that of the lowest polysulfide (**3**, $m$ = 3.5). The latter had its strongest band centered at ~1000 $cm^{-1}$ in common with the di- and trisulfide (**3**, $m$ = 2, 3);[1h] this band became inconspicuous when $m$ exceeded 3. Hence **3** ($m$ = 3.5) evidently contained considerable trisulfide. Astonishingly, all of the polysulfide spectra showed strong bands at 1230–1120 and 1080–1025 $cm^{-1}$ characteristic of sulfonate salts.[9] The extreme improbability that significant oxidation had occurred of $SO_2Na$ to $SO_3Na$, however, followed from several facts: (a) presence of such bands in the analytically pure trisulfide **3** ($m$ = 3) but not in the disulfide;[1h] (b) the improbability of equivalent oxidation that would produce *congruent* polysulfide (disulfinate) spectra; (c) the lack of exposure to $O_2$ or oxidants (Ar-purged solvents, Ar atmosphere), together with the short time from the beginning of reaction to the final product (<6 h); (d) resistance to oxidation of aqueous solutions of the disulfinate **3** ($m$ = 3) under ambient conditions in excess of 1 week (Table I); (e) the facile loss of sulfur (cf. Scheme II), which contrasts with the stability of a sulfonate disulfide ($AcNH(CH_2)_2SS(CH_2)_4SO_3Na$; trace of disproportionation to symmetrical disulfides in 96 h at 61 °C) but accords with that of a sulfinate disulfide ($AcNH(CH_2)_2SS(CH_2)_4SO_2Na$; ~50% disproportionation in 0.5 h at 61 °C).[1i] Nevertheless, for certainty, the identity of **3** ($m$ = 4.9) as a sulfinate was confirmed in two ways. (a) An aqueous solution of **3** ($m$ = 4.9) was treated with 6 equiv of 30% aqueous $H_2O_2$ and a trace of HCl, allowed to stand for 1 h, neutralized, and freeze-dried. Absence of the strong band at 1070 $cm^{-1}$ in this resulting solid showed oxidation of $SO_2Na$ to $SO_3Na$ and confirmed assignment of the band at 1070 $cm^{-1}$ to $SO_2Na$; loss of the band at 1020 $cm^{-1}$ appeared to occur but was less clear. Strong bands appeared in the product at 1230–1120 and 1090 $cm^{-1}$, as expected for $SO_3Na$.[9] (b) Reflux of **3** ($m$ = 4.9) with 2 equiv of 2,4-dinitrochlorobenzene for 3 h in EtOH led to a yellow precipitate having the strong bands characteristic of a nitrosulfone [1530–1500 ($NO_2$), 1360–1320 (3 bands; $NO_2$, $SO_2$), 1140 $cm^{-1}$ ($SO_2$)].[12] Absence again of the 1070-$cm^{-1}$ band of **3** ($m$ = 4.9), through conversion of $SO_2Na$ to $SO_2Ar(NO_2)_2$, confirmed the assignment to $SO_2Na$; the 1180-$cm^{-1}$ band also had disappeared and perhaps also that at 1020 $cm^{-1}$. Hence the IR bands for polythiobis(butanesulfinates) include that at 1070 $cm^{-1}$ and perhaps 1180 and/or 1020 $cm^{-1}$.

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**Registry No.** **2**, 18321-15-8; **3** ($m$ = 3), 56527-86-7; **3** ($m$ = 4), 76832-43-4; **3** ($m$ = 5), 76832-44-5; **3** ($m$ = 6), 76832-45-6; **4**, 76832-46-7; **5**, 76832-47-8; **6**, 76832-48-9; **7**, 76832-49-0; **8**, 76832-50-3; **9**, 25331-82-2; **10**, 76832-51-4; **13**, 76832-52-5; sodium polysulfide, 1344-08-7; 2,4-dinitrochlorobenzene, 97-00-7; *S*-benzylthiouronium chloride, 538-28-3.

# Metalated Unsaturated Amides. Regio- and Stereoselective γ-Alkylation[1,2]

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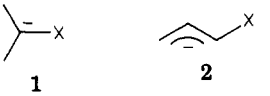
The reactions of lithiated and dilithiated unsaturated amides **4**, **5**, **12**, **15**, **18**, **34**, and **36** with a variety of electrophiles have been shown to produce deconjugated, α-alkylated products **6**, **7**, **13**, **16**, **19**, **35**, and **37**, respectively, in good to excellent yields (Tables I, II, IV, and VI). Whereas lithiated **4** and dilithiated **5** do not undergo γ-alkylation, the corresponding species of **12** and **15**, when converted to their cuprates by using cuprous iodide, afford γ products **4** and **17** with good regio- (67–90%) and *Z* stereoselectivity (67–80%) for E = allyl, prenyl, and geranyl. Differences between the reactions of cuprated, unsaturated amides and unsaturated carboxylic acids with nonallylic alkylating agents are discussed. The reaction of dicuprated *N*-methylsenecioamide (**15**) with prenyl bromide leads to a complex mixture of products which have been separated and characterized (Scheme III). The reaction of lithiated *N*,*N*-dimethylsenecioamide (**18**) with aromatic and pyridine aldehydes and some ketones has been shown to provide α (**19**) or γ (**20**) products, depending on the conditions of the reaction (Table VI). In this reaction, the reversible formation of the α product **19** and its conversion into the γ product **20** have been demonstrated (Scheme IV). The utility of the α- and γ-alkylated unsaturated amide products is illustrated by the syntheses of the monoterpenoid lavandulol (**42**) and the amide alkaloid piperlonguminine (**43**), respectively.

Carbon–carbon bond formation by alkylation of charge-stabilized carbanions of the type **1** ($d^2$ reagents)[3] is a fundamental organic reaction whose synthetic utility has been revolutionized in recent years by the availability of strong bases and chelating or basifying solvents[4,5] which allow great latitude in the conditions under which species **1** may be derived.[6] Dimetalated carboxylic acids, already



**1** **2**

X = CHO, COR, CH=NR, CH=$NNR_2$, CN, $CO_2R$, $CO_2^-$, $CONR_2$, $CON^-R$

recognized by Grignard in 1904 and extensively investigated by Ivanov,[7] have had a considerable impact in synthetic practice.[8] Metalated carboxamides, on the other hand, although first described by Hauser[9] as part of his

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(2) Results reported in this paper are based in part upon the work of: Oakleaf, J. A. M.Sc., University of Waterloo, 1977.
(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(4) Stowell, J. C. "Carbanions in Organic Synthesis"; Wiley: New York, 1979; pp 10–18.
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(6) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509.
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(8) Creger, P. L. *Annu. Rep. Med. Chem.* **1977**, *12*, 278.
(9) Meyer, R. B.; Hauser, C. R. *J. Org. Chem.* **1961**, *26*, 3696.

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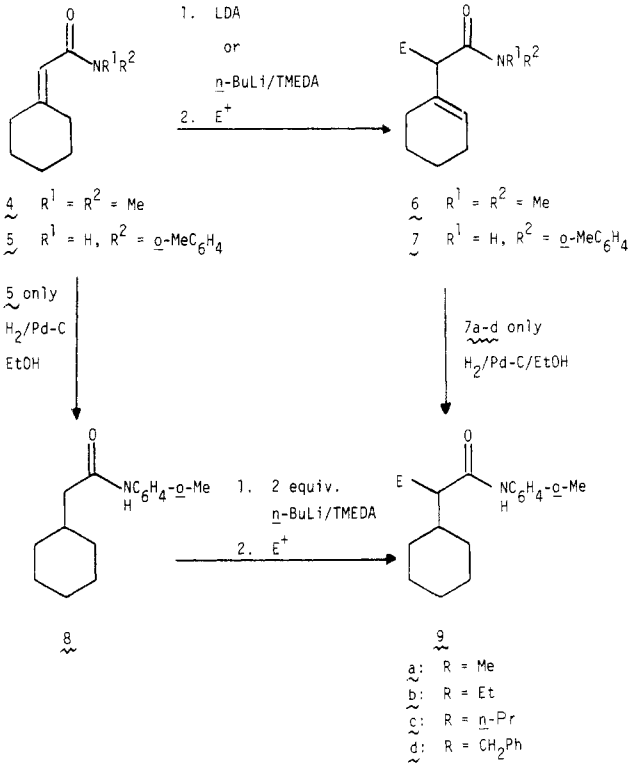
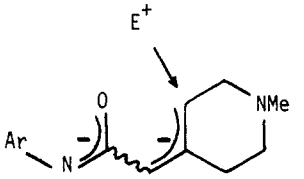
pioneering work in multianion chemistry,[10] have only recently seen substantial methodological development.[6,11,12] The vinylogous carbanions **2** have similarly attracted considerable attention.[6,8,13-22] In particular, effort has focussed on devising regimens for regioselective γ-alkylations[23] of **2** with the intent of using them for the elaboration of terpenoid natural products.[21b-d,f,23d,g]

Scheme I




While engaged in the synthesis of indole alkaloids, we discovered and found propitious use for a regioselective γ-alkylation reaction of the dimetalated heterocyclic unsaturated amide **3**.[24] This discovery and literature evidence for limited work on usaturated amide anions[25-29]




3

(10) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. Harris, T. M.; Harris, C. M. *Ibid.* **1969**, *17*, 155.

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(24) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057.

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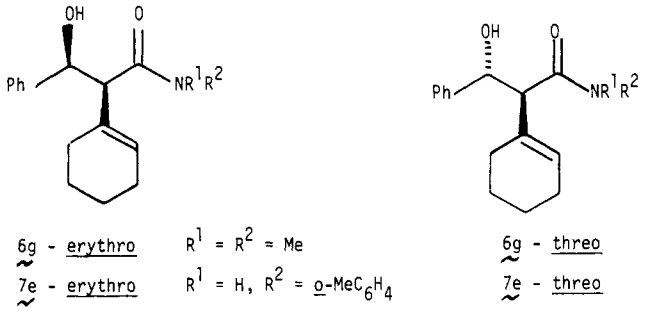
motivated our examination of the reaction between lithiated and cuprated secondary and tertiary unsaturated amides with a series of electrophiles.[1] Herein we present the details and extensions of these studies and compare the utility of metalated unsaturated amides with the corresponding carboxylic acids[21,55] in regio- and stereoselective γ-alkylation reactions. In addition, we describe the application of these intermediates to the synthesis of simple monoterpenoids and amide alkaloids.

