A drop of ethanol was added, and the mixture was stirred for 1 h and then poured into water. The ether layer was washed (H_2O) and the combined aqueous layers were acidified with 0.5 mL of 6 N HCl and extracted with ether. The ether solution was washed (aqueous $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated in vacuo. The crude product was flash chromatographed (1 to 10% EtOAc/hex) to give 95.5 mg of an unstable colorless oil (87%): TLC R_f 0.55 (10% EtOAc/hex); ^1H NMR ($CDCl_3$) δ 15.00–15.12 (m, 0.9 H, enolic H), 9.58 (d, 0.05 H, J = 1.7 Hz), 9.56 (d, 0.05 H, J = 4.0 Hz), 7.88–7.98 (m, 1 H), 5.20–5.52 (m, 2 H), 2.40 (br t, 2 H), 1.8–2.32 (m, 4 H), 1.50–1.70 (m, 4 H), 1.25 (br s, 20 H), 0.87 (br t, 6 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 197.62, (177.75, 177.00, 176.71, 176.55), (132.25, 131.70, 131.58, 131.18), (128.99, 128.48, 128.22, 127.52), (112.65, 112.59, 111.83), 31.87, 31.51, 31.39, 31.26, 29.55, 29.41, 29.29, 29.15, 27.35, 25.01, 22.64, 22.59, 14.08; IR 1580–1640 cm^{-1} (broad peak). Analytical data were obtained on the more stable isoxazole derivatives (see below).

Mixture of [6,7-$^3H_2$]-(*Z*)-10-Formyl-6-heneicosen-11-one and 12-Formyl Isomer (3b). The labeled ketone (143 mCi, ca. 0.76 mg) was formylated with 50 μL of ethyl formate and 5 mg of NaH in 1.00 mL of dry ether and 1 μL of absolute ethanol. The mixture was allowed to stir at 30 °C overnight. The reaction was worked up by using the same procedure described for the unlabeled reaction. Flash chromatography of the product (1 to 10% EtOAc/hex) gave 103 mCi (ca. 0.6 mg) (72% radiochemical yield) of the homogeneous formylated ketone isomers **3b**.

Mixture of (*Z*)-10-Diazo-6-heneicosen-11-one and 12-Diazo Isomer (4a). To a stirred and ice-cold solution of **3a** (85.5 mg, 0.25 mmol) and 50 mg of Et_3N (0.5 mmol) in dry CH_2Cl_2 (4 mL) was added a solution of *p*-toluenesulfonyl azide (50 mg, 0.25 mmol) in 1 mL of CH_2Cl_2 dropwise. Stirring was continued for 3 h as the ice melted, then 1 mL of 1 N KOH was added and the mixture was stirred for 0.5 h at room temperature. The methylene chloride layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with dilute aqueous KOH and water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed four times with 0.5% EtOAc/hex in a long thin column of silica gel packed in *n*-hexane to eliminate the unreacted tosyl azide and to give 55 mg of a yellow oil (65%): TLC R_f 0.48 (10% EtOAc/hex); ^1H NMR ($CDCl_3$) δ 5.2–5.6 (m, 2 H), 2.2–2.5 (m, 4 H), 1.8–2.1 (m, 2 H), 1.5–1.8 (m, 4 H), 1.25 (br s, 20 H), 0.85 (br t, 6 H, J = 6 Hz); IR 2050 (strong), 1730, 1640 cm^{-1}; UV (ethanol) λ_{max} 287 nm ($n \rightarrow \pi^*$, ϵ 6120); 248 nm ($\pi \rightarrow \pi^*$, ϵ 12 740); LR-MS, 70 eV, m/z (rel abund) 306 (0.7, $M^+ - N_2$), 279 (1.2, $M^+ - N_2 - C_2H_3$), 249 (2.8, $M^+ - N_2 - C_4H_7$), 235 (4.8), 221 (10.5), 165 (13.7, $M^+ - N_2 - C_{10}H_{21}$), 149 (57.3, $M^+ - N_2 - C_{10}H_{21}O$), 109 (39.8), 97 (54.2), 95 (69.6), 81 (65.2), 69 (77), 55 (100, $C_3H_3O^+$); HR-MS, calcd for $C_{21}H_{38}O$ (loss of N_2) 306.2922, found 306.2922.

