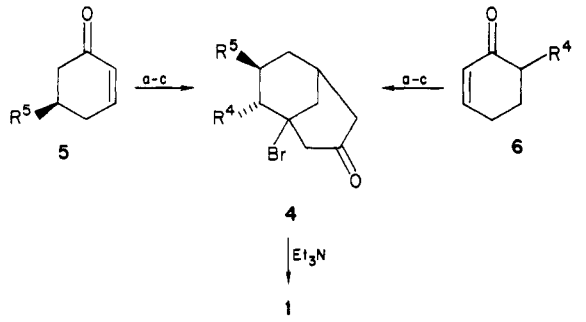
Scheme II[a]



[a] (a) $CH_3COCH_2CO_2Et$, NaOEt; (b) KOH; (c) PBr_3.

Table I. Diels-Alder Reactions of Bridgehead Enones

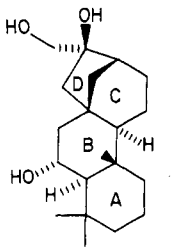
1 + 2 → 3-exo

entry	R^1	R^2	R^3	R^4	R^5	% yield	cmpd
1	$OSiMe_3$	$-(CH_3)_4-$		PhS	H	97	8
2	$OSiMe_3$	$-(CH_3)_4-$		H	CH_3	52	9
3	H	H	H	PhS	H	41	10
4	$OSiMe_3$	H	OCH_3	PhS	H	98	11
5	H	H	OAc	PhS	H	63	12
6	H	H	OAc	H	CH_3	55	13

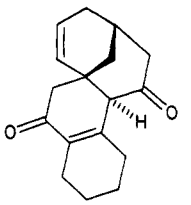
carbon atom would have a partial positive charge, a regioselective reaction should result. It is not clear how the exo/endo ratio will be affected by the nonplanarity of the enone. While House has determined an exo/endo ratio of 2.3 with furan, literature data indicate that furan often exhibits a slight exo preference, even with dienophiles which afford largely endo adducts with other dienes.[6] Adducts may be generated by endo (3-endo) or exo (3-exo) modes of addition (Scheme I).

The bromo ketone precursors to the bridgehead enones were constructed by using literature procedures.[7] In both cases the substituted cyclohexenones were treated with ethyl acetoacetate and a slight excess of base. Subsequent decarbalkoxylation produced hydroxy ketones by using phosphorus tribromide in benzene. Both bromo ketones were recrystallized and were only one diastereomer as evidenced by ^{13}C NMR. The structure of 4 (R_4 = SPh, R_5 = H) was determined by X-ray crystallography.[8] The bridgehead enones were generated by adding 2 equiv of triethylamine to a solution of 4 (1 equiv) and the diene (1.5 equiv) in methylene chloride at 0 °C (Scheme II). Table I indicates that dienes bearing electron-donating groups afforded high yields of Diels–Alder adducts. The ^{13}C NMR spectrum of each purified adduct showed that the reactions were highly stereoselective. In each case in Table I only a single set of resonances was observed: For adducts 11 and 12, decoupling experiments gave a coupling constant of 7 Hz for the two adjacent methine protons. This value is consistent with a trans diaxial relationship and therefore an exo adduct. Additional evidence for the exo mode of addition was provided by an X-ray crystal structure of the acid hydrolysis product of 8.

Adduct 8 represents an attractive intermediate for the synthesis of members of the kaurane family of diterpenes.[9] One member of this family, corymbol, is shown. The key



corymbol



7

transformation involves the introduction of the tetrasubstituted enone. As illustrated in eq 1, the requisite enone

$$8 \xrightarrow{a\text{-}c} 7 \qquad (1)$$

(a) $Pd(OAc)_2$; (b) $NaIO_4$, MeOH; (c) 180 °C

was constructed from 8 by oxidation of the enol silyl ether with palladium acetate and benzoquinone.[10] Reduction of the ketone prior to silyl ether oxidation afforded mostly the isomeric enone, as evidenced by a vinyl hydrogen absorption at 6.9 ppm in the spectra.[11] Sulfide oxidation with sodium metaperiodate in methanol at ambient temperature followed by sulfoxide elimination at 180 °C produced ketone 7 in approximately 60% overall yield from adduct 8. Ketone 7 contains the appropriate functionality for eventual conversion to corymbol. Importantly, ketone 7 also permits the introduction, via conjugate addition, of a hydroxymethyl group, which is common to the more biologically active members of this class.[12]