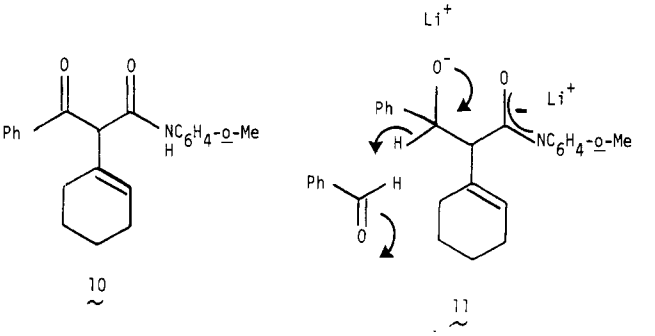
**Alkylation of Metalated Cyclohexylidene Acetamides (Scheme I).** Our initial study was concerned with the extension of the result observed with dianion **3**[24] to systems **4** and **5** which lack heterocyclic nitrogen (Scheme I). The results of alkylation of mono- and dilithiated species derived by treatment of **4** and **5** with LDA or *n*-BuLi in THF at room temperature are summarized in Table I. In contrast to the heterocyclic system **3**,[30] compounds **4** and **5** undergo deconjugative α-alkylation to give products **6** and **7** in moderate to excellent yields. The reaction of lithiated **4** with electrophiles has broader scope than that of dilithiated **5** which fails with isopropyl iodide, crotyl bromide, and 1,3-dichlorobut-2-ene, possibly owing to hydrogen halide elimination. Sharply contrasting with the results observed for the senecioamides **12** and **15** (see below), attempts to promote γ-alkylation by treatment of the initial mono- and dilithiated species of **4** and **5** with CuI were unsuccessful. For example, the reaction of cuprated **4** with methyl iodide and allyl bromide gave only α products **6a** (38%) and **6c** (47%), respectively, in addition to recovered starting material (25–40%). All products **6** and **7** showed spectral properties consistent with the α-alkylation structural formulation. In several cases (**7a–d**), chemical verification was carried out by hydrogenation to the corresponding saturated amides **9a–d** which were prepared by alkylation of the common cyclohexyl acetamide **8** (Experimental Section).

The reaction of lithiated **4** and dilithiated **5** with benzaldehyde was briefly studied as a function of time and temperature. Generation of lithiated dimethyl amide **4** in THF at 0–20 °C followed by cooling to −78 °C, treatment with benzaldehyde for 10 s, and quenching at −78 °C resulted in the formation of a mixture of amide alcohols **6g** with essentially complete erythro stereoselectivity (erythro/threo ratio of 98:<2). However, when lithiated **4**, generated in the same way, was treated with benzaldehyde at 20 °C for 4–8 h, the resulting diasteriomeric mixture of **6g** was rich in the threo isomer (erythro/threo ratio of 1:5). The threo and erythro assignments are based on the differences of $^1$H NMR coupling constants of the diastereomeric hydrogens[31b] (see Experimental Section).




The identical sets of conditions used for **4** when applied to the reaction of dilithiated *o*-toluidide **5** with benzaldehyde gave amide alcohol **7e** as a 1:1 erythro/threo mixture (10% yield) and as exclusively the threo isomer (26% yield), respectively. In both cases the material balance consisted of recovered starting amide **5**. These observations are consistent with the general trends of stereoselectivity observed in aldol condensations using kinetic vs. thermodynamic control considerations.[31] However, the inability to generate the amide dienolates of **4** and **5** under conditions which approximate kinetic control[31c] and the lack of knowledge concerning their *Z*/*E* isomer ratio preclude any interpretation of these results.[56] Further studies are planned.

In addition to the diasteriomeric amide alcohols *erythro*-**7e** and *threo*-**7e**, a minor product (<5%) was detected in the condensations of dilithiated **5** with benzaldehyde under several experimental conditions. This product was obtained in isolable amounts from reactions carried out for 4–8 h and was identified as the keto amide **10**. Furthermore, compound **10** (38%) and benzyl alcohol (~38%) were the sole reaction products when 2 equiv of benzaldehyde was used, the product balance consisting of starting material. This result may be mechanistically described by structure **11** for which precedent is available.[32] In contrast, treatment of lithiated dimethyl amide **4** under the same conditions (2 equiv of PhCHO) produced only the *erythro*-**6e**/*threo*-**6e** product mixture; a keto amide corresponding to **10** was not detected, suggesting that the neighboring amide anion may be a driving force for the hydride transfer shown in **11**.




**Alkylation of Metalated Senecioamides (Scheme II).** Compared to the sometime sluggish reactions of **4** and **5**, the mono- and dilithiated dienolates of the senecioamides **12** and **15** undergo rapid and efficient alkylation to give mainly the α products **13** and **16**, respectively (Scheme II, Table II). The lithiated *N*,*N*-diisopropyl amide **12**, in particular, is α-alkylated within minutes at room temperature, a result which is perhaps a manifestation of the release by deconjugation of the steric con-

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(30) The implication that the heterocyclic nitrogen in **3** is essential for γ-alkylation is under study.

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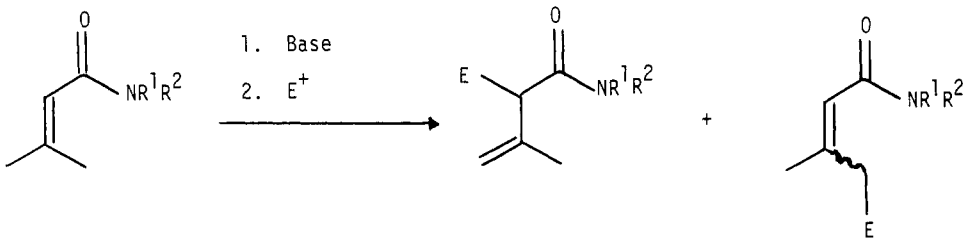
Table I. Physical and Spectral Data for Cyclohexylidene Acetamides 6 and 7

| product[a,b] | E[c] | yield, % | mp (solvent) or bp (mmHg),[d] °C | IR ($CHCl_3$), $cm^{-1}$ | NMR ($CDCl_3$),[f] δ | MS,[e] *m/e* (rel intensity) |
|---|---|---|---|---|---|---|
| **6a** | Me | 58 | 75 (1.0) | 1630 | 1.2 (d, 3 H, *J* = 7), 1.43-2.17 (2 m, 8 H), 2.97 (br s, 6 H), 3.2 (q, 1 H, *J* = 7), 5.53 (br s, 1 H) | 181 ($M^+$, 21), 166 (50), 109 (33), 72 (100) |
| **6b** | *i*-Pr | 83 | 85-90 (0.2) | 1630 | 0.75 (d, 3 H, *J* = 3), 0.87 (d, 3 H, *J* = 3), 1.40-2.60 (m, 9 H), 2.77 (d, 1 H, *J* = 10), 2.97 (d, 6 H), 5.6 (br s, 1 H) | 209 ($M^+$, 6), 166 (100) |
| **6c** | $CH_2$=$CHCH_2$ | 65 | 105 (0.2) | 1635 | 1.40-2.65 (m, 10 H), 2.98 (d, 6 H), 3.13 (hidden t, 1 H, *J* = 7), 4.77-5.20, 5.37-6.13 (2 m, 4 H) | 207 ($M^+$, 6), 166 (100), 72 (50) |
| **6d** | $Me_2C$=$CHCH_2$ | 71 | 120 (0.2) | 1630 | 1.27-2.53 (m including 1.63, br s, 16 H), 2.98 (d, 6 H), 3.07 (hidden t, 1 H, *J* = 7), 5.07 (br t, 1 H, *J* = 8), 5.53 (br s, 1 H) | 235 ($M^+$, 10), 166 (100) |
| **6e** | MeC(Cl)=$CHCH_2$ | 73 | 125-130 (0.2) | 1640, 1670 | 1.45-2.67 (m including 2.03, s, 13 H), 2.93 (s, 3 H), 3.17 (hidden m, 1 H), 5.53 (m, 2 H) | 257 ($M^+$, ~1), 255 ($M^+$, 4), 166 (100) |
| **6f** | $PhCH_2$ | 76 | 70-71 (petroleum ether) | 1635 | 1.37-2.13 (m, 8 H), 2.78-3.63 (m, 3 H), 2.83, 2.87 (2 s, 6 H), 5.48 (br s, 1 H), 7.20 (s, 5 H) | 257 ($M^+$, 8), 166 (100) |
| **6g** (threo) | PhCH(OH) | 61 | 118-119 (petroleum ether-PhH) | 1625 | 1.27-2.13 (br, 8 H), 2.97, 3.0 (2 s, 6 H), 3.27 (d, 1 H, *J* = 8), 4.65 (s, 1 H, exchangeable with $D_2O$), 5.05 (d, 1 H, *J* = 8), 5.50 (br s, 1 H), 7.37 (s, 5 H) | 273 ($M^+$) |
| **6g** (erythro) | PhCH(OH) | 13 | 65-66 ($Et_2O$-hexane) | 1625 | 1.27-2.05 (m, 8 H), 2.90, 2.93 (2 s, 6 H), 3.23 (d, 1 H, *J* = 4), 4.95 (br, 1 H, exchangeable with $D_2O$), 5.25 (d, 1 H, *J* = 4), 5.38 (br s, 1 H), 7.33 (s, 5 H) | 273 ($M^+$) |
| **6h** | PhCO | 43 | 96-97 (petroleum ether-PhH) | 1645, 1685, 1700 | 1.48-2.33 (m, 8 H), 2.98, 3.03 (2 s, 6 H), 5.03 (s, 1 H), 5.63 (br s, 1 H), 7.42-7.68, 7.92-8.13 (m, 5 H) | 271 ($M^+$, 12), 166 (100), 105 (69) |
| **6i** | PhSe | 32 | 120 (1.0) | 1635 | 1.42-2.17 (m, 8 H), 2.95 (s, 6 H), 4.62 (s, 1 H), 5.13 (br s, 1 H), 7.13-7.70 (m, 5 H) | 323 ($M^+$, <3), 321 ($M^+$, <3), 166 (100), 121 (30) |
| **7a** | Me | 80 | 74-75 ($C_6H_{12}$-$Et_2O$) | 1670 | 1.32 (d, 1 H, *J* = 7), 1.5-2.42 (m, 8 H), 2.23 (s, 3 H), 3.15 (q, 1 H, *J* = 7), 5.87 (br s, 1 H), 7.0-7.67 (m, 4 H), 7.97 (br d, 1 H) | 243 ($M^+$, 8), 229 (64), 123 (89), 107 (100) |
| **7b** | Et | 80 | 79-80 ($C_6H_{12}$-$Et_2O$) | 1670 | 0.90 (t, 1 H, *J* = 7), 1.05-2.47 (m including 2.17, s, 13 H), 2.83 (m, 1 H), 5.80 (br s, 1 H), 6.93-7.67 (m, 4 H), 7.90 (br s, 1 H) | 275 ($M^+$) |
| **7c** | $CH_2$=$CHCH_2$ | 50 | 85-86 (EtOH-$H_2O$) | 1635 (br) | 1.20-3.20 (m including 2.20, s, 14 H), 4.87-5.33 and 5.50-6.10 (2 m, 4 H), 6.90-7.55 (m, 4 H), 7.93 (br s, 1 H) | 269 ($M^+$, 29), 229 (29), 147 (53), 123 (100), 107 (59) |
| **7d** | $PhCH_2$ | 43 | 127-128 (EtOH-$H_2O$) | 1675, 1645 | 1.30-2.33 (m, including 2.10, s, 11 H), 2.70-3.52 (m, 3 H), 5.72 (br s, 1 H), 7.02-7.43 (m, 4 H), 7.90 (br s, 1 H) | 319 ($M^+$, 100), 123 (44), 91 (56) |
| **7e** (threo) | PhCH(OH) | 14 | 139-140 ($Et_2O$-hexane) | 3390, 1660 | 1.50 (m, 4 H), 1.90 (m, 4 H), 2.18 (s, 3 H), 3.28 (d, 1 H, *J* = 8.5), 4.70 (m, 1 H, $D_2O$ exch), 5.13 (d, 1 H, *J* = 8.5), 5.63 (m, 1 H), 6.9-7.9 (m, 10 H) | 317 ($M^+$ - 18, 2), 229 (47), 122 (100), 117 (56) |
| **7e** (erythro) | PhCH(OH) | 28 | 151-152 (EtOH) | 3400, 1665 | 1.55 (m, 4 H), 2.05 (m, 4 H), 2.10 (s, 3 H), 3.20 (d, 1 H, *J* = 5.5), 3.38 (d, 1 H, *J* = 2.5), 5.40 (m, 1 H), 5.65 (br s, 1 H), 7.0-7.5 (m, 9 H), 7.7 (br, 1 H) | 317 ($M^+$ - 18, 1), 229 (41), 122 (100), 117 (62) |