Mixture of [6,7-$^3H_2$]-(*Z*)-10-Diazo-6-heneicosen-11-one and 12-Diazo Isomer (4b). The reaction was conducted as described above in a conical microflex vial by using the crude formylated ketone (103 mCi, ca. 0.6 mg), excess tosyl azide (ca. 10 mg), and 20 μL of Et_3N in 1 mL of dry CH_2Cl_2. After aqueous workup, the crude product was chromatographed four times as above to eliminate the excess tosyl azide and Et_3N to give ca. 35 mCi (ca. 0.2 mg) of the labeled diazo ketone **4b** (34% radiochemical yield).

Mixture of Isoxazoles. The crude formyl ketone mixture (10 mg, 0.03 mmol) was diluted with 1.5 mL of absolute ethanol, 70 mg of dry K_2CO_3, and 70 mg of hydroxylamine hydrochloride at 0 °C and then stirred for 1 h at 20 °C and 16 h at reflux.[10] The reaction was quenched with 1 mL of 2 N HCl, the isoxazoles **5** were extracted with 1:1 hexane/ether, and the crude product was purified by alumina chromatography (1% EtOAc–hexane) to give 8 mg (81%) of TLC-homogeneous isoxazoles: TLC R_f 0.5 (10% EtOAc/hex). While GC on a DB-5 Megabore column (15 m × 1 mm) showed a single peak, analysis on a 30 m × 0.25 mm DB-5 column (T_i = 150 °C, T_f = 250 °C, T_p = 10 °C/min) showed eight peaks with relative abundances of 38.2, 28.4, 15.3, 11.9, 2.3, 1.7, 1.5, 0.6. These were not assigned to individual regio- or stereoisomers. ^1H NMR ($CDCl_3$): δ 8.09 (s, 0.3 H), 8.06 (s, 0.7 H), 5.2–5.6 (m, 2 H), 2.70 (t, 2 H, J = 7.4 Hz), 2.15–2.45 (m, 2 H), 1.95–2.20 (m, 4 H), 1.2–1.86 (m, 20 H), 0.89 (br t, 6 H, J = 6 Hz). FT-IR (neat): 1736, 1628, 1467, 1378 cm^{-1}. HR-MS of mixed TLC-homogeneous isoxazole isomers: calcd for $C_{22}H_{39}ON$ 333.3033, found 333.3030.

Acknowledgment. We thank the Herman Frasch Foundation and the U.S. Department of Agriculture (85-CRCR-11736) for grants in support of this work. B.L. acknowledges support of the Ministry of Science of Algeria for a fellowship. Unrestricted funds to G.D.P. from the Camille and Henry Dreyfus Foundation and from the Rohm and Haas Company have facilitated these studies. Special thanks are due to Dr. H. Morimoto (NTLF), Dr. P. G. Williams (NTLF), S. McG. Graham (Stony Brook), and M. F. Boehm (Stony Brook) for assistance in tritium labeling and tritium NMR. Dr. R. G. Vogt (Stony Brook) first suggested this system for biochemical study, and Dr. G. E. Daterman (USDA, Corvallis, OR) generously provided *O. pseudotsugata* eggs, pupae, and bioassay data.

(10) Prestwich, G. D.; Collins, M. S. *J. Org. Chem.* **1981**, *46*, 2383.

