enone	enolate	E/Z ratio[b]	temp, °C	time, min	yield, %	1,2/1,4 ratio	syn/anti (1,4 adduct)
1	3	1		−78	15	73	<3:97	13:87[c]
2	3	2		−78	15	85	<3:97	95:5[c]
3	4	1	12:88	−78	15	49	<3:97	5:95[c]
4	4	2	94:6	−78	15	86	<3:97	91:9[d]
5	5	1		−78	15	0		
6	5	1		25	90	25	<3:97	<3:97[c,d]
7	5	2		−78	15	65	>97:3	
8	5	2		25	90	46	<3:97	38:62[c,d]
9	6	1	11:89	−78	15	88	14:86	7:93[d]
10	6	1	11:89	25	90	76	<3:97	11:89[d]
11	6	2	95:5	−78	15	95	40:60	94:6[d]
12	6	2	95:5	25	90	96	<3:97	94:6[d]

[a] Reactions with enolate 2 were carried out in THF. Enolate 1 was prepared by the Ireland method, employing a mixture of HMPT and THF as solvent; thus, its reactions were carried out in a 23% (volume/volume) solution of HMPT and THF. [b] See ref 2 for the definition of E and Z as used in this paper. [c] Stereoisomer ratios determined by ^{13}C NMR spectroscopy. [d] Stereoisomer ratios determined by capillary GLPC.

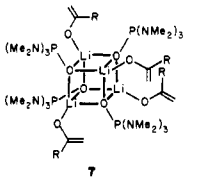
Scheme I



comparable to those observed with amide enolates.

The most striking aspect of the data in Table I is the clear correlation between enolate geometry and 1,4 adduct stereostructure. In all cases except one (entry 8), Z enolate 1 gives the anti-Michael adduct and E enolate 2 gives the syn isomer.[7] The observed stereoselectivity is in accord with the four open transition states depicted in Scheme I. Transition states A and B transform the E enolate 2 to the syn and anti 1,4 adducts, respectively. It is proposed that the dominant steric control element is the nonbonded interaction between R and either t-BuO or LiO. If the reaction occurs on the enolate tetramer,[8] as is likely, then the enolate oxygen is actually tetracoordinated, and LiO may be considered to be large, relative to t-BuO. Thus, transition state B is disfavored, and 2 shows high syn selectivity. Correspondingly, the Z enolate 1 should lead through transition state D to the anti 1,4 adduct.

With Z enolate 1 the picture is somewhat clouded by the presence of HMPT in the solvent. Seebach has suggested that HMPT does not disrupt enolate tetramers.[8d] Rather, it has been proposed that this polar aprotic solvent may reorganize the tetramer to a form such as 7.[9] However, even in this form, LiO is probably much more sterically demanding than t-BuO.



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One further complication that must be considered is the possibility of E-Z equilibration in the reactions that proceed by initial 1,2 addition, followed by 1,2 to 1,4 equilibration. Rathke has shown that aldol–retroaldol processes can provide a mechanism for E–Z equilibration in reactions of ketone enolates.[10] The relative stabilities of the E and Z isomers of the *tert*-butyl propionate lithium enolates have not been determined. However, Wilcox has examined the corresponding *tert*-butyldimethylsilyl ketene acetals and finds a Z/E ratio of about 10:1 at 32 °C.[11,12] Furthermore, Corey and Gross have recently suggested that the Z lithium enolate is more stable than the E lithium enolate.[13,14] This suggestion is also consistent with our results, as E–Z equilibration nicely explains the low stereoselectivity seen in the reaction of enolate 2 with enone 5 (Table I, entry 8), the sole departure from the otherwise strong E-syn,Z-anti correlation. In fact, E→Z equilibration might explain the fact that reactions carried out with the HMPT-derived enolate often show higher anti/syn ratios than the Z/E ratio of the enolate (Table I, entries 3 and 9). The indication from these experiments, and others recently carried out in our laboratories,[15] is that the thermodynamic Z/E ratio for the *tert*-butyl propionate enolates is >97:3.