[a] γ products were not detected (<2%) by GLC analysis. [b] Anal. Calcd (Found) for **6a** ($C_{11}H_{19}NO$): C, 72.88 (72.99); H, 10.56 (10.80); N, 7.73 (8.05). **6b** ($C_{13}H_{23}NO$): C, 74.59 (74.18); H, 11.07 (11.11); N, 6.69 (7.09). **6c** ($C_{13}H_{21}NO$): C, 75.32 (75.35); H, 10.21 (10.39); N, 6.76 (6.72). **6d** ($C_{15}H_{25}NO$): C, 76.55 (76.14); H, 10.71 (10.43); N, 5.95 (5.75). **6e** ($C_{14}H_{22}NOCl$): C, 65.75 (66.07); H, 8.61 (8.73); N, 5.48 (5.51). **6f** ($C_{17}H_{23}NO$): C, 79.33 (79.18); H, 9.01 (9.18); N, 5.44 (5.58). *threo*-**6g** ($C_{17}H_{23}NO_2$): C, 74.69 (74.60); H, 8.48 (8.80); N, 5.12 (4.90). *erythro*-**6g**: C, 74.69 (74.41); H, 8.48 (8.73); N, 5.12 (4.83). **6h** ($C_{17}H_{21}NO_2$): C, 75.25 (74.99); H, 7.80 (8.12); N, 5.16 (5.18). **6i** ($C_{16}H_{21}NOSe$): analysis precluded by instability. **7a** ($C_{16}H_{21}NO$): C, 78.97 (79.06); H, 8.70 (8.84); N, 5.76 (6.07). **7b** ($C_{17}H_{23}NO$): C, 79.33 (79.53); H, 9.01 (9.29); N, 5.44 (5.38). **7c** ($C_{18}H_{23}NO$): C, 80.26 (80.49); H, 8.61 (8.58); N, 5.20 (5.41). **7d** ($C_{22}H_{25}NO$): C, 82.72 (82.64); H, 7.89 (7.89); N, 4.38 (4.32). *threo*-**7e** ($C_{22}H_{25}NO_2$): C, 78.77 (78.56); H, 7.51 (7.53); N, 4.18 (3.92). *erythro*-**7e**: C, 78.77 (78.47); H, 7.51 (7.62); N, 4.18 (3.96). [c] The following halides were used: MeI, EtBr, *i*-PrI, $CH_2$=$CHCH_2Br$, $Me_2C$=$CHCH_2Br$, MeC(Cl)=$CHCH_2Cl$, $PhCH_2Br$, PhSeBr. [d] Molecular distillation. [e] With the exception of the $M^+$ peak, relative intensities of >30% only are recorded. [f] *J* values are in hertz.

Scheme II

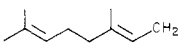
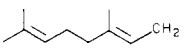



12 $R^1 = R^2 =$ i-Pr
15 $R^1 =$ H, $R^2 =$ Me
18 $R^1 = R^2 =$ Me

13 $R^1 = R^2 =$ i-Pr
16 $R^1 =$ H, $R^2 =$ Me
19 $R^1 = R^2 =$ Me

14 $R^1 = R^2 =$ i-Pr
17 $R^1 =$ H, $R^2 =$ Me
20 $R^1 = R^2 =$ Me

Table II. Regio- and Stereoselectivity in Alkylation of Senecioamides 12 and 15

| | | | | | products[c] | |
|---|---|---|---|---|---|---|
| entry | substrate | metal | E[a] | yield, %[b] | regioselectivity,[d] α/γ | γ stereoselectivity,[e] Z/E |
| 1 | 12 | Li | Me | 98 | 98/2 (13/14) | |
| 2 | | Cu | Me | 95 | 98/2 (13/14) | |
| 3 | 12 | Li | *i*-Pr | 87 | 86/14 (13/14) | 91/9 (14) |
| 4 | | Cu | *i*-Pr | 87 | 86/14 (13/14) | 91/9 (14) |
| 5 | 12 | Li | $CH_2$=$CHCH_2$ | 85 | 86/14 (13/14) | 92/8 (14) |
| 6 | | Cu | $CH_2$=$CHCH_2$ | 85 | 67/33 (13/14) | 80/20 (14) |
| 7 | 12 | Li | $Me_2C$=$CHCH_2$ | 90 | 96/4 (13/14) | |
| 8 | | Cu | $Me_2C$=$CHCH_2$ | 85 | 33/67 (13/14) | 67/33[f] (14) |
| 9 | 12 | Li | $PhCH_2$ | 83 | 98/2 (13/14) | |
| 10 | | Cu | $PhCH_2$ | 83 | 98/2 (13/14) | |
| 11 | 15 | Li | Me | 98 | 98/2 (16/17) | |
| 12 | | Cu | Me | 80 | 59/41 (16/17) | 91/9 (17) |
| 13 | 15 | Li | *i*-Pr | 93 | 80/20 (16/17) | 60/40 (17) |
| 14 | | Cu | *i*-Pr | 72 | 60/40 (16/17) | 62/38 (17) |
| 15 | 15 | Li | $CH_2$=$CHCH_2$ | 90 | 98/2 (16/17) | |
| 16 | | Cu | $CH_2$=$CHCH_2$ | 90 | 30/70 (16/17) | 60/40 (17) |
| 17 | 15 | Li | $Me_2C$=$CHCH_2$ | 96 | 98/2 (16/17) | |
| 18 | | Cu | $Me_2C$=$CHCH_2$ | 95 | 17/83[g] (16/17) | 75/25[g] (17) |
| 19 | 15 | Li |  | 88 | 94/6 (16/17) | |
| 20 | | Cu |  | 80 | 10/90 (16/17) | 80/20 (17) |
| 21 | 15 | Li | $PhCH_2$ | 90 | 98/2 (16/17) | |
| 22 | | Cu | $PhCH_2$ | 80 | 75/25 (16/17) | 80/20 (17) |

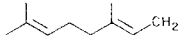
[a] See footnote *c* in Table I. In entries 19 and 20, the electrophile used was geranyl bromide. [b] Isolated yield (percent) after primary cleanup by column chromatography (silica gel) or distillation. [c] Except where noted, α/γ isomer separation was effected by distillation or silica gel chromatography, and Z/E isomer separation was carried out by chromatography. The results given represent averages of three to five experiments in all cases. [d] Determined by GLC and NMR; 2% γ products refer to the lower limit of detection by GLC. [e] Determined by GLC and NMR (including benzene-induced chemical shift studies). Absence of entry indicates an insufficient quantity of γ product for determination of the Z/E ratio. For entries 18, 20, and 22, pure γ-Z isomers were obtained by column chromatography; purification of the γ-E isomer from the remaining fraction was not attempted. [f] Contains ~5% of transposed ($S_N2'$) product, 2(Z)-$CH_2$=$CHC(Me_2)CH_2C(Me)$=$CHCON(i\text{-}Pr)_2$, as estimated by GLC and NMR (integration of singlet at δ 1.08 representing the allyl methyl groups). [g] Ratio based on product distribution shown in Scheme III.

