(24 μL, 0.025 mmol) was added dropwise to a solution of the diol **3** (7 mg, 0.023 mmol) in anhydrous acetone (5 mL) at 0 °C. The reaction mixture was stirred for 10 min, then quenched with excess 2-propanol (1 drop) and water (5 mL). The acetone was removed in vacuo and the aqueous residue extracted with ether (3 × 10 mL). The combined ether extracts were dried over sodium sulfate and the solvent was evaporated to yield the ketone **18** (4 mg, 57% theoretical) as an oil: IR ($CHCl_3$) 3500, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.95 (d, 3 H, $J$ = 7 Hz), 0.96 (s, 3 H), 1.18 (s, 6 H), 1.44 (s, 3 H), 2.62 (m, 1 H), 2.80 (d, 1 H, $J$ = 10 Hz), 2.93 (d, 1 H, $J$ = 10 Hz), 3.23 (d, 1 H, $J$ = 10 Hz), 5.20 (m, 2 H).

**Jones Oxidation of Triol 9.** One equivalent of Jones reagent was added to a solution of the triol **9** (14 mg, 0.043 mmol) in acetone (5 mL) and the reaction was allowed to proceed according to the procedure above to give the ketone **19** (8 mg, 58% theoretical): IR ($CDCl_3$) 3500, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.99 (d, 3 H, $J$ = 7 Hz), 1.09 (s, 3 H), 1.13 (s, 3 H), 1.14 (s, 3 H), 1.23 (s, 3 H), 1.50 (m, 4 H), 1.93 (m, 2 H), 2.16 (m, 1 H), 2.59 (m, 2 H), 2.48 (m, 2 H), 2.83 (d, 1 H, $J$ = 10 Hz), 5.16 (d, 1 H, $J$ = 16 Hz), 5.23 (m, 1 H), 5.30 (m, 1 H), 5.47 (d, 1 H, $J$ = 16 Hz).

**Jones Oxidation of Triol 13.** One equivalent of Jones reagent was added to a solution of the triol **13** (20 mg, 0.062 mmol) in acetone (5 mL) and the reaction was allowed to proceed according to the procedure above to give the dione (11 mg, 56% theoretical): IR ($CHCl_3$) 3500, 1710, 1680 $cm^{-1}$; $\lambda_{max}$ 247 nm; $^1H$ NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.10 (d, 3 H, $J$ = 7 Hz), 1.21 (s, 3 H), 1.91 (s, 3 H), 2.46 (br s, 2 H), 2.70 (m, 1 H), 2.95 (d, 1 H, $J$ = 11 Hz), 3.05 (d, 1 H, $J$ = 11 Hz), 3.39 (d, 1 H, $J$ = 11 Hz), 5.19 (d, 1 H, $J$ = 16 Hz), 5.49 (dd, 1 H, $J$ = 16, 7 Hz), 5.98 (s, 1 H).

**Acknowledgments.** We wish to thank J. R. Lance for the identification of opisthobranchs. This research was supported by a grant from the National Science Foundation (BMS 72-02539). The NMR Facility at UCSD was supported by a grant from the National Institutes of Health (RR-00708).

**Registry No.**—**13** dione, 62861-24-9; **16**, 62861-25-0; **18**, 62861-26-1; **19**, 62861-27-2.

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# A Convenient Synthesis of γ-Lactams via Michael Addition

