diverse and evergrowing structure class. Further applications of this methodology to the construction of rigid "ball-shaped" polyethers is in progress.[15,16]

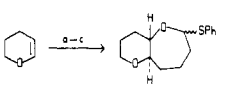
**Acknowledgment.** We are indebted to the National Institutes of Health for their support of these investigations. We thank Dr. J. Abola and Mr. J. Mandel for the X-ray structure determination which was carried out on the NIH supported (Grant 1 S1O RR02381-01) X-ray facility of the University of Pittsburgh Chemistry Department.

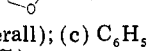
**Registry No.** **1**, 92056-26-3; **2**, 97102-43-7; **3**, 97102-44-8; **4**, 97102-45-9; **4**-one, 97102-61-9; **5**, 60378-39-4; **5** (Grignard adduct), 97102-72-2; **6a**, 97102-46-0; **6b**, 97102-47-1; **7**, 97102-48-2; **8** (isomer 1), 97134-64-0; **8** (isomer 2), 97169-11-4; **9** (isomer 1), 2396-74-9; **9** (isomer 2), 3021-94-1; **10**, 97102-49-3; **10**-ol, 97102-64-2; **10**-ol (THP), 97102-66-4; **10**-diol (THP), 97102-68-6; **10**-alol (THP), 97102-70-0; **11**, 97102-50-6; **11**-ol, 97102-65-3; **11**-ol (THP), 97102-67-5; **11**-diol (THP), 97102-69-7; **11**-al (THP), 97102-71-1; **12**, 97102-51-7; **12**-ol, 97102-73-3; **13** (isomer 1), 97102-52-8; **13** (isomer 2), 97134-65-1; **14**, 82921-66-2; **14** (allyl deriv.), 82921-70-8; **15**, 97102-53-9; **15**-ol, 97134-66-2; **16**, 97102-54-0; **17** (isomer 1), 97112-50-0; **17** (isomer 2), 97102-55-1; **18**, 92619-83-5; **18** (benzyl ether), 97134-67-3; **19**, 97102-56-2; **20**, 97102-57-3; i, 97102-58-4; ii, 97112-51-1; iii, 97102-59-5; 6-(phenylthio)octahydro-2*H*-pyrano[3,2-*b*]oxepin, 97102-60-8; dihydropyran, 110-87-2; 3-iodopropionaldehyde ethylene acetal, 83665-55-8; *cis*-2,3-dihydroxytetrahydropyran, 97102-62-0; *trans*-2,3-dihydroxytetrahydropyran, 97102-63-1; 3-bromopropionaldehyde ethylene acetal, 18742-02-4; allyl bromide, 106-95-6; allyltrimethylsilane, 762-72-1.

**Supplementary Material Available:** Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **13** and the physical and spectral data for **4**, **5**, **6a**, **8**, **13**, **17**, and **20** (11 pages). Ordering information is given on any current masthead page.

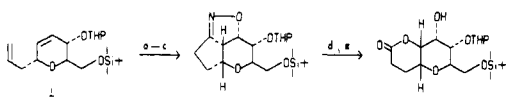
(15) For some other recent approaches to pyranopyrans, see: Nicoll-Griffith, D.; Weiler, L. *J. Chem. Soc., Chem. Commun.* **1984**, *659*. Martin, O. R.; Szarek, W. A. *Carbohydr. Res.* **1984**, *130*, 195. Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 5049.

(16) We have also assembled the pyran system below containing a fused seven-membered ring using the type a methodology.



(a) *t*-BuLi, TMEDA;  ; HMPA; (b) $BH_3$·THF/$H_2O_2$, NaOH (67% overall); (c) $C_6H_5SH$, TsOH, $CH_2Cl_2$, room temperature (96%).

(17) The INOC reaction can also serve as a device for the construction of cis-fused pyranolactones as illustrated below.



(prepared as in ref 14e)

(a) 9-BBN/$H_2O_2$, NaOH; (b) Swern oxidation (82% overall); (c) $NH_2OH$·HCl, py; NaOCl, $Et_3N$, $CH_2Cl_2$ (89%); (d) Raney Ni, *i*-PrOH, $H_2O$; (e) MCPBA, $CH_2Cl_2$ (88% overall from ii).