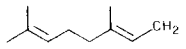
straints imposed by the diisopropyl groups. A further difference between the reactions of mono- and dilithiated **4,5** and **12,15** is the formation in some cases (Table II, entries 3, 5, and 13) of significant amounts of γ products **14** and **17** with the latter set of substrates. Separation of α (**13**, **16**) and γ (**14**, **17**) products was achieved by distillation and/or column chromatography, and an assignment of structure was readily made by NMR spectroscopy (Table III). The γ-*Z* and γ-*E* isomers of **14** and **17** were separated, whenever possible, by column chromatography. The assignment of stereochemistry for these geometrical isomers, either pure or in an unseparable mixture, is based on benzene-induced chemical shift studies which is an established method for distinguishing geometrical isomers of α,β-unsaturated ketones.[33] A typical analysis is given in the Experimental Section.

Significant enhancement in γ regioselectivity was observed in the reactions of mono- and dicuprated dienolates of amides **12** and **15** (Table II) which were generated from the corresponding lithiated species by treatment with CuI as described by Katzenellenbogen and Crumrine.[21b,55] Although the anion of **12** undergoes deconjugative α-methylation (**13**) irrespective of cation (Table II, entries 1, 2), a shift toward γ-alkylation (**14**) is evident in the reactions of cuprated **12** with allyl bromide (entry 6), and γ-attack becomes clearly dominant with 3,3-dimethylallyl

(33) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: London and New York, 1969; p 246.

Table III. Physical and Spectral Data for α- and γ-Alkylated Senecioamides 13, 14, 16, and 17

| product[a] | E | mp (solvent) or bp (mmHg),[b] °C | IR ($CHCl_3$) $\nu_{CO}$, $cm^{-1}$ | NMR ($CDCl_3$),[d] δ | MS, *m/e* (rel intensity)[c] |
|---|---|---|---|---|---|
| **13a** | Me | 62.5-63 (EtOH-$H_2O$) | 1630 | 1.0-1.55 (m, 15 H), 1.75 (m, 3 H), 3.3 (q, $J$ = 7, 1 H), 3.45 (septet, 1 H, $J$ = 7), 4.0 (septet, 1 H, $J$ = 7), 4.88 (m, 2 H) | 197 ($M^+$, 5), 86 (100) |
| **13b** | *i*-Pr | 37.5-38 (sublimed) | 1622 | 0.7-1.50 (m, 18 H), 1.70 (m, 3 H), 2.30 (m, 1 H), 2.81 (d, 1 H, $J$ = 10), 3.35 (septet, 1 H, $J$ = 7), 4.30 (septet, 1 H, $J$ = 7) | 225 ($M^+$, 6), 86 (85) |
| **13c** | $CH_2$=$CHCH_2$ | 56-58 (0.25) | 1630 | 1.0-1.5 (m, 12 H), 1.74 (m, 3 H), 2.45 (m, 2 H), 2.95-3.65 (m, 2 H), 4.16 (septet, 1 H, $J$ = 7), 4.90 (m, 2 H), 4.85-5.25 (m, 2 H), 5.85 (m, 1 H) | 223 ($M^+$, 15), 182 (34), 128 (33), 95 (32), 86 (100) |
| **13d** | $Me_2C$=$CHCH_2$ | 76-78 (0.2) | 1625 | 1.03-1.53 (m, 12 H), 1.56-1.83 (m, 9 H), 2.4 (m, 2 H), 3.2 (t, 1 H, $J$ = 7), 3.4 (septet, 1 H, $J$ = 7), 4.15 (septet, 1 H, $J$ = 7), 4.9 (m, 2 H), 5.1 (m, 1 H) | 251 ($M^+$, 9), 86 (100) |
| **13e** | $PhCH_2$ | 90-94 (0.2) | 1628 | 0.7-1.50 (m, 12 H), 1.75 (m, 3 H), 2.45-3.65 (m, 4 H), 4.0 (septet, 1 H, $J$ = 7), 4.85 (m, 2 H), 7.2 (s, 5 H) | 273 ($M^+$, 3), 128 (30), 86 (86) |
| **14b** | *i*-Pr | 65-67 (0.2) | 1606 | 0.85 (d, 6 H, $J$ = 6), 1.28 (br, 12 H), 1.78 (d, 3 H, $J$ = 1.5), 2.22 (m, 2 H), 3.75 (br, 2 H), 5.80 (m, 1 H) | 225 ($M^+$, 18), 125 (79), 85 (79), 84 (55) |
| **14c** | $CH_2$=$CHCH_2$ | 64-66 (0.2) | 1610 | 1.0-1.6 (br, 12 H), 1.80 (m, 3 H), 2.15-2.45 (m, 4 H), 3.2-4.4 (br, 2 H), 5.05 (m, 2 H), 5.82 (m, 1 H), 5.85 (m, 1 H) | 223 ($M^+$, 21), 180 (47), 123 (99), 86 (100), 84 (63) |
| **14d** | $Me_2C$=$CHCH_2$ | 96-98 (0.25) | 1610 | 1.0-1.6 (br, 12 H), 1.70 (m, 6 H), 1.80 (s, 3 H), 2.10 (m, 4 H), 3.2-4.4 (br, 2 H), 5.05 (m, 2 H), 5.2 (m, 1 H), 5.8 (m, 1 H) | 251 ($M^+$, 24), 100 (32), 86 (100), 84 (67) |
| **16a** | Me | 64-66 (0.25) | 1660 | 1.15 (d, 3 H, $J$ = 7), 1.75 (s, 3 H), 2.80 (d, 3 H, $J$ = 5), 3.10 (q, 1 H, $J$ = 7), 4.95 (s, 2 H), 6.4 (br s, 1 H) | 127 ($M^+$, 11), 112 (66), 70 (81) |
| **16b** | *i*-Pr | 79-81 ($Et_2O$-petroleum ether) | 1670 | 0.90 (t, 6 H, $J$ = 7), 1.65 (m, 1 H), 1.75 (s, 3 H), 2.80 (d, 3 H, $J$ = 5), 2.50 (d, 1 H, $J$ = 6), 4.95 (s, 2 H), 6.4 (br s, 1 H) | 155 ($M^+$, 3), 112 (70), 83 (58) |
| **16c** | $CH_2$=$CHCH_2$ | 76-78 (0.2) | 1645 | 1.75 (s, 3 H), 2.80 (d, 3 H, $J$ = 5), 2.5 (m, 2 H), 2.95 (m, 1 H), 4.95 (s, 2 H), 5.07 (m, 2 H), 5.7 (m, 1 H) | 153 ($M^+$, 18), 124 (68), 112 (37), 96 (80), 95 (99), 81 (100) |
| **16d** | $Me_2C$=$CHCH_2$ | 96-98 (0.2) | 1645 | 1.5-1.9 (m, 9 H), 2.40 (m, 2 H), 2.75 (d, 3 H, $J$ = 5), 2.95 (m, 1 H), 4.90 (s, 2 H), 5.02 (m, 1 H), 6.3 (br s, 1 H) | 181 ($M^+$, 14), 124 (49), 123 (98), 113 (100), 112 (54), 98 (69), 83 (99), 81 (92) |
| **16e** | $PhCH_2$ | 77-78 (sublimed) | 1655 | 1.75 (s, 3 H), 2.65 (d, 3 H, $J$ = 5), 2.9-3.45 (m, 1 H), 4.85 (s, 2 H), 6.10 (br s, 1 H), 7.20 (s, 5 H) | 203 ($M^+$, 12), 145 (100), 112 (94), 91 (43) |
| **16f** |  | 130-134 (0.3) | 1645 | 1.65 (m, 12 H), 2.0 (s, 4 H), 2.45 (m, 2 H), 2.75 (d, 3 H, $J$ = 5), 2.80 (m, 1 H), 4.85 (s, 2 H), 5.02 (m, 2 H), 6.20 (br s, 1 H) | 249 ($M^+$, 18), 180 (58), 127 (50), 123 (100), 113 (98), 112 (74), 83 (82), 81 (95) |
| **24** | $Me_2C$=$CHCH_2$ | 63-64 (EtOH) | 1645 | 1.05 (d, 6 H, $J$ = 6), 1.75 (s, 6 H), 2.60 (m, 1 H), 2.90 (d, 3 H, $J$ = 5), 5.90 (br s, 1 H), 6.10 (m, 2 H) | 181 ($M^+$, 42), 166 (100), 81 (37) |
| **17a** | Me | 70-72 (0.25) | 1640 | 1.10 (t, 3 H, $J$ = 7), 1.80 (s, 3 H), 2.65 (q, 2 H, $J$ = 7), 2.80 (d, 3 H, $J$ = 5), 5.60 (s, 1 H), 6.05 (br s, 1 H) | 127 ($M^+$, 55), 97 (83) |
| **17b** | *i*-Pr | 88-92 (0.2) | 1645 | 0.85 (d, 6 H, $J$ = 5), 1.7 (m, 1 H), 1.85 (s, 3 H), 2.50 (m, 2 H), 2.80 (d, 3 H, $J$ = 5), 5.50 (s, 1 H), 5.90 (br s, 1 H) | 155 ($M^+$, 43), 112 (84), 97 (100) |
| **17c** | $CH_2$=$CHCH_2$ | 94-96 (0.2) | 1630 | 1.85 (s, 3 H), 2.20-3.0 (m, 4 H), 2.80 (d, 3 H, $J$ = 5), 5.0 (m, 2 H), 5.60 (s, 1 H), 5.95 (m, 1 H), 6.15 (br s, 1 H) | 153 ($M^+$, 11), 112 (96) |
| **17d** | $Me_2C$=$CHCH_2$ | 102-105 (0.25) | 1630 | 1.65 (m, 6 H), 1.85 (s, 3 H), 2.20 (m, 2 H), 2.65 (m, 2 H), 2.85 (d, 3 H, $J$ = 5), 5.20 (t, 1 H, $J$ = 6), 5.65 (s, 1 H), 6.25 (br s, 1 H) | 181 ($M^+$, 20), 113 (100), 98 (46), 83 (90) |
| **17e** | $PhCH_2$ | 80-81 (EtOH) | 1635 | 1.80 (s, 3 H), 2.85 (m, 4 H), 2.80 (d, 3 H, $J$ = 5), 5.60 (s, 1 H), 6.20 (br s, 1 H), 7.25 (s, 5 H) | 203 ($M^+$, 21), 145 (41), 131 (50), 112 (99), 91 (100) |

| | | | | | |
|---|---|---|---|---|---|
| **17f** |  | 144–146 (0.3) | 1630 | 1.65 (m, 12 H), 2.10 (m, 8 H), 2.80 (d, 3 H, $J$ = 5), 5.05 (m, 2 H), 5.60 (s, 1 H), 6.20 (br s, 1 H) | 249 ($M^+$, 25), 180 (65), 127 (43), 123 (100), 113 (99), 112 (68), 83 (90), 81 (99) |