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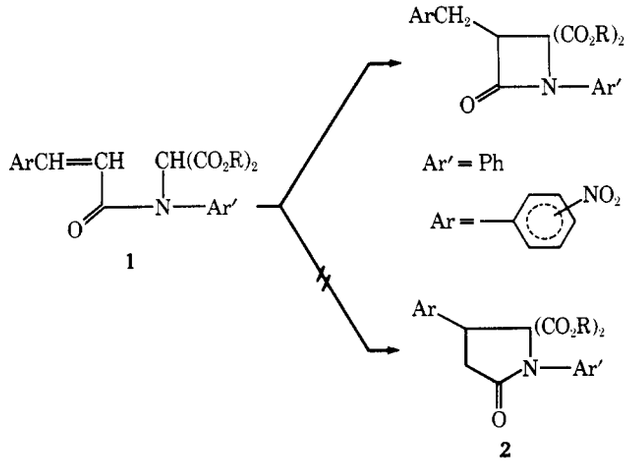
A convenient synthesis of 1-aryl-2,2-dicarboalkoxy-5-pyrrolidinones from substituted anilinomalonates by way of intermolecular Michael addition followed by amidification has been developed. This is probably the first report on a Michael addition involving an acid chloride as a Michael acceptor. The mechanism suggested has been convincingly established. A large number of γ-lactam derivatives have been prepared in good to excellent yields.

It has been demonstrated by Bose et al.[1] that *N*-acryloylanilinomalonate does not undergo intramolecular Michael addition to yield γ-lactam because the acrylic amide moiety is a poor Michael acceptor. A strong electron-withdrawing substituent in the β position of the acrylamide, however, does activate the double bond to such an extent as to lead to the formation of β- and γ-lactams[2] from suitable substrates by way of Michael addition.




Though much work has not been reported on the formation of β- or γ-lactams by intramolecular Michael addition, many γ-lactams have been conveniently synthesized by intermolecular Michael addition. Cocolas and Hartung[3] have reported that the Michael adduct between diethyl acetamidomalonate and ethyl acrylate or crotonate in ethanol gave 2-pyrrolidinones at reflux temperature. The formation of γ-lactams from the simple Michael adduct has been explained on the basis that the conformation of the molecule places the groups in question in very close proximity with each other for the attack of nitrogen on the γ-carbonyl carbon.

A detailed and exhaustive study on the synthesis of γ-lactams has been made by Pachaly et al.[4] It has been shown that *N*-acetylglycine esters also undergo similar intermolecular Michael addition provided that a strong base such as sodium hydride is used. The reaction follows a stereoselective path leading to the formation of the trans isomer of the γ-lactam.

An attempt to throw some light on the intramolecular Michael addition leading to γ-lactam formation led us to work on amide **1e** (Ar = Ph; Ar' = *p*-nitrophenyl).

Table I.[a] 1-Aryl-2,2-dicarboalkoxy-3-phenyl-5-pyrrolidinone (2)

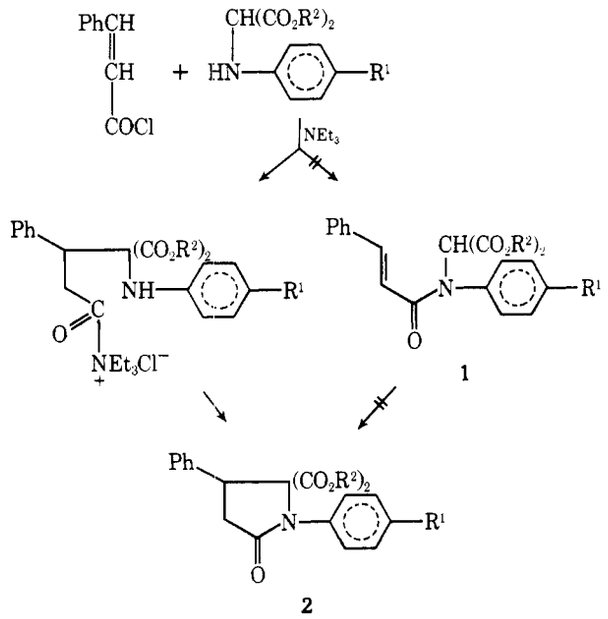
| Registry No. | Compd | Yield, % | Mp, °C | IR, $cm^{-1}$ ν C=O | NMR[b] $C_3$ proton (t) | NMR[b] $C_4$ protons (d) |
|---|---|---|---|---|---|---|
| 62851-28-9 | **2a** | 36.0 | 92 | 1730, 1721, 1718 | 5.48 | 7.15 |
| 32285-86-2 | **2b**[7] | 24.0 | 128–129 | 1735, 1720, 1710 | 5.58 | 7.23 |
| 62851-29-0 | **2c** | 66.7 | 125–127 | 1740, 1730, 1715 | 5.43 | 7.02 |
| 62851-30-3 | **2d** | 71.6 | 108–110 | 1742, 1720, 1706 | 5.41 | 6.97 |
| 62851-31-4 | **2e** | 85.4 | 106 | 1742, 1735, 1710 | 5.63 | 6.97 |
| 62905-87-7 | **2f** | 76.1 | 134–135 | 1739, 1724, 1714, 1698 | 5.46 | 6.97 |
| 19038-40-5 | **2g**[8] | 45.0 | 130 | 1758, 1740, 1720 | 5.34 | 6.91 |
| 62882-93-3 | **2h** | 78.7 | 135–136 | 1760, 1740, 1720 | 5.47 | 6.92 |
| 62851-32-5 | **2i** | 75.1 | 100–101 | 1759, 1724, 1709 | 5.40 | 6.92 |
| 62905-88-8 | **2j** | 79.7 | 136–137 | 1754, 1724, 1706 | 5.46 | 7.01 |

