with brine (2 × 3 mL), and dried ($MgSO_4$). After evaporation of the solvents under reduced pressure, pure **3** was obtained (10 mg, 80%) as a colorless oil by flash chromatography (hexanes/ethyl acetate, 4:1). ^1H NMR (500 MHz): δ 6.55 (dd, 1 H, J = 1.0, 4.7 Hz), 3.54 (s, 1 H), 2.86 (tp, 1 H, J = 1.0, 6.9 Hz), 2.72 (s, 3 H), 2.55 (d, 1 H, J = 7.0 Hz), 2.46 (m, 1 H, J = 4.7, 8.0, 10 Hz), 2.26 (tdd, 1 H, J = 1.4, 6.0, 12.7 Hz), 2.06 (m, 1 H, J = 1.0, 7.0, 8.0, 10.0 Hz), 1.89 (m, 1 H, J = 6.0, 7.0, 12.5, 12.7 Hz), 1.38–1.27 (comp, 4 H), 1.03 (d, 3 H, J = 6.9 Hz), 0.96 (d, 3 H, J = 6.9 Hz). ^{13}C NMR (125 MHz): δ 194.7, 176.8, 143.9, 140.9, 70.4, 55.5, 47.1, 44.7, 33.9, 29.6, 28.7, 27.3, 26.9, 22.0, 21.1. IR (CCl_4): ν 2940, 2860, 1700, 1675, 1465, 1395, 1240 cm^{-1}. Mass spectrum: m/e 247.15723 ($C_{15}H_{21}NO_2$ requires 247.15769), 124, 111 (base).

Acknowledgment. We thank the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation for generous financial support of this research. We are grateful to Dr. Franz Scheidl (Hoffmann-LaRoche, Nutley, NJ) for performing the combustion analyses.

Registry No. (±)-**1**, 30646-45-8; (±)-**3**, 40142-12-9; (±)-**7**, 129872-08-8; (±)-**7** methyl ester, 83747-57-3; (±)-**8**, 118495-26-4; **9a**, 129872-10-2; **9a** aldehyde, 123-73-9; **9b**, 129872-11-3; **9c**, 129872-12-4; **9d**, 129872-13-5; (*E,E*)-**9e**, 129872-14-6; (*E,Z*)-**9e**, 129872-15-7; **9e** aldehyde, 59819-88-4; **9f**, 129895-36-9; **9f** aldehyde, 129872-09-9; (*E,E*)-**9g**, 129872-16-8; (*E,Z*)-**9g**, 129872-17-9; (±)-**10a**, 118495-12-8; (±)-**10b**, 118495-13-9; **10c** (isomer 1), 129872-18-0; **10c** (isomer 2), 129872-28-2; (±)-**10d**, 118495-15-1; (±)-**10e**, 129872-19-1; (±)-**10f**, 129872-20-4; (±)-**10g**, 118495-24-2; (±)-**11a**, 118495-16-2; (±)-**11b**, 118495-17-3; **11c**, 112899-11-3; **11c'**, 129940-03-0; (±)-**11d**, 118495-18-4; (±)-**11e**, 129872-21-5; (±)-**11f**, 129872-22-6; (±)-**11g**, 118495-25-3; (±)-**12a**, 118574-41-7; (±)-**12b**, 118574-42-8; **12c**, 118574-40-6; (±)-**12d**, 118574-43-9; (±)-**12e**, 129940-01-8; (±)-**12f**, 129940-02-9; (±)-**12g**, 118574-44-0; (±)-**13a**, 118495-19-5; (±)-**13b**, 118495-20-8; **13c**, 118495-21-9; (±)-**15**, 129872-23-7; (±)-**16**, 129872-25-9; (±)-**16** (*N*-demethyl derivative), 129872-24-8; (±)-**17**, 129872-26-0; (±)-**18**, 129872-27-1; (±)-**22**, 118495-27-5; (±)-**23**, 118574-45-1; $MeNH_2$, 74-89-5; $PhCH_2NH_2$, 100-46-9; (*R*)-Ph(Me)CHNH$_2$, 3886-69-9; Ph_2CHNH_2, 91-00-9.

Supplementary Material Available: A summary of X-ray crystallographic data and ORTEP plots are provided for compounds **11c,d**, **18**, and **23** (45 pages). Ordering information is given on any current masthead page.

Stereochemical Control in the Ester Enolate Claisen Rearrangement. 1. Stereoselectivity in Silyl Ketene Acetal Formation[1]

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Received June 5, 1990

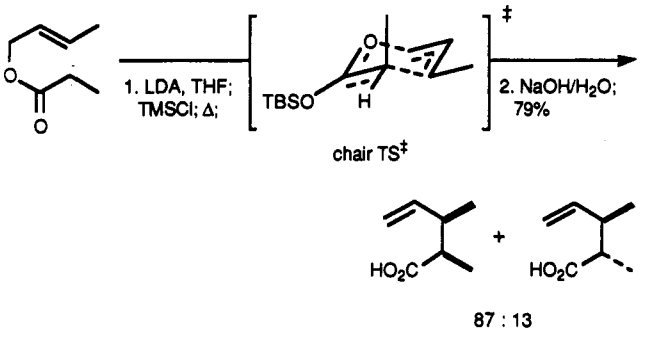
Methods for the stereoselective deprotonation and silylation of esters were systematically investigated. A kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective formation of (*E*)- and (*Z*)-silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS. A thermodynamic equilibration mechanism seems to be of minor significance with ester enolates. Improved reaction conditions were exemplified in a highly stereoselective Claisen rearrangement in THF/45% DMPU.

Introduction

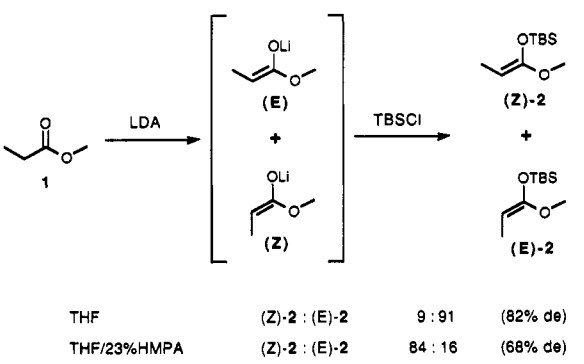
Since its introduction in 1972,[2] the silyl ketene acetal variant of the Claisen rearrangement has become increasingly popular in organic synthesis.[3] A wide field of applications includes the preparation of polyether antibiotics,[4] sesquiterpenes,[5] iridoids,[6] tetronates,[7] marine natural products,[8] amino acids,[9] *C*-glycosides,[10] large carbocycles,[11] and monochiral stannanes and silanes.[12]

Several factors contribute to the versatility of the ester

Scheme I



Scheme II



(1) Grateful acknowledgment is made for support of this investigation by a grant from NIH (GM-39998).

(2) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *46*, 3975. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Chem. Soc.* **1976**, *98*, 2868.

(3) For recent reviews, see: (a) Blechert, S. *Synthesis* **1989**, 71. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(4) Monensin: (a) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285. Lasolocide: (b) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (c) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.