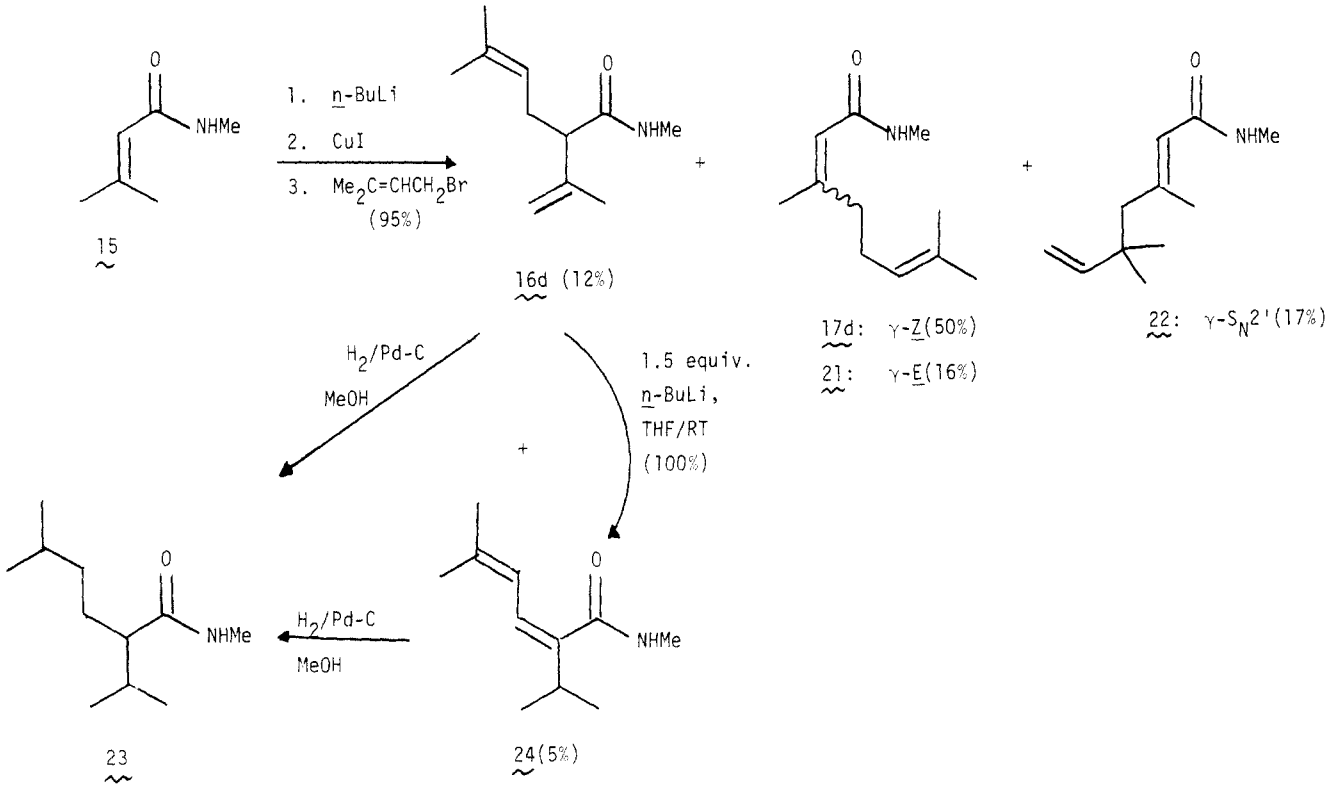
[a] With exception of **14d**, **17d**, and **17e**, for which analyses of pure $\gamma$-$Z$ isomers are given, all data for $\gamma$ products are those obtained on $Z/E$ mixtures. Anal. Calcd (Found) for **13a** ($C_{12}H_{23}NO$): C, 73.04 (72.88); H, 11.75 (11.79); N, 7.10 (7.14). **13b** ($C_{14}H_{27}NO$): C, 74.61 (74.69); H, 12.08 (12.21); N, 6.21 (6.18). **13c** ($C_{14}H_{25}NO$): C, 75.28 (75.43); H, 11.28 (11.32); N, 6.27 (6.26). **13d** ($C_{16}H_{29}NO$): C, 76.44 (76.41); H, 11.63 (11.60); N, 5.57 (5.63). **13e** ($C_{18}H_{27}NO$): C, 79.07 (79.11); H, 9.95 (9.98); N, 5.12 (5.11). **14b** ($C_{14}H_{27}NO$): C, 74.61 (74.82); H, 12.08 (12.10); N, 6.21 (6.23). **14c** ($C_{14}H_{25}NO$): C, 75.28 (75.19); H, 11.28 (11.35); N, 6.27 (6.31). **14d** ($C_{16}H_{29}NO$): C, 76.44 (76.74); H, 11.63 (11.73); N, 5.57 (5.62). **16a** ($C_7H_{13}NO$): C, 66.11 (66.12); H, 10.30 (10.32); N, 11.01 (11.00). **16b** ($C_9H_{17}NO$): C, 69.63 (69.49); H, 11.04 (11.01); N, 9.02 (9.01). **16c** ($C_9H_{15}NO$): C, 70.55 (70.76); H, 9.87 (9.89); N, 9.14 (9.13). **16d** ($C_{11}H_{19}NO$): C, 72.88 (73.15); H, 10.56 (10.60); N, 7.73 (7.71). **16e** ($C_{13}H_{17}NO$): C, 76.81 (76.85); H, 8.43 (8.45); 6.89 (6.88). **16f** ($C_{16}H_{27}NO$): C, 77.11 (77.10); H, 10.84 (11.50); N, 5.62 (5.61). **24** ($C_{11}H_{19}NO$): C, 72.88 (72.75); H, 10.56 (10.81); N, 7.73 (7.52). **17a** ($C_7H_{13}NO$): C, 66.11 (66.15); H, 10.30 (10.41); N, 11.01 (11.09). **17b** ($C_9H_{17}NO$): C, 69.63 (69.41); H, 11.04 (10.95); N, 9.02 (9.08). **17c** ($C_9H_{15}NO$): C, 70.55 (71.01); H, 9.87 (9.58); N, 9.14 (9.02). **17d** ($C_{11}H_{19}NO$): C, 72.88 (72.45); H, 10.56 (10.21); N, 7.73 (7.41). **17e** ($C_{13}H_{17}NO$): C, 76.81 (76.53); H, 8.43 (8.22); N, 6.89 (7.05). **17f** ($C_{16}H_{27}NO$): C, 77.11 (77.56); H, 10.84 (11.34); N, 5.62 (5.34). [b] See footnote *d*, Table I. [c] See footnote *e*, Table I. [d] $J$ values are given in hertz.