Overall, the dissection A + CD → ABCD constitutes an entirely new approach to the synthesis of diterpenes bearing a bicyclo[3.2.1]octane subunit. The convergent approach plus the flexibility and good overall yields combine to make this synthetic route a significant one.

(6) House, H. O.; DeTar, M. B.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 3793.
(7) For synthesis, see: ref 5 and also House, H. O.; Outcalt, R. J.; Cliffton, M. D. *J. Org. Chem.* **1982**, *47*, 2413.
(8) Ketone 1 (R_4 = PhS, R_5 = H) was produced as a mixture of diastereomers. The major isomer was used in this study.
(9) Corymbol: Perezamador, M. C.; Jimenez, F. G. *Tetrahedron* **1966**, 1937.
(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(11) The reduction with sodium borohydride in ethanol afforded largely one diastereomer. It was tentatively assigned the β configuration on the basis of steric hindrance on the top face of the molecule.
(12) For example, the trichorabdals: Node, M.; Sai, M.; Fujita, E.; Fuji, K. *Heterocycles* **1984**, *22*, 1701.

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2 + 3 Dipolar Cycloadditions of a Monomeric Thioaldehyde

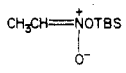
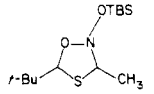
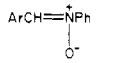
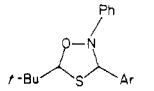
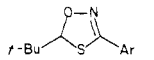
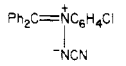
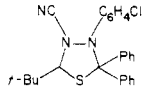
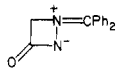
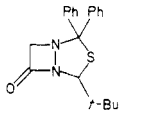
Summary: Thiopivaldehyde is a highly reactive dipolarophile toward nitrones, nitrile *N*-oxides, diazo compounds, azomethine *N*-imines, thiomunchnones, and sydnones.

Sir: Thioketones are recognized as highly reactive dipolarophiles[1] and even higher reactivity would be expected for thioaldehydes.[2,3] The recent preparation of reasonably

(1) For example: (a) Gotthard, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1968**, *101*, 1056. (b) Schönberg, A.; Fateen, A. E. K.; Samous, A. E.-M-A. *J. Am. Chem. Soc.* **1957**, *79*, 6020. (c) Middleton, W. J. *J. Org. Chem.* **1969**, *34*, 3201. (d) Black, D. St. C.; Watson, K. G. *Aust. J. Chem.* **1973**, *26*, 2491. (e) Katada, T.; Eguchi, S.; Sasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2641.
(2) Diazoalkanes + transient thioaldehyde: Burri, K. F.; Paioni, R.; Woodward, R. B., unpublished results. We thank Dr. Burri for informing us of this work.
(3) Nitronate ester + transient thioaldehyde: Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

0022-3263/86/1951-0117$01.50/0

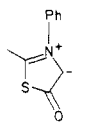
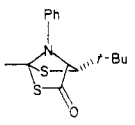
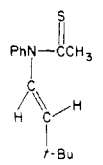
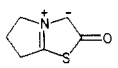
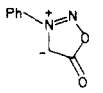
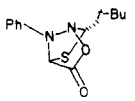
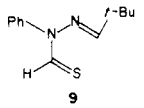
Table I. Thiopivaldehyde + 1,3-Dipoles; Stable Adducts

entry	dipole	adduct	rel yield
1			1[a]
2[b]			0.7
3[b]	ArCNO		0.7
4			0.8
5			0.7

