Acknowledgment. This work was supported by the National Science Foundation–Solid State Chemistry Grant DMR-8307693. We gratefully acknowledge Dr. Knud Lerstrup, Dr. Kurt Loening, Dr. Aravinda Kini, and Dr. Long-Yong Chiang for their helpful discussions.

Novel Reaction of 2-(Methylthio)-1-pyrroline with Acyl Chlorides in the Presence of Triethylamine

Hiroki Takahata and Takao Yamazaki*

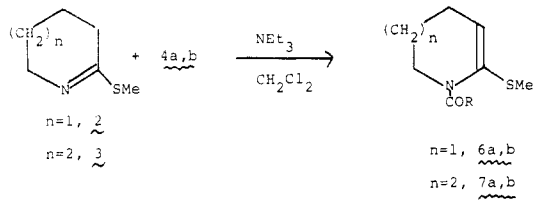
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan

Keiichi Aoe

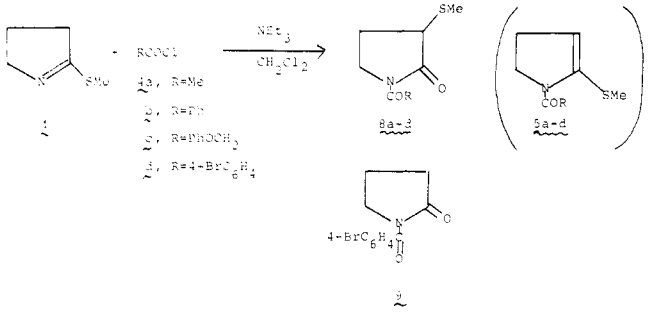
Analitical Center, Tanabe Seiyaku, Co., Ltd. Toda, Saitama 335, Japan

Received January 21, 1985

In connection with our research on activated lactams,[1] we required a variety of *N*-acyl ketene *S,N*-acetals.[2] Bose et al.[3] reported that the reaction of 2-(methylthio)-1-pyrroline (**1**) with phenoxyacetyl chloride (**4c**) in the presence of triethylamine gave *N*-phenoxyacetyl ketene *S,N*-acetal (**5c**). We tried the similar reaction of cyclic thioimidates (**1**, **2**, and **3**) with acetyl chloride (**4a**) and benzoyl chloride (**4b**). Although *N*-acyl ketene *S,N*-acetals (**6a,b** and **7a,b**) were obtained as expected from **2** and **3**, respectively, the corresponding *N*-acyl-2-(methylthio)-2-pyrrolines (**5a,b**) were not isolated. The ^{1}H NMR spectra



of **6a,b** and **7a,b** showed peaks of vinyl protons at C-3 position as characteristic triplets (Table I). However, compounds **8a,b** obtained from **1** have no peaks for vinyl protons in the ^{1}H NMR. Microanalyses data of **8a,b** were consistent with the addition of one oxygen atom to the molecular formulas of the corresponding *N*-acyl ketene *S,N*-acetals (**5a,b**). Next, **1** was allowed to react with **4c** and 4-bromobenzoyl chloride (**4d**) to give **8c** and **8d** together with the lactam **9**, respectively. The spectral patterns of **8c** and **8d** were similar to those of **8a,b**.



(1) (a) Takahata, H.; Tomiguchi, A.; Nakano, M.; Yamazaki, T. *Synthesis* **1982**, 156; (b) Takahata, H.; Nakano, M.; Yamazaki, T. *Synthesis* **1983**, 225; (c) Takahata, H.; Nakajima, T.; Yamazaki, T. *Synthesis* **1983**, 226; (d) Takahata, H.; Nakajima, T.; Yamazaki, T. *Synthesis* **1984**, 703.

(2) Takahata, H.; Tomiguchi, A.; Hagiwara, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1982**, *30*, 1300.

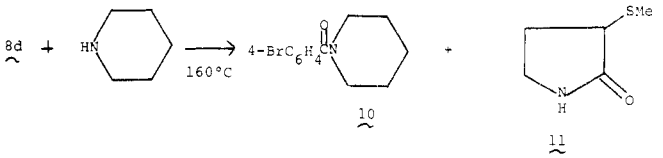
(3) Bose, A. K.; Fahey, J. L. *J. Org. Chem.* **1974**, *39*, 115.