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## Stereoselection in the Michael Addition Reaction. 2. Stereochemistry of the Kinetic Michael Reaction of Amide Enolates with Enones[1]

*Summary:* An extensive study of structure–stereoselectivity relationships in the kinetic Michael addition of preformed lithium enolates to enones has uncovered some reactions of sufficiently high diastereoselectivity as to be synthetically attractive and has allowed the formulation of a coherent transition state hypothesis that incorporates the lithium enolate cluster as a dominant stereocontrol element.

*Sir:* The conjugate addition of enolates to unsaturated carbonyl compounds (Michael processes,[17] we one of the most widely used carbon–carbon bond-forming reactions.[3] However, in spite of its scope, the Michael reaction is not without limitations, which revolve mainly about the problems of regioselective enolate generation, the tendency for many enones to undergo polymerization under strongly basic conditions, and the availability of an attractive alternative reaction path in many cases (1,2 addition).[4,5] A number of methods for achieving stoichiometric enolate Michael additions have been devised.[6-16]

Because of our interest in the stereochemistry of carbon–carbon bond-forming processes,[17] we have initiated an investigation of the diastereoselectivity of the Michael addition reaction. In a previous communication[1] we reported results of a study of the acid-catalyzed process (Mukaiyama–Michael reaction); in this communication, we report preliminary results of a study of the stereochemistry of addition of amide enolates to enones. The results to date have revealed some kinetic Michael additions of sufficiently high diastereoselectivity as to be synthetically attractive. More importantly, the structure–stereoselectivity trends that have emerged from the study have allowed us to formulate for this important reaction a coherent transition state hypothesis, involving the lithium enolate cluster as a dominant stereocontrol element.

(1) Part 30 in the series "Acyclic Stereoselection". For part 29, see: Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

(2) (a) Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349. (b) Michael, A.; Schulthess, O. *Ibid.* **1892**, *45*, 55. (c) Michael, A. *Ibid.* **1894**, *49*, 20. (d) Michael, A. *Am. Chem. J.* **1887**, *9*, 112. (e) Michael, A. *Chem. Ber.* **1894**, *27*, 2126. (f) Michael, A. *Ibid.* **1900**, *33*, 3731.

(3) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React. (N.Y.)* **1959**, *10*, 179.

(4) House, H. O. In "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, 1972; 595–615.

(5) (a) House, H. O.; Lusch, M. J. *J. Org. Chem.* **1977**, *42*, 183. (b) See also: Bertrand, J.; Cabrol, N.; Gorrichon-Guigon, L.; Maroni-Barnard, Y. *Tetrahedron Lett.* **1973**, 4683.

(6) (a) Stork, G. A.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Stork, G. A.; Ganem, B. *Ibid.* **1974**, *96*, 6181.

(7) (a) Boeckman, R. K. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (b) Boeckman, R. K. *Ibid.* **1974**, *96*, 6179.

(8) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544.

(9) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.

(10) Mulzer, J.; Chucholowski, A.; Lammer, O.; Jibril, I.; Huttner, G. *J. Chem. Soc., Chem. Commun.* **1983**, 869.

(11) Oppolzer, W.; Pitteloud, R.; Bernardinelli, G.; Baettig, K. *Tetrahedron Lett.* **1983**, *24*, 4975.

(12) (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.

(13) Mulzer, J.; Hartz, G.; Kühl, U.; Brüntrup, G. *Tetrahedron Lett.* **1978**, 2949.

(14) Viteva, L. Z.; Stefanovsky, Y. N. *Monatsh. Chem.* **1982**, *113*, 181 and previous papers in this series.

(15) (a) Bertrand, J.; Gorrichon, L.; Maroni, P. *Tetrahedron* **1984**, *40*, 4127. (b) Bertrand, J.; Gorrichon, L.; Maroni, P., Meyer, R. *Bull. Soc. Chim. (Fr.)*, submitted for publication.

(16) Häner, R.; Laube, T.; Seebach, D. *Chimia* **1984**, *38*, 255.

(17) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395.