Finally, we would like to draw attention to the similarities and differences between our results and those recently reported by Yamaguchi and co-workers.[16] The

(6) In the case of the ester enolate reactions, part of this preference is undoubtedly due to the fact that the initial 1,2 adduct is less stable in the presence of HMPT than in pure THF. Thus, with enone 5 and enolate 1 (Table I, entry 5), 1,2-addition is probably more rapid than 1,4-addition, but is thermodynamically unfavorable under the reaction conditions (HMPT/THF). At higher temperature, the slower, thermodynamically favorable 1,4 addition occurs (entry 6).

(7) For a definition of the syn/anti convention, see: Masamune, S.; Ali, Sk, A.; Snitman, D. L., Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(8) (a) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. (c) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (d) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (e) Seebach, D. "Proceedings of the R. A. Welch Foundation Conference", Houston, Nov 7–9, 1983. (f) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972.

(9) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(10) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

(11) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.

(12) Note that the Z silyl ketene acetal has the same configuration as the E lithium enolate, using the Evans convention.[2]

(13) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(14) Scolastico and co-workers have recently observed thermal isomerization of an E enolate to its Z isomer. In this case, however, the more stable isomer may benefit from internal chelation. Banfi, L.; Bernardi, A.; Colombo, L; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784.

(15) If less than a stoichiometric amount of *tert*-butyl propionate in THF is added slowly (syringe pump) to a solution of LDA in 23% (v/v) HMPT in THF, by the classic Ireland procedure (ref 4), the Z/E ratio is usually in the range 85:15 to 90:10. However, if excess ester (1.1–1.5 equiv) is added rapidly to a solution of LDA in HMPT/THF, Z/E ratios as high as 97:3 are observed.

Japanese group have found that the *E* lithium enolate of ethyl propionate reacts with ethyl (*E*)-crotonate to give the anti and syn 1,4 adducts in a ratio of 71:29[16a] and that the stereoselectivity is increased to 10:1 if HMPT is added *subsequent* to enolate formation and to >20:1 if HMPT is added prior to enolate formation.[16b] The latter observation is consistent with our finding that the *Z* enolate **1**, formed by deprotonation of *tert*-butyl propionate in the presence of HMPT,[4] gives predominantly the anti-Michael adduct. However, we observe high syn selectivity with the enolate formed in THF alone and have not observed a reversal to anti selectivity if HMPT is added after formation of the enolate. In agreement with our results, Yamaguchi and co-workers also found that the *E* enolate of *tert*-butyl propionate (**2**), formed by deprotonation of *tert*-butyl propionate in the absence of HMPT, reacts with ethyl (*E*)-crotonate to give the syn diastereomer (stereoselectivity >20:1).[16b]

In summary, our investigations with the stereoisomeric *E* and *Z* enolates of *tert*-butyl propionate have demonstrated that there is a relationship between enolate geometry and Michael adduct stereostructure, as has been previously found in the aldol addition reactions of lithium enolates.[3] Experiments aimed at further defining the mechanism and scope of the kinetic Michael reaction and at the synthetic exploitation of the stereoselective processes reported in this communication are in progress.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service (AI15027).

Supplementary Material Available: A listing of the ^{13}C NMR chemical shifts of the products summarized in Table I (1 page). Ordering information is given on any current masthead page.

(16) (a) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Chem. Lett.* **1984**, 375. (b) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661.

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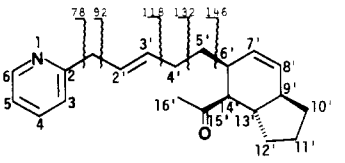
An Intriguing C_{16}-Alkadienone-Substituted 2-Pyridine from a Marine Mollusk[1]

Summary: A minor metabolite of the caphalaspidean mollusk *Philinopsis speciosa* is an uncommon pyridine derivative, substituted at C-2 by a bicyclic polyketide derived C_{16}-alkadienone. Its structure was elucidated largely by ^1H NMR techniques.

