H, d, J = 3.0), 5.10 (1 H, d, J = 11), 5.25 (1 H, d, J = 18), 5.49 (1 H, s), 5.63 (1 H, d, J = 3), 6.38 (1 H, dd, J = 18, 11); IR ($CHCl_3$) 1720, 1715 cm^{-1}.

1,3-Ochtodien-3,6(*R)-diol (15).** Silica gel column chromatography (25% EtOAc in CH_2Cl_2) and further purification by high-pressure LC with 35% ethyl acetate in isooctane yielded pure **15**: $[\alpha]^{20}_D$ −14.8° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3600, 1610 cm^{-1}; low-resolution mass spectrum (for $C_{10}H_{16}O_2$), *m/e* 168.

Ketone **32**: ^1H NMR ($CDCl_3$) δ 1.20 (3 H, s), 1.27 (3 H, s), 2.04 (1 H, d, J = 14), 2.15 (1 H, d, J = 14), 5.20 (1 H, d, J = 11), 5.23 (1 H, d, J = 17), 6.01 (1 H, d, J = 10), 6.08 (1 H, dd, J = 11, 17) 6.68 (1 H, dd, J = 10); IR ($CHCl_3$) 3500, 1690, 1600 cm^{-1}; low-resolution mass spectrum (for $C_{10}H_{14}O_2$), *m/e* 166.

Fish Toxicity Bioassay. Compounds **1** and **4–15** were tested for fish toxicity by using the tropical Pacific damselfish *Pomacentrus coeruleus*. *P. coeruleus* is an abundant macroalgal herbivore in many tropical Pacific ecosystems and was locally available in pet stores. Compounds, at the concentrations in Table III, were stirred into seawater by using a small amount of ethanol. A damselfish was placed in water, observed for 1 h, and then placed in fresh seawater. At concentrations effecting sedation, the fish would darken, often stop swimming, and turn over on its side or back. When placed in fresh seawater, the symptoms would disappear, and the fish would return to "normal". At slightly greater concentrations, compounds **1** and **4–6** resulted in the death of *P. coeruleus*. For each compound this bioassay was repeated four times with identical results.

Feeding Inhibition Bioassay. Known concentrations of each compound were made in ether and volumetrically applied to 10 mg of fish food. The ether was evaporated at 60 °C, and the cooled food was dropped into a tank of ten fish. In most cases, the fish would pick the food up in their mouths but immediately reject it, thus indicating a positive avoidance reaction. After several fish rejected the food, it would drop to the bottom of the aquarium and no other fish would indicate interest. At concentrations where no feeding inhibition was observed, the fish would continue to compete for the food source until it was totally comsumed.

Acknowledgment. We wish to thank Dr. Jim Norris, Smithsonian Institution, for the opportunity to participate in research activities in the Galapagos Islands and for advice and help with algal taxonomy. We gratefully acknowledge financial support for this work from the National Science Foundation, Oceanography Section, under Grant OCE78-17202. We express our appreciation to Professor Phil Crews, University of California, Santa Cruz, for providing numerous ^{13}C NMR spectra.

Registry No. **1**, 73872-74-9; **2**, 57461-72-0; **3**, 57496-04-5; **4**, 73872-75-0; **5**, 73872-76-1; **6**, 73872-77-2; **7**, 73872-78-3; **8**, 73872-79-4; **9**, 73872-80-7; **10**, 73872-81-8; **11**, 73891-29-9; **12**, 73872-82-9; **13**, 73872-83-0; **14**, 73872-84-1; **15**, 73872-85-2; **16**, 67237-07-4; **18**, 73872-86-3; **19**, 73872-87-4; **20**, 73872-88-5; **21**, 73872-89-6; **22**, 73872-90-9; **23**, 73872-91-0; **24**, 73872-92-1; **25**, 73872-93-2; **26**, 73872-94-3; **27**, 73872-95-4; **28**, 73872-96-5; **29**, 73872-97-6; **30**, 73872-98-7; **31**, 73872-99-8; **32**, 73873-00-4.

Stereospecific Alkylation of 3,5,5-Trisubstituted-4-hydroxy-1-*p*-tosyl-2-pyrazolines by Trimethylaluminum. An Efficient Synthesis of 3,3,5,5-Tetrasubstituted-1-pyrazolin-4-ones

William H. Pirkle* and Dennis J. Hoover

The Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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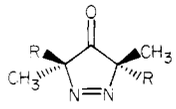
Isomeric *p*-tosylpyrazolines **5** and **6** are obtained in high yield by cyclization of the tosylhydrazones of various β,β-disubstituted-α,β-epoxy ketones **4**. Oxidation of these mixtures to pyrazolones **9** followed by selective reduction affords isomers **5**. Reaction of **5** with 8 equiv of trimethylaluminum in toluene stereospecifically produces the trans, tetrasubstituted 4-hydroxy-1-pyrazolines **7** in high yield. Methylmagnesium bromide and methyllithium are less effective in producing a similar conversion as competing elimination reactions occur. Oxidation of pyrazolols **7** gives the corresponding pyrazolones **1**.

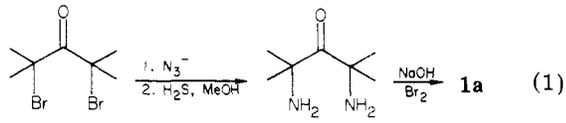
In connection with our current interest in the stereochemistry of several 1-pyrazoline transformations, we required a series of trans, tetrasubstituted pyrazolones **1**



1a, R = CH_3
b, R = C_2H_5
h, R = Ph

containing various alkyl and aryl substituents R. Three members of this series (**1a,b,h**) were reported prior to the present investigation, having served as precursors to allenes[1] and functionalized cyclopropanes.[2]

Although recent interest has also been demonstrated in 4-alkylidene derivatives of **1a**[3] and other bicyclic 4-alkylidene-1-pyrazolines as precursors to trimethylenemethanes,[4] a general approach to compounds **1** has not been described previously. The method described by Mock (eq 1) for the preparation of **1a**[5] is not satisfactory as a



(1)

synthesis of our desired trans targets. This procedure gave a mixture of **1b** and the corresponding cis isomer[6] in ap-

(1) Pirkle, W. H.; Kalish, R. *J. Am. Chem. Soc.* **1967**, *89*, 2781–2.
(2) Convers, R. J. Ph.D. Thesis, University of Illinois, Urbana, IL, 1974.
(3) See: Bushby, R. J.; Pollard, M. D. *Tetrahedron Lett.* **1978**, 3855–60; Bushby, R. J.; Pollard, M. D. *Ibid.* **1977**, 3671–2.
(4) Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 446–53 and references therein.
(5) Mock, W. L. Ph.D. Thesis, Harvard University, Cambridge, MA, 1964; *Diss. Abstr.* **1966**, *26*, 6374. A variation of this sequence has been used to prepare **1a**. See: Crawford, R. J.; Tokunaga, H. *Can. J. Chem.* **1974**, *52*, 4033–9.
(6) Thornburg, K. A. Ph.D. Thesis, University of Illinois, Urbana, IL, 1970.