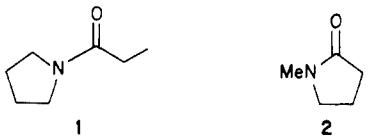
0022-3263/85/1950-3019$01.50/0 

**Table I. Stereochemistry of Addition of Amides 1 and 2 to Enones (Eq 1, 2)**

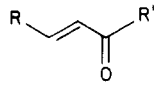
| entry | amide | enone | reactn temp, °C | reactn time | yield, % | 1,2/1,4 | syn/anti (1,4 adduct) |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 3 | −78 | 20 min | 78 | >97:3 | |
| 2 | 1 | 3 | 25 | 12 h | 26 | 4:96 | 43:57 |
| 3 | 2 | 3 | −78 | 60 min | 50 | >97:3 | |
| 4 | 2 | 3 | 25 | 10 h | 60 | >97:3 | |
| 5 | 1 | 4 | −78 | 45 min | 84 | 29:71 | 40:60 |
| 6 | 1 | 4 | 25 | 12 h | 85 | <3:97 | 40:60 |
| 7 | 2 | 4 | −78 | 60 min | 64 | 80:20 | 10:90 |
| 8 | 2 | 4 | 25 | 10 h | 76 | 50:50 | 10:90 |
| 9 | 1 | 5 | −78 | 60 min | 90 | <3:97 | 45:55 |
| 10 | 2 | 5 | −78 | 60 min | 72 | 14:86 | 10:90 |
| 11 | 2 | 5 | 25 | 10 h | 99 | <3:97 | 10:90 |
| 12 | 1 | 6 | −78 | 60 min | 56 | 40:60 | 45:55 |
| 13 | 1 | 6 | 25 | 14 h | 51 | <3:97 | 45:55 |
| 14 | 2 | 6 | −78 | 60 min | 93 | 68:32 | 10:90 |
| 15 | 2 | 6 | 25 | 13 h | 56 | 20:80 | 10:90 |
| 16 | 1 | 7 | −78 | 60 min | 92 | 12:88 | 87:13 |
| 17 | 1 | 7 | 25 | 10 h | 86 | <1:99 | 85:15 |
| 18 | 2 | 7 | −78 | 60 min | 67 | 63:37 | 5:95 |
| 19 | 2 | 7 | 25 | 10 h | 96 | <5:95 | 5:95 |
| 20 | 1 | 8 | −78 | 60 min | 84 | 50:50 | 80:20 |
| 21 | 1 | 8 | 25 | 13 h | 40 | <3:97 | 80:20 |
| 22 | 2 | 8 | −78 | 30 min | 77 | 70:30 | 5:95 |
| 23 | 2 | 8 | 25 | 14 h | 90 | 58:42 | 5:95 |
| 24 | 1 | 9 | −78 | 60 min | 72 | 35:65 | 75:25 |
| 25 | 1 | 9 | 25 | 19 h | 58 | <3:97 | 75:25 |
| 26 | 2 | 9 | −78 | 60 min | 49 | 72:28 | 10:90 |
| 27 | 2 | 9 | 25 | 12 h | 60 | <3:97 | 10:90 |
| 28 | 1 | 10 | −78 | 15 min | 95 | <3:97 | 37:63 |
| 29 | 2 | 10 | −78 | 15 min | 58 | 31:69 | 8:92 |
| 30 | 2 | 10 | 25 | 90 min | 87 | <3:97 | 7:93 |
| 31 | 1 | 11 | −78 | 15 min | 46 | 7:93 | 33:67 |
| 32 | 1 | 11 | 25 | 90 min | 65 | <3:97 | 27:73 |
| 33 | 2 | 11 | −78 | 15 min | 73 | 57:43 | 7:93 |
| 34 | 2 | 11 | 25 | 90 min | 62 | <3:97 | 20:80 |
| 35 | 1 | 12 | −78 | 15 min | 70 | 54:46 | <3:97 |
| 36 | 1 | 12 | 25 | 90 min | 86 | <3:97 | <3:97 |
| 37 | 2 | 12 | −78 | 15 min | 60 | >97:3 | |
| 38 | 2 | 12 | 25 | 23 h | 0[a] | | |
| 39 | 1 | 13 | −78 | 15 min | 69 | <3:97 | 9:91 |
| 40 | 2 | 13 | −78 | 15 min | 55 | 55:45 | 32:68 |
| 41 | 2 | 13 | 25 | 90 min | 68 | <3:97 | 40:60 |

[a] Extensive decomposition indicated by proton NMR spectrum; no product was isolated.

The amides chosen for study were *N*-propionylpyrrolidine (1), which has been shown to form the *Z* enolate with LDA in THF,[18] and *N*-methylpyrrolidone (2), which must form the *E* enolate for geometric reasons. For Michael receptors, we employed enones **3**–**13**.