(5) e.g. Guaianolide: (a) Knight, D. W.; Begley, M. J.; Cameron, A. G. *J. Chem. Soc., Chem. Commun.* **1984**, 827. Widdrol: (b) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891. Aphidicolin: (c) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446.

(6) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030.

(7) Chlorothricolide: (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. Streptolic acid: (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

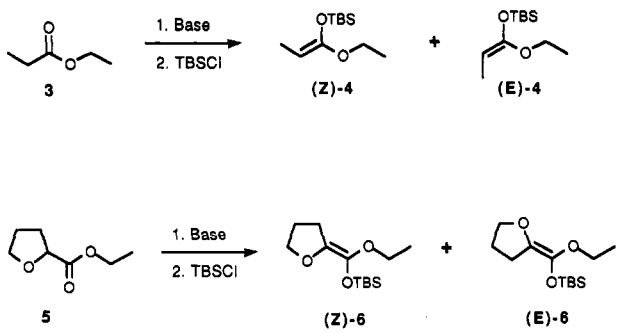
(8) Ophiobolin C: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735.

(9) (a) Barlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, 3933. (b) Knight, D. W.; Dell, C. P.; Khan, K. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1812.

(10) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743.

0022-3263/91/1956-0650$02.50/0

Scheme III



enolate Claisen rearrangement. Among these are the ability to use a stoichiometric combination of the alcohol and the acid components, the relatively low temperature[2c,13] of the pericyclic process that allows for the assembly of complex, highly functionalized structures, and the transformation of a carbon–oxygen into a carbon–carbon bond that lends itself easily to the assembly of contiguous quaternary centers.[14] Another particularly important aspect to this process is that, through an efficient control of ketene acetal geometry, a highly reliable and predictable transfer of stereochemistry from starting material to product can be realized (Scheme I). It is important to note, however, that an observed erosion of diastereoselectivity can be attributed to either the geometric integrity of the silyl ketene acetals or the selectivity of the chairlike vs boatlike transition states, which renders interpretation and improvement of experimental stereoselectivities rather delicate.

Silyl ketene acetal geometry is controlled by the selective formation of the *E* and *Z* ester enolate.[15] Deprotonation of methyl propionate (**1**) with LDA in THF at −78 °C gives, upon silylation with TBSCl, a 9:91 ratio of the "thermodynamic" ((*Z*)-**2**) and "kinetic" ((*E*)-**2**) silyl ketene acetals (Scheme II).[2,16]

A change in the reaction solvent results in a reversal in selectivity. In a THF/23% HMPA mixture, the silyl ketene acetals are isolated in a 84:16 ratio. The use of bulkier amide bases such as lithium *tert*-octyl-*tert*-butyl amide in THF leads to a slight increase of the *Z*:*E* ratio to 5:95 (de = 90%).[17] The degree of stereoselectivity for the formation of the (*Z*)-silyl ketene acetal (68% de, with present methodology), however, clearly deserves further optimization. In this paper, a systematic variation of reaction parameters such as solvent, ester to base ratio, and the type of base is reported that results in the enhancement of the selectivity for the formation of the (*Z*)-silyl ketene acetal and explores possible hypotheses for the change in selectivity observed in the combined use of THF and dipolar aprotic solvents.[18]

Table I. Effect of Solvent on Stereoselectivity of Silyl Ketene Acetal Formation of Ethyl Propionate (3) with LDA (Scheme III)

entry	solvent	ester:base	(*Z*)-4:(*E*)-4	yield, %
1	THF	1:1	6:94	90
2	THF/25% TMEDA	1:1	60:40	50
3	THF/50% TMEDA	1:1	–	0
4	THF/15% DMPU	1:1	37:63	90
5	THF/30% DMPU	1:1	67:31	85
6	THF/45% DMPU	1:1	93:7	90
7	THF/23% HMPA	1:1	85:15	90

Table II. Effect of Ester to Base Ratio on Stereoselectivity in Silyl Ketene Acetal Formation of Ethyl Propionate (3) with LDA (Scheme III)

entry	solvent	ester:base	(*Z*)-4:(*E*)-4	yield, %
1	THF	1.4:1	1:1	5
2	THF	1 + 0.2:1[a]	20:80	35
3	THF	1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30% DMPU	1.2:1	≥98:2	70
6	THF/30% DMPU	0.95:1	67:33	90
7	THF/30% DMPU	0.8:1	68:32	85
8	THF/30% DMPU	0.5:1	60:40	95
9	THF/30% DMPU	0.3:1	60:40	95
10	THF/45% DMPU	1.05:1	≥98:2	80
11	THF/45% DMPU	0.95:1[b]	≥98:2	80
12	THF/45% DMPU	0.8:1	93:7	90
13	THF/45% DMPU	0.8:1[c]	95:5	80
14	THF/45% DMPU	0.5:1	84:16	85
15	THF/23% HMPA	1.2:1	93:7	65
16	THF/23% HMPA	1:1	85:15	80
17	THF/23% HMPA	0.8:1	59:41	40
18	THF/23% HMPA	0.8:1[c]	64:36	35
19	THF/23% HMPA	0.6:1	55:45	35
20	THF/23% HMPA	0.4:1	54:46	40

[a] 0.2 equiv of the ester was added after DMPU addition. [b] 0.15 equiv of DMSO was added after enolization. [c] 0.22 equiv of DMSO was added after enolization.

Results

The enolization and silylation of ethyl propionate (**3**) and ethyl 2-tetrahydrofuroate (**5**) served as a model system to test the influence of various parameters on the stereoselectivity of lithium enolate formation (Scheme III).[19]

Effect of Solvent on Stereoselectivity of Silyl Ketene Acetal Formation. As reported,[2] enolization of 1 equiv of ethyl propionate with 1 equiv of LDA in THF leads, after silylation, to a 6:94 ratio of silyl ketene acetals (*Z*)-4 and (*E*)-4 (Scheme III, Table I). In a reaction medium containing 25% TMEDA, this ratio changes to 60:40 and is accompanied by a significant drop in yield. At a TMEDA concentration of 50% no desired product could be isolated.

In THF/15% DMPU,[20] enolization of ethyl propionate with LDA affords a 37:63 ratio of silyl ketene acetals. Increasing the amounts of DMPU led to a maximum *Z* isomer content of 93% in THF/45% DMPU (Table I, entry 6). The THF/45% DMPU solvent mixture results therefore in a significantly higher selectivity for *E* enolate formation than the THF/23% HMPA solvent system that is currently used for *E*-selective lithium enolate formation (Table I, entry 7). The higher efficiency of DMPU in the