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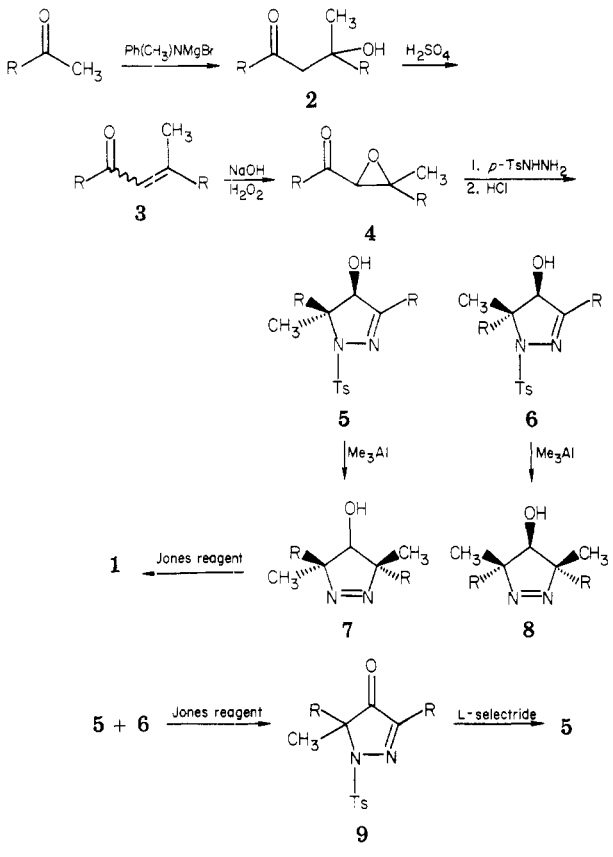
Scheme I[a,b]



[a] a, R = CH_3; b, R = C_2H_5; c, R = $(CH_2)_2CH_3$; d, R = $(CH_2)_5CH_3$; e, R = $CH_2CH(CH_3)_2$; f, R = $(CH_2)_2Ph$; g, R = $CH(CH_3)_2$; h, R = Ph; i, R = $C(CH_3)_3$. [b] Consult the text for variations.

proximately 25% overall yield from 3,5-dimethyl-4-heptanone. Borohydride reduction of this mixture afforded the three possible pyrazolols; separation of the trans material by chromatography and oxidation gave pure **1b**. The diaryl pyrazolone **1h** could not be prepared by the same sequence,[2] as dibromination of 2,4-diphenyl-3-pentanone could not be accomplished. Alternatively, **1h** was derived from *r*-3,*t*-5-diphenyl-3,5-dimethyl-4-nitro-1-pyrazoline, which was available[2] in low (6%) yield by reaction of 1-diazo-1-phenylethane and 1-methyl-2-nitrostyrene. Examination of a variety of analogous cycloadditions failed to provide a more attractive approach to this compound. Because neither of these methods was satisfactory as a means of preparing useful quantities of the desired trans pyrazolones **1**, necessity dictated that a conveniently implemented sequence be developed which would provide preparative quantities of the stereochemically pure pyrazolones from readily available precursors.

In this report, we describe the successful implementation of the sequence outlined in Scheme I in the synthesis of our desired targets **1b–h** and note that the method also accommodates the stereospecific preparation of the corresponding cis isomers.

Results and Discussion

Preparation of Keto Epoxides 4. Olefins **3b**, **3h**, and **3i** were previously reported and were prepared accordingly.

Ketols **2c–g** were prepared by dimerization (PhN(CH$_3$)MgBr, ether) of the corresponding methyl ketones and were conveniently dehydrated to a mixture of olefins containing predominantly the α,β-unsaturated isomers **3** by treatment with cold sulfuric acid. Dehydration of the ketols by refluxing with iodine or under basic conditions (Et_3N–MsCl or $SOCl_2$–pyridine) was decidedly inferior as substantial amounts (15–40%) of the β,γ-unsaturated isomers were produced. Purification of the olefins **3** thus obtained was unnecessary and on several occasions (in the preparation of **3d** and **3f**) detrimental, as double bond isomerization occurred during distillation. Oxidation (MeOH, NaOH, H_2O_2, 5–10 °C) of the olefinic ketones gave epoxides **4**, generally as a mixture of isomers, which were (except for **4h**) purified by distillation. **4i** was prepared as a single isomer by peracid oxidation of **3i** and was identical by NMR to the single (presumably *E*) isomer obtained by epoxidation of **3i** with basic hydrogen peroxide. The epoxy ketones **4** were thus obtained in 38–66% overall yields from the methyl ketones.

Formation of *p*-Tosylpyrazolines 5 and 6. A survey of the literature revealed but one report[7] describing the preparation of **5a** and three other 4-hydroxy-3,5,5-trisubstituted-1-*p*-tosyl-2-pyrazolines in moderate (25–48%) yield by reaction of β,β-disubstituted-α,β-epoxy ketones with *p*-tosylhydrazine in refluxing chloroform/acetic acid.[8] We found the reaction to proceed with somewhat improved yields when conducted in refluxing THF with *p*-toluenesulfonic acid catalysis (0.05–0.10 equiv); in this manner, epoxides **4a–g** provided mixtures of the corresponding *p*-tosylpyrazolines **5** and **6** in 40–75% yields. Under these conditions, **4h** gave complex mixtures, and **4i** was unreactive. With the exception of **4g**, which routinely gave the single crystalline pyrazolol **6g** in 70–75% yield, this method was less than satisfactory, as products of acceptable purity were obtained from the dark reaction mixtures only after one or more chromatographic operations. Closer scrutiny produced a greatly improved procedure. Epoxides **4a–d** reacted completely with a slight excess of *p*-tosylhydrazine in methylene chloride at 0 °C within 48 h or within 4–5 h in the presence of 4 equiv of acetic acid, providing the corresponding tosylhydrazones[9] as a syn/anti mixture. Even with added acetic acid, the slightly more hindered epoxides **4e** and **4f** required a reaction period of 36–48 h. The progress of this transformation was easily monitored by NMR, the carbinyl singlets in the tosylhydrazone isomers replacing the slightly downfield ($\Delta\delta$ = 0.05–0.10 ppm) epoxide carbinyl resonances. Treatment of the dried methylene chloride solution of the tosylhydrazones with HCl gas cleanly converted the latter to the tosylpyrazolines. These two-step conversions for epoxides **4a–f** proceeded in near-quantitative yields, and the tosylpyrazoline mixtures, several as solids and homogeneous by ^{1}H NMR, were used in subsequent steps without further purification.

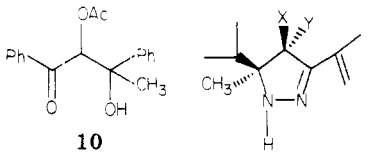
(*E*)-Dypnone oxide (**4h**) failed to react with *p*-tosylhydrazine in methylene chloride in the presence of several equivalents of acetic acid at 0 °C; increasing the reaction temperature (reflux) caused condensation to occur but also resulted in appreciable epoxide acetolysis (formation of **10**).[10] When allowed to react at 0 °C in 1:1 acetic acid/

(7) Hamon, D. P. G.; Holding, H. *J. Chem. Soc. D* **1970**, 1330.

(8) Disubstituted 4-hydroxy-1-*p*-tosyl-2-pyrazolines from various chalcones and *p*-tosylhydrazine are reported. See: Dhar, D. N.; Munjal, R. C. *Z. Naturforsch.* **1973**, *28b*, 369–70 and references therein.

(9) The preparation and isolation of several α,β-epoxytosylhydrazones has been reported: Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935–7.