1

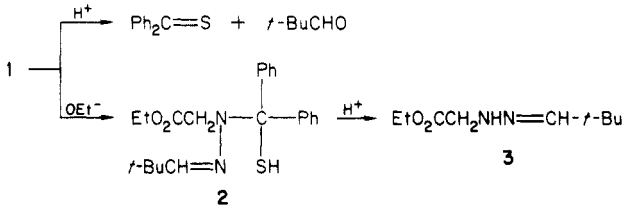
[a] The reaction of entry 1 is used for color end point titration of thiopivaldehyde solutions and occurs in >90% yield. [b] Ar = *p*-$CH_3OC_6H_4$. [c] TBS = *tert*-butyldimethylsilyl.

Table II. Unstable Adducts

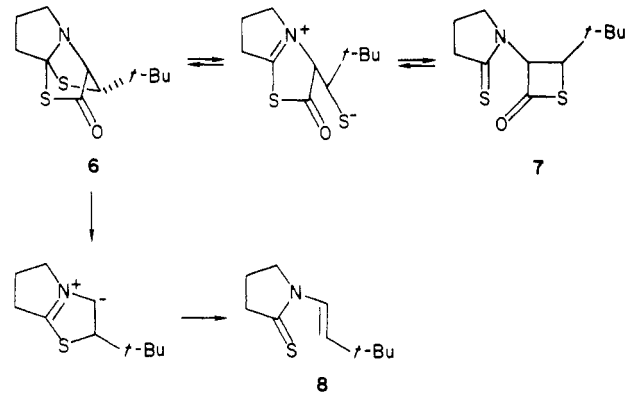
entry	dipole	initial adduct	isolated products	rel yield
6		 4	4 +  5 (4:5 = 1:9)	0.4
7		6	7	0.4
8			 9	0.5

stable solutions of thiopivaldehyde in our laboratory offered an opportunity to study this question.[4] As expected, the thioaldehyde reacts readily with representative 1,3-dipoles (Tables I and II), usually within minutes at room temperature.

In entries 1–5, the initially formed 2 + 3 adducts are sufficiently stable for isolation, and their structures are obvious from spectral data.[5] The diazetidinone dipole[6] (entry 5) gves an adduct **1** consisting of two diastereomers at pyramidal nitrogen which interconvert slowly on the NMR time scale, but too rapidly to allow separation. This is consistent with the behavior of the previously known 1,2-diaryldiazetidinones.[7] Attempts to observe coalescence of the NMR signals for **1** at higher temperatures result in decomposition to thiobenzophenone (intensely blue solution!), a reaction which is greatly accelerated by acid catalysis. Further characterization of **1** is provided by base cleavage to give **2** which affords the hydrazone **3** upon treatment with acid.



Entries 6–8 (Table II) describe systems where the initial adducts are not stable. Only in the thiomunchnone example (entry 6) can the 2 + 3 adduct **4** be isolated at room temperature (4% yield), and the major product is the cycloreversion-derived *N*-thioacetyl enamine **5**.[8] Brief heating in toluene converts **4** into **5** via loss of COS and electrocyclic ring opening. The bicyclic thiomunchnone[9] (entry 7) affords a more peculiar product to which we assign structure **7** on the basis of the β-thio lactone carbonyl frequency at 1760 cm^{-1} and the ^{13}C NMR spectrum (SC=O, 188.1 ppm; NC=S, 203 ppm). This product can be derived from the expected **6** by acyl transfer, a reaction which appears to be reversible. Thus, heating **7** eventually affords the cycloreversion product **8**, which is most easily explained starting from **6** by loss of COS as in the monocyclic thiomunchnone example (entry 6). The syndnone



(entry 8) gives **9** by a similar 2 + 3 addition, cycloreversion sequence, a transformation which is also observed in sydnone–thioketone reactions.[1a]

With regard to regiochemistry, all of the products in Table I are derived from that orientation which has the thioaldehyde *tert*-butyl group near the less hindered end of the dipole. The same trends are seen with thioketones,[1] and there are indications that steric effects may dominate[1e] over FMO interactions.[10] However, one should note that the FMO approximation[10] clearly predicts the same product as does the steric effect in all of the examples with the possible exception of entry 8. According to calculations on simpler model structures,[11,12] the sydnone reaction

(4) Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 1683.