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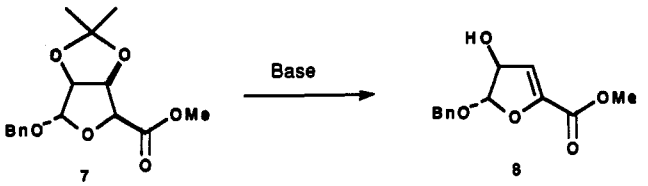
(12) (a) Ritter, K. *Tetrahedron Lett.* **1990**, *31*, 869. (b) Procter, G.; Murphy, P. J.; Spencer, J. L. *Tetrahedron Lett.* **1990**, *31*, 1051.
(13) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.
(14) (a) Birch, A. J.; Stobbe, J. *Tetrahedron Lett.* **1976**, 2079. (b) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1986**, *51*, 4485.
(15) The *E*/*Z* notation is adopted for the definition of the geometries of silyl ketene acetals as well as metal enolates. An a consequence, silylation of (*E*)-lithium ester enolates leads to (*Z*)-silyl ketene acetals.
(16) The configurational assignment for the enolate intermediate was confirmed by an X-ray analysis: Seebach, D.; Amstutz, R.; Laube, R.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. Silylation of enolates proceeds with retention of alkene geometry: Wilcox, C. S.; Babston, R. E.; Lynch, V. *Tetrahedron Lett.* **1989**, *30*, 447.
(17) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
(18) For a highly stereoselective formation of silyl ketene acetals from esters and trialkylsilyl perchlorates see: Wilcox, C. S.; Babston, R. E. *Tetrahedron Lett.* **1984**, *25*, 699.
(19) The stereochemistry of the enolate formed in THF is virtually unchanged by the subsequent addition of HMPA or DMPU; the trapping agent (TBSCl) may be present during the enolization or added afterwards with no change in outcome, cf. ref 2.
(20) DMPU = *N*,*N*'-dimethyl-*N*,*N*'-propyleneurea = 1,3-dimethyl-2-oxo-hexahydropyrimidine, a noncarcinogenic substitute for HMPA: Seebach, D.; Mukhopadhyay, T. *Helv. Chim. Acta* **1982**, *65*, 385. Melting point of DMPU: ca. −20 °C. HMPA: ca. 7 °C; THF/45% DMPU mixtures are still homogenous at −78 °C.

Table III. Rates of β-Elimination of Bicyclic Ester 7



entry	base	solvent	$t_{1/2}$, min	temp, °C
1	LHMDS	THF	45	−60
2	LHMDS	THF	no reaction	−80
3	LHMDS	THF/12% HMPA	15	−85
4	LHMDS	THF/12% HMPA	8	−78
5	KHMDS	THF	no reaction	−75
6	KHMDS	THF/12% HMPA	30	−75
7	KHMDS	THF/12% HMPA	1	−50

stereoselective formation of *E* enolates (leading to (*Z*)-silyl ketene acetals upon silylation) compared to HMPA is very likely due to the higher concentration of the former reagent that can be obtained in THF at −78 °C.[20]

Effect of Ester to Base Ratio on Stereoselectivity in Silyl Ketene Acetal Formation. In THF, a decrease of the ester to base ratio does not effect the (*E*)-silyl ketene acetal selectivity, whereas in the mixed solvent systems a slight (DMPU) or significant (HMPA) drop in (*Z*)-silyl ketene acetal selectivity is observed (Table II).

Addition of an excess of ester to 1 equiv of base in THF at −78 °C leads to a sharp drop in yield and an increase in the relative amount of (*Z*)-silyl ketene acetal (*Z*)-4. In THF/DMPU solvent systems, the presence of a small excess of ester leads to a spectacular increase in *Z* selectivity. If the ester to base ratio is kept below 1, *Z* selectivity is slightly attenuated until approximately a 0.5:1 ester to base ratio is reached, after which further dilution of the ester concentration in the reaction medium has no effect on the ratio of isolated silyl ketene acetals. A similar trend is observed for THF/23% HMPA solvent mixtures, for which the decrease in selectivity is even more pronounced at ester to base ratios less than 1.

The influence of the ester to base ratio on the stereoselectivity of silyl ketene acetal formation has not previously been systematically investigated. In a recent article, Heathcock states that the highest percentage of (*Z*)-ketene acetal isomer is obtained from rapid addition of a slight excess of neat ester to a solution of the base.[21] In fact, with various amounts of DMPU or HMPA in THF, addition of more than 1 equiv of ester to the base is accompanied by a significant increase in (*Z*)-silyl ketene acetal formation. Interestingly, addition of small amounts of DMSO after enolization leads to the same result. The increase in selectivity is invariably accompanied by a slight drop in yield, and a number of side products, such as apparent Claisen condensation products, can be observed in the NMR spectra of the crude reaction mixtures.

Effect of the Base on Stereoselectivity in Silyl Ketene Acetal Formation. LHMDS/THF was reported to be equivalent to LDA/THF/23% HMPA for the generation of (*E*)-lithium enolates.[22] Deprotonation studies with β-alkoxy ester 7 demonstrate that addition of HMPA is crucial for a rapid ester deprotonation at low temperature (Table III). Between −60 and −80 °C, enolization of bicyclic ester 7 (unambiguously indicated by a fast β-elimination process[23]) is a very sluggish reaction in the absence of HMPA with both LHMDS and KHMDS. Enolization in THF/12% HMPA with LHMDS (detected by TLC analysis of quenched aliquots with authentic samples of esters 7 and 8) is complete within ca. 20 min at −78 °C. The presence of a dipolar solvent seems to be essential for an efficient enolization of esters with hexamethyldisilazide bases at low temperatures,[24] and the deprotonation studies with ethyl propionate were therefore conducted in a THF/23% HMPA solvent mixture (Table IV).

Table IV. Effect of the Base on the Stereoselectivity in Silyl Ketene Acetal Formation of Ethyl Propionate (3) (Scheme III). Solvent System: THF/23% HMPA

entry	base	ester:base	*Z*:*E*	yield, %
1	LDA	1:1	85:15	80
2	LHMDS	1:1	>91:9	85
3	LHMDS	0.8:1	>90:10	90
4	LHMDS	0.5:1	>90:10	90
5	LHMDS	1.1:1	>95:5	60
6	LHMDS	0.9:1[a]	>95:5	60

[a] 0.22 equiv of DMSO was added after enolization.

Table V. Effect of the Nature of the Base on the Stereoselectivity in Silyl Ketene Acetal Formation of Ethyl Tetrahydrofuroate (5) (Scheme III)

entry	base	solvent	(*Z*)-6:(*E*)-6	yield, %
1	LDA	THF	90:10	80
2	LDA	THF/45% DMPU	72:28	85
3	LDA	THF/23% HMPA	63:37	90
4	LHMDS	THF/23% HMPA	ca. 2:1	35
5	KHMDS	THF/23% HMPA	ca. 2:1	40

For an ester to base ratio of 1:1, LHMDS is slightly more efficient for *E*-selective enolate formation than LDA in THF/23% HMPA. The selectivity for (*Z*)-silyl ketene acetal formation can be increased to higher than 95:5 by addition of an excess of ester or small amounts of DMSO to the reaction mixture but is also accompanied with a drop in yield to ca. 60%. In contrast to the LDA systems, no change in selectivity or yield was observed when less than one equivalent of ester was used (Table IV, entries 3 and 4). The results obtained with KHMDS closely paralleled the selectivities observed with LHMDS.

Effect of an α-Oxygen Substituent on the Stereoselectivity in Silyl Ketene Acetal Formation. A number of groups have investigated the effect of chelating and nonchelating α-heteroatom substituents on ester enolization and subsequent Claisen rearrangement.[25] As a consequence of our studies in the monensin series,[4a,26] we are particularly interested in the stereochemical outcome of deprotonation in alkyl tetrahydrofuroates. The results of various enolization protocols are summarized in Table V.