Facile Synthesis of Protected β,β-Dialkylcysteine Derivatives Suitable for Peptide Synthesis

Nelson C. F. Yim, Heidemarie Bryan, William F. Huffman, and Michael L. Moore*

Department of Peptide Chemistry, Smith Kline & French Laboratories, King of Prussia, Pennsylvania 19406

Received May 12, 1988

The use of β,β-dialkylcysteine derivatives has begun to find widespread use in conformation–activity studies of peptides due to the conformational constraint imposed by the *gem*-dialkyl substituent on the adjacent disulfide bond.[1] This type of substitution has produced antagonists of oxytocin[2,3] and vasopressin[4,5] and has produced enkephalin agonist analogues with δ-receptor subtype selectivity.[6]

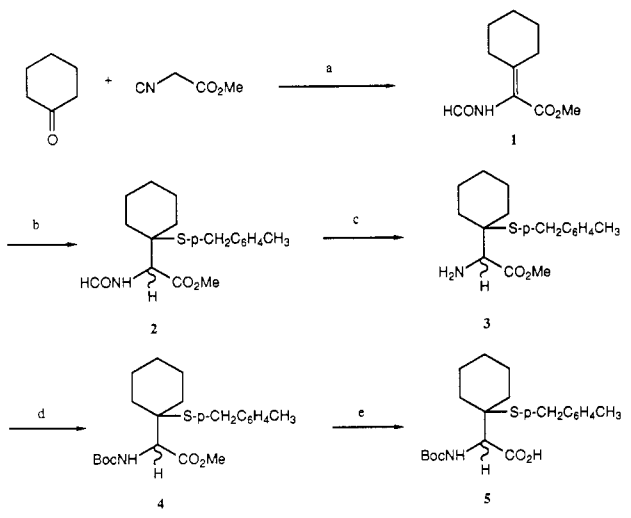
While β,β-dimethylcysteine (penicillamine) is readily available, other dialkylcysteines have been more difficult to obtain. A report of a general synthesis for dialkylcysteine derivatives by Stanfield et al. has appeared recently.[7] Their synthesis involves the addition of sulfur to an α,β-dehydro amino acid derivative using phosphorus pentasulfide, hydrolysis of the resulting thiazoline to the free mercapto amino acid, and sequential protection of the mercapto and amino groups. Protection of the mercapto group requires a sodium/liquid ammonia reaction.

A simpler and more direct approach is the introduction of the protected mercaptan directly by Michael addition of a sulfur nucleophile to the dehydro amino acid derivative. It has been shown, for example, that benzyl mercaptan will undergo Michael addition to oxazolones of α,β-dehydro amino acids to yield *S*-benzyl-β-alkylcysteines upon hydrolysis.[8] We have previously used the Michael addition of *p*-methylbenzyl mercaptan to β,β-dialkyl-

(1) Meraldi, J.-P.; Hruby, V. J.; Brewster, A. I. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 1373.
(2) Schulz, H.; du Vigneaud, V. J. *J. Med. Chem.* **1966**, *9*, 647.
(3) Chan, W. Y.; Fear, R.; du Vigneaud, V. *Endocrinology (Baltimore)* **1967**, *81*, 1267.
(4) Sawyer, W. H.; Pang, P. K. T.; Seto, J.; McEnroe, M.; Lammek, B.; Manning, M. *Science (Washington, D.C.)* **1981**, *212*, 49.
(5) Yim, N. C. F.; Moore, M. L.; Huffman, W. F.; Bryan, H. G.; Chang, H.-L.; Kinter, L. B.; Edwards, R.; Stassen, F. L.; Schmidt, D.; Heckman, G. *J. Med. Chem.* **1986**, *29*, 2425.
(6) Mosberg, H. I.; Hurst, R.; Hruby, V. J.; Gee, Y.; Yamamura, H. I.; Galligan, J. J.; Burks, T. F. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5871.
(7) Stanfield, C. F.; Cody, W. L.; Ruby, V. J. *J. Org. Chem.* **1986**, *51*, 5153.
(8) Carter, H. E.; Stevens, C. M.; Ney, L. F. *J. Biol. Chem.* **1941**, *139*, 247.