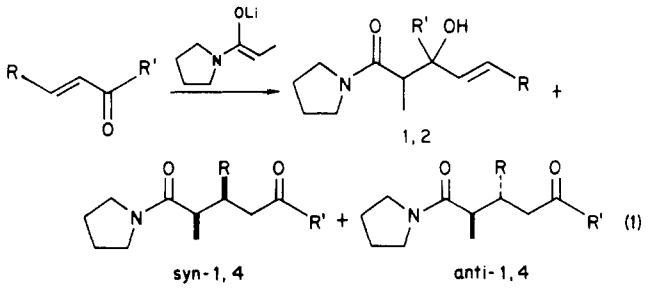
1 2



**3**, R = Me; R' = Et
**4**, R = Me; R' = *iso*-Pr
**5**, R = Me; R' = *t*-Bu
**6**, R = Me; R' = *c*-$C_6H_{11}$
**7**, R = Me; R' = Ph
**8**, R = Me; R' = *p*-$BrC_6H_4$
**9**, R = Me; R' = *p*-$MeOC_6H_4$
**10**, R = Et; R' = *t*-Bu
**11**, R = *iso*-Pr; R' = *t*-Bu
**12**, R = *t*-Bu; R' = *t*-Bu
**13**, R = Ph; R' = *t*-Bu

Enolates were preformed in THF at −78 °C by addition of the amide to a solution of lithium diisopropylamide (LDA). Workup by addition of aqueous $NH_4Cl$ after short reaction times (5–30 min) at −78 °C allowed us to determine the kinetic ratio of 1,2 to 1,4 addition. Control experiments showed that 1,2 to 1,4 equilibration does not occur at −78 °C. In agreement with the observations of Schultz,[9] we found that 1,2 to 1,4 equilibration occurs when the reaction solution is brought to a higher temperature for an appropriate period of time. Product structures were determined by a variety of methods, including single-crystal X-ray analysis, conversion to materials of known stereostructure, chemical interconversion, and $^{13}C$ NMR chemical shift correlation.[19]

As expected, at −78 °C amide 1 gives mixtures of 1,2 and 1,4 adducts, with the 1,2/1,4 ratio being related to the steric bulk of R and R′ (eq 1, Table I).[13,15] The 1,4 adducts



syn-1,4 anti-1,4 (1)

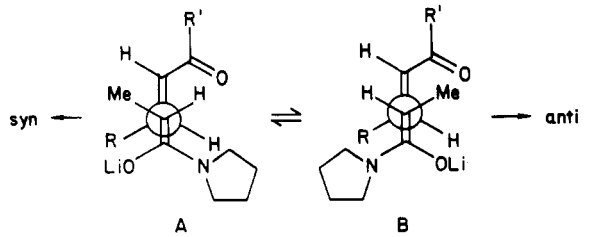
are a mixture of syn and anti isomers, with the anti isomer generally being moderately favored.[20] However, with

(18) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876.

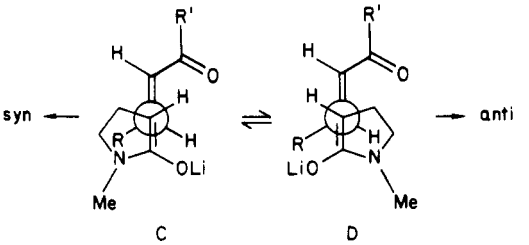
(19) Full details are presented in the Supplementary Material; see statement at the end of this paper.

(20) 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.

**Scheme I**

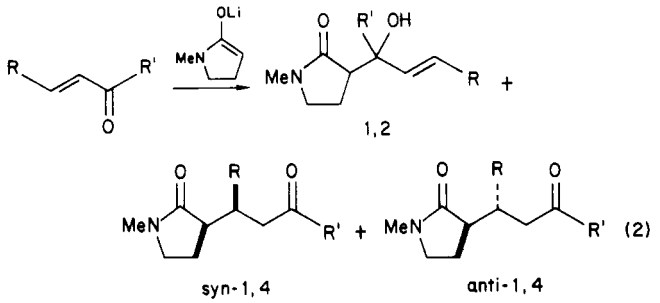



**Scheme II**




enones **12** and **13** the anti preference is very high (entries 35/36 and 39). With the phenyl enones **7–9**, amide **1** shows relatively high syn selectivity. The diastereoselectivity of the 1,4 addition seems to be little affected by reaction temperature; syn/anti ratios observed in the kinetic products (−78 °C data) are virtually identical with those obtained from the 1,2 to 1,4 equilibration.