As expected, with ethyl tetrahydrofuroate (5) the formation of the chelated enolate leading to the (*Z*)-silyl ketene acetal (*Z*)-6 is predominant under all reaction conditions. These results closely parallel those observed with acyclic, α-alkoxy-substituted esters. The 90:10 ratio

(21) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.
(22) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479.
(23) Formation of β-eliminated ester 8 occurs instanteneously at −78 °C by treatment with LDA.
(24) Heathcock reported similar problems in deprotonation of propionic esters and amides with LHMDS in neat THF at −70 °C, cf. ref 32.
(25) (a) Bartlet, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619. Bartlett, P. A.; Barstow, J. F. *Ibid.* **1982**, *23*, 623. (b) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (c) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (d) Fujisawa, T.; Sato, T.; Tajima, K. *Tetrahedron Lett.* **1983**, *24*, 729. (e) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177. (f) Fujisawa, T.; Tajima, K.; Sato, T. *Chem. Lett.* **1984**, 1669. T. Sato, Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Ibid.* **1986**, 1553. (g) Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1987**, 1372.
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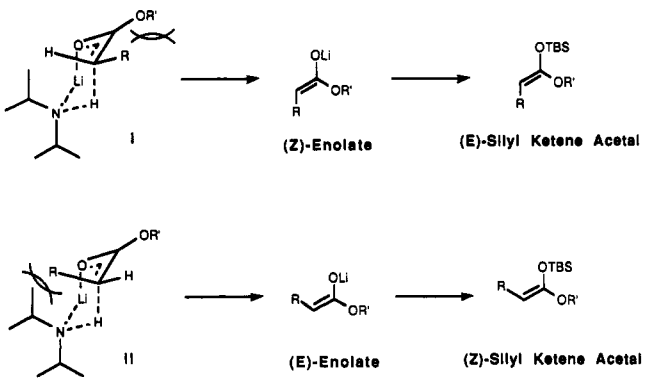
Scheme IV



of (*Z*)- to (*E*)-silyl ketene acetals obtained in THF is moderated to a 72:28 or a 63:37 ratio by the addition of 45% DMPU or 23% HMPA, respectively. Even with LHMDS and KHMDS the formation of the chelated enolate remains the major process.

The selective formation of the (*E*)-silyl ketene acetal (*E*)-6 via ester enolization and O-silylation therefore remains a challenging problem.

Discussion

Despite the frequent appearance of ester enolate anions in synthetic organic chemistry, the role of additives such as HMPA, DMPU, or TMEDA in the control of enolate stereochemistry has not yet found a comprehensive explanation. In 1976, a cyclic transition state model for the enolization of carbonyl esters with amide bases was proposed.[2c] In THF solution, the metal cation is coordinated to the carbonyl oxygen and the base. In the absence of additives, the kinetic enolization of esters in THF is expected to operate through a pericyclic transition state I, that enables a close interaction between Li^+ cation, carbonyl oxygen, and base (Scheme IV).[27,28]

A switch from a preference of TS* I in THF to TS* II for deprotonation in the presence of dipolar solvents appears questionable at first, due to a severe 1,3-diaxial interaction between the *N*-isopropyl group and the R substituent in TS* II. However, the presence of additives such as HMPA or DMPU results in a greater degree of solvation of the lithium cation and a weakened Li^+–carbonyl oxygen interaction. Accordingly, the association between base and ester is diminished and the 1,3-diaxial strain in TS* II is reduced, whereas TS* I is still destabilized by $A_{1,3}$-strain. A decrease in polarization of the carbonyl oxygen bond also results in a significantly less reactant-like transition state, as the α-C,H-bond becomes more difficult to extend and break.[29,30]

It is important to note that a strong solvation of Li^+ ions may lead to a relative stabilization of TS* II over TS* I through the occurrence of a late transition state. Additionally, the same effect will be exerted by bulky substituents on the carbonyl carbon, due to an increase in $A_{1,3}$-strain in TS* I. Not surprisingly, therefore, deprotonation of *tert*-butyl alkyl ketones and amides in THF/LDA leads exclusively to *Z* enolate formation.[31,32]

In very strongly complexing solvent systems, a continual change from an expanded cyclic to an acyclic transition state is expected. In fact, an acyclic transition state can be considered as an extreme situation of an expanded cyclic transition state with a strongly solvated base counterion.[32]

As an alternative to the occurrence of kinetic cyclic or acyclic sterocontrol in ester deprotonation, a thermodynamic enolate equilibration process has to be considered. In 1980, Rathke reported clear evidence that the predominant *Z* stereoselectivity in the deprotonation of 3-pentanone with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in a THF/HMPA solvent mixture is in fact a consequence of thermodynamic control.[33] A reversible aldol condensation appeared to be the most likely mechanism for the rapid isomerization of the (*E*)- to (*Z*)-lithium ketone enolate and was in accordance with all experimental findings.

In an often cited report, Corey and Gross confirmed Rathke's findings of a kinetic ratio of ca. 1:1 (*E*)- to (*Z*)-lithium enolates in THF/HMPA in the 3-pentanone system by internal quenching experiments.[17] Erroneously, the latter results with 3-pentanone have been interpreted as a proof of a thermodynamic equilibration of ester enolates during deprotonation in the presence of HMPA,[28b] even though no data in the Corey and Gross report indicated an application of the quenching experiments to esters or a possible mechanism of ester enolate equilibration. Clearly, a simple aldol-type equilibration is too slow or irreversible with acid derivatives such as esters or amides and thus cannot account for the results obtained with ester enolate systems.

Although initially the goal of this work was evidence and a plausible mechanism for thermodynamic control in the LDA/THF/23% HMPA or LDA/THF/DMPU systems, the experimental data presented above compelled the abandonment of this hypothesis. An equilibration process, based, for example, on direct proton exchange between ester enolate and ester or diisopropylamine in a solvent cage might account for the large differences in (*Z*)- to (*E*)-silyl ketene acetal ratios found with increasing concentrations of DMPU in THF. Such a process, however, could hardly explain the exceedingly high stereoselectivity observed with ester to base ratios higher than 1.[34,35]

(27) Due to the oligomeric structure of lithium amides and lithium enolates in solution the actual transition state structure quite likely involves a number of other coordinating species. For a recent compilation of structural data information on lithium enolates, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(28) Based on X-ray structural information, the coordinative bond between a Li^+ cation and a carbonyl oxygen atom is estimated at 1.9–2.0 Å; the standard Li^+–nitrogen distance in lithium amides is measured between 2.0 and 2.1 Å: (a) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. (b) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta*, *68*, 1373.

(29) Moreland, D. W.; Dauben, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2264. Based on a molecular mechanics model for the formation of lithium enolates, Moreland and Dauben also concluded a much more loosely organized but still cyclic transition state for the kinetic deprotonation of carbonyl compounds in a THF/HMPA solvent mixture.