0022-3263/88/1953-4605$01.50/0

Scheme I[a]



[a] (a) NaH (1.2 equiv), THF; (b) NaH (0.1 equiv), *p*-methylbenzyl mercaptan (1 equiv), toluene; (c) 10% HCl/MeOH, ether, 4 °C; (d) NaOH (1 equiv), di-*tert*-butyl dicarbonate (1.1 equiv), water/*tert*-butyl alcohol; (e) K_2CO_3 (1 equiv), MeOH, water, reflux.

acrylate esters to prepare S-protected β,β-dialkylmercaptopropionic acid analogues.[9,10] We now report that this procedure can be extended to the synthesis of an S-protected β,β-dialkylcysteine directly by Michael addition of *p*-methylbenzyl mercaptan to a dehydro amino acid derivative using a catalytic amount of sodium hydride.[11] This scheme elimiates the tedious sodium/liquid ammonia reaction in the Stanfield et al. synthesis.

The synthesis of Boc-*S*-(*p*-methylbenzyl)-β,β-pentamethylenecysteine (**5**, Scheme I) exemplifies the approach. The *N*-formyl cyclohexylideneglycine methyl ester was prepared by addition of cyclohexanone to methyl isocyanoacetate as described previously.[12] As we had reported earlier in the synthesis of β,β-pentamethylene-β-mercaptopropionic acid,[9] the key to the synthesis is the use of catalytic rather than stoichiometric amounts of sodium hydride in the Michael addition. This suppresses such side reactions as retro-Michael elimination of the *p*-methylbenzyl mercaptan and migration of the double bond in **1**, which can occur when stoichiometric amounts of sodium hydride are employed. The reactions are all straightforward and proceed cleanly in generally good yields. The methodology avoids the use of sodium/liquid ammonia and should be applicable to the preparation of a wide range of β-mono- and β,β-dialkylcysteine derivatives.

Experimental Section

Tetrahydrofuran and toluene were stored over 4-Å molecular sieves. Cyclohexanone, methyl isocyanoacetate, and di-*tert*-butyl dicarbonate were obtained from Aldrich. *p*-Methylbenzyl mercaptan was obtained from Fairfield Chemical Co. NMR spectra were obtained at 90 MHz on a Varian EM-390 spectrometer. Chemical shifts are reported relative to tetramethylsilane. Thin-layer chromatography was done on Analtech silica gel Uniplates using the following systems: (1) cyclohexane–ethyl acetate, 1:1 (v/v); (2) cyclohexane–ethyl acetate, 12:1 (v/v); (3) cyclohexane–ethyl acetate–glacial acetic acid, 18:2:1 (v/v). Spots were visualized by charring with sulfuric acid.

Methyl *N*-Formyl-α-cyclohexylideneglycinate (1). To a suspension of NaH (2.88 g, 120 mmol, 60% oil dispersion) in dry THF (100 mL) was added dropwise over 1 h a solution of cyclohexanone (11.35 mL, 100 mmol) and methyl isocyanoacetate (10 g, 100 mmol) in dry THF (100 mL). The reaction mixture was stirred at room temperature for 2 h and cooled to 0 °C, and 10% aqueous acetic acid (100 mL) was then added dropwise. The organic solvent was removed in vacuo, and the resulting aqueous solution was extracted with three portions of CH_2Cl_2. The combined extracts were washed with one portion of water, dried over Na_2SO_4, and evaporated to dryness. The crude product was recrystallized from ether–CH_2Cl_2, yielding 11.6 g (59%) of pure **1**: mp 106–107.5 °C; R_f (1) 0.41; ^{1}H NMR ($CDCl_3$) δ 8.2–7.8 (dd, 1 H, *H*CONH, syn and anti isomers), 7.0 (br m, 1 H, NH), 3.76 (s, 3 H, CO_2CH_3), 2.75 (m, 2 H, $CH_2C{=}C$), 2.35 (m, 2 H, $CH_2C{=}C$), 1.65 (m, 6 H, CH_2).