[a] All compounds presented here have satisfactory elemental analyses. [b] $CDCl_3$, $Me_4Si$ as internal standard. Chemical shift in τ.

Chatterjee and co-workers[5] have shown that the carbonyl character of similar nitro-substituted amides is greatly enhanced because of the increased delocalization of Np electrons across the π orbital of the *p*-nitrophenyl system causing a decrease in the strength of N-p:C=O π overlap. Amide **1e**, therefore, is expected to be a suitable substrate for intramolecular Michael addition.

When *p*-nitroanilinomalonate could not be amidified with cinnamoyl chloride under nonbasic conditions,[6] the reaction was carried out in the presence of triethylamine. We hoped that amidification would be followed by intramolecular Michael addition in presence of the base, resulting in the formation of γ-lactam. The product from the above reaction was isolated in excellent yield and was characterized to be a γ-lactam by IR and NMR spectra as well as the elemental analysis.

A conceivable mechanism, however, for the formation of γ-lactam involves intermolecular Michael addition followed by intramolecular amidification.



**2a**, $R^1$ = H; $R^2$ = Et
**b**, $R^1$ = $CH_3$; $R^2$ = Et
**c**, $R^1$ = Cl; $R^2$ = Et
**d**, $R^1$ = Br; $R^2$ = Et
**e**, $R^1$ = $NO_2$; $R^2$ = Et
**f**, $R^1$ = $CO_2Et$; $R^2$ = Et
**g**, $R^1$ = H; $R^2$ = Me
**h**, $R^1$ = Cl; $R^2$ = Me
**i**, $R^1$ = Br; $R^2$ = Me
**j**, $R^1$ = $CO_2Et$; $R^2$ = Me

A conclusive evidence for this alternative mechanism will be to experimentally rule out the first one. The amide **1e** was ultimately prepared in 80% yield from *p*-nitroanilinomalonate with cinnamoyl chloride in the presence of pyridine, a base weak enough not to create complications by abstracting the methine proton. We were surprised to find that the amide **1e** did not yield γ-lactam in the presence of various bases normally used as catalysts in the Michael addition. This establishes the alternative mode of γ-lactam formation suggested by us.

Since the yield of lactam **2e** was about 85%, it follows that addition–elimination reaction leading to the formation of α,β-unsaturated ketone does not seriously compete with the Michael addition.