(10) Complete solvolysis of (*E*)-dypnone oxide occurred (<3 h) in refluxing chloroform/acetic acid (1:1), providing **10** in high yield as the principal product. **10** was characterized spectrally: ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3 H), 1.97 (s, 3 H), 3.30 (br s, 1 H, exchanges with D_2O), 6.08 (s, 1 H), 7.16–7.52 (m, 8 H), 7.84 (overlapping d, 2 H); IR (neat) 3500, 1740, 1680 cm^{-1}. The presence of an α-acetoxy substituent in **10** was indicated by the low-field carbinyl resonance and was further confirmed by its reduction (Zn, NH_4Cl, EtOH/H_2O/Et_2O, 25 °C, 48 h) to 1,3-diphenyl-3-hydroxy-1-butanone.[21]



10

11, X = OH; Y = H
12, X = H; Y = OH

methylene chloride, **4h** afforded a mixture of a tosylhydrazone and pyrazoline **6h**, plus some (10–20%) previously encountered **10**. Using isobutyric acid in place of acetic acid substantially reduced the amount of epoxide solvolysis. Cyclization of the remaining epoxytosylhydrazone with dry HCl afforded crude **6h** which was obtained in 50% yield (from crude **4h** containing about 10% of the *Z* isomer) after chromatographic purification and crystallization from ether. (*Z*)-Dypnone oxide reacted under these conditions to form **5h** in a similar yield, but this *p*-tosylpyrazoline was (vide infra) much more conveniently derived from **6h**. Epoxide **4i** was recovered unchanged even after prolonged exposure to refluxing chloroform/acetic acid (1:1).

In each case, the ratio of the crude *p*-tosylpyrazolols **5** and **6** was the same as the *Z*/*E* isomeric ratio of the starting epoxides, providing the initial stereochemical assignment of structure **6** to the major isomers (derived from the major (*E*) isomers of epoxides **4**). The *p*-tosylpyrazolols **5** and **6** were separable by chromatography (silica, hexane/ethyl acetate), and the elution order was consistent (compounds **6b–h** more polar than their respective **5b–h** isomers) with this structural assignment.

Additional structure proof was (Scheme I) obtained by chromic acid oxidation of each tosylpyrazolol mixture to the stereochemically homogeneous ketones **9b–h**, which could then in turn be cleanly reduced in high yield with 85–100% stereoselectivity (**9e** was an exception, 55:45 **5e**/**6e**) to the more hindered alcohols **5** by lithium tri-*sec*-butylborohydride[11] (−78 °C, THF) or as in the case of **9g** simply by treatment with sodium borohydride in ethanol (94% selectivity). Removal of the minor isomers **6** was easily accomplished by either crystallization or chromatography.

Reaction of 5 and 6 with Organometallic Reagents. Having achieved access to the *p*-tosylpyrazolines, we investigated methods whereby they might be transformed into the desired tetrasubstituted 1-pyrazolines. Our hope was that nucleophilic addition of a methyl group at C-3 of the tosylpyrazoline (via an appropriate organometallic reagent) might be induced and that subsequent elimination of *p*-toluenesulfinate would generate the azo function. We felt it probable that the direction of such an addition would be strongly influenced by the hydroxyl (alkoxide) function at C-4, so that one isomer (**5** or **6**) would generate predominantly the *trans*-1-pyrazolines **7**, and the other would give rise to the cis isomers **8**.

We were pleased to discover that *p*-tosylpyrazolines **5b–h** react cleanly with trimethylaluminum in toluene, producing the desired (trans) pyrazolols **7b–h** in high yield. Similarly, **6g** and **6h** furnished the corresponding cis compounds **8g** and **8h**. The stereochemistry of these tetrasubstituted pyrazolols is readily apparent from their ^{1}H NMR spectra, which show separate resonances for the nonequivalent substituents in the trans compounds **7b–h** and but single resonances for the substituents in the cis compounds. An excess of trimethylaluminum (5–6 mmol of trimethylaluminum/mmol of pyrazoline) is required for complete transformation within a reasonable time regardless of the reaction temperature (**5b** reacts completely with 6 equiv of trimethylaluminum in 48 h at 55 °C or in 6 h at toluene reflux). These conditions, however, give crude pyrazolols **7** and **8** contaminated with 5–20 mol % of methyl *p*-tolyl sulfoxide (increased amounts at elevated temperatures and short reaction times), a contaminant which is removed only by careful chromatography. This difficulty is obviated by employing a larger excess of trimethylaluminum (8 equiv) and conducting the reaction at ca. 70 °C for 48–72 h; no sulfoxide is then encountered,[12] and the pure pyrazolols are conveniently isolated in high yield. Although the hindered *p*-tosylpyrazolines **5g** and **5h** react more slowly (5–7% of **5g** was recovered after 66 h at 55 °C), pure pyrazolols **7b–h**, **8g**, and **8h** were isolated in 78–95% yields.

Careful examination of the NMR spectra of crude **7b** and **8g** revealed the addition in both cases to be highly stereospecific, as the products of methyl addition to the *p*-tosylpyrazolol face opposite the hydroxyl (the known *r*-3,*c*-5-diethyl-3,5-dimethyl-*c*-4-hydroxyl-1-pyrazoline[6] and **7g**, respectively) could not be detected. The hydroxyl function is clearly a requirement for this transformation,[13] as the methyl ether of **5g** was recovered unchanged after exposure to excess trimethylaluminum in refluxing toluene.

Methylmagnesium bromide and methyllithium were unable to effect the same transformation cleanly.[14] The *p*-tosylpyrazolines bearing unbranched alkyl substituents at C-3 (**5a–d**) reacted with excess (>3 equiv) methylmagnesium bromide in refluxing THF in 3–8 h, producing exclusively (>97%) the trans compounds **7a–d** in 30–65% yield. The more hindered **5e** and **5f** reacted extremely slowly with methylmagnesium bromide, producing the 1-pyrazolines with poor conversion, and the isopropyl and phenyl compounds **5g** and **5h** were totally unreactive. Reaction of **5g** with methylmagnesium bromide in higher boiling solvents (benzene, toluene, or anisole) produced complex mixtures of products.

Elimination of *p*-toluenesulfinic acid clearly competed with alkylation to varying degrees in the reactions of **5** and **6** with methyllithium. The unhindered compounds **5a** and **5b** gave alkylation products **7a** and (stereospecifically) **7b**, respectively, but in low (20–40%) yield together with unidentified basic byproducts. With both isopropyl-substituted diastereomers **5g** and **6g**, no alkylation occurred; reaction with methyllithium produced amines **11** and **12**, respectively, in high yield. These compounds presumably arise by abstraction of the isopropyl methine proton and tautomerization of the initially formed 3-isopropylidene-1-pyrazolines. A more delicate balance between alkylation and elimination was observed with the diphenyl-*p*-tosylpyrazolines **5h** and **6h**. While **6h** produced the tetrasubstituted pyrazolol **8h** in 70% yield on treatment with methyllithium, **5h** gave a 1:5 mixture of trans pyrazoline **7h** and a tertiary alcohol **13**. **13** probably arises by addition of methyllithium to the 2-pyrazolin-4-one anion generated by elimination of *p*-toluenesulfinic acid from the alkoxide of **5h**.

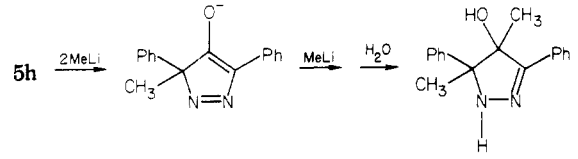
Other organolithium and magnesium reagents also behaved merely as strong bases toward the tosylpyrazolines.

(11) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–61.

(12) Complete reduction of the *p*-toluenesulfinate to the volatile methyl *p*-tolyl sulfide occurs.

(13) Hydroxyl-mediated regiospecific opening of an epoxide with dialkylalkynylalanes has been reported: Fried, J.; Sil, J. C.; Dalven, P. *J. Am. Chem. Soc.* **1972**, *94*, 4343–5.

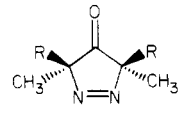
(14) 3,3,5,5-Tetramethyl-1-pyrazoline has been prepared in moderate yield by reaction of 3,5,5-trimethyl-1-*p*-tosyl-2-pyrazoline with methyllithium: Engel, P. S.; Hayes, R. A.; Keifer, L.; Szilaggi, S.; Timberlake, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 1876–82.