Methyl *N*-Formyl-*S*-(*p*-methylbenzyl)-β,β-pentamethylenecysteinate (2). To a suspension of NaH (80 mg, 2.0 mmol, 60% oil dispersion) in dry toluene (7 mL) was added *p*-methylbenzyl mercaptan (2.76 g, 20 mmol). The reaction mixture was stirred at room temperature for 30 min. A portion of **1** (1.97 g, 10 mmol) was suspended in dry toluene (10 mL) and added to the reaction, followed by the addition of dry DMF (2 mL) to clarify the reaction mixture. After being stirred at room temperature for 16 h, the reaction mixture was poured into 200 mL of ice–water and extracted with three portions of ether. The combined ether extracts were washed once with 10% aqueous NaOH, dried over Na_2SO_4, and evaporated to dryness, yielding 2.7 g (80%) of pure **2**: R_f (1) 0.63; ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1 H, *H*CONH), 7.25–7.05 (dd, 4 H, C_6H_4), 6.85 (br d, 1 H, NH), 4.85 (d, 1 H, α-CH), 3.75 (s, 3 H, CO_2CH_3), 3.6 (s, 2 H, SCH_2), 2.3 (s, 3 H, $C_6H_4CH_3$), 1.9–1.5 (m, 10 H, CH_2); mass spectrum, *m/z* 336 (M + H$^+$). Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.28; H, 7.74; N, 4.17. Found: C, 64.36; H, 7.46; N, 4.32.

Methyl *S*-(*p*-Methylbenzyl)-β,β-pentamethylenecysteinate (3). A portion of **2** (3.1 g, 9.2 mmo6) was dissolved in ether (150 mL) and 10% HCl in methanol (77 mL) and kept at 4 °C for 2 days. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed once with 15% aqueous NH_4OH and once with saturated aqueous $NaHCO_3$. The solution was dried over Na_2SO_4 and evaporated to yield 2.3 g of **3** (81.4%): mp 160–161 °C; R_f (1) 0.52; ^{1}H NMR ($CDCl_3$) δ 7.3–7.0 (dd, 4 H, C_6H_4), 5.25 (s, 1 H, α-CH), 3.73 (s, 3 H, CO_2CH_3), 3.56 (s, 2 H, SCH_2), 2.3 (s, 3 H, $C_6H_4CH_3$), 1.9–1.45 (m, 10 H, CH_2); mass spectrum, *m/z* 308 (M + H$^+$).

Methyl *N*-Boc-*S*-(*p*-methylbenzyl)-β,β-pentamethylenecysteinate (4). A portion of **3** (2.3 g, 7.5 mmol) was dissolved in 46 mL of H_2O and 46 mL of *tert*-butyl alcohol containing 7.5 mL of 1 N NaOH. Di-*tert*-butyl dicarbonate (1.8 g, 8.25 mmol) was added dropwise over 30 min and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was extracted with three portions of hexane. The combined hexane extracts were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was triturated with petroleum ether and the solid collected by filtration and air-dried to yield 2.4 g of pure **4** (79%): mp 108–109 °C; R_f (2) 0.28; ^{1}H NMR ($CDCl_3$) δ 7.3–7.0 (dd, 4 H, C_6H_4), 5.5 (br d, 1 H, α-CH), 4.4 (br d, 1 H, NH), 3.8 (s, 3 H, CO_2CH_3), 3.6 (s, 2 H, SCH_2), 2.35 (s, 3 H, $C_6H_4CH_3$), 1.95–1.5 (m, 10 H, CH_2). Anal. Calcd for $C_{22}H_{33}NO_4S$: C, 64.86; H, 8.11; N, 3.44. Found: C, 65.53; H, 8.27; N, 3.37.

***N*-Boc-*S*-(*p*-methylbenzyl)-β,β-pentamethylenecysteine (5).** To 32 mL of a solution of 12.5% aqueous K_2CO_3 in 25% aqueous methanol (4 mmol) was added **4** (1.6 g, 4 mmol). The reaction mixture was refluxed for 16 h. After cooling, the methanol was removed under reduced pressure and the remaining solution was diluted with water, washed with one portion of ether–hexane (1:1), cooled to 0 °C, and carefully acidified to pH 2 with 3 N HCl. This was then extracted with three portions of ether, and the combined ether extracts were dried over $MgSO_4$, evaporated, and recrystallized from cyclohexane, yielding 0.89 g of pure **5** (56.5%):

(9) Yim, N. C. F.; Huffman, W. F. *Int. J. Pept. Protein Res.* **1983**, *21*, 568.