Table I. Reaction of Cyclic Thioimidates (1, 2, and 3) with Acyl Halides (4a-d)

compd	yield, %	^{1}H NMR (C_3-H), δ
6a	73	5.50 (t, J = 4 Hz)
6b	83	5.47 (t, J = 4 Hz)
7a	54	5.70 (t, J = 7 Hz)
7b	73	5.67 (t, J = 6 Hz)
8a	50	3.47 (dd, J = 8 and 4 Hz)
8b	39	3.37 (dd, J = 9 and 5 Hz)
8c	48	3.55 (dd, J = 8 and 4 Hz)
8d	64	3.47 (dd, J = 8 and 4 Hz)
	69[a]	
	17[b]	
9	2	
	0[a]	
	54[b]	

[a] Reaction was carried out in an atmosphere of O_2. [b] Reaction was carried out with exclusion with O_2.

Since no physical and spectral data for **5c** were reported by Bose, we decided to determine the structures of **8a–d**. Heating of **8d** with piperidine at 160 °C afforded the amide (**10**) and 3-(methylthio)pyrrolidin-2-one (**11**)[4] in 85% and 96% yields, respectively. Formation of **11** suggested the



existence of a methylthio group at C-3 position in **8d**. The structure of **8d** was then determined finally by X-ray crystallography (Figure 1). In order to speculate on potential mechanisms for this unusual transformation, the following experiments were carried out. The reaction of **1** with **4d** in an atmosphere of oxygen gas (O_2) resulted in a little increase of **8d** (69%) and no isolation of **9**. Next, the similar reaction with exclusion of O_2 was carried out (Experimental Section). ^{1}H NMR spectrum of a crude product before chromatography revealed a signal at δ 5.00 (t, J = 3 Hz) due to a vinyl proton at C_3 position, supporting the structure of **5d**. After chromatography, **8d** and **9** were obtained in 17% and 54% yields, respectively. These results suggested the participation of an oxygen molecule in this reaction.[5]

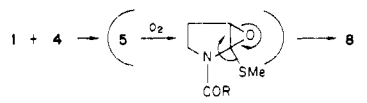
On the other hand, the reaction of 2-(methylthio)-3-methyl-1-pyrroline (**12**) with **4d** gave only the normal product, *N*-acyl ketene *S,N*-acetal (**13**), in 79% yield. It was found that the novel products were formed only in the reaction using 3-unsubstituted 2-(methylthio)-1-pyrroline.

Experimental Section

^{1}H NMR spectra were recorded on a JEOL PMX (60 MHz) spectrometer and a Varian XL-200 (200 MHz) spectrometer in

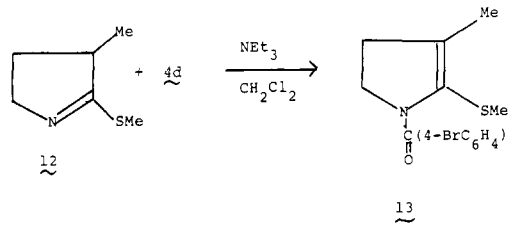
(4) Murakami, Y.; Koga, K.; Matsuo, H.; Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 543.

(5) Although insufficient experimental evidence deter us from offering a mechanism, we have a temporary explanation as shown below.



The formation of *N*-acyl ketene *S,N*-acetals **5** followed by the epoxidation with air (oxygen) and rearrangement of the methylthio group accompanied with the cleavage of the epoxide ring might afford the products (**8**). The existence of **5** would be supported by the reaction with exclusion of O_2. In this reaction, **5d** would be hydrolyzed to give compound **9** by chromatography. It is known that cyclic alkenes were epoxidated with O_2. (van Sickle, D. E.; Mayo, F. R.; Arluck, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 4824.) However, the precise mechanism remains unclear.

0022-3263/85/1950-4648$01.50/0



$CDCl_3$, unless otherwise noted and were reported in ppm (δ units) downfield of internal tetramethylsilane (Me_4Si). ^{13}C NMR spectra were obtained on a Varian XL-200 (50.3 MHz) spectrometer. MS spectra were obtained with a JEOL-TMS-D200 spectrometer at 70 eV. IR spectra were taken with a JASCO A-102 spectrophotometer. Melting points are uncorrected. Cyclic thioimidates (**1**, **2**, and **3**) were prepared from the corresponding thiolactams and methyl iodide by the procedure previously reported.[6] Their spectral data and boiling points were identical with the samples prepared previously.