Sir: Our search for ecologically meaningful metabolites of coral reef invertebrates has prompted us to study the endemic Hawaiian opisthobranch mollusk *Philinopsis speciosa*. *P. speciosa* belongs to the order Cephalaspidea, characterized by a prominent head shield; it has a thin shell enclosed in the mantle and feeds on other mollusks at night, when it may be found in sandy tidepools during June and July.[2] Its principal organic constituents are C_{24}- and C_{25}-polypropionate compounds to be described elsewhere. Here we report on the structure of pulo'upone[3] (**1**),



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a minor (0.008% of freeze-dried animal) metabolite, which is an uncommon pyridine derivative substituted at C-2 by a bicyclic C_{16}-polyketide. Hexane extraction of 59 freeze-dried animals (77.5 g) yielded 1.17 g of residue. Chromatography on Sephadex LH-20 (1:1 CH_2Cl_2/2-PrOH) yielded four fractions; the last (613 mg) was triturated with MeCN and then passed through a C_{18} Bond Elut[4] cartridge (MeCN). The eluate after HPLC on Bondapak C_{18} (MeCN) was split into three fractions. Rechromatography of the middle fraction on Bondapak C_{18} (85:15 MeCN/H_2O) furnished pulo'upone (**1**, 6.5 mg) as a colorless oil, $[\alpha]_D$ −10° (*c* 0.20, hexane).

HRMS revealed a composition of $C_{21}H_{27}NO$ (*m/z* 309.2095, calcd 309.2093), which together with UV bands (EtOH) at 260 (ε 10 700), 257 (3870), 263 (4200), and 269 (3130) nm suggested a substituted pyridine. MS fragments[6] at *m/z* 78, 92, 118, 132, and 146 (see formula *1*) were indicative of an unbranched C_5 monoolefinic side chain. Four downfield proton signals in the ^1H NMR spectrum of **1** (Table I) require a monosubstituted pyridine; an acetyl group (δ 2.09 (s, 3 H) and ν_{max} 1713 cm^{-1}) defines the terminus of the side chain. Full ^1H NMR data are given in Table I.

A ^1H NMR COSY experiment and extensive decoupling in C_6D_6 showed that the pyridine ring was 2-substituted

Table I. ^1H NMR Data (300 MHz) for 1 in Cd_2Cl_2 and C_6D_6

	CD_2Cl_2		C_6D_6	
^1H	δ	*J*	δ	*J*
3	7.14 br d	8.2	6.78 d	7.6
4	7.63 ddd	1.7, 7.7, 8.2	7.02 ddd	1.8, 7.3, 7.6
5	7.13 br dd	5.0, 7.7	6.56 dd	4.9, 7.3
6	8.48 dd	0.8, 5.0	8.46 dd	1.8, 4.9
1′a,b	3.50 br d	6.6	3.51 d	6.9
2′	5.65 br dd	6.6, 15.3	5.72 ddd	6.9, 6.9, 15.0
3′	5.51 ddd	5.3, 6.6, 15.3	5.36 ddd	6.7, 6.8, 15.0
4′a	2.15 m		2.05 m	
4′b	2.00 m		1.87 m	
5′a	1.3 m		1.38 m	
5′b	1.2 m		1.28 m	
6′	2.65 m		2.35 m	
7′	5.70 ddd	2.6, 3.9, 9.9	5.57 ddd	2.4, 3.3, 9.8
8′	5.86 d	9.9	5.82 d	9.8
9′	2.0 m		2.3 m	
10′a	1.3 m		1.4 m	
10′b	1.2 m		1.4 m	
11′a	1.7 m		1.6 m	
11′b	1.6 m		1.6 m	
12′a	0.93 m		1.1 m	
12′b	1.15 m		0.9 m	
13′	1.54 m	6, 9, 10, 11.0	1.6 m	
14′	2.75 dd	6.2, 11.0	2.40 br d	7.3
16′	2.09 s	CH_3	1.71 s	CH_3

(1) A preliminary account was presented at the PacChem Congress, Honolulu, HI, Dec 16-21, 1984, Abstract *ORGN* 10 E 23.

(2) Kay, E. A. "Hawaiian Marine Shells"; Bishop Museum Press: Honolulu, HI, 1979; p 430.
(3) Pulo'u is the Hawaiian word for head covering.
(4) Analytichem International, Harbor City, CA.
(5) Waters Associates, Inc., Milford, MA.
(6) EIMS, *m/z* 309 (5%), 267 (18), 266 (91), 173 (7), 172 (6), 147 (10), 146 (62), 133 (66), 132 (39), 131 (15), 130 (28), 119 (30), 118 (72), 106 (15), 93 (59), 92 (13), 91 (44), 79 (22), 78 (10), 77 (15), 67 (11), 43 (100).
(7) IR (film) ν_{max} 2924, 2856, 1713, 1456, 1435, 1354, 970 cm^{-1}.

0022-3263/85/1950-3024$01.50/0