(30) According to the Hammond principle the transition state for an exothermic ester deprotonation has to be considered basically reactant-like; cf.: Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(31) Cf.: (a) Tsunoda, T.; Sasaki, O.; Ito, S. *Tetrahedron Lett.* **1990**, *31*, 727. (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press: Orlando, 1984; Vol. 3, p 1 and references cited therein.

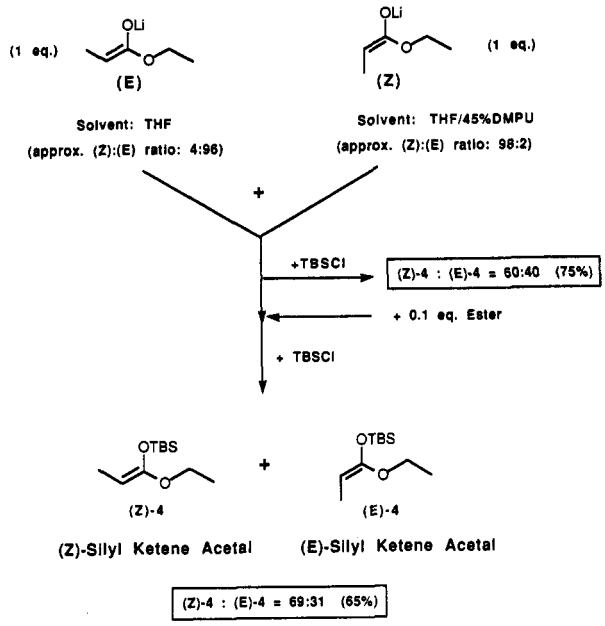
(32) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

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

(34) The relative thermodynamic stabilities of *cis*- and *trans*-lithium ester enolates are still subject to discussions. However, it is known that the cis diastereomer is more stable for potassium enolates, enol acetates, and enol ethers: (a) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362. (b) Taskinen, E.; Liukas, P. *Acta Chem. Scand.; Ser. B* **1974**, *B28*, 114.

(35) The thermodynamic equilibrium for (*E*)- and (*Z*)-silyl ketene acetals was determined to be ca. 1:9. Cf.: Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451. In the presence of dipolar solvents, aggregation of the lithium enolates is decreased and, consequently, this value is likely to be an upper limit for the thermodynamic ratio of the corresponding ester (*Z*)- and (*E*)-lithium enolates. Cf.: Spears, G. W.; Caufield, C. E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 1226.

Scheme V



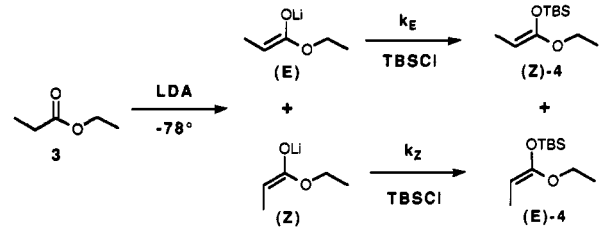
Whereas Rathke had been able to control the deprotonation of 3-pentanone in THF solution to produce predominantly *Z* ketone enolate by addition of a slight excess of ketone to base, the analogous experiment with ethyl propionate in THF, even in presence of 30% DMPU (added *after* the enolization of 1 equiv of ester by 1 equiv of LDA, Table II, entry 2), led only to a 1:4 ratio of (*Z*)- and (*E*)-silyl ketene acetals. More significantly yet, addition of 0.1 equiv of ester to a preformed 60:40 ratio[36] of 2 equiv of (*E*)- to (*Z*)-lithium ester enolates led only to a change in ratio to 69:31 (Scheme V).

A significant increase in selectivity from 67:33 or 93:7 ((*Z*)- to (*E*)-silyl ketene acetal ratios) in THF/30% DMPU or THF/45% DMPU to >98:2 could be obtained by addition of a small excess of ester or DMSO. The same tendency was observed in the THF/23% HMPA solvent systems.

These observations render a thermodynamically controlled equilibration mechanism to the more stable isomer an unlikely explanation for the high selectivity of enolization in THF/dipolar solvent systems. Instead they indicate a *kinetic resolution* process. An initially formed ratio of *Z* and *E* ester enolates can be altered not only by thermodynamic equilibration but also by addition of a small amount of a trapping agent that reacts at different rates with the two isomers. The presence of a slight excess of ester or DMSO in the enolate mixture could thus induce an irreversible reaction predominantly with the more reactive enolate.[37]

In order to test this theory, competitive trapping with TBSCl was used as a means to detect and quantify reactivity differences between the (*E*)- and the (*Z*)-lithium enolates. A 30:70 ratio[36] of (*E*)- to (*Z*)-lithium enolates in

Table VI. Competition Experiments



entry	solvent	ester:base	TBS-Cl, equiv	(*Z*)-4:(*E*)-4
1	THF/15% DMPU	0.8:1	0.9	30:70
2	THF/15% DMPU	0.8:1	0.08	14:86
3	THF/23% HMPA	0.8:1	0.9	73:27
4	THF/23% HMPA	0.8:1	0.08	66:34
5	THF	1:1	1.1	6:94
6	THF	1:1	0.9	4:96

Table VII. Relative Change in Ratio of Silyl Ketene Acetals (*Z*)-4 and (*E*)-4 on Warm Up from −78 °C to Room Temperature (Initial Ratio = 30:70)

conditions	(*Z*)-4:(*E*)-4
THF/23% HMPA	30:70
THF/23% HMPA + LiCl	30:70
THF/23% HMPA + LiCl + LDA	39:61

THF/15% DMPU led, upon trapping with 0.01 equiv of TBSCl, to a 14:86 ratio of (*Z*)- to (*E*)-silyl ketene acetals (Table VI). The significant change in ratios accounts for a competition constant of $K = k_Z/k_E = 2.6$ for the silylation of the two enolates.[38] This experiment cannot quantify the rate difference between the two lithium enolates in the reaction with excess ester or DMSO. It does establish, however, that there are significant differences in the kinetic properties of (*E*)- and (*Z*)-lithium enolates; the *Z* isomer is the more reactive one at least upon silylation.[39]

The analogous set of experiments in THF/23% HMPA led to competition constant $K = k_Z/k_E = 1.4$. Although this result still confirms the greater reactivity of the (*Z*)-lithium enolate, this factor is surprisingly lower than the one observed in 15% DMPU. It was found, however, that in the presence of HMPA and a strongly basic medium, a significant decomposition of the silyl ketene acetals occurs. The (*E*)-silyl ketene acetal proves to be more strongly affected by this decomposition process, which results in a change of the (*Z*)- to (*E*)-silyl ketene acetal ratio in favour of the (*Z*)-silyl ketene acetal (Table VII).[40]

A 30:70 ratio of (*Z*)- to (*E*)-silyl ketene acetals, previously generated in THF/15% DMPU and purified by distillation, changed in a controlled experiment in THF/23% HMPA in the presence of LDA upon warming from −78 °C to room temperature to an isomer ratio of 39:61. Thus, both the (*Z*)-lithium enolate and the (*E*)-silyl ketene acetal show a significantly enhanced reactivity over the corresponding (*E*)-lithium enolate and (*Z*)-silyl ketene acetal isomers.[41] The instability of the silyl ketene acetals in an

(36) The ratio of (*Z*)- to (*E*)-silyl ketene acetals was assayed by removal of an aliquot from the reaction mixture.