Amide **2** gives a somewhat greater amount of 1,2 adduct at −78 °C, and the 1,2 to 1,4 equilibration is slower (eq 2, Table I). On the other hand, this reactant gives generally




(2)

greater stereoselectivity. The anti isomer is the major product with amide **2**, generally in synthetically useful ratios of >10:1. Again, enone **13** is exceptional, giving only a modest preference for the anti adduct.

The results of this study may be understood in terms of an open transition state, as illustrated in Scheme I. We believe that the reaction takes place on the lithium enolate tetramer,[21] and that "OLi" in Scheme I is actually a rather large group. With amide **1** little syn/anti selectivity is seen with most enones, presumably because the gauche interactions in A and B are comparable in magnitude. The syn selectivity observed with amide **1** and phenyl enones may be the result of a charge-transfer interaction between the $\pi$-systems of the aromatic ring and the enolate.

On the other hand, the stereocontrol element in the reactions of amide **2** is interaction of R with the pyrrolidone ring (conformation C). Thus, this amide reacts primarily through conformation D, and gives anti products (Scheme II).

Previous discussions of the stereochemistry of the kinetic Michael reaction have mainly invoked closed transition states, in which the metal ion is chelated in an eight-membered ring between the oxygens of the enone and enolate.[10-11,13-16,22] If our notion of an open transition state is valid, it follows that ester enolates should show higher stereoselectivity than amide enolates and that there should be a good correlation between enolate geometry and Michael adduct stereostructure, with the *Z* enolate giving the anti adduct and the *E* enolate giving the syn adduct. Further support for this mechanistic rationale has been found in parallel studies of the reactions of *E* and *Z* enolates derived from *tert*-butyl propionate with enones **5**, **10**, **12**, and **13**. Details of this investigation are reported in the following communication.[23]

**Acknowledgment.** This work was supported by a research grant from the United States Public Health Service (AI15027). M.A.H. acknowledges financial support in the form of a University of California Regents Fellowship, 1983–84.