In order to study the effect of substituents on the formation of γ-lactams, a number of substituted anilinomalonates were prepared. It was observed (Table I) that with an electron-withdrawing substituent which decreased the basicity of aminomalonate the yields obtained ranged from 67 to 86%, whereas with electron-releasing groups such as $CH_3$ the yields were tremendously reduced because of simultaneous formation of α,β-unsaturated amides. Amidification, therefore, does compete with Michael addition and the amides if formed do not isomerize to γ-lactams.

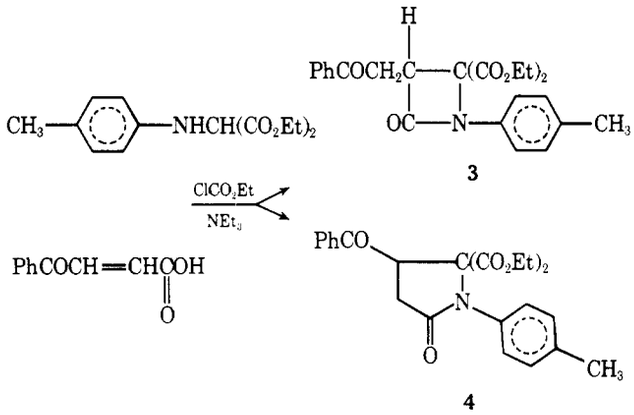
Recently Baldwin[9] has examined a number of polyfunctional molecules as substrates for the 5-endo-trigonal ring-forming reaction. It has been found that for first-row elements this is a disfavored process. The failure of amide **1e** to undergo intramolecular Michael addition to form **2e** is an additional reinforcement to Baldwin's hypothesis.[10]

The mechanism suggested by us shows the final step to be a 5-exo-trigonal ring-forming process and hence it will be favored.

Since α,β-unsaturated acid chlorides have never been employed in Michael addition, we felt that additional convincing evidences were necessary in support of the mechanism suggested by us.

The mixed anhydride from β-benzoylacrylic acid and ethyl chloroformate was treated with ethyl *p*-toluidinomalonate in the presence of triethylamine. If the keto carbonyl group alone be responsible for the activation of the double bond, then both intermolecular Michael addition followed by amidification and amidification followed by intramolecular Michael addition would lead only to the formation of β-lactam **3**. But if γ-lactam be isolated even in minor yield from this comparatively more basic amino ester, it would definitely establish the validity of the mechanism suggested by us.

The reaction product as expected was a mixture from which we isolated a solid product by chromatography in 10% yield. Since β- and γ-lactams are isomeric, elemental analysis cannot differentiate them. Since both of them contain four carbonyl functions, the IR spectrum too could not be profitably used



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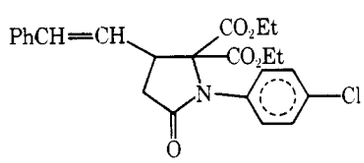
for eliminating one structure in favor of the other. The NMR spectrum, however, was helpful in characterizing the product as a γ-lactam (4). Since this reaction product was characterized as a γ-lactam, no attempt was made to investigate the nature of other products of the reaction.

In all NMR spectra of the γ-lactams prepared by us we find the ring methine proton as a triplet between τ 5.4 and 5.6 and the ring methylene proton as multiplets between τ 6.9 and 7.2. The spectrum of the isolated product shows a triplet centered at τ 4.93 (1 H) and a multiplet at τ 7.03. A keto group present adjacent to the ring methine proton in this compound obviously is responsible for the shift in position from τ 5.4 to τ 4.93. The β-lactam ring methine proton in a similar environment has never been observed by us at such low field.