**Table IV. Alkylation of Crotonamides 34 and 36**

| product[a] | E | mp (solvent) or bp (mmHg), °C | yield, % | IR ($CHCl_3$), $cm^{-1}$ | NMR[f] ($CDCl_3$), $\delta$ |
|---|---|---|---|---|---|
| **35a**[b] | Me | 65 (1.0) | 53 | 1630 | 1.0–1.47 (m, 15 H), 3.40 (septet, 2 H), 4.07 (m, 1 H), 4.93 (m, 1 H), 5.17 (br d, 1 H), 5.97 (septet, 1 H) |
| **35b** | $PhCH_2$ | 130 (1.0) | 41 | 1628 | 0.85, 1.05, 1.25, 1.37 (4 d, 12 H, $J$ = 7), 2.53–4.18 (m, 5 H), 4.97 (dd, 1 H, $J$ = 1, 5), 5.17 (s, 1 H), 5.85–6.33 (m, 1 H), 7.27 (s, 5 H) |
| **35c**[c] | PhCH(OH) | 72–73 (petroleum ether) | 42 | 1630 | 0.72–1.52 (m, 12 H), 3.0–4.07 (m, 3 H), 4.70–6.33 (m, 5 H), 7.35 (s, 5 H) |
| **37a** | 3,4-$(OCH_2O)C_6H_3CH_2$ | 61–63 ($Et_2O$-petroleum ether) | 65 | 1650 | 0.8 (d, 6 H, $J$ = 6), 1.7 (m, 1 H), 3.0 (m, 5 H), 5.1 (m, 2 H), 5.8 (m, 1 H), 5.9 (s, 2 H), 6.7 (s, 3 H) |
| **38a** | 3,4-$(OCH_2O)C_6H_3CH_2$ | 104–105[d] (PhH-petroleum ether) | 22 | 1670, 1620 | 0.9 (d, 6 H, $J$ = 6), 1.7 (m, 1 H), 2.6 (m, 4 H), 3.1 (m, 2 H), 5.8 (d, 1 H, $J$ = 16), 5.9 (s, 2 H), 6.7 (s, 3 H), 6.8 (m, 1 H) |
| **37b**[c] | $CH_3(CH_2)_{14}CH(OH)$ | 85–87 ($Et_2O$-petroleum ether) | 54[e] | 1655 | 0.75 (d, 6 H, $J$ = 6), 0.8 (m, 3 H), 1.05 (m, 28 H), 1.6 (m, 1 H), 2.03 (s, 1 H, $D_2O$ exch), 2.6 (m, 1 H), 2.8 (m, 1 H), 3.4–3.9 (m, 1 H), 5.0 (m, 2 H), 5.5–5.9 (m, 2 H) |
| **38b** | $CH_3(CH_2)_{14}CH(OH)$ | 82–84 ($Et_2O$-petroleum ether) | 13 | 1630 | 0.9 (d, 6 H, $J$ = 6), 0.9 (m, 3 H), 1.3 (m, 28 H), 1.7 (m, 1 H), 2.0–2.5 (m, 3 H), 3.05 (m, 2 H), 3.6 (m, 1 H), 5.8 (d, 1 H, $J$ = 15), 6.8 (m, 1 H) |
| **37c**[c] | 3,4-$(OCH_2O)C_6H_3CH(OH)$ | 105–108 ($CCl_4$) | 56 | 1660 | 1.0 (d, 6 H, $J$ = 6), 1.8 (m, 1 H), 3.15 (m, 3 H), 4.8–5.4 (m, 4 H), 5.75 (m, 1 H), 6.0 (s, 2 H), 6.02 (br s, 1 H), 6.9 (m, 3 H) |
| **38c** | 3,4-$(OCH_2O)C_6H_3CH(OH)$ | 130–131 ($CHCl_3$) | 28 | 1670, 1625 | 0.95 (d, 6 H, $J$ = 6), 1.75 (m, 1 H), 2.50 (m, 2 H), 3.0 (m, 2 H), 4.65 (m, 1 H), 5.15 (br s, 1 H), 5.90 (d, 1 H, $J$ = 16), 6.05 (s, 2 H), 6.95 (m, 3 H), 7.90 (br s, 1 H) |

[a] Anal. Calcd (Found) for **35a** ($C_{11}H_{21}NO$): C, 72.08 (72.70); H, 11.55 (12.30); N, 7.64 (7.22). **35b** ($C_{17}H_{25}NO$): C, 78.72 (78.91); H, 9.71 (9.55); N, 5.40 (5.37). **35c** ($C_{17}H_{25}NO_2$): C, 74.19 (73.90); H, 9.15 (9.44); N, 5.09 (5.22). **37a** ($C_{16}H_{21}NO_3$): C, 69.79 (69.61); H, 7.69 (7.74); N, 5.09 (5.29). **37b** ($C_{24}H_{47}NO_2$): C, 75.59 (75.68); H, 12.33 (12.21); N, 3.67 (3.88). **38b** ($C_{24}H_{47}NO_2$): C, 75.59 (75.43); H, 12.33 (12.22); N, 3.67 (3.53). **37c** ($C_{16}H_{21}NO_4$): C, 65.98 (66.01); H, 7.22 (7.48); N, 4.81 (5.14). **38c** ($C_{16}H_{21}NO_4$): C, 65.98 (65.88); H, 7.22 (7.47); N, 4.81 (5.14). [b] Highly unstable product. [c] Diasteriomeric mixture. [d] Known compound lit. mp 90–94 °C (Dwuma-Badu, D.; Ayim, J. S. K.; Dabra, T. T.; El Sohly, H. N.; El Sohly, M. A.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L., Jr. *Phytochemistry* **1976**, *15*, 822). [e] Starting material (30%) was recovered. [f] $J$ values are given in hertz.

Scheme III




bromide (entry 8). The dicuprated dienolate of **15**, generated by reaction of the corresponding dilithiated species with 2 equiv of CuI, provided mainly $\alpha$-alkylated product in reaction with benzyl bromide (entry 22) but gave roughly equal amounts of $\alpha$ and $\gamma$ isomers with isopropyl iodide and even methyl iodide (entries 12, 14). Synthetically useful $\gamma$ regioselectivity was observed with the allylic electrophiles (entries 16, 18, 20). Treatment of dilithiated species of **15** with *only 1 equiv* of CuI followed by alkylation with any of the electrophiles listed in Table III gave results identical with those observed when 2 equiv of CuI was used (see Experimental Section).[34] Pitzele and coworkers have made similar observations in reactions of dianions of unsaturated carboxylic acids.[21c]

All $\gamma$-product mixtures **14** and **17** obtained from **12** and **15**, respectively, showed a high $Z/E$ ratio (i.e., the predominance of the thermodynamically less stable isomer), independent of the use of lithiated or cuprated intermediates (Table II). For tertiary amide **12**, high $Z$ stereoselectivity was uniformly observed whereas for secondary amide **15**, the $\gamma$-$Z/E$ ratio was highest for methyl iodide (entry 12) and only slightly lower for allylic and benzylic halides (entries 18, 20, 22). Separation of pure $\gamma$-$Z$ isomers was carried out by column chromatography in several cases (footnote *e* in Table II); in general, however, $\gamma$-$Z/E$ isomer ratios were determined by NMR solvent shift studies (vide supra). Cope rearrangement of $\alpha$ product **16c** at 190–200 °C afforded $\gamma$ isomer **17c** as a 1:1 $Z/E$ mixture whereas the dimethyallyl analogue **16d** did not undergo rearrangement under identical conditions. It was established that $\gamma$-allylated products, e.g., **17c**, did not arise by a Cope rearrangement of the corresponding $\alpha$ isomer under the basic conditions of the reaction. Furthermore, it was shown that both lithiated and cuprated $\gamma$-$Z$ products (e.g., **17d**) did not undergo isomerization into the $\gamma$-$E$ isomers under the reaction conditions (see Experimental Section).

The reaction of cuprated **15** with 3,3-dimethylallyl bromide gave a complex mixture of products (Scheme III). In addition to the $\alpha$ (**16d**) and $\gamma$-$Z$ (**17d**) isomers which could be separated by careful column chromatography, there was obtained a three-component mixture consisting of the double bond isomer of the $\alpha$ product (**24**), the $\gamma$-$E$ isomer (**21**), and the transposed ($S_N2'$) $\gamma$ product (**22**). Compound **24** most likely arises by base-catalyzed rearrangement of the normal $\alpha$ product **16d** since it can be obtaned from the latter in quantitative yield under the conditions of the reaction. Identity was established by comparison of GLC retention times. The structure of **24** was assigned on the basis of its NMR spectrum (Table III) and hydrogenation to the tetrahydro derivative **23** which was also obtained by identical reduction of the $\alpha$ product (**16d**).

Further chromatography of the $\gamma$-$E$ (**21**), $\gamma$-$S_N2'$ (**22**), and rearranged $\alpha$ (**24**) product mixture provided a sample containing only **21** and **22**. Resolution of this mixture was achieved by preparative GLC. The $\gamma$-$E$ product (**21**) showed the expected differences in its NMR spectrum compared to that of the corresponding $\gamma$-$Z$ isomer (**17d**). The NMR spectrum of the $\gamma$-$S_N2'$ isomer and benzene-induced solvent shift data were fully consistent with the structure and $E$ stereochemistry represented by **22** (see Experimental Section).

Comparison of our data (Table II) with those reported by Katzenellenbogen and Crumrine for the alkylation of cuprated unsaturated esters[18b] and dicuprated unsaturated acids[21b,55] reveals some significant differences. Although cuprated unsaturated esters and amide **12** behave similarly toward methyl and benzyl halides (exclusive deconjugative $\alpha$-alkylation, entries 2, 10), a marked difference is observed in reactions of allylic halides. Thus cuprated unsaturated esters yield only $\alpha$ products with allyl and 3,3-dimethylallyl bromides, whereas cuprated amide **12** furnishes moderate to good $\gamma$ regioselectivity with these halides (entries 6, 8). In addition, reaction with a secondary halide yields a

(34) On the other hand, use of catalytic amounts (0.2 equiv) of CuI led to a 95:5 $\alpha/\gamma$ product ratio for the reactions of dilithiated **15** with allyl bromide and 3,3-dimethylallyl bromide. For contrast, see ref 57.

significant amount of γ product (entry 4).