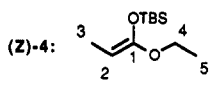
(37) A kinetic resolution process cannot only occur with an excess of ester over base but also at ester to base ratios smaller than 1:1, due to local high concentrations of ester and enolate especially at the end of the addition of the ester solution to the reaction mixture. This explains the initial drop in selectivity observed when the ester to base ratio is decreased from 1:1 to ca. 0.5:1 (Table II, entries 6 and 8). The stability of the (*E*)- to (*Z*)-silyl ketene acetal ratio in THF at ester to base ratios of 1:1 and smaller (Table II, entries 3 and 4) indicates that the rate of such a kinetic resolution process in THF is significantly lower (but not zero, Table II, entry 1 and 2) than in THF/DMPU.

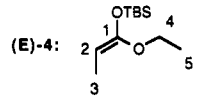
(38) For a discussion of the method of competing reactions for the study of relative reactivity, see: Hammett, L. P. In *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; Chapter 4.23, p 91 and references cited therein.

(39) The difference in reactivity between the (*Z*)- and the (*E*)-lithium ester enolates is possibly due to the higher steric energy of *E* enolates. Not surprising in this context is the observation that *E* ester enolates (or *Z* ketone enolates) are generally more stereoselective in aldol-type reactions than their *Z* counterparts (or *E* ketone enolates). Cf.: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 111 and references cited therein.

(40) The mixture of silyl ketene acetals used in this experiment was added to the THF/HMPA reaction mixture at −78 °C.

Table VIII. NMR Data for Silyl Ketene Acetals (*Z*)-4 and (*E*)-4 (δ in ppm)

(Z)-4: 

(E)-4: 

^{1}H NMR	CH(2)	CH_3(3)	CH_2(4)	CH_3(5)	OTBS
(*Z*)-4	3.40 (q, *J* = 6.5)	1.50 (d, *J* = 6.5)	3.62 (q, *J* = 6.9)	1.23 (q, *J* = 6.9)	0.93 (s), 0.12 (s)
(*E*)-4	3.70 (q, *J* = 6.4)	1.47 (d, *J* = 6.4)	3.82 (q, *J* = 6.9)	1.19 (t, *J* = 6.9)	0.92 (s), 0.14 (s)

^{13}C NMR	C(1)	C(2)	C(3)	C(4)	C(5)	OTBS
(*Z*)-4	156.2	70.4	10.0	63.0	14.9	26.1, 18.5, −3.9
(*E*)-4	153.5	80.6	9.9	63.2	15.2	26.0, 18.5, −4.7

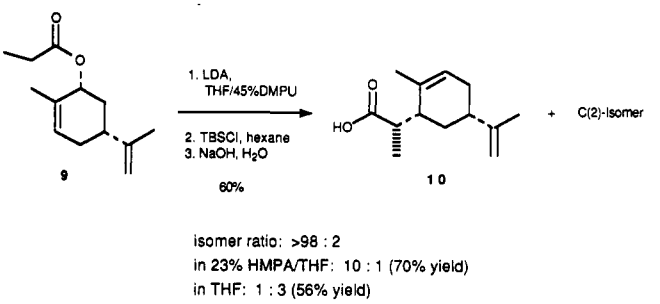
excess of base in a THF/HMPA solvent system also explains the sharp drop in yields and selectivity observed with ester to base ratios smaller than 1 (Table II, entries 16–20). Addition of 0.9 equiv of TBSCl to 1 equiv of ester enolate generated in THF leads, as expected, to a slight increase in *E*-selective silyl ketene acetal formation (Table VI, entries 5 and 6).

The kinetic resolution of (*Z*)- and (*E*)-lithium enolates also explains the shift in the ratio of isolated silyl ketene acetals in the differential trapping experiment (Scheme V) and the usually observed small drop in yield after addition of excess of ester or DMSO.[42]

Therefore, it is assumed that in all solvent systems the initially generated ratio of (*E*)- to (*Z*)-lithium enolates is based on a kinetically controlled ester enolization through a cyclic or expanded cyclic transition states. Upon addition of a trapping agent such as excess ester or DMSO, a kinetic resolution process leads through preferential destruction of the (*Z*)-lithium enolate to a relative increase of the amount of (*E*)-lithium enolate formed. The basic kinetic differences between the THF and the THF/dipolar additive solvent systems are exemplified by the isomer ratios obtained with a significant excess of base over ester (e.g. from 6:94 (*Z*)-4 to (*E*)-4 in THF to 60:40 in THF/30% DMPU to 84:16 in THF/45% DMPU, Table II, entries 3, 9, and 14). These differences are likely to have their origin in the partial involvement of both cyclic transition states I and II (Scheme IV).

In neat THF, a reactant-like, early transition state I seems to be of lowest energy and directs the course of ester enolization. With increasing amounts of dipolar solvents the more productlike, cyclic transition state II and acyclic transition states become operational as well and lead to a decreased level of stereoselectivity. In the presence of large percentages of dipolar additives and high solvation of Li^+ ions, enolization will quite possibly take its course almost exclusively via acyclic transition states and thus be influenced by the relative stability of the ground state ester conformations.[32,43,44] This extreme case is probably most closely reached with LHMDS and KHMDS in THF/23% HMPA, and accounts for a >9:1 ratio of *E* to *Z* enolates at all ester to base ratios. In addition to the presence of dipolar solvents, the decreased basicity of LHMDS, combined with its monomeric structure in THF solution,[45] leads to the occurrence of a late, less reactant-like transition state. A similar situation presents itself in the THF/45% DMPU system, which leads at low ester to base ratios to a kinetic ratio of 14:86 (*E*)- to (*Z*)-silyl ketene acetals, only slightly less than the 93:7 ratio obtained at an ester to base ratio of 0.8:1.

Scheme VI



This work was initiated with the goal of increasing the stereoselectivity of the ester enolate Claisen rearrangement by an optimization and a better theoretical understanding of the stereoselective formation of silyl ketene acetals. Direct experimental consequences of this study are illustrated in Scheme VI. Through application of highly *E*-selective enolization conditions (THF/45% DMPU, 1.05:1 ratio of ester to base), the diastereoselectivity of the formation of acid **10** through Claisen rearrangement of allyl ester **9** could be increased from 84% (obtained in THF/23% HMPA) to better than 96%.

Conclusions

A kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective formation of (*E*)- and (*Z*)-silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS. A thermodynamic equilibration mechanism seems to be of minor significance with ester enolates. The reactivity of (*Z*)-lithium enolates and (*E*)-silyl ketene acetals is significantly higher than the reactivity of the corresponding (*E*)-lithium enolate and (*Z*)-silyl ketene acetal systems. This observation is of significance for the highly stereoselective preparation of (*Z*)-silyl ketene acetals. Further investigations are directed toward the application of these findings to the transition-state analysis of the ester enolate Claisen rearrangement and will be reported in due course.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, *N,N'*-dimethyl-*N,N'*-propyleneurea = 1,3-dimethyl-2-oxohexahydropyrimidine (DMPU), and hexamethylphosphoric triamide

(41) An obviously related difference in reactivity was very recently used for the separation of *E*/*Z* isomeric silyl enol ethers by a kinetic resolution process: Hippeli, C.; Basso, N.; Dammast, F.; Reissig, H.-U. *Synthesis* **1990**, 26.