Encouraged by our above results, we tried to investigate the comparative ease of formation of five- vs. seven-membered rings. β-Styrylacryloyl chloride was reacted with *p*-chloroanilinomalonate in the presence of triethylamine. The NMR spectrum of the reaction product shows the following pattern: τ 2.81 (m, 9 H), 3.72 (m, 2 H), 5.97 (m, 5 H), 7.36 (d, 2 H), and 8.97 (m, 6 H). The doublet at τ 7.36 can be assigned to the ring methylene protons of a γ-lactam. The ring methine proton, which also is an allylic proton, appears merged with the ester methylene (4 H) protons giving a complicated splitting pattern. The characteristic splitting pattern centered at τ 3.72 of two protons is very similar to that of a β-substituted styrene derivative.[11] The NMR spectrum, therefore, is compatible with the formulation of the product as a γ-lactam (5) rather than a seven-membered cyclic amide.



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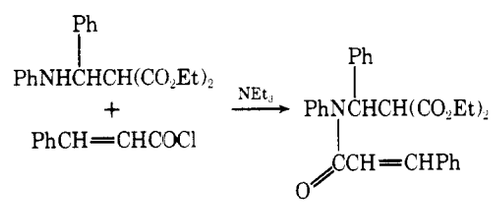
We wish to report here that an attempt to synthesize a 2-piperidinone derivative from ethyl β-anilinobenzylmalonate and cinnamoyl chloride by the method developed by us was not met with success. An α,β-unsaturated amide (6) was obtained in 70% yield. This suggests that amidification outweights other competitive processes in the case of this basic amino ester.



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## Experimental Section[12]

**A Typical Preparation of γ-Lactam. 1-(*p*-Nitrophenyl)-2,2-dicarboethoxy-3-phenyl-5-pyrrolidinone (2e).** A mixture of 3.0 g (10 mmol) of *p*-nitroanilinomalonate,[5] 3.03 g (30 mmol) of triethylamine, and 2.46 g (15 mmol) of freshly distilled cinnamoyl chloride in 60 mL of anhydrous benzene was refluxed for 6 h. The reaction mixture was cooled and washed successively with 2 N HCl, 5% $NaHCO_3$ solution, and finally with water. After drying ($Na_2SO_4$), the solvent was stripped out to give a crude solid which on fractional crystallization from methanol (two times) afforded 3.68 g (85.4%) of off-white, crystalline solid: mp 106 °C; IR (Nujol) 1742, 1735, 1710 $cm^{-1}$; NMR ($CDCl_3$) τ 1.72 (d, 2 H), 2.52 (m, 7 H), 5.63 (t, 1 H), 5.88 (q, 2 H), 6.39 (q, 2 H), 6.97 (d, 2 H), 9.05 (t, 3 H), and 9.2 (t, 3 H).

Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.16; N, 6.74. Found: C, 61.67; H, 5.47; N, 6.40.

**Ethyl *N*-Cinnamyl-*p*-nitroanilinomalonate (1e).** A mixture of 0.9 g (3 mmol) of *p*-nitroanilinomalonate and 0.67 g (4 mmol) of cinnamoyl chloride in 10 mL of pyridine and 20 mL of benzene was refluxed on a water bath for 6 h. It was washed with 2 N HCl and water, dried ($Na_2SO_4$), and evaporated at reduced pressure to give a crude solid. This on repeated fractional crystallization from ethanol and petroleum ether mixture yielded 1.29 g (79.8%) of light green needles: mp 99–100 °C; IR (Nujol) 1740, 1728, 1665 $cm^{-1}$; NMR ($CDCl_3$) τ 2.1 (d, 2 H), 2.54 (m, 7 H), 3.37 (d, 1 H, $J$ = 10 Hz), 3.47 (d, 1 H), 5.17 (d, 1 H), 5.67 (q, 4 H), and 9.03 (t, 6 H).

Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.16. Found: C, 62.00; H, 4.88.