(5) Partial NMR data: [entry 2] ^1H NMR δ 6.27 (1 H, s), 5.38 (1 H, s), [entry 3] 5.95 (1 H, s), [entry 4] 4.39 (1 H, s), [entry 5 (**1**), major isomer] 5.23 (1 H, s), 4.07 (1 H, d, *J* = 13.9 Hz), 3.09 (1 H, d, *J* = 13.9 Hz), [entry 5 (**1**), minor isomer] 3.93 (1 H, d, *J* = 15.0 Hz), 3.90 (1 H, s), 3.69 (1 H, d, *J* = 15.0 Hz), [entry 6 (**4**)] 4.79 (1 H, br s), 3.81 (1 H, br s), 2.18 (3 H, s), [**5**] 7.50–7.06 (6 H, m), 4.67 (0.5 H, d, *J* = 5.1 Hz), 4.01 (0.5 H, d, *J* = 5.2 Hz), 2.30 (1.5 H, s), 2.08 (1.5 H, s), 1.13 (4.5 H, s), 1.10 (4.5 H, s), [entry 7 (**7**)] 6.77 (1 H, d, *J* = 5.2 Hz), [**8**] 7.50 (1 H, d, *J* = 14.8 Hz), 5.38 (1 H, d, *J* = 14.8 Hz), [entry 8, (**9**)] 10.00 (1 H, s), 6.75 (1 H, s).

(6) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567.

(7) (a) Fahr, E.; Fisher, W.; Jung, A.; Sauer, L.; Mannschreck, A. *Tetrahedron Lett.* **1967**, 161. (b) Mannschreck, A.; Seitz, W. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 212. (c) Fahr, E.; Rohfing, W.; Thiedemann, R.; Mannschreck, A.; Rissmann, G.; Seitz, W. *Tetrahedron Lett.* **1970**, 3605.

(8) For analogous cycloreversions, see: Funk, E.; Huisgen, R.; Schaefer, R. C. *Chem. Ber.* **1971**, 1550. Kumar, A.; Hartke, K.; Köster, J. *Chem. Ztg.* **1982**, *106*, 144. Reference 1a.

(9) Generated from the thiolactam carboxylate salt and MsCl, followed by 1 equiv of Et_3N.

(10) (a) Houk, K. N.; Yamaguchi, K. "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 407. (b) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569. (c) Huisgen, R., ref 10a; Vol. 1, p 1.

(11) For thioaldehyde HOMO/LUMO coefficients, see: Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999.

should be dipole HOMO controlled, and the HOMO polarization is modestly weighted toward carbon rather than nitrogen due to the effect of sydnone carbonyl.[12] Since thial LUMO polarization also has the larger FMO coefficient at carbon,[11] the regiochemistry seen for entry 8 would have to be due to other factors (sterics, lone pair repulsions, dipole LUMO–thial HOMO interactions, etc).

So far, only the previously reported reaction of thiopivaladehyde with ethyl diazoacetate gives detectable products from the more hindered 2 + 3 cycloadduct (ca. 1:1 mixture of regioisomers is formed).[4] A comparison of FMO energies and coefficients for the reactants[11,13] in this case is instructive because both possible FMO interactions (dipole HOMO + thial LUMO; dipole LUMO + thial HOMO) now favor the more hindered regioisomer. The behavior of thioketones with diazo esters is again very similar and opposing steric vs. FMO factors result in regioisomer mixtures.

Overall, there is a close analogy in the behavior of thiopivaldehyde and the previously studied thioketone 2 + 3 cycloadditions. The same trend has also been noted in 2 + 4 cycloadditions and ene insertions which are discussed in other papers from our laboratory.[11,14]

Acknowledgment. This work was supported by the National Science Foundation.