13

Compound **5a** was not alkylated by isopropyllithium, phenyllithium, or the corresponding Grignard reagents, and reaction with the lithium acetylide/ethylenediamine complex similarly produced mixtures of basic products which appeared to be derived by initial elimination of *p*-toluenesulfinic acid.

The target pyrazolones **1b–h** were obtained in uniformly excellent yields by oxidation of the pyrazolols **7b–h** with excess chromic acid in acetone. Oxidation of **8g** and **8h** gave **14** and **15**, respectively.



14, R = $CH(CH_3)_2$
15, R = Ph

Experimental Section

General Methods. Melting points were determined on a Buchi apparatus and are uncorrected. ^1H NMR spectra were recorded by using a Varian EM-390 or HR-220 spectrometer at 30 °C. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. IR spectra were obtained by using a Beckman IR-12 or Perkin-Elmer Infracord spectrophotometer. Elemental analyses were performed by Mr. J. Nemeth and colleagues at the University of Illinois. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$ before use. Toluene was dried by azeotropic distillation. Reactions involving air- or moisture-sensitive reagents were conducted under a nitrogen atmosphere. Organic solutions were dried over $MgSO_4$. Brinkman Polygram SIL G/UV_{254} silica gel plates were used for TLC work. Preparative chromatography was performed on silica gel. Isomer ratios were determined by ^1H NMR.

4,5-Epoxy-5-methyl-3-heptanone (4b). Homomesityl oxide was prepared as previously described.[15] NMR analysis ($CDCl_3$) revealed this material to be a 5:4:1 mixture of 5-methyl-4-hepten-3-one (**3b**) and two other (presumably isomeric) olefins, the first two displaying vinyl multiplets at δ 6.03 and 5.35, the minor component possessing absorptions at δ 4.80 and 4.90. A 355-g sample of this mixture was epoxidized with excess hydrogen peroxide in methanol (as described below for the preparation of **4g**). The crude product was isolated by pentane extraction and was fractionally distilled, affording 161 g of **4b** as a 1.5:1 mixture of isomers: bp 76–79 °C (10 mm); NMR ($CDCl_3$) δ 1.26 and 1.42 (s, 3 H total, major and minor isomers, respectively), 0.8–1.2 (overlapping t, 6 H), 1.2–1.8 (m, 2 H), 2.5 (q, 2 H), 3.40 (s, 1 H). Material purified by GC (120 °C, Carbowax) showed the following: IR (CCl_4) 2970, 2930, 2870, 1730, 1715, 1465, 1410, 1380, 1180, 1110 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.51; H, 9.92. Found: C, 67.31; H, 9.71.

General Procedure for the Preparation of Keto Epoxides 4c–g. These compounds were prepared in a three-step sequence in which the intermediates were not purified. Dimerization of the appropriate methyl ketone was conducted according to the procedure of Grignard[16] and in all cases produced the ketols in high yield. The ketols were dehydrated by being stirred (neat, 0 °C) with concentrated H_2SO_4, producing a mixture of α,β and β,γ olefinic ketones as indicated. The crude olefins were subjected to basic peroxide,[17] and the resulting epoxides were separated (when necessary) by fractional distillation from the lower boiling β,γ-unsaturated isomers. The procedures described for the preparation of **4g** is illustrative.

4,5-Epoxy-2,5,6-trimethyl-3-heptanone (4g). To an ice-cooled solution of *N*-methylaniline (53.5 g, 0.5 mol) in ether (100 mL) was added methylmagnesium bromide (0.5 mol of a 3 M solution in ether) over a 0.5-h period. The resulting solution was cooled to 5 °C, and a solution of methyl isopropyl ketone (86 g, 1.0 mol) in ether (250 mL) was added at such a rate that the temperature did not exceed 15 °C. After the addition was complete the reaction mixture was stirred for 2 h and poured onto ice. Cold, aqueous, 6 N HCl (180 mL) was added, and the layers were separated. The aqueous layer was extracted twice with pentane (200 mL), and the combined organic layers were dried and concentrated on a steam bath. Concentration at reduced pressure (<35 °C) gave crude ketol **2g**: NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 1.12 (d, 6 H, J = 7 Hz), 1.23 (s, 3 H), 1.78 (septet, 1 H, J = 7 Hz), 2.61 (septet, 1 H, J = 7 Hz), 2.65 (s, 2 H), 4.10 (br s, 1 H). To the chilled ketol (0 °C, neat) was added concentrated H_2SO_4 (5 mL), and the mixture was stirred overnight at room temperature. The NMR spectrum indicated the material thus treated to be a mixture of only the α,β-unsaturated isomers: ($CDCl_3$) δ 1.08 (d, 12 H, J = 7 Hz), 2.08 and 1.76 (d, J = 1–2 Hz, and d, J = 1–2 Hz, major and minor isomers, respectively, 3 H total), 2.32 (septet, 1 H, J = 7 Hz), 2.56 (septet, 1 H, J = 7 Hz), 5.97 and 6.06 (m, J = 1–2 Hz and m, J = 1–2 Hz, minor and major isomers, respectively, 1 H total).

The lower layer of H_2SO_4 was withdrawn, and the chilled olefin was dissolved in methanol (500 mL), cooled to 5 °C, treated first with aqueous 6 N NaOH (30 mL) and then with 30% H_2O_2 (60 g, 530 mmol), and stirred at 5–10 °C for 18 h. The reaction mixture was poured into water (1 L) and extracted with pentane (200 mL and then 5 × 100 mL). The pentane extracts were dried and concentrated, and the crude product was distilled (200-cm Vigreux column) to give 55 g (65% from methyl isopropyl ketone) of **4g** [bp 60–65 °C (1.3 mm)] as predominantly (>90%) a single isomer: NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.27 (d, 3 H, J = 7 Hz), 1.26 (s, 3 H), 1.62 (septet, 1 H, J = 7 Hz), 2.81 (septet, 1 H, J = 7 Hz), 3.36 (s, 1 H); IR (CCl_4) 2980, 2940, 2885, 1727, 1715, 1470, 1405, 1385, 1075, 975, 925 cm^{-1}. GC (125 °C, 20% SE-30 on 60/80-mesh Chromosorb W) gave an analytical sample.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.94; H, 10.91.

2,2,5,6,6-Pentamethyl-4,5-epoxy-3-heptanone (4i). 2,2,5,6,6-Pentamethyl-4-hepten-3-one[18] (5.5 g, 30 mmol; a single isomer by NMR) in CH_2Cl_2 (100 mL) was treated with *m*-chloroperoxybenzoic acid (8.0 g of 85%, 40 mmol), and the mixture was heated at reflux for 8 h. The cooled solution was washed with aqueous 5% Na_2CO_3 (2 × 75 mL) and dried, and most of the solvent was removed on a steam bath. The product was concentrated to an oil (7.0 g, 98%) at reduced pressure. The NMR indicated complete conversion to a single compound. A sample purified by GC (130 °C, SE-30) showed the following: NMR (CCl_4) δ 1.00 (s, 9 H), 1.09 (s, 3 H), 1.20 (s, 9 H), 3.68 (s, 1 H); IR (CCl_4) 2980, 1720, 1480, 1400, 1380, 1365, 1300, 1260, 1220, 1160, 1070, 960, 875 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.20. Found: C, 72.56; H, 11.20.