**1-(*p*-Tolyl)-2,2-dicarboethoxy-3-benzoyl-5-pyrrolidinone (4).** A solution of 1.33 g (5 mmol) of β-benzoylacrylic acid[13] and 1.54 g (15 mmol) of triethylamine in 30 mL of anhydrous chloroform was maintained at 0 °C with stirring. To this, 0.56 g of ethyl chloroformate was added at a time. After 20 min of stirring, a solution of 1.33 g (5 mmol) of ethyl *p*-toluidinomalonate in 20 mL of anhydrous chloroform was added dropwise while not allowing the temperature of the reaction mixture to rise above 5 °C. The stirring was continued for 0.5 h after the addition was over. The product, isolated in the usual fashion, was a viscous, dark brown liquid which on chromatography over silica gel with ethyl acetate–petroleum ether afforded 0.36 g (10%) of colorless cubes (recrystallized from ethanol): mp 138–139 °C; IR (Nujol) 1758, 1738, 1728, 1688 $cm^{-1}$; NMR ($CDCl_3$) τ 2.00 (m, 2 H), 2.53 (m, 2 H), 2.90 (m, 5 H), 4.93 (t, 1 H), 5.87 (q, 2 H), 6.07 (q, 2 H), 7.03 (q, 2 H), 7.65 (s, 3 H), 9.00 (t, 3 H), and 9.08 (t, 3 H).

Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.11; H, 5.91. Found: C, 68.70; H, 5.33.

**1-(*p*-Chlorophenyl)-2,2-dicarboethoxy-3-styryl-5-pyrrolidinone (5).** β-Styrylacryloyl chloride (obtained by heating 1.7 g of the acid[14] with 3 mL of thionyl chloride in 20 mL of benzene) was taken in 25 mL of benzene and to it was added 1.3 g (5 mmol) of ethyl *p*-chloroanilinomalonate and 5 mL of triethylamine. The mixture was refluxed for 5 h, cooled, and washed successively with 2 N HCl, 5% $NaHCO_3$, and water. After drying over $Na_2SO_4$, the solvent was stripped off to yield 2.1 g of a viscous liquid which on chromatography over alumina using petroleum ether–ethyl acetate as eluent afforded 0.95 g (22.2%) of a golden yellow, viscous liquid: IR ($CHCl_3$) 1740, 1720, 1690 $cm^{-1}$; NMR ($CCl_4$) τ 2.81 (m, 9 H), 3.72 (m, 2 H), 5.97 (m, 5 H), 7.36 (d, 2 H), and 8.97 (m, 6 H).

**Diethyl *N*-Cinnamyl-β-anilinobenzylmalonate (6).** A mixture of 1.71 g (5 mmol) of ethyl β-anilinobenzylmalonate,[15] 1.0 g (6 mmol) of cinnamoyl chloride, and 2.02 g (20 mmol) of triethylamine in 40 mL of benzene was refluxed on a water bath for 6 h. The reaction mixture was worked up by the usual procedure to afford 1.38 g of colorless needles (recrystallized from benzene–petroleum ether): mp 144–145 °C; IR (Nujol) 1745, 1724, 1637 $cm^{-1}$. Identical product was obtained when the reaction was carried out under nonbasic condition.

Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.89; H, 6.15. Found: C, 73.50; H, 6.09.

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**Registry No.**—**1e**, 62851-33-6; **4**, 62851-34-7; **5**, 62851-35-8; **6**, 62851-36-9; cinnamoyl chloride, 102-92-1; β-benzoylacrylic acid, 583-06-2; ethyl chloroformate, 541-41-3; ethyl *p*-toluidinomalonate, 5634-67-3; β-styrylacryloyl chloride, 40926-86-1; ethyl *p*-chloroanilinomalonate, 5203-01-0; ethyl β-anilinobenzylmalonate, 58929-06-9; diethyl anilinomalonate, 6414-58-0; diethyl *p*-nitroanilinomalonate,

22815-39-0; diethyl *p*-chloroanilinomalonate, 5203-01-0; diethyl *p*-bromoanilinomalonate, 5500-48-1; diethyl *p*-ethoxycarbonylanilinomalonate, 28268-31-7; dimethyl anilinomalonate, 35757-92-7; dimethyl *p*-chloroanilinomalonate, 62851-37-0; dimethyl *p*-bromoanilinomalonate, 62851-38-1; dimethyl *p*-ethoxycarbonylanilinomalonate, 62851-39-2.