Reaction of Cyclic Thioimidates (1, 2, and 3) with Acyl Halides (4a–d). General Procedure. To a stirred solution of **1**, **2**, and **3** (5 mmol) and triethylamine (5.5 mmol) in dichloromethane (100 mL), cooled to 0 °C, was slowly added during 30 min a solution of **4a–d** (5 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 4 h at room temperature and evaporated to leave a residue. The residue was extracted with ether (50 mL) 3 times. The extracts were evaporated to leave a residue. The residue was purified by distillation or column chromatography on silica gel to give **6a,b**, **7a,b**, **8a–d**, and **9**.

1-Acetyl-1,4,5,6-tetrahydro-2-(methylthio)pyridine (6a): bp 90–91 °C (0.06 mmHg); ^1H NMR 2.20 (s, 6 H, SCH_3 and CH_3), 5.50 (t, J = 4 Hz, 1 H, 3-H); IR (neat) 1690 cm^{-1}; mass spectrum, m/z 171 (M^+). Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18. Found: C, 56.00; H, 7.68; N, 8.03.

1-Benzoyl-1,4,5,6-tetrahydro-2-(methylthio)pyridine (6b): bp 129 °C (0.01 mmHg); ^1H NMR 2.17 (s, 3 H, SCH_3), 5.47 (t, J = 4 Hz, 1 H, 3-H); IR (neat) 1670 cm^{-1}; mass spectrum, m/z 233 (M^+). Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 67.18; H, 6.42; N, 5.88.

1-Acetyl-4,5,6,7-tetrahydro-2-(methylthio)-1*H*-azepine (7a): bp 103–104 °C (0.4 mmHg); ^1H NMR 2.03 (s, 3 H, SCH_3), 2.23 (s, 3 H, CH_3), 5.70 (t, J = 7 Hz, 1 H, 3-H); IR (neat) 1670 cm^{-1}; mass spectrum, m/z 185 (M^+). Anal. Calcd for $C_9H_{15}NOS$: C, 58.33; H, 8.16; N, 7.56. Found: C, 57.99; H, 8.38; N, 7.48.

1-Benzoyl-4,5,6,7-tetrahydro-2-(methylthio)-1*H*-azepine (7b): bp 135 °C (0.0004 mmHg); ^1H NMR 1.97 (s, 3 H, SCH_3), 5.67 (t, J = 6 Hz, 1 H, 3-H); IR (neat) 1650 cm^{-1}; mass spectrum, m/e 247 (M^+). Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.62; H, 7.10; N, 5.42.

1-Acetyl-3-(methylthio)pyrrolidin-2-one (8a): bp 79 °C (0.002 mmHg); ^1H NMR 2.27 (s, 3 H, SCH_3), 2.43 (s, 3 H, CH_3), 3.47 (dd, J = 8 and 4 Hz, 1 H, 3-H); IR (neat) 1700, 1690, 1650 cm^{-1}; mass spectrum, m/z 173 (M^+). Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.79; H, 6.38; N, 7.83.

1-Benzoyl-3-(methylthio)pyrrolidin-2-one (8b): bp 161 °C (0.8 mmHg); ^1H NMR 2.23 (s, 3 H, SCH_3); 3.37 (dd, J = 9 and 5 Hz, 1 H, 3-H); IR (neat) 1740 cm^{-1}; mass spectrum, m/z 235 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.62; H, 5.40; N, 5.81.

1-(Phenoxyacetyl)-3-(methylthio)pyrrolidin-2-one (8c): mp 89–90 °C (from isopropyl ether/dichloromethane); benzene/ethyl acetate (5:2) as eluant; ^1H NMR 2.39 (s, 3 H, SCH_3), 3.55 (dd, J = 8 and 4 Hz, 1 H, 3-H), 5.21 (s, 2 H, $CH_2OC_6H_5$); ^{13}C NMR 14.7 (SCH_3), 25.3 (C-4), 42.9 (C-5), 45.8 (C-3), 68.7 ($CH_2OC_6H_5$), 114.8 (Ar), 121.5 (Ar), 129.5 (Ar), 157.8 (Ar), 169.4 (C=O), 173.8 (C=O); IR (Nujol) 1720, 1620 cm^{-1}; mass spectrum, m/z 249 (M^+). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 58.84; H, 5.70; N, 5.27. Found: C, 58.49; H, 5.69; N, 5.31.