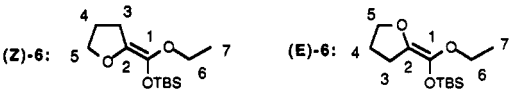
(42) The effect of DMSO might be due to a preferred decomposition of (*E*)-silyl ketene acetals upon warm up of the reaction mixture.

(43) Cyclic transition states I and II and their acyclic counterparts differ only in the degree of the association of the Li^+ cation to the carbonyl oxygen and the extent of pericyclic character in the enolization.

(44) For considerations of the stereoselectivity of acyclic transition states, see: (a) McKee, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 559. (b) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 4119.

(45) Kimura, B. Y.; Brown, T. L. *J. Organomet. Chem.* **1971**, *26*, 57.

Table IX. NMR Data for Silyl Ketene Acetals (*Z*)-6 and (*E*)-6 (δ in ppm)



^{1}H NMR	CH_2(3)	CH_2(4)	CH_2(5)	CH_2(6)	CH_3(7)	OTBS
(*Z*)-6	2.47 (t, *J* = 7.5)	1.89 (m)	3.94 (t, *J* = 6.6)	3.75 (q, *J* = 7.2)	1.16 (t, *J* = 7.2)	0.93, 0.10
(*E*)-6	2.40 (t, *J* = 7.5)	1.89 (m)	3.95 (t, *J* = 6.6)	3.79 (q, *J* = 7.2)	1.18 (t, *J* = 7.2)	0.93, 0.10

^{13}C NMR	C(1)	C(2)	C(3), C(4)	C(5)	C(6)	C(7)	OTBS
(*Z*)-6	136.9	128.0	25.3, 26.2	70.3	65.4	15.3	26.1, 18.6, −4.4
(*E*)-6	138.2	128.0	25.3, 25.8	70.5	65.7	15.4	26.1, 18.6, −4.3

(HMPA) were distilled from CaH_2 immediately prior to use. Diisopropylamine and tetramethylethylenediamine (TMEDA) were distilled from KOH. Solvent concentration was accomplished with a Büchi rotary evaporator. Ethyl tetrahydrofuroate (**5**) was prepared by catalytic hydrogenation of 2-furoic acid in methanol, followed by esterification with ethanol and Amberlite IR-120 and purification with flash chromatography.[46] Bicyclic ester **7** was prepared according to Ireland and Norbeck.[26b,47] Ester **9** was prepared according to Ireland and Maienfisch.[48,49] All enolization and silylation reactions were conducted under a nitrogen or argon atmosphere. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were measured with $CDCl_3$ solutions. Multiplicities are given as s (singlet), d (duplet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants are in hertz.

General Procedure A for the Enolization and Silylation of Esters in THF. A solution of 1.11 g (10 mmol) of diisopropylamine in 10 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added slowly by syringe. This mixture was stirred for 3 min at 0 °C and subsequently cooled to −78 °C. From 6 to 14 mmol of the ester as a solution in 10 mL of THF was added by syringe over a 2-min time period under intensive stirring. After 20 min, from 4.2 to 9.9 mL (6.6 to 15.4 mmol, 1.1 equiv) of a 1.56 M solution of TBSCl in hexanes was added, followed by 8 mL of DMPU. The reaction mixture was stirred for an additional 5 min at −78 °C and subsequently allowed to warm up to room temperature. After a 45-min period the reaction mixture was quenched with 10 mL of a saturated aqueous solution of $NaHCO_3$ and diluted with 100 mL of cold pentane. The resulting solution was extracted with H_2O (4 × 50 mL); the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The isomer ratio and the yield were determined by ^{1}H NMR and ^{13}C NMR spectroscopy of the crude product (for NMR assignments, see Tables VIII and IX).

General Procedure B for the Enolization and Silylation of Esters in THF/DMPU. A solution of 1.11 g (10 mmol) of diisopropylamine in 6 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added slowly by syringe. This mixture was stirred for 3 min at 0 °C and cooled to −78 °C, and 3.5, 7.5, or 14 mL of DMPU (for an ca. 15%, 30%, or 45% solution of DMPU in THF) was added dropwise by syringe. After 5 min, from 3 to 12 mmol of the ester as a solution in 10 mL of THF was added by syringe over a 2-min time period under intensive stirring. After 15 min, from 2.1 to 8.5 mL (3.3 to 13.2 mmol, 1.1 equiv) of a 1.56 M solution of TBSCl in hexanes was added. The reaction mixture was stirred for an additional 5 min at −78 °C, allowed to warm up to room temperature, and subsequently treated as described in the general procedure A.

General Procedure C for the Enolization and Silylation of Esters in THF/HMPA. A solution of 1.11 g (10 mmol) of diisopropylamine in 8 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added slowly by syringe. This mixture was stirred for 3 min at 0 °C and cooled to −78 °C, and 3.0 mL of HMPA was added dropwise by syringe. After 5 min, from 4 to 12 mmol of the ester as a solution in 10 mL of THF and 3.0 mL of HMPA was added by syringe over a 2-min time period under intensive stirring. After 15 min, from 2.8 to 8.5 mL (4.4 to 13.2 mmol, 1.1 equiv) of a 1.56 M solution of TBSCl in hexanes and from 0.8 to 3.0 mL of HMPA were added. The reaction mixture was stirred for an additional 5 min at −78 °C, allowed to warm up to room temperature, and subsequently treated as described in the general procedure A.

General Procedure D for the Enolization and Silylation of Esters in THF/TMEDA. A solution of 1.11 g (10 mmol) of diisopropylamine in 6 mL of THF was cooled to 0 °C, and 4 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added slowly by syringe. This mixture was stirred for 3 min at 0 °C and cooled to −78 °C, and 6 or 15 mL of TMEDA (for ca. 25% or 50% solution of TMEDA in THF) were added dropwise by syringe. After 5 min, 10 mL (10 mmol) of a 1 M solution of the ester in THF was added by syringe over a 2-min time period under intensive stirring. After 15 min, 7.1 mL (11 mmol) of a 1.56 M solution of TBSCl in hexanes were added. The reaction mixure was stirred for an additional 5 min at −78 °C, allowed to warm up to room temperature, and subsequently treated as described in the general procedure A.

General Procedure E for the Enolization of Esters with LHMDS and KHMDS in THF/23% HMPA. A solution of 10 mmol of LHMDS or KHMDS in 10 mL of THF was cooled to −78 °C, and 6.0 mL of HMPA was added dropwise by syringe. After 5 min, from 5 to 11 mmol of the ester as a solution in 10 mL of THF was added by syringe over a 2-min time period under intensive stirring. After 20 min, from 3.5 to 7.8 mL (5.5 mmol to 12.1 mmol, 1.1 equiv) of a 1.56 M solution of TBSCl in hexanes was added. The reaction mixture was stirred for an additional 5 min at −78 °C and subsequently treated as described in the general procedure A.