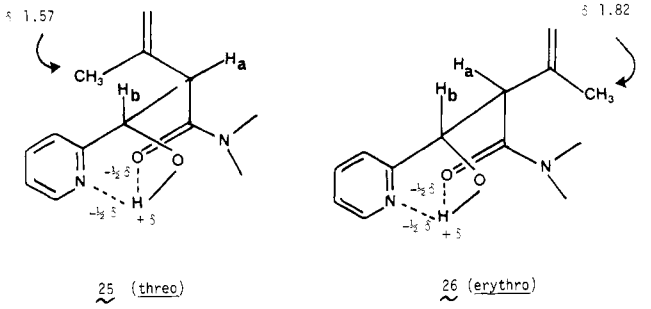
Both dicuprated senecioic acid[21b,55] and the corresponding amide **15** (or cuprated–lithiated species: vide supra; Table II, entries 16, 18, 20) exhibit high γ regioselectivity in reactions with allylic halides. Alkylation using geranyl bromide (entry 20) offers a slight advantage in that it provides a 10:90 α/γ product ratio compared to the 20:80 ratio achieved in the corresponding reaction of the dicuprated senecioic acid described by Pitzele and coworkers.[21c] However, substantial γ product is formed from the reaction of dicuprated **15** with benzyl bromide (entry 22), and this effect is more pronounced in the corresponding reactions with methyl iodide (entry 12) and isopropyl iodide (entry 14). In contrast, reactions of primary and benzylic halides with dicuprated senecioic acid (and other unsaturated acids) do not yield γ-alkylated products.[21b]

The major difference between the reactions of dicuprated amide **15** and the corresponding acid[21b,55] concerns γ-*Z*/*E* stereoselectivity. Good to excellent γ-*Z* stereoselectivity was observed in alkylation of **15** with all halides tested but particularly with 3,3-dimethylallyl, geranyl, and benzyl bromides (entries 18, 20, 22). In contrast, the reactions of dicuprated senecioic acid with allylic bromides result in almost equal amounts of γ-*Z*/*E* isomers [$CH_2$=$CHCH_2Br$ (50:50), MeC=$CHCH_2Br$ (45:55), geranyl bromide (54:46)] while, as noted earlier, benzyl bromide yields only α-alkylated product.[21b]

**Reaction of Metalated Senecioamides with Carbonyl Compounds (Table VI).** The reaction of dimetalated unsaturated carboxylic acids with carbonyl compounds has been shown to provide mixtures of α and γ products whose composition is diversely dependent on the structure of both reactants, the nature of cations associated with the dianion, and the temperature and solvent of the reaction.[21b,f,55] After some initial confusion and inadequate observation concerning this reaction, it has been generally demonostrated[21f] (within certain structural constraints) that (1) α-substituted products obtain from reactions carried out under kinetic control while the corresponding γ isomers result from thermodynamic control conditions, (2) α products may be dissociatively equilibrated to the more stable γ isomers under appropriate conditions, and (3) γ-substituted products usually show a high *Z*/*E* stereoselectivity. Points 2 and 3 have proved to be useful in the synthesis of insect juvenile hormone analogues[21a] and a simple acyclic sesquiterpenoid.[21b] The reaction of dilithiated (*E*)-β-methylcinnamanilide with benzophenone and 9-fluorenone, apparently the only previous study[25b] concerning the reaction of unsaturated amides with carbonyl compounds, gave only γ-substituted products under thermodynamic control conditions.[28]

The results of the reaction of lithiated *N*,*N*-dimethylsenecioamide (**18**) with aromatic and aliphatic aldehydes and ketones are summarized in Table VI. When effected at −78 °C for 10 s, the reaction of **18** with benzaldehyde produced a mixture of *erythro*- and *threo*-**19** diastereomers, favoring the threo isomer (Table VI, entry 1). At longer reaction times (5–15 min, conditions A), aromatic aldehydes (entries 2, 4, 6) gave α- and γ-substituted product mixtures, **19** and **20**, highly favoring the α isomer (α/γ ratio >80:20). In agreement with the general result for the stereoselectivity of the aldol condensation under thermodynamic control[31] and the observations of the present study (α products **6g** and **7e**, vide supra), the α isomer **19** consisted of an erythro–threo mixture in which the threo isomer predominated. However, *threo*-**19** is favored after only 10 s. Interpretation of these results in terms of kinetic vs. thermodynamic control without knowledge of the *Z*/*E* ratio of the dienolate of **18** is not meaningful. The reaction of lithiated **18** with aromatic aldehydes under conditions B (16 h) resulted in exclusive formation of γ-*Z* products **20** (entries 3, 5, 7). A similar trend in product composition has been observed in the condensation of the analogous dienolate anions of senecioic acid and ester with benzaldehyde except that the γ-*Z* product was isolated as the 5,6-dihydro-2-pyrone owing to facile lactonization.[18g,21f]

The reactions of **18** with pyridine-3-carboxaldehyde (Table VI, entries 12, 13), and *n*-butyraldehyde (entries 18, 19) provided similar results with variation in yields to that observed for benzaldehyde. In contrast, the pyridine-2- and -4-carboxaldehydes (entries 10, 11 and 14, 15) gave α products exclusively under both sets of conditions A and B. Reaction with cyclohexanone (entry 16) and benzophenone (entry 17) according to conditions A gave the α product in excellent and moderate yields, respectively. When the α products were subjected to conditions B or the reactants themselves were combined at 0 °C, no α or γ product was obtained, indicating the highly reversible nature of these reactions and the (presumed) polymerization of lithiated **18** under long reaction times. The α products obtained from the reaction with *n*-butyraldehyde (entries 18, 19) partially underwent retroaldol reaction to starting materials upon column chromatography. This behavior parallels that found for products derived from condensation of saturated amides with aromatic aldehydes.[35] In contrast to γ-*Z* stereoselectivity in the reactions of lithiated **18** with aromatic aldehydes, *n*-butyraldehyde provided the γ-*E* product **20d**. Spectral data for all products is given in Table V. The stereochemistry of the α-threo and α-erythro isomers of **19** was deduced from the differences in the $^1H$ NMR coupling constants of the diasteriomeric hydrogens[31b] while that of the γ isomer (**20**) was assigned on the basis of $^1H$ NMR data, including benzene-induced solvent shift studies (see Experimental Section). The erythro–threo pairs of products **19g,h**, **19i,j**, and **19k,l** derived from reaction of **18** with the pyridine aldehydes showed similar NMR coupling constants, $J_{a,b}$ for the respective diastereomeric hydrogens. The 3- and 4-pyridyl erythro and threo products, **19i,j** and **19k,l** could be differentiated on the basis of a somewhat larger $J_{a,b}$ (threo) = 7 Hz as compared with $J_{a,b}$ (erythro) = 5 Hz by following normal practice.[31b] However, the 2-pyridyl erythro–threo pair **19g,h** showed almost identical and low coupling constants of $J_{a,b}$ = 4–5 Hz. The abnormally low $J_{a,b}$ (threo) for **19h** could be attributed to a conformational preference **25** in which

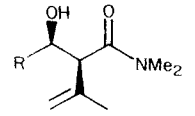



**25** (threo) **26** (erythro)

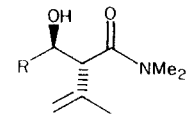
hydrogen bonding is stronger than normal, owing to the availability of two electronegative sites, the pyridine nitrogen and the amide carbonyl, between which OH hydrogen could exchange. Such interaction may also be

(35) von Schriltz, D. M.; Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 2610.

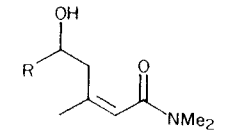
**Table V. Physical and Spectral Data of Products 19 and 20**




**19-Er**

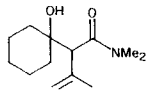
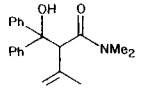