1-(4-Bromobenzoyl)-3-(methylthio)pyrrolidin-2-one (8d) and 1-(4-Bromobenzoyl)pyrrolidin-2-one (9): benzene/dichloromethane (1:1) as eluant; **8d**: mp 100–102 °C (from ethanol); ^1H NMR 2.27 (s, 3 H, SCH_3), 3.47 (dd, J = 8 and 4 Hz, 1 H, 3-H);

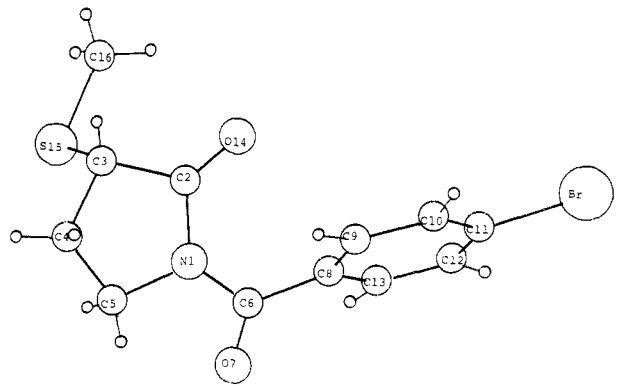


Figure 1. Perspective view of 1-(4′-bromobenzoyl)-3-(methylthio)pyrrolidin-2-one (**8d**).

^{13}C NMR 14.9 (SCH_3), 25.0 (C-4), 44.4 (C-5), 46.0 (C-3), 126.9 (Ar), 130.5 (Ar), 131.1 (Ar), 132.8 (Ar), 169.7 (C=O), 172.5 (C=O); IR (Nujol) 1725, 1665 cm^{-1}; mass spectrum, m/z 313, 315 (M^+). Anal. Calcd for $C_{12}H_{12}BrNO_2S$: C, 45.86; H, 3.85; N, 4.43. Found: C, 45.87; H, 3.88; N, 4.55.

9: mp 125–126 °C (from isopropyl ether/dichloromethane); IR (Nujol) 1730 cm^{-1}; mass spectrum, m/z 267, 269 (M^+). Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.27; H, 3.76; N, 5.23. Found: C, 48.94; H, 3.87; N, 5.03.

1-(4-Bromobenzoyl)piperidine (10) and 3-(Methylthio)-pyrrolidin-2-one (11). A mixture of **8d** (0.7 g, 2.23 mmol) and piperidine (0.19 g, 2.23 mmol) was heated in a sealed tube at 160 °C for 3 h. The reaction mixture was subjected to column chromatography on silica gel to afford **10** (0.51 g, 88%) using dichloromethane as eluant and **11** (0.288 g, 96%) using dichloromethane/methanol (100:1) as eluant.

10: mp 93–95 °C (from isopropyl ether/petroleum ether); IR (Nujol) 1620 cm^{-1}; mass spectrum, m/z 283, 285 (M^+). Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 53.75; H, 5.26; N, 5.22. Found: C, 53.88; H, 5.35; N, 5.08.

11:[4] mp 62–63 °C (from isopropyl ether/ether); ^1H NMR 2.27 (s, 3 H, SCH_3), 7.10 (br s, 1 H, NH); IR ($CHCl_3$) 3450, 1695 cm^{-1}. Anal. Calcd for C_5H_9NOS: C, 45.77; H, 6.91; N, 10.68. Found: C, 45.72; H, 6.95; N, 10.45.

1-(4-Bromobenzoyl)-2-(methylthio)-3-methyl-2-pyrroline (13). Analogous to the method described for **8d**, a solution of **12** (0.5 g, 3.8 mmol) and triethylamine (0.5 g, 4.9 mmol) in dichloromethane (50 mL) was reacted with a solution of **4d** (1 g, 4.6 mmol) in dichloromethane (20 mL) to give **13** (1.12 g, 79%) using benzene/dichloromethane (1:1) as eluant. **13**: mp 122–123 °C (from isopropyl ether/dichloromethane); ^1H NMR 1.90 (s, 3 H, CH_3), 2.07 (s, 3 H, SCH_3); IR (Nujol) 1630, 1610 cm^{-1}; mass spectrum, m/z 311, 313 (M^+). Anal. Calcd for $C_{13}H_{14}BrNOS$: C, 50.00; H, 4.52; N, 4.49. Found: C, 49.88; H, 4.64; N, 4.37.