***p*-Tosylpyrazolines 5 and 6 from Epoxy Ketones 4a–f.** The procedure is illustrated for the preparation of **5b** and **6b**. The preparation of **5e** and **6e** and **5f** and **6f** requires the addition of acetic acid (4 equiv) in the first step. A solution of keto epoxide **4b** (150 g, 1.06 mol) and *p*-tosylhydrazine (232 g, 1.25 mol) in CH_2Cl_2 (1 L) was stirred at 0 °C for 48 h. The solution was dried, filtered, saturated at 0 °C with anhydrous HCl, and stirred for an additional hour at 0 °C. The solution was filtered and washed with three 200-mL portions of aqueous 5% Na_2CO_3 containing several drops of aqueous benzyltrimethylammonium chloride and with brine (200 mL), dried, and concentrated to give 330 g (100%) of a 1:1.5 mixture of compounds **5b** and **6b** as a light orange solid. This material was subsequently oxidized (see below) without

(15) Powell, S. G.; Secoy, C. H. *J. Am. Chem. Soc.* **1931**, *53*, 765–8.
(16) Grignard, V.; Colonge, J. *Bull. Soc. Chim. Rom.* **1933**, *15*, 5–12; *Chem. Abstr.* **1934**, *28*, 101.
(17) Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327–44.
(18) Bartlett, P. D.; Roha, M.; Stiles, M. *J. Am. Chem. Soc.* **1954**, *76*, 2349–53.

further purification. These isomers could be separated by chromatography (TLC R_f values of 0.21 and 0.17 with 5% 2-propanol in hexane), and the low-R_f component was identified as **3,*t*-5-diethyl-*r*-4-hydroxy-5-methyl-1-*p*-tosyl-2-pyrazoline (6b):** mp 147–148 °C (aqueous ethanol); NMR ($CDCl_3$) δ 0.83 (t, 3 H, J = 7 Hz), 1.12 (t, 3 H, J = 7 Hz), 1.26 (s, 3 H), 1.7–2.0 (m, 2 H), 2.2–2.4 (m, 2 H), 2.37 (s, 3 H), 4.47 (s, 1 H), 7.25 (d, 2 H, J = 8 Hz), 7.75 (d, 2 H, J = 8 Hz); IR ($CHCl_3$) 3600, 3450, 2980, 2940, 2880, 1600, 1350, 1165, 1095, 820 cm^{-1}.

Preparation of 3,*t*-5-Diisopropyl-*r*-4-hydroxy-5-methyl-1-*p*-tosyl-2-pyrazoline (6g). A solution of epoxy ketone **4g** (20.0 g, 117 mmol), *p*-tosylhydrazine (23.8 g, 128 mmol), and *p*-toluenesulfonic acid (1.0 g, 5.4 mmol) in THF (300 mL) was heated at reflux for 8 h. The solvent was removed on a rotary evaporator, and the remaining oil was dissolved in CH_2Cl_2 (300 mL). This solution was washed with aqueous 2 N NaOH containing a few drops of benzyltrimethylammonium chloride (2 × 50 mL), dried, and concentrated. The oil which remained was crystallized from 250 mL of hot benzene to give 29.0 g (73%) of **6g** as a colorless solid. Recrystallization from benzene gave an analytical sample: mp 154–156.5 °C; NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 1.26 (s, 3 H), 2.12 (br s, 1 H), 2.37 (s, 3 H), 2.47 (septet, 1 H, J = 7 Hz), 2.70 (septet, 1 H, J = 7 Hz), 4.68 (s, 1 H), 7.21 (d, 2 H, J = 8 Hz), 7.79 (d, 2 H, J = 8 Hz); IR ($CHCl_3$) 3700–3300, 3620, 2980, 2960, 2880, 1600, 1470, 1350, 1165, 1090, 1070, 820, 670 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}N_2O_3S$: C, 60.32; H, 7.74; N, 8.28; S, 9.47. Found: C, 60.37; H, 7.56; N, 7.97; S, 9.30.

Preparation of 3,*t*-5-Diphenyl-*r*-4-hydroxy-5-methyl-1-*p*-tosyl-2-pyrazoline (6h). (*E*)-Dypnone oxide[19] (16.8 mmol, 4.00 g) and *p*-tosylhydrazine (18.8 mmol, 3.50 g) were dissolved in a mixture of CH_2Cl_2 (20 mL) and isobutyric acid (20 mL), and the mixture was stirred at 0 °C for 110 h. The solution was dried, filtered, and saturated at 0 °C with anhydrous HCl. After being stirred for 1 h, the reaction mixture was washed repeatedly with portions of aqueous 5% Na_2CO_3 solution containing a few drops of benzyltrimethylammonium chloride until effervescence ceased. The dried solution was concentrated to give 6.74 g of a brown syrup which was chromatographed on silica gel, eluting with hexane/ethyl acetate (3:1). The product so obtained was crystallized from ether, giving 3.27 g (48%) of **6h** as a light pink powder, mp 165–166 °C. Recrystallized material showed the following: mp 165–166 °C; NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.34 (d, 1 H, J = 9 Hz, vanishes with added D_2O), 2.38 (s, 3 H), 5.11 (d, 1 H, J = 9 Hz, collapses to s in D_2O), 7.08–7.40 (m, s at 7.26, 10 H total), 7.65 (d, 2 H, J = 8 Hz), 7.82 (dd, 2 H, J = 2–3, 7 Hz); IR (KBr) 3500, 1600, 1500, 1450, 1360, 1175, 1060, 770, 700, 680, 590 cm^{-1}.

Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.95; H, 5.46; N, 6.89; S, 7.89. Found: C, 67.88; H, 5.39; N, 6.91; S, 8.15.

General Procedure for the Chromic Acid Oxidation of Hydroxypyrazolines 5–8 to the Corresponding Pyrazolones. Chromic acid solution[20] was added dropwise to a stirred solution of the pyrazolol(s) in acetone (~3 mL/mmol pyrazolol) chilled in an ice bath at such a rate that the temperature did not exceed 10 °C. When TLC (10% 2-propanol in hexane) indicated complete reaction (most useful for the *p*-tosylpyrazolines) or when the orange color of excess reagent persisted for 30 min, the excess oxidant was destroyed by the addition of 2-propanol, the mixture was filtered through Celite, and the salts were washed well with acetone. Most of the acetone was removed on a steam bath and the remainder by concentration in vacuo (<35 °C). The residue was dissolved in ether, washed with brine, 5% aqueous Na_2CO_3, and brine, dried, and concentrated in vacuo. In all cases the oxidation proceeded without noticeable side reactions to provide the crude pyrazolones in 85–100% yields.

3,5-Diethyl-5-methyl-1-*p*-tosyl-2-pyrazolin-4-one (9b) was obtained from crude **5b** and **6b** as a light yellow oil which crystallized on standing. Recrystallization from methanol typically returned 70–80% of **9b**: mp 66–68 °C; NMR ($CDCl_3$) δ 0.62 (t, 3 H, J = 7 Hz), 1.16 (t, 3 H, J = 7 Hz), 1.34 (s, 3 H), 1.89 (dq, 1 H, J = 7, 7 Hz), 2.24 (dq, 1 H, J = 7, 7 Hz), 2.41 (s, 3 H), 2.45 (q, 2 H, J = 7 Hz), 7.30 (d, 2 H, J = 8 Hz), 7.86 (d, 2 H, J = 8 Hz); IR ($CHCl_3$) 3020, 2960, 2920, 2860, 1735, 1600, 1465, 1360, 1170, 1100, 1060, 665 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.41; H, 6.54; N, 9.09; S, 10.40. Found: C, 58.07; H, 6.36; N, 9.34; S, 10.59.