(10) Yim, N. C. F.; Moore, M. L.; Huffman, W. F.; Bryan, H. G.; Chang, H.-L.; Kinter, L. B.; Edwards, R.; Stassen, F. L.; Schmidt, D.; Heckman, G. *J. Med. Chem.* **1986**, *29*, 2425.

(11) Subsequent to the submission of this paper, a similar Michael addition of benzyl mercaptans to protected dehydro amino acids was reported by Stanfield and Hruby. They use stoichiometric or greater amounts of the lithium thiolate formed using *n*-butyllithium at −78 °C rather than a catalytic amount of the sodium thiolate formed using sodium hydride at room temperature. Stanfield, C. F.; Hruby, V. J. *Synth. Commun.* **1988**, *18*, 531.

(12) Suzuki, M.; Nunami, K.-I.; Matsumoto, K.; Yoneda, N.; Kasuga, O.; Yoshida, H.; Yamaguchi, T. *Chem. Pharm. Bull.* **1980**, *28*, 2374.

mp 120–122 °C (lit.[7] mp 123–124 °C); R_f (3) 0.32; mass spectrum m/z 394 ($M + H^+$); ^1H NMR ($CDCl_3$) δ 7.3–7.1 (dd, 4 H, C_6H_4), 5.8–5.2 (br s, 1 H, NH), 5.5 (d, 1 H, α-CH), 3.65 (s, 2 H, SCH_2), 2.3 (s, 3 H, $C_6H_4CH_3$), 1.8–1.5 (m, 10 H, CH_2).

Registry No. 1, 67654-35-7; 2, 115797-97-2; 3, 115797-98-3; 4, 115797-99-4; 5, 105563-00-6; 4-$MeC_6H_4CH_2SH$, 4498-99-1; cyclohexanone, 108-94-1; methyl isocyanoacetate, 39687-95-1.

Diels–Alder Reactions of Cycloalkenones. 13. Reactions of 2-Cyclohexenones with (*E*)-1-Methoxy-1,3-butadiene[1]

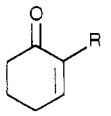
Francesco Fringuelli,*[2a] Lucio Minuti,[2a] Lajos Radics,*[2b] Aldo Taticchi,*[2a] and Ernest Wenkert[2c]

Dipartimento di Chimica, Università di Perugia, 06100 Perugia, Italy, Central Research Institute of Chemistry, P.O. Box 17, H-1525 Budapest, Hungary, and Department of Chemistry (D-006), University of California—San Diego, La Jolla, California 92093

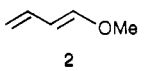
Received November 23, 1987

Introduction

Several years ago we undertook a broad study on the Lewis acid catalyzed Diels–Alder reaction of conjugated cycloalkenones with simple dienes such as 1,3-butadiene, isoprene and (*E*)-piperylene.[3] In the course of this investigation we analyzed the effects of specific reaction parameters on the reaction yield[4] and then examined the diastereofacial selectivity,[5] the exo–endo diastereoselectivity,[6] and the regioselectivity[7] of the reactions of these dienes with several substituted 2-cyclohexenones. In continuation of this study and in consideration of the relatively modest functionalities incorporated into the dienic framework used so far, we focused our attention on the reactions of cycloalkenones with alkoxybutadienes, a diene class interesting for its introduction of valuable functional groups into the adducts. These dienes have been used widely in cycloadditions with highly reactive dienophiles, their use being limited in reactions with poor dienophiles such as conjugated cycloalkenones.[8] In this connection we now report the Diels–Alder reaction of 2-cyclohexenone (**1a**) and 2-methyl-2-cyclohexenone (**1b**) with (*E*)-1-methoxy-1,3-butadiene (**2**).