Reaction of 1 with 4d in an Atmosphere of Oxygen. According to the procedure described above, a solution of **4d** (5 mmol) in dichloromethane (20 mL) was added to a solution of **1** (5 mmol) and triethylamine (5.5 mmol) in dichloromethane (100 mL). After the completion of addition, oxygen gas was streamed into the reaction mixture for 4 h. Analogous workup gave **8d** in 69% yield, identical with the above sample, with respect to IR and ^1H NMR data and chromatographic behaviors.

Reaction of 1 with 4d with Exclusion of O_2. Dichloromethane bubbled by argon gas (99.999%) under reflux for 1 h and argon gas was continuously bubbled through the reaction. In the same manner described above, the reaction of **1** (5 mmol) with **4d** (5.5 mmol) gave a crude product before chromatography. The crude product: ^1H NMR 5.00 (t, J = 3 Hz, 3-H); mass spectrum, m/z 297, 299. These peaks corresponded to molecular ion peaks of **5d**. The separation of the crude product by chromatography gave **8d** (17%) and **9** (54%).

Single-Crystal X-ray Analysis of 8d. Crystal Data: $C_{12}H_{12}BrNO_2S$, M = 314.2, monoclinic a = 15.4924 (18) Å, b = 5.8167 (5) Å, c = 7.058 (18) Å, β = 103.774 (8)°, V = 1255.34 (30) Å^3, D_c = 1.662 g/cm^{-1}, z = 4, space group $P2_1/c$.

Crystallographic Measurements. Single crystals of **8d** were obtained from ethanol. The intensity data were collected by 2θ–ω scanning technique by using graphite-monochromated Cu Kα

(6) Takahata, H.; Tomiguchi, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1980**, *28*, 1000.

radiation on a four-circle diffractometer (Rigaku AFC-5). Of the total of 2140 independent reflections, 1799 had intensities above the 2.667σ (1) level, and they were used for structure determination.

Determination of the Structure. The structure was solved by direct methods using MULTAN and refined by the block-diagonal least-square method with anisotropic temperature factors for all non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final R value was 0.053 (Tables II–V, in supplementary material section).

Registry No. 1, 40051-83-0; **2**, 19766-29-1; **3**, 39488-50-1; **6a**, 85312-20-5; **6b**, 98612-86-3; **7a**, 85312-21-6; **7b**, 98612-87-4; **8a**, 98612-88-5; **8b**, 98612-89-6; **8c**, 98612-90-9; **8d**, 98612-91-0; **9**, 98612-92-1; **10**, 98612-93-2; **11**, 98612-94-3; **12**, 98612-95-4; **13**, 98612-96-5; CH_3COCl, 75-36-5; PhCOCl, 98-88-4; $PhOCH_2COCl$, 701-99-5; 4-BrC_6H_4COCl, 586-75-4.

Supplementary Material Available: Tables II–V containing atomic coordinates, bond lengths, and bond angles for **8d** (4 pages). Ordering information is given on any current masthead page.

Variations in the Stereochemistry of the Boron Trifluoride Mediated Cyclocondensation Reaction of Aldehydes with Siloxy Dienes

Samuel Danishefsky,* Kuo-Hua Chao, and Gayle Schulte

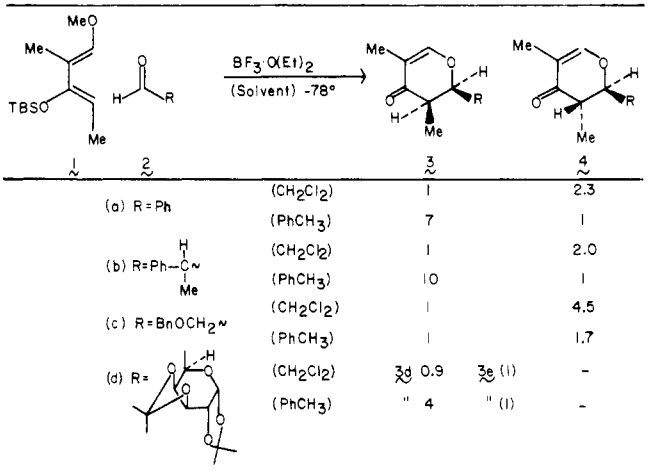
Department of Chemistry, Yale University, New Haven, Connecticut 06511