3,5-Diisopropyl-5-methyl-1-*p*-tosyl-2-pyrazolin-4-one (9g) was obtained in quantitative yield from **6g** as a slightly yellow oil which refused to crystallize from a variety of solvents but required no purification: NMR ($CDCl_3$) δ 0.73 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.16 (d, 3 H, J = 7 Hz), 1.20 (d, 3 H, J = 7 Hz), 1.42 (s, 3 H), 2.42 (s, 3 H), 2.55 (septet, 1 H, J = 7 Hz), 2.83 (septet, 1 H, J = 7 Hz), 7.29 (d, 2 H, J = 8 Hz), 7.83 (d, 2 H, J = 8 Hz); IR (CCl_4) 2980, 1730, 1600, 1380, 1165, 1250, 1040, 1095, 1055, 870, 690 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.68; H, 7.19; N, 8.33; S, 9.53. Found: C, 61.00; H, 7.36; N, 8.10; S, 9.59.

***r*-3,*t*-5-Diethyl-3,5-dimethyl-1-pyrazolin-4-one (1b).** Oxidation of crude **7b** gave pure **1b** in 77% overall yield from **5b** after distillation: bp 36–42 °C (0.05 mm); NMR (CCl_4) δ 0.84 (t, 6 H, J = 8 Hz), 1.28 (s, 6 H), 1.66–1.97 (m, 4 H); IR ($CHCl_3$) 1757, 1520, 1460 cm^{-1}. These data are consistent with those previously reported for **1b**.[6]

***r*-3,*t*-5-Diisopropyl-3,5-dimethyl-1-pyrazolin-4-one (1g),** as an oil in 93% yield from **7g**, sublimed (10 mm, 90 °C), giving a low-melting solid: NMR ($CDCl_3$) δ 1.01 (d, 6 H, J = 7 Hz), 1.03 (d, 6 H, J = 7 Hz), 1.34 (s, 6 H), 2.07 (septet, 2 H, J = 7 Hz); IR ($CHCl_3$) 1750, 1520, 1460, 1380, 1360, 1060 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.29; N, 10.24; N, 14.42.

General Procedure for the Selective Reduction of Pyrazolones 9 to Pyrazolols 5. The procedure described below for the conversion of **9b** to **5b** is illustrative. To a mechanically stirred −78 °C solution of lithium tri-*sec*-butylborohydride (Aldrich L-Selectride, 225 mL, 1 M in THF) and THF (100 mL) was added a solution of **9b** (48.7 g, 158 mmol) in THF (100 mL) at such a rate that the temperature did not exceed −70 °C. [In other reductions a smaller excess (1.1–1.2 equiv) of L-Selectride was satisfactorily employed.] TLC of an aliquot quenched at −78 °C in methanol indicated the reaction to be complete, the solution was allowed to warm to −45 °C, and excess hydride was quenched cautiously with methanol (5 mL). At −10 °C aqueous 6 N NaOH (125 mL) was added, followed by 30% H_2O_2 (100 g, 0.89 mol) at such a rate that the temperature was maintained at 35–40 °C. After addition of the peroxide, the reaction mixture was maintained at 40 °C for an additional hour. The reaction mixture was diluted with water (~1 L) and extracted thoroughly with ether (200 mL and then 6 × 50 mL). The extracts were washed with brine, dried, and concentrated at reduced pressure. Residual 2-butanol was removed by several concentrations at reduced pressure in the presence of added toluene, leaving 42.6 g (94%) of pyrazolols **5b** and **6b** as a white powder. NMR (integration of carbinyl resonances) indicated an 88:12 ratio with **5b** in excess. Recrystallization from aqueous ethanol gave 32.0 g (65.2% from **9b**) of diastereomerically pure **3,*c*-5-diethyl-*r*-4-hydroxy-5-methyl-1-*p*-tosyl-2-pyrazoline (5b):** mp 127–130 °C; NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 8 Hz), 1.14 (t, 3 H, J = 8 Hz), 1.23 (s, 3 H), 1.8–2.6 (m, 4 H), 2.07 (d, 1 H, J = 9 Hz, exchanges with D_2O), 4.23 (d, 1 H, J = 9 Hz, collapses to s with added D_2O), 7.25 (d, 2 H, J = 8 Hz), 7.75 (d, 2 H, J = 8 Hz); IR ($CHCl_3$) 3600, 3450, 2980, 2940, 2880, 1600, 1460, 1350, 1165, 1095, 820 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.03; H, 7.14; N, 9.03; S, 10.33. Found: C, 58.04; H, 7.35; N, 9.08; S, 10.66.

Borohydride Reduction of 9g. 3,*c*-5-Diisopropyl-*r*-4-hydroxy-5-methyl-1-*p*-tosyl-2-pyrazoline (5g). A stirred solution of crude **9g** (101 mmol, 34.0 g) in absolute ethanol (300 mL) was cooled in an ice bath and treated with $NaBH_4$ (200 mmol, 7.6 g) in portions. After 1 h the reaction mixture was poured onto ice and excess 3 N HCl and concentrated at reduced pressure to remove most of the ethanol. CH_2Cl_2 (300 mL) was added, the aqueous layer was discarded, and the organic layer was washed with 5% aqueous Na_2CO_3 and dried. Filtration and concentration afforded 32.0 g (93%) of **5g** as a colorless solid, contaminated with

(19) Wasserman, H.; Aubrey, N.; Zimmerman, H. *J. Am. Chem. Soc.* **1953**, *75*, 96–8. Dypnone was prepared by the method of Calloway and Green: Calloway, N. O.; Green, L. D. *J. Am. Chem. Soc.* **1937**, *59*, 809–11.

(20) Prepared as described in: "Organic Syntheses"; Wiley, New York, 1973; Collect. Vol. V, p 310.

(21) Canonne, P.; Bilodeau, H. *Can. J. Chem.* **1966**, *44*, 2849–54.

4–6% (NMR) of isomer **6g** [TLC R_f values (5% 2-propanol in hexane) of 0.27 and 0.22, respectively]. Crystallization from aqueous ethanol was not effective in removing the minor isomer; the crude product was used without purification. For **5g**: NMR ($CDCl_3$) δ 1.10–1.22 (overlapping doublets, 12 H, J = 7 Hz), 1.19 (s, 3 H), 2.02 (br s, 1 H, exchanges with D_2O), 2.40 (s, 3 H), 2.56 (septet, 1 H, J = 7 Hz), 2.70 (septet, 1 H, J = 7 Hz), 4.41 (br s, 1 H, sharpens with added D_2O), 7.25 (d, 2 H, J = 8 Hz), 7.84 (d, 2 H, J = 8 Hz). A sample was chromatographed (silica, 5% 2-propanol in hexane) for analysis.

Anal. Calcd for $C_{17}H_{26}N_2O_3S$: C, 60.32; H, 7.74; N, 8.28; S, 9.47. Found: C, 59.99; H, 7.81; N, 8.23; S, 9.59.

Reaction of *p*-Tosylpyrazolines 5 and 6 with Trimethylaluminum. Tetrasubstituted 4-Hydroxy-1-pyrazolines 7 and 8. The procedure described below for the preparation of **7g** appears optimal for this transformation, providing pure products with minimal purification effort.