(12) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786.
(13) The FMO coefficients for diazoacetate are given in ref 10c where they are attributed to: Sustmann, R., private communication.
(14) Vedejs, E.; Wilde, R. G., unpublished results. Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.*, submitted for publication.

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The Temperature-Dependent Regioselective Deprotonation of Fluoroacetone Cyclohexylimine

Summary: The temperature-dependent regioselective deprotonation of fluoroacetone cyclohexylimine was developed as a procedure for the regioselective alkylation of fluoroacetone.

Sir: The importance of metalated imines (azaallyl metal reagents) in selective asymmetric synthesis is widely recognized.[1] Regioselective deprotonation, critical when acyclic ketimines are employed, is dependent upon temperature, the nitrogen alkyl substituent, and the steric bulk of the base among other factors.[2] In the course of our studies on the stereoselective synthesis of fluorinated compounds, we sought to develop methods for the selective deprotonation and alkylation of fluorinated imines. As fluorine is not a sterically demanding substituent, fluorination is a severe test of the sensitivity of deprotonation to steric effects. At the same time fluorination will have pronounced electronic effects on the reaction.

Table I. Temperature-Dependent Deprotonations of Fluoroacetone Cyclohexylimine

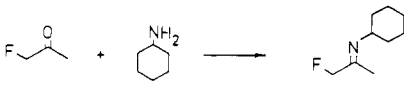
entry	alkyl halide	temp, °C	product composition[a] RCHFO-CH_3	product composition[a] CH_2FCO-CH_2R	yield, %
1	CH_3I	−30	11	89	48[b]
2	CH_3I	−80	96	4	43[b]
3	CH_2=$CHCH_2Br$	−30	9	91	62
4	CH_2=$CHCH_2Br$	−80	97	3	69
5	$CH_3CH_2CH_2CH_2I$	−30	3	97	60
6	$CH_3CH_2CH_2CH_2I$	−80	97	3	81
7	$C_6H_5CH_2Br$	−30	18	82	71
8	$C_6H_5CH_2Br$	−80	93	7	81
9	C_6H_5CH=$CHCH_2Br$	−30	8	92	88
10	C_6H_5CH=$CHCH_2Br$	−80	28	72	79

[a] Product composition determined by gas chromatography and ^{19}F NMR spectroscopy. [b] Yield of crude product.

The utility of stereospecifically fluorinated biologically active compounds, such as γ-fluoroglutamic acid,[3] fluorocitric acid,[4] or 2-deoxy-2-fluoroarabinose,[5] in descerning biochemical pathways is limited only by the difficulty of their preparation. This challenge has been addressed in our[6] and others'[7] earlier investigations of fluorinated enolates. Deprotonated fluorinated imines are particularly attractive enolate equivalents, where the sensitivity of imine deprotonation to subtle steric and electronic effects may be probed.

Halogenated imines[8] have been reported to react with nitrogen bases by intra- or intermolecular displacement of halide.[9] Organometallic reagents also effect displacement reactions as well as imine dimerization.[10] Although fluoro imines have been implicated as intermediates in action of pyridoxal 5′-phosphate with fluoroaspartates in NMR studies,[11] much less is known about the chemistry of fluorinated imines.

We have found that the cyclohexylimine of fluoroacetone may be simply prepared by treatment of fluoroacetone with cyclohexylamine in the presence of anhydrous potassium carbonate. Distillation under reduced pressure



(1) (a) Bergbreiter, D. E.; Newcomb, M. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: Orlando, 1983; Vol. 2, pp 243–273. (b) Fraser, R. R. In "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Part B, pp 65–105.
(2) Smith, J. K.; Newcomb, M.; Bergbreiter, D. E.; Williams, D. R.; Meyers, A. I. *Tetrahedron Lett.* **1983**, *24*, 3559–3562.
(3) Dubois, J.; Gaudry, M.; Bory, S.; Azerad, R.; Marque, A. *J. Biol. Chem.* **1983**, *258*, 7897–7899.
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