Received June 10, 1985

Variation of the Lewis Acid catalyst results in remarkable changes in the stereochemical outcome of the cyclocondensation of aldehydes with siloxy dienes.[1] Given the accessibility of the substrates which go into this reaction, the generality of the process, and the valuable functionality of the resultant products,[2] the issue of stereochemical control is of no small moment. Accordingly, we have continued to investigate the effects of modifications on the selectivity of the process. In these studies, some rather striking results were encountered. The findings are summarized herein.

This inquiry was confined to the use of boron trifluoride–etherate as the catalyst. In the first instance, we focused on the use of (*tert*-butyldimethylsilyl)oxy diene **1**. This stereochemically homogeneous diene is readily prepared from the reaction of (*E*)-1-methoxy-2-methylpent-1-en-3-one[3] with *tert*-butyldimethylsilyl triflate.[4] In all cases, reactions were carried out at −78 °C. The combined yields (see Experimental Section) of cis (**3**) and trans (**4**) products were only marginally affected by solvent changes. As recorded in Table I, a notable contrast was observed when the reaction was carried out in toluene as opposed to methylene chloride. With benzaldehyde (**2a**) and phenylpropanal (**2b**), reaction in toluene afforded a substantial increase in the proportions of cis product relative to those encountered in methylene chloride. In the case of the α-oxygenated aldehydes **2c** and **2d**, the

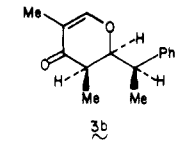
Table I



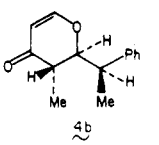
		3	4
(a) R = Ph	(CH_2Cl_2)	1	2.3
	$(PhCH_3)$	7	1
(b) R = Ph–C(H)(Me)–	(CH_2Cl_2)	1	2.0
	$(PhCH_3)$	10	1
(c) R = $BnOCH_2$–	(CH_2Cl_2)	1	4.5
	$(PhCH_3)$	1	1.7
(d) R =	(CH_2Cl_2)	3d 0.9	3e (1)
	$(PhCH_3)$	" 4	" (1)

situation is more complex. For **2c**, the methylene chloride–toluene trend is also in the same direction. However, the consequence of the effect was to erode the trans selectivity manifested in the former solvent. With the galactose-derived aldehyde **2d**, cis selectivity is manifested in both solvents; the impact of the solvent effect was only on the ratio of diastereofacial isomers (vide infra).

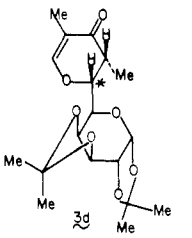
The facial sense of the reaction of **1** with aldehyde **2b** was apparently specific in both solvents. Thus, pyrones **3b** and **4b** are identical with those previously prepared.[1] The formation of these compounds corresponds to that predicted by the Cram[5] or Felkin[6] models. The structure of trans dihydropyrone **4b** had been rigorously demonstrated by its conversion to the well-known Prelog–Djerassi lactone. That the cis isomer **3b** corresponds to the same facial series had been previously inferred.[1,7]



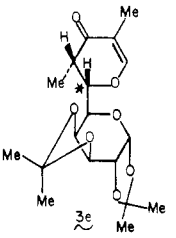
3b



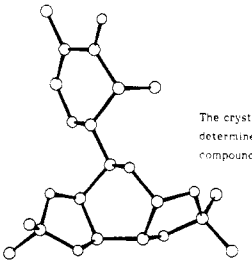
4b



3d



3e



The crystallographically determined structure of compound **3d**.

The full stereochemistry of the major cis pyrone **3d**, mp 150–151 °C, was unambiguously demonstrated to be as shown by an X-ray crystallographic determination.[8] We

(1) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457.
(2) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6715.
(3) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R.; McCurry, P. Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.
(4) Emde, H.; Domsch, D.; Feger, H.; FrickU.; Bötz, H.; Hergoth, H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
(5) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245 and references therein.
(6) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(7) Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

0022-3263/85/1950-4650$01.50/0