A mechanically stirred suspension of crude **5g** (42.2 g, 125 mmol, containing 4–6% of **6g**) in toluene (500 mL) was treated slowly with trimethylaluminum (500 mL of a 2 M solution in toluene, 8 equiv). The resulting solution was stirred at 75 °C for 90 h. The cooled mixture was slowly forced (with nitrogen pressure) through a flexible double-tipped needle into a vigorously stirred mixture of ice, 6 N HCl (500 mL), and ether (750 mL). When effervescence ceased, the layers were separated, and the aqueous layer was thoroughly extracted with ether (4 × 250 mL). The extracts were washed with 1.5 N HCl, 5% aqueous Na_2CO_3, and brine, dried, and concentrated. Crystallization of the crude product from hexane gave 20.5 g (83%) of diastereomerically pure **7g** as a colorless solid. The recrystallized material showed mp 93–96.5 °C; NMR ($CDCl_3$) δ 0.87 (d, 3 H, J = 7 Hz), 1.09 (d, 3 H, J = 7 Hz), 1.14 (d, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 1.24 (s, 3 H), 1.25 (s, 3 H), 1.39 (d, 1 H, J = 6 Hz, exchanges with D_2O), 1.87 (septet, 1 H, J = 7 Hz), 2.09 (septet, 1 H, J = 7 Hz), 3.65 (d, 1 H, J = 6 Hz, collapses to s in D_2O); IR (KBr) 3400–3200, 3000–2900, 1565, 1465, 1385, 1370, 1325, 1070 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 170 ($M^+ - N_2$, 1.5), 155 ($M^+ - CH_3N_2$, 8.0), 127 ($M^+ - C_3H_7N_2$, 14.9), 85 (50.6), 67 (27.5), 57 (12.6), 55 (48.5), 43 (100), 41 (45.6), 29 (22.1), 27 (19.7).

Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.76; H, 11.43; N, 14.41.

***r*-3,*t*-5-Diethyl-3,5-dimethyl-4-hydroxy-1-pyrazoline (7b).** Reaction of diastereomerically pure **5b** (165 mmol) with 5 equiv of Me_3Al at 55 °C for 50 h gave crude **7b** in a 110% yield. NMR indicated 4–7% of unreacted **5b**. This material was directly oxidized to pyrazolone **1b** without purification. Pure **7b** could be obtained by chromatography (silica, CH_2Cl_2/ether) and sublimation (0.05 mm, 60 °C): mp 65–68 °C; NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 8 Hz), 1.10 (t, 3 H, J = 8 Hz), 1.31 (s, 3 H), 1.34 (s, 3 H), 1.50 (dq, 1 H, J = 6, 8 Hz), 1.87 (dq, 1 H, J = 6, 8 Hz), 1.86 (br s, 1 H, exchanges with D_2O), 3.59 (s, 1 H); IR ($CHCl_3$) 3620, 3400, 1560, 1465, 1080 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 171 (M^+ + 1, 3.7), 142 ($M^+ - N_2$, 11.4), 127 ($M^+ - CH_3N_2$, 11.92), 114 (9.4), 113 ($M^+ - C_2H_5N_2$, 57.3), 109 (7.3), 95 (35.6), 86 (13.5), 85 (41.0), 71 (40.7), 69 (14.6), 67 (38.6), 57 (46.9), 56 (39.3), 55 (31.8), 43 (100), 42 (8.4), 41 (45.0), 29 (11.6), 28 (7.8), 27 (6.8).

Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.65; N, 16.46. Found: C, 63.74; H, 10.44; N, 16.49.

Reaction of 5b with Methylmagnesium Bromide. Preparation of 7b. To a stirred solution of **5b** (23.3 g, 75 mmol) in THF (240 mL) was added slowly 75 mL of a 3 M solution of methylmagnesium bromide in Et_2O. The resulting solution was held at reflux under nitrogen for 16 h. The reaction mixture was poured onto ice and acidified with 3 N HCl (150 mL). Et_2O (500 mL) was added, and after separation the aqueous layer was extracted with Et_2O (3 × 150 mL). The extracts were combined with the organic layer, and the mixture was washed with aqueous 5% $NaHCO_3$ (50 mL) and brine (50 mL) and dried. Removal of the solvent afforded an oil which was chromatographed on 170 g of silica gel, with elution first with two column volumes of CH_2Cl_2 and then with two column volumes of CH_2Cl_2/Et_2O (2:1). The CH_2Cl_2/Et_2O eluent was concentrated to give a colorless solid which was sublimed (0.5 mm, 80 °C), giving 7.33 g (57%) of **7b** as a colorless solid, identical with that prepared above. The high-R_f (CH_2Cl_2) eluent contained a mixture of methyl and ethyl *p*-tolyl sulfides which were separated by GC and readily identified by their microanalyses and NMR and mass spectra.

Reaction of 5g with Methyllithium. *r*-4-Hydroxy-3-isopropenyl-*c*-5-isopropyl-5-methyl-2-pyrazoline (11). A stirring solution of crude **5g** (1.0 mmol, 340 mg) in THF (5 mL) was treated slowly at 5 °C with methyllithium in ether (3.0 equiv, 1.8 mL of a 1.7 M solution) and stirred overnight at 25 °C. The mixture was poured into H_2O (10 mL) and extracted twice with ether (10-mL portions). The extracts were washed with aqueous bicarbonate, dried, and concentrated to give 155 mg of a yellowish solid. NMR suggested the crude product to be a mixture of **11** (vide infra) and an undetermined (<20%) amount of another compound which apparently possessed absorptions only at δ 4.13 and 1.23 as singlets in a ratio of ~1:6. This mixture was readily soluble in 1.5 N aqueous HCl and was recovered by ether extraction of the basified solution. The major component was readily purified by trituration with cold (−20 °C) ether, giving a colorless solid which darkened and liquefied on standing at room temperature but appeared stable for months when stored in a freezer. The structure of this compound was readily apparent from its NMR spectrum, which indicated an isopropenyl substituent, a single isopropyl substituent in a chiral molecule, a pseudo-allylic carbinyl resonance, and a high-field singlet characteristic of the C-5-methyl resonance of N^1-unsubstituted 2-pyrazolines. For **11**: NMR ($CDCl_3$) δ 0.93 (s, 3 H), 0.97 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.98 (br s, 3 H), 2.1 (m, 1 H, J = 7 Hz), 4.25 (s, 1 H), 5.25 (m, 1 H, $J \simeq$ 1 Hz), 5.36 (s, 1 H); IR ($CHCl_3$) 3600, 3360, 2980, 1650, 1620, 1460, 1370, 1060, 900 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.95; N, 15.37. Found: C, 66.09; H, 10.18; N, 15.34.

Reaction of 6g with methyllithium as described above furnished (with 2.4 equiv of MeLi) a single compound in high yield as an oil, which was identified as ***r*-4-hydroxy-3-isopropenyl-*t*-5-isopropyl-5-methyl-2-pyrazoline (12)** on the basis of its NMR spectrum: NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 1.15 (s, 3 H), 1.69 (septet, 1 H, J = 7 Hz), 1.98 (br s, 3 H), 2.30 (br s, 1 H, exchanges with D_2O), 4.69 (br s, 1 H, sharpens in D_2O), 5.24 (br s, 1 H), 5.47 (br s, 1 H), 5.50 (br s, 1 H, exchanges with D_2O).

Reaction of 5h with Methyllithium. Compound **5h** (1.0 mmol, 406 mg) in THF (5 mL) was cooled in an ice bath and treated with methyllithium in ether (3 mL of a 1.7 M solution). After being stirred at 5 °C for 1 h, the mixture was poured into H_2O (10 mL) and extracted twice with ether (10-mL portions). The extracts were washed with aqueous bicarbonate (5 mL of 5%) and dried. Removal of solvent at reduced pressure gave 0.254 g (95%) of a (6:1) mixture of **3,5-diphenyl-4,5-dimethyl-4-hydroxy-2-pyrazoline (13)** and **7h** (NMR). Pure **13** was obtained after two recrystallizations from hot ethanol: mp 169.5–171.5 °C (inserted 165 °C); NMR ($CDCl_3$) δ 1.56 (s, 3 H), 1.61 (s, 3 H), 1.7 (br s, 1 H, exchanges with D_2O), 5.82 (br s, 1 H, exchanges with D_2O), 7.21–7.57 (m, 8 H), 7.75–7.92 (m, 2 H); IR (KBr) 3340, 3280, 3000, 1600, 1570, 1555, 1500, 1470, 1450, 1390, 1120, 1070, 955, 925, 815, 770, 730, 705, 695 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 266 (M^+, 10.4), 205 (9.7), 148 (100), 120 (99.8), 104 (55.8), 77 (29.2), 42 (29.1).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.82; H, 6.76; N, 10.69.