1a, R=H
b, R=Me



2

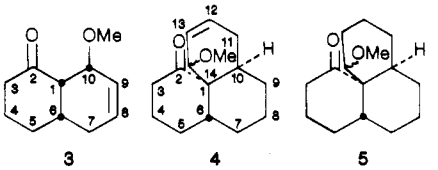
Results and Discussion

Thermal cycloaddition of 2-cyclohexenone (**1a**) with (*E*)-1-methoxy-1,3-butadiene (**2**) at 160 °C in the presence of hydroquinone affords the endo adduct **3** in moderate yield (47%). In order to improve the yield, Lewis acid catalyzed reactions were executed. Lewis acids have been known for some time to increase remarkably the rates and yields of Diels–Alder reactions.[9] On the other hand, care had to be exercised to avoid polymerization of the dienes, especially electron-rich dienes.

When 2-cyclohexenone (**1a**) and diene **2** interact in toluene solution under the influence of the most common Lewis acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, $EtAlCl_2$, $SnCl_4$), resinous materials (formed by the Friedel–Crafts reaction between diene and solvent or diene polymerization) were produced, only traces of adducts being detected. The recent Danishefsky discovery[10] of the ability of certain lanthanide complexes to act as mild Lewis acid catalysts in a variety of Diels–Alder and homo-Diels–Alder reactions induced us to explore this new type of catalyst in the present case.

The reaction of (*E*)-1-methoxy-1,3-butadiene (**2**) with 2-cyclohexenone (**1a**) under $Yb(fod)_3$ catalysis[11] in toluene solution at 110 °C for 110 h afforded a 1.5:1 mixture (55%) of two compounds, neither of which was adduct **3**.

Structure analysis by IR and ^1H and ^{13}C NMR spectroscopy showed these compounds to be methoxy dienic ketone stereoisomers having a tricyclic skeleton with three fused, six-membered rings and differing from one another only in the configuration of the methoxy group. For the determination of the complete stereochemistry the hydrogen coupling characteristics in the ^1H NMR spectra were inspected but were found to leave ambiguities of interpretation for the J_{HH} values of the allylic hydrogens of the two cyclohexene moieties of each compound. Hence the dienes **4a** and **4b** were hydrogenated, yielding the saturated ketones **5a** and **5b**, respectively. On the basis of the structure analysis of the latter two substances, it was possible to assign rigorously structure **4a** with an equatorial 14β-methoxy group to the major product and structure **4b** with an axial 14α-methoxy group to the minor component of the reaction mixture. Both ring junctions of the tricycles could be shown to be cis and the carbon–carbon double bonds of the unsaturated ketones to be positioned at C(8)–C(9) and C(12)–C(13).



3 **4** **5**

a, β-OMe; **b**, α-OMe

The sequence of events leading to the tricyclic ketones **4** was examined next. When octalone **3**, prepared by the thermal cycloaddition, was treated with (*E*)-1-methoxy-1,3-butadiene (**2**) in toluene solution under $Yb(fod)_3$ catalysis at 100 °C for 13 h, there was obtained a mixture of the tricyclic ketones **4a** and **4b**, identical with that from the reaction of 2-cyclohexenone (**1a**) and (*E*)-1-methoxy-1,3-butadiene (**2**). Heating a toluene solution of octalone

(1) For the previous paper, see: Angell, E. C.; Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 1424.
(2) (a) Università di Perugia. (b) Central Research Institute of Chemistry. (c) University of California.
(3) (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391. (b) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.
(4) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.
(5) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642.
(6) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2649.
(7) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 5177.
(8) (a) Ireland, R. E.; Aristoff, P. A.; Hoyng, C. F. *J. Org. Chem.* **1979**, *44*, 4318. (b) Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 1133. (c) Carreno, M. C.; Farina, F.; Garcia Ruano, J. L.; Puebla, L. *J. Chem. Res., Synop.* **1984**, 288.
(9) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.
(10) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721. (c) Danishefsky, S.; Uang, B.-J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453. (d) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 2507.
(11) $Yb(fod)_3$ is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium.

0022-3263/88/1953-4607$01.50/0