β-Elimination of Benzyl 2,3-*O*-(1-Methylethylidene)-α-D-lyxofuranosiduronic Acid Methyl Ester (7). A solution of 0.32 mmol (2 equiv) of LDA, LHMDS, or KHMDS in 5 mL of THF was treated at −78 °C with the solution of 50 mg (0.16 mmol) of bicyclic ester **7** in 0.5 mL of THF, followed by 0.8 mL of HMPA if a THF/12% HMPA solvent system was desired. The rate of β-elimination was determined by thin layer chromatography after quenching 0.1-mL aliquots in wet ether (solvent system, ethyl acetate/hexanes 1:3; R_f of the bicyclic ester **7**, 0.45; R_f of the β-elimination product **8**, 0.15).

Competition Experiments. Ethyl propionate (**3**) was enolized according to the general procedure A, B, or C in THF, THF/15% DMPU, or THF/23% HMPA, respectively. Silylation of the ester enolates was accomplished by addition of an excess (1.1 equiv) or 0.1 equiv (0.9 equiv in the case of neat THF) of TBSCl in hexanes, followed by the standard workup. The results of these competition experiments are summarized in Table VI.

Relative Change in the Ratio of Silyl Ketene Acetals (*Z*)-4 and (*E*)-4 on Warm Up from −78 °C to Room Temperature. A 30:70 mixture of (*Z*)-4 and (*E*)-4, generated following the general procedure B in THF/15% DMPU and purified by Kugelrohr destillation, was added to THF/23% HMPA at −78 °C. The change in the ratio of (*Z*)- to (*E*)-silyl ketene acetals in the presence of LiCl and LDA was essayed by removal of aliquots upon warm up of the solution to room temperature. Whereas the presence of 2 equiv of LiCl did not effect the silyl ketene acetal ratio, addition of 1 equiv of LDA led to the appearance of ca. 20% decomposition products in the crude mixture and a change in the (*Z*)-4 to (*E*)-4 ratio to 39:61, as determined by ^{13}C NMR.

Ester Enolate Claisen Rearrangement of (−)-*cis*-Carvyl Propionate (9). A solution of 437 mg (2.1 mmol) of (−)-*cis*-carvyl propionate (**9**) in THF was enolized and silylated according to general procedure B. The clear solution was heated at reflux for

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6 h, quenched with 8 mL of a 2 N solution of NaOH, and stirred at room temperature for 15 min. The resulting solution was diluted with ether and extracted with 2 N NaOH (3 × 10 mL). The base phases were combined, acidified with a 6 N solution of HCl (pH ~ 2) at 0 °C, and extracted with ether (4 × 15 mL). The etheral extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 261 mg (60%) of 2(*S*)-[2-methyl-5(*S*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic acid (10): ^{13}C NMR δ 182.4, 150.2, 134.7, 125.2, 109.1, 44.0, 42.1, 41.3, 32.2, 31.4, 21.9, 21.2, 13.2. For additional data, see ref 48. Neither the ^{13}C NMR nor the ^1H NMR spectra indicated the presence of the C(2) isomer, which was the major isomer in the absence of dipolar solvents in the enolization mixture.[50]

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Reaction of Aminopropanedinitrile 4-Methylbenzenesulfonate [Aminomalononitrile *p*-Toluenesulfonate (Tosylate)] with Aromatic Aldehydes

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Received August 16, 1990

Aminopropanedinitrile 4-methylbenzenesulfonate (ammoniopropanedinitrile *p*-toluenesulfonate, aminomalononitrile *p*-toluenesulfonate (tosylate), 1) reacts with aromatic aldehydes in methanolic sodium ethanoate to give diastereoselectively (*E,E*)-4-amino-1-aryl-3-cyano-4-methoxy-2-aza-1,3-butadienes (3) and *trans*-3,6-diaryl-2,2,5,5-tetracyanopiperazines (4). The product distribution (3:4) depends on the ratio of reactants and the structures of the substrates. Electron-releasing groups on the 4-position of the phenyl ring favor piperazine (4) formation (method B.) The formation of piperazines (4) may involve synthetically useful N-protonated aryl- and cyano-stabilized azomethine ylide (prototropic 1,3-dipoles) intermediates which could have resulted from an imine–azomethine ylide tautomerism of prior formed 1-aryl-3,3-dicyano-2-aza-1-propenes. 1,3-Dipolar cycloaddition [4 + 2] reactions of the highly reactive azomethine ylides with dimethyl 1,2-ethynedicarboxylate (DMAD) give 3,4-dicarbomethoxy-2-cyano-5-aryl-3-pyrrolines, which undergo facile dehydrocyanation to 3,4-dicarbomethoxy-2-cyano-5-arylpyrroles. The possible intermediacy of ketenimines and of aryl- and cyano-stabilized 2-azaallyl anionic intermediates in equilibrium with azomethine ylides is also considered.

Aminopropanedinitrile 4-methylbenzenesulfonate (ammoniopropanedinitrile *p*-toluenesulfonate, aminomalononitrile *p*-toluenesulfonate (tosylate), AMNT, 1)[1-6] reacts with aromatic aldehydes to give a wide variety of products, depending on experimental conditions and the structures of the substrates.[7,8] 1-Aryl-3,3-dicyano-2-aza-1-propenes (2) have been reported[8] as the products from the reaction of aminopropanedinitrile (aminomalononitrile)[2,3,9-11] and aromatic aldehydes. Aminomalononitrile tosylate (AMNT, 1) reacts with aromatic aldehydes in methanolic sodium ethanoate to give diastereoselectively (*E,E*)-4-amino-1-aryl-3-cyano-4-methoxy-2-aza-1,3-butadienes (3) in good to excellent yields.[7] This report describes experimental conditions for the concurrent formation of 2-aza-1,3-butadienes (3) and *trans*-3,6-diaryl-2,2,5,5-tetracyanopiperazines (4) from the reaction of AMNT (1) and aromatic aldehydes (Table I).[7,8] Some products precipitate during the reaction, and other product mixtures are easily separated by column chromatography. Highly functionalized 2-aza-1,3-butadienes are important in the Diels–Alder reactions of heterodienes and in mechanistic studies of cycloaddition reactions[7] and piperazine and its derivatives are well known for their bioactivity[12] and for their roles in the preparation of pharmaceuticals such as β-adrenergic blocking agents,[13a] medicinally important amino steroids,[13b] and antibiotics.[13c]

Table I shows that the yields of piperazines (4) increase on going from a mol ratio of sodium ethanoate:aldehyde = 1.0 (method A) to a molar ratio of 1.5 (method B) with phenylmethanal. It was also observed that the reaction of AMNT (1) with phenylmethanal did not proceed at a measurable rate in the absence of sodium ethanoate. Using a molar ratio of 2.0 (sodium ethanoate:aldehyde) with phenylmethanal gave a lower overall yield while a molar ratio of 0.5 led to a sluggish reaction that afforded a complex product mixture. An increase in methanol concentration from 494 to 741 mmol in method A (11 h) with

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