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Registry No. **1a**, 30467-62-0; **1b**, 74097-35-1; **1c**, 74097-36-2; **1d**, 74097-37-3; **1e**, 74097-38-4; **1f**, 74097-39-5; **1g**, 74097-40-8; **1h**, 74097-41-9; **1i**, 74097-42-0; **2c**, 54862-90-7; **2d**, 74097-43-1; **2e**, 59357-11-8; **2f**, 74097-44-2; **2g**, 54862-89-4; **3b**, 1447-26-3; (*E*)-**3g**, 61010-47-7; (*Z*)-**3g**, 74097-45-3; **3i**, 3205-31-0; **4a**, 4478-63-1; *cis*-**4b**, 58609-86-2; *trans*-**4b**, 58609-87-3; *cis*-**4c**, 74097-46-4; *trans*-**4c**, 74097-47-5; *cis*-**4d**, 74097-48-6; *trans*-**4d**, 74113-05-6; *cis*-**4e**, 74097-49-7; *trans*-**4e**, 74097-50-0; **4f**, 74113-06-7; **4g**, 74097-51-1; *trans*-**4h**, 19804-81-0; **4i**, 74097-52-2; **5a**, 29984-95-0; **5b**, 74097-53-3; **5c**, 74097-54-4; **5d**, 74097-55-5; **5e**, 74097-56-6; **5f**, 74097-57-7; **5g**, 74097-58-8; **5h**, 74097-59-9; **5i**, 74097-60-2; **6b**, 74097-61-3; **6c**, 74097-62-4; **6d**, 74097-63-5; **6e**, 74097-64-6; **6f**, 74097-65-7; **6g**, 74097-66-8; **6h**, 74097-67-9; **6i**, 74097-68-0; **7a**, 74097-69-1; **7b**, 74097-70-4; **7c**, 74097-71-5; **7d**, 74097-72-6; **7e**, 74097-73-7; **7f**, 74097-74-8; **7g**, 74097-75-9; **7h**, 74097-76-0; **7i**, 74097-77-1; **8b**,

74097-78-2; **8c**, 74097-79-3; **8d**, 74097-80-6; **8e**, 74097-81-7; **8f**, 74097-82-8; **8g**, 74097-83-9; **8h**, 74097-84-0; **8i**, 74097-85-1; **9a**, 29984-96-1; **9b**, 74097-86-2; **9c**, 74097-87-3; **9d**, 74113-07-8; **9e**, 74097-88-4; **9f**, 74097-89-5; **9g**, 74097-90-8; **9h**, 74097-91-9; **9i**, 74097-92-0; **10**, 74097-93-1; **11**, 74097-94-2; **12**, 74097-95-3; **13**, 74097-96-4; **14**, 74097-97-5; **15**, 74097-98-6; methyl isopropyl ketone, 563-80-4; *p*-tosylhydrazine, 1576-35-8; 2-pentanone, 107-87-9; 2-octanone, 111-13-7; benzylacetone, 2550-26-7; methyl isobutyl ketone, 108-10-1; acetone, 67-64-1; 2-butanone, 78-93-3; acetophenone, 98-86-2; *tert*-butyl methyl ketone, 75-97-8; *r*-3,*c*-5-diethyl-3,5-dimethyl-1-pyrazolin-4-one, 74097-99-7; *r*-3,*c*-5-dipropyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-00-3; *r*-3,*c*-5-dihexyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-01-4; *r*-3,*c*-5-diisobutyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-02-5; *r*-3,*c*-5-diphenethyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-03-6; *r*-3,*c*-5-di-*tert*-butyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-04-7.

Supplementary Material Available: Complete descriptions of isolation and purification methods, yields, physical constants, and ^{1}H NMR, IR, and analytical data for compounds **4c–f**, **5a**, **5c–f**, **5h**, **7c–f**, **7h**, **8g**, **8h**, **9c–f**, **9h**, **1c–f**, **1h**, **14**, and **15** (18 pages). Ordering information is given on any current masthead page.

Preparation of β-Lactams by the Condensation of Lithium Ester Enolates with Aryl Aldimines

Charles Gluchowski, Lynn Cooper, David E. Bergbreiter,* and Martin Newcomb*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

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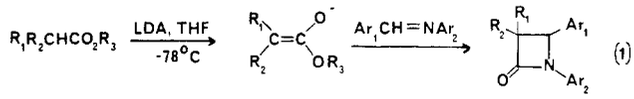
The condensation of simple lithium ester enolates with appropriately substituted aryl imines produces β-lactams in yields from 35 to 95%. Excellent stereoselectivity is observed in the preparation of β-lactams with chiral centers at C-3 and C-4 of the β-lactam ring. When chiral ester enolates are used, asymmetric induction occurs to yield optically active β-lactams with up to 60% ee. Synthetic and mechanistic details of these reactions are discussed.

β-Lactams are known to be key components of many biologically active compounds such as penicillin and cephalosporin antibiotics.[1] Recent syntheses of norcardicin,[2] thienamycin,[3] and totally synthetic penems[4] and the apparent antibiotic potential for simple β-lactams have provided a continuing impetus for research on β-lactam chemistry.[5] Here we report a rather simple procedure for synthesis of certain aryl-substituted β-lactams by condensation of ester enolates and aryl aldimines. These ester–imine condensation reactions we describe are analogous to corresponding stereoselective hydroxylation reactions of enolates with ketones or aldehydes.[6]

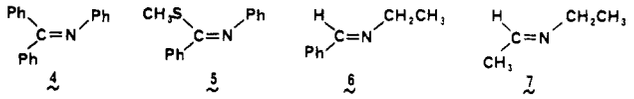
The most common procedure for preparing β-lactams is based on the cycloaddition of a ketene and an imine.[7] However, preparations of β-lactams by the reaction of a carbanionic reagent and an imine have been reported.[8-10] Related titanium tetrachloride promoted condensation reactions on imines with silylated ester enolates have also been reported.[11] Advantages of our procedure over those procedures described above include the use of readily available esters as starting materials, high yields resulting from the use of LDA as a base, and the ability to prepare optically active β-lactams by using chiral esters as starting materials. Recent work in both this laboratory and others has shown that alkylations of chiral esters can proceed in high synthetic yield with good stereoselectivity.[12] Here we show that asymmetric synthesis of β-lactams is feasible using chiral ester enolates in these enolate–imine condensation reactions.

Results and Discussion

Our procedure for the synthesis of β-lactams involves an electrophilic substitution by an imine on a nucleophilic ester enolate (eq 1). Examples of β-lactams prepared by



using this procedure are listed in Table I along with their melting points. It is evident from these results that a variety of β-lactams are accessible by reaction 1. However, a major limitation of our procedure is the apparent requirement that an aryl aldimine containing an aryl substituted nitrogen be used in the ester enolate–imine condensation. As a result, the β-lactams listed in Table I contain aromatic substituents on N-1 and C-4, the part of the β-lactam ring corresponding to the imine used. This required imine substitution is evidently due to the fact that the imine must be both electrophilic and unhindered for successful 1,2 addition to occur. For example, attempts to affect the reaction of benzophenone anil **4** with the



enolate of **li** led to recovered starting material, presumably

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