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# Exploitation of the Vinylogous Wolff Rearrangement. An Efficient Total Synthesis of (±)-Mayurone, (±)-Thujopsene, and (±)-Thujopsadiene


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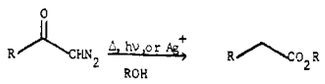
A synthetic route to (±)-mayurone, (±)-thujopsene, and (±)-thujopsadiene employing in turn a vinylogous Wolff rearrangement, a photochemical Wolff rearrangement, and an intramolecular copper-catalyzed cyclopropanation reaction is described.


Since the pioneering studies of Arndt and Eistert in the early 1940's $\alpha$-diazo ketones have found wide application in organic syntheses.[1] Principal among the synthetically useful reactions of this functionality are the Wolff rearrangement (eq 1) and the intramolecular insertion into olefinic bonds (eq 2). The former transformation can be effected thermally,[2] photochemically,[3] and by silver ion[1] catalysis, while the latter is best effected by copper.[4] Recently, we and others have described what appears, formally at least, to be a special case of the latter reaction.[5-7] Specifically, $\beta,\gamma$-unsaturated diazo ketones in the presence of a nucleophile and under the influence of copper lead efficiently via skeletal rearrangement to $\gamma,\delta$-unsaturated acid derivatives (eq 3). This transformation, a synthetic alternative to the Claisen rearrangement (eq 4),



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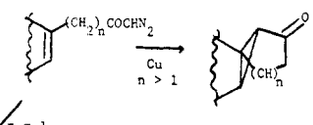

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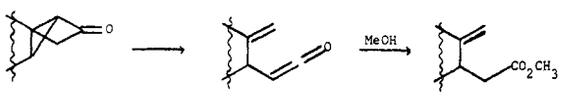
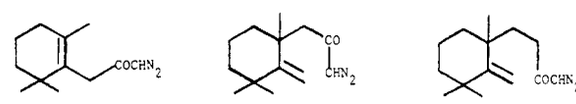


(3)

(4)

was termed[5] the vinylogous Wolff rearrangement and was suggested to involve the intermediacy of a bicyclo[2.1.0]pentanone, which under the reaction conditions fragments to a $\beta,\gamma$-unsaturated ketene (eq 3).[5-7] In order to illustrate dramatically the synthetic flexibility of the diazo ketone functionality in general, and the use of the vinylogous Wolff rearrangement in particular, we describe here an efficient route to the thujopsene class of sesquiterpenes including mayurone, thujopsene, and thujopsadiene (**1-3**). Our approach, employing the three diazo ketones listed below, exploits in turn a vinylogous Wolff rearrangement, a photochemical Wolff rearrangement, and an intramolecular copper-catalyzed cyclopropanation reaction.




The salient structural feature of the thujopsene class of sesquiterpenes is the cis disposition of the angular methyl group and the cyclopropane ring. Dihydromayurone (**4**) occupies a central place in any synthetic strategy to this class of natural products as it embodies the requisite stereochemical features and furthermore is easily transformed to each member of this class. The first solution of this interesting architectural problem was achieved in 1963 by Dauben and Ashcraft through application of their then recent discovery: the hydroxyl-mediated stereospecific Simmons–Smith reaction (**5** → **6**).[8] Subsequent oxidation yielded (±)-dihydromayurone (**4**), which was transformed into (±)-thujopsene. The second approach, solely to (±)-thujopsene and avoiding the intermediacy of dihydromayurone, was elegantly conceived by Buchi to involve intramolecular cyclization of the carbene derived from tosyl hydrazone **7**.[9] Finally, Anderson[10a] and more recently Mori[10b] and McMurry[11] demonstrated that the intramolecular cyclization of $\delta,\epsilon$-unsaturated diazo ketones