**Registry No.** **1**, 4553-05-3; **1** (Li enolate), 76943-99-2; **2**, 872-50-4; **2** (Li enolate), 55259-75-1; **3**, 50396-87-7; **4**, 50396-90-2; **5**, 20971-19-1; **6**, 15378-40-2; **7**, 35845-66-0; **8**, 97060-28-1; **9**, 97060-29-2; **10**, 38343-01-0; **11**, 38343-04-3; **12**, 20859-13-6; **13**, 29569-91-3; *N*-(3-ethyl-3-hydroxy-2-methyl-4-hexenoyl)pyrrolidine, 97060-30-5; *syn*-*N*-(2,3-dimethyl-5-oxoheptanoyl)pyrrolidine, 97060-31-6; *anti*-*N*-(2,3-dimethyl-5-oxoheptanoyl)pyrrolidine, 97060-32-7; 3-(4-hydroxy-2-hexen-4-yl)-*N*-methylpyrrolidone, 97060-33-8; 3-(4-oxo-2-hexyl)-*N*-methylpyrrolidone, 97060-34-9; *N*-(3-hydroxy-3-isopropyl-2-methyl-4-hexenoyl)pyrrolidine, 97060-35-0; *syn*-*N*-(5-oxo-2,3,6-trimethylheptanoyl)pyrrolidine, 97060-36-1; *anti*-*N*-(5-oxo-2,3,6-trimethylheptanoyl)pyrrolidine, 97060-37-2; 3-(4-hydroxy-5-methyl-2-hexen-4-yl)-*N*-methylpyrrolidone, 97060-38-3; *syn*-3-(5-methyl-4-oxo-2-hexyl)-*N*-methylpyrrolidone, 97060-39-4; *anti*-3-(5-methyl-4-oxo-2-hexyl)-*N*-methylpyrrolidone, 97060-40-7; *N*-(3-*tert*-butyl-3-hydroxy-2-methyl-4-hexenoyl)pyrrolidine, 97060-41-8; *syn*-*N*-(5-oxo-2,3,6,6-tetramethylheptanoyl)pyrrolidine, 97060-42-9; *anti*-*N*-(5-oxo-2,3,6,6-tetramethylheptanoyl)pyrrolidine, 97060-43-0; 3-(5,5-dimethyl-4-hydroxy-2-hexen-4-yl)-*N*-methylpyrrolidone, 97060-44-1; *syn*-3-(5,5-dimethyl-4-oxo-2-hexyl)-*N*-methylpyrrolidone, 97060-45-2; *anti*-3-(5,5-dimethyl-4-oxo-2-hexyl)-*N*-methylpyrrolidone, 97060-46-3; *N*-(3-cyclohexyl-3-hydroxy-2-methyl-4-hexenoyl)pyrrolidine, 97060-47-4; *syn*-*N*-(5-cyclohexyl-2,3-dimethyl-5-oxopentanoyl)pyrrolidine, 97060-48-5; *anti*-*N*-(5-cyclohexyl-2,3-dimethyl-5-oxopentanoyl)pyrrolidine, 97060-49-6; 3-(1-cyclohexyl-1-hydroxy-2-butenyl)-*N*-methylpyrrolidone, 97060-50-9; *syn*-3-(4-cyclohexyl-4-oxo-2-butyl)-*N*-methylpyrrolidone, 97060-51-0; *anti*-3-(4-cyclohexyl-4-oxo-2-butyl)-*N*-methylpyrrolidone, 97060-52-1; *N*-(3-hydroxy-2-methyl-3-phenyl-4-hexenoyl)pyrrolidine, 97060-53-2; *syn*-*N*-(2,3-dimethyl-5-oxo-5-phenylpentanoyl)pyrrolidine, 97060-54-3; *anti*-*N*-(2,3-dimethyl-5-oxo-5-phenylpentanoyl)pyrrolidine, 97060-55-4; 3-(1-hydroxy-1-phenyl-2-butenyl)-*N*-methylpyrrolidone, 97060-56-5; *syn*-3-(4-oxo-4-phenyl-2-butyl)-*N*-methylpyrrolidone, 97060-57-6; *anti*-3-(4-oxo-4-phenyl-2-butyl)-*N*-methylpyrrolidone, 97060-58-7; *N*-[3-(*p*-bromophenyl)-3-hydroxy-2-methyl-4-hexenoyl]pyrrolidine, 97060-59-8; *syn*-*N*-[5-(*p*-bromophenyl)-2,3-dimethyl-5-oxopentanoyl]pyrrolidine, 97060-60-1; *anti*-*N*-[5-(*p*-bromophenyl)-2,3-dimethyl-5-oxopentanoyl]pyrrolidine, 97071-45-9; 3-[1-(*p*-bromophenyl)-1-hydroxy-2-butenyl]-*N*-methylpyrrolidone, 97060-61-2; *syn*-3-[4-(*p*-bromophenyl)-4-oxo-2-butyl]-*N*-methylpyrrolidone, 97060-62-3; *anti*-3-[4-(*p*-bromophenyl)-4-oxo-2-butyl]-*N*-methylpyrrolidone, 97060-63-4; *N*-[3-

(21) (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.

(22) In Mulzer's work on kinetic Michael addition of $\beta$-lactone enolates to dimethyl maleate, high anti selectivity is observed, as in the reactions of lactam **2**. A closed transition state, in which the enolate and maleate double bonds are approximately parallel, was invoked to explain the high stereoselectivity observed. However, examination of the suggested transition state (transition state A in ref 10) reveals that it would actually afford the syn Michael adduct. An open transition state, such as we propose, nicely accounts for Mulzer's result.

(23) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.*, following communication in this issue.

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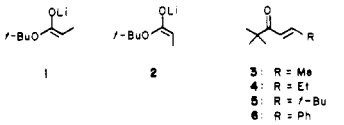
## Stereoselection in the Michael Addition Reaction. 3. Relationship between Ester Enolate Geometry and Adduct Stereochemistry in the Kinetic Michael Reaction of Lithium Enolates with Enones[1]

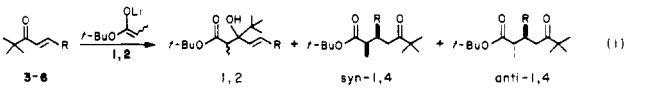
*Summary:* A systematic study of the stereochemistry of the kinetic Michael addition of the *Z* and *E* lithium enolates of *tert*-butyl propionate has provided conclusive evidence that the stereostructure of a lithium enolate determines the stereostructure of the resulting Michael adduct.

*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.

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