**19-T**




**(*Z*)-20**

| product[a-c] | R | mp, °C (solvent)[d] | IR[e] ($CHCl_3$), $cm^{-1}$ | NMR[h] ($CDCl_3$), δ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $CH_3C{=}C$ | $N(CH_3)_2$ | CHCO | CH(OH) | OH[f] | $C{=}CH_2$ | other |
| 19a-Er | Ph | 59–61 (hexane–$Et_2O$) | 3430, 1625 | 1.60 (s, 3 H) | 2.84 (s, 6 H) | 3.39 (d, 1 H, $J$ = 4) | 5.18 (d, 1 H, $J$ = 4) | 4.55 (br, 1 H) | 4.55, 4.85 (2 m, 2 H) | 7.23 (m, 5 H) |
| 19b-T | Ph | 114–114.5 ($Et_2O$) | 3450, 1625 | 1.58 (d, 3 H, $J$ = 0.5) | 2.87, 2.92 (2 s, 6 H) | 3.38 (d, 1 H, $J$ = 7) | 5.05 (d, 1 H, $J$ = 7) | 5.1 (br, 1 H) | 4.80, 4.98 (2 m, 2 H) | 7.25 (s, 5 H) |
| 19c-Er | 3,4-$(OMe)_2C_6H_3$ | 100–101.5 (hexane–$Et_2O$) | 3400, 1622 | 1.67 (s, 3 H) | 2.88 (s, 6 H) | 3.40 (d, 1 H, $J$ = 4) | 5.18 (d, 1 H, $J$ = 4) | 4.65 (br, 1 H) | 4.65, 4.98 (2 m, 2 H) | 3.87 (s, 6 H, 2 $OCH_3$), 6.75–7.02 (m, 3 H) |
| 19d-T | 3,4-$(OMe)_2C_6H_3$ | 118 | 3430, 1620 | 1.60 (br s, 3 H) | 2.92, 2.90 (2 s, 6 H) | 3.35 (d, 1 H, $J$ = 7) | 5.02 (d, 1 H, $J$ = 7) | 4.58 (d, 1 H, $J$ = 5) | 4.58–4.98 (m, 2 H) | 3.83, 3.85 (2 s, 6 H, 2 $OCH_3$), 6.77 (s, 2 H), 6.87 (br s, 1 H) |
| 19e-Er | 3,4-$(OCH_2O)C_6H_3$ | 93–95 | 3500, 1623 | 1.65 (br s, 3 H) | 2.92 (s, 6 H) | 3.37 (d, 1 H, $J$ = 4.5) | 5.15 (d, 1 H, $J$ = 4.5) | 4.66 (br s, 1 H) | 4.80 (br s, 1 H), 5.01 (m, 1 H) | 5.93 (s, 2 H, $OCH_2O$), 6.68–6.93 (br d, 3 H) |
| 19f-T | 3,4-$(OCH_2O)C_6H_3$ | 137–138 ($Et_2O$–$CH_2Cl_2$) | 3450, 1620 | 1.60 (br s, 3 H) | 2.90, 2.93 (2 s, 6 H) | 3.35 (d, 1 H, $J$ = 7) | 4.98 (d, 1 H, $J$ = 7) | 4.51 (d, 1 H, $J$ = 5) | 4.75 (br s, 1 H), 4.90 (m, 1 H) | 5.90 (s, 2 H, $OCH_2O$), 6.73 (s, 2 H), 6.83 (d, 1 H) |
| 19g-Er | 2-pyridyl | 76–77 | 3330, 1625 | 1.82 (s, 3 H) | 2.84, 2.98 (2 s, 6 H) | 4.06 (d, 1 H, $J$ = 5) | | 4.98 (m, 4 H) | | 8.55 (d, 1 H), 7.62 (m, 2 H), 7.20 (m, 1 H) |
| 19h-T | 2-pyridyl | 123–124 | 3400, 1622 | 1.58 (s, 3 H) | 2.95 (s, 6 H) | 3.88 (d, 1 H, $J$ = 4) | 5.25 (d, 1 H, $J$ = 4) | 6.3 (br s, H) | 4.88 (br s, 1 H), 4.55 (br s, 1 H) | 7.13 (m, 1 H), 7.58 (dd, 2 H, $J$ = 2, 6), 8.48 (br d, 1 H, $J$ = 5) |
| 19i-Er | 3-pyridyl | oil[g] | 3330, 1630 | 1.75 (s, 3 H) | 2.85, 3.00 (2 s, 6 H) | 3.46 (d, 1 H, $J$ = 5) | 5.30 (d, 1 H, $J$ = 5) | 4.66 (s, 1 H) | 5.02 (m, 1 H), 4.72 (s, 1 H) | 8.50 (m, 2 H), 7.72 (m, 1 H), 7.28 (m, 1 H) |
| 19j-T | 3-pyridyl | 127–128 | 3335, 1630 | 1.63 (br s, 3 H) | 2.93 (s, 6 H) | 3.38 (d, 1 H, $J$ = 7) | 5.07 (d, 1 H, $J$ = 7) | 4.5–5.0 (br, 1 H) | 4.70 (br s, 1 H), 4.88 (m, 1 H) | 7.20 (m, 1 H), 7.70 (m, 1 H), 8.47 (dd, 2 H, $J$ = 1.5, 5) |
| 19k-Er | 4-pyridyl | 98–99 | 3380, 1625 | 1.68 (s, 3 H) | 2.90 (s, 6 H) | 3.42 (d, 1 H, $J$ = 5) | 5.20 (d, 1 H, $J$ = 5) | 5.30 (br s, 1 H) | 4.53–5.07 (m, 2 H) | 7.27 (dd, 2 H, $J$ = 1, 6), 8.45 (dd, 2 H, $J$ = 1, 6) |
| 19l-T | 4-pyridyl | 128–129 | 3390, 1630 | 1.70 (s, 3 H) | 2.90 (s, 6 H) | 3.40 (d, 1 H, $J$ = 7) | 5.02 (masked d, 1 H, $J$ = 7) | 5.20 (br s, 1 H) | 4.75, 4.95 (2 br s, 2 H) | 7.27 (dd, 2 H, $J$ = 1, 6), 8.50 (dd, 2 H, $J$ = 1, 6) |
| 19m-T | PhCH=CH | 74–75 | 3410, 1625 | 1.78 (s, 3 H) | 2.95 (s, 6 H) | 3.25 (d, 1 H, $J$ = 6) | 4.63 (dd, 1 H, $J$ = 6, 6) | 4.27 (d, 1 H, $J$ = 6) | 4.90 (br s, 1 H), 5.0 (m, 1 H) | 6.20 (q, 1 H, $J$ = 6, 16), 6.67 (d, 1 H, $J$ = 16), 7.28 (m, 5 H) |
| 19n-Er | *n*-Pr | 44–46 (hexane–$Et_2O$) | 3400, 1620 | 1.83 (s, 3 H) | 2.95, 3.02 (2 s, 6 H) | 3.20 (d, 1 H, $J$ = 4) | 4.07 (m, 1 H) | 4.33 (d, 1 H, $J$ = 2) | 4.90 (br s, 1 H), 5.13 (m, 1 H) | 0.70–1.75 (m, 7 H) |
| 19o-T | *n*-Pr | 70 | 3360, 1620 | 1.78 (d, 3 H, $J$ = 0.5) | 2.98, 3.0 (2 s, 6 H) | 3.18 (d, 1 H, $J$ = 6) | 4.02 (m, 1 H) | 3.90 (br s, 1 H) | 4.92 (br s, 1 H), 5.03 (t, 1 H) | 0.70–1.67 (m, 7 H) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
|  **19p** | | 102–106 (bp at 0.2 mm) | 3360, 1620 | 1.88 (s, 3 H) | 3.0, 3.08 (2 s, 6 H) | 3.24 (s, 1 H) | | 5.68 (s, 1 H) | 5.06 (s, 1 H), 4.88 (s, 1 H) | 1.50 (br, 10 H) |
|  **19q** | | 145–146 (hexane–$Et_2O$) | 3200, 1645 | 1.55 (s, 3 H) | 2.83, 3.08 (2 s, 6 H) | 4.22 (s, 1 H) | | 6.93 (s, 1 H) | 4.63 (br s, 1 H), 4.85 (m, 1 H) | 7.03–7.55 (m, 10 H) |
| **20a** | Ph | 76–76.5 | 3300, 1640 | 1.93 (d, 1 H, $J$ = 0.5) | 3.0, 3.03 (2 s, 6 H) | | 4.90 (q, 1 H, $J$ =3, 11) | 6.98 (br s, 1 H) | 6.18 (br s, 1 H) | 2.32 (q, 1 H, $J$ = 3, 11), ~3.0 (masked s, 1 H), 7.18–7.65 (m, 5 H) |
| **20b** | 3,4-$(OMe)_2C_6H_3$ | 78–80 | 3200, 1645 | 1.93 (d, 1 H, $J$ = 0.5) | 2.98, 3.02 (2 s, 6 H) | | 4.75 (m, 1 H) | 6.65 (d, 1 H, $J$ = 6) | 6.10 (br s, 1 H) | 2.30 (q, 1 H, $J$ = 3, 12), 3.85, 3.90 (2 s, 6 H), 6.85 (br, 2 H), 7.03 (s, 1 H) |
| **20c** | 3,4-$(OCH_2O)C_6H_3$ | 99–100 ($Et_2O$–$CH_2Cl_2$) | 3340, 1648 | 1.93 (s, 3 H) | 3.0, 3.03 (2 s, 6 H) | | 4.82 (q, 1 H, $J$ = 3, 12) | 6.72 (d, 1 H, $J$ = 6) | 6.18 (br s, 1 H) | 2.30 (q, 1 H, $J$ = 3, 12), 5.97 (s, 2 H), 6.88 (br, 2 H), 7.05 (s, 1 H) |
| **20d** | *n*-Pr | oil[g] | 3340, 1645 | 1.95 (s, 3 H) | 3.06, 2.95 (2 s, 6 H) | | 3.80 (m, 1 H) | 4.68 (d, 1 H, $J$ = 6) | 6.15 (br s, 1 H) | 0.95 (m, 3 H, $CH_3$), 1.50 (m, 4 H, 2 $CH_2$), 2.22, 3.80 (overlapping m, 2 H, $CH_2CH$=) |

[a] T = threo and Er = erythro according to configurational representation shown above. [b] Anal. Calcd (Found) for **19a** ($C_{14}H_{19}NO_2$): C, 72.07 (71.79); H, 8.21 (8.40); N, 6.00 (6.09). **19b** ($C_{14}H_{19}NO_2$): C, 72.07 (72.08); H, 8.21 (8.26); N, 6.00 (5.87). **19c** ($C_{16}H_{23}NO_4$): C, 65.51 (65.34); H, 7.90 (8.11); N, 4.77 (4.70). **19d** ($C_{16}H_{23}NO_4$): C, 65.51 (65.37); H, 7.90 (8.19); N, 4.77 (4.66). **19e** ($C_{15}H_{19}NO_4$): C, 64.97 (65.25); H, 6.91 (7.04); N, 5.05 (5.04). **19f** ($C_{15}H_{19}NO_4$): C, 64.97 (64.86); H, 6.91 (7.04); N, 5.05 (4.85). **19g** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.84); H, 7.74 (7.92); N, 11.96 (11.95). **19h** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.34); H, 7.74 (7.68); N, 11.96 (12.01). **19i** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.39); H, 7.74 (7.90); N, 11.96 (12.00). **19j** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.38); H, 7.74 (7.87); N, 11.96 (11.64). **19k** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.96); H, 7.74 (7.84); N, 11.96 (11.70). **19l** ($C_{13}H_{18}N_2O_2$): C, 66.64 (66.96); H, 7.74 (7.79); N, 11.96 (11.86). **19m** ($C_{16}H_{21}NO_2$): C, 74.10 (74.51); H, 8.16 (8.58); N, 5.40 (5.54). **19n** ($C_{11}H_{21}NO_2$): C, 66.29 (66.14); H, 10.62 (10.67); N, 7.03 (6.98). **19o** ($C_{11}H_{21}NO_2$): C, 66.29 (66.61); H, 10.62 (10.81); N, 7.03 (6.86). **19p** ($C_{13}H_{23}NO_2$): C, 69.29 (69.00); H, 10.29 (10.54); N, 6.22 (6.44). **19q** ($C_{20}H_{23}NO_2$): C, 77.64 (77.70); H, 7.49 (7.75); N, 4.53 (4.24). **20a** ($C_{14}H_{19}NO_2$): C, 72.07 (72.30); H, 8.21 (8.32); N, 6.00 (5.97). **20b** ($C_{16}H_{23}NO_4$): C, 65.51 (65.21); H, 7.90 (8.08); N, 4.77 (4.36). **20c** ($C_{15}H_{19}NO_4$): C, 64.97 (65.25); H, 6.91 (7.04); N, 5.05 (5.08). **20d** ($C_{11}H_{21}NO_2$): C, 66.29 (66.01); H, 10.62 (10.84); N, 7.03 (6.89). [c] All compounds gave mass spectra with low relative intensity correct molecular ions ($M^+$) and base peaks at $m/e$ 127. [d] A hexane–$CH_2Cl_2$ mixture was used as the solvent of recrystallization unless otherwise indicated. [e] All $\nu \approx 3400$ $cm^{-1}$ due to OH absorption are very broad. [f] Highly concentration dependent absorption, exchangeable with $D_2O$ with concomitant simplification of absorption due to CH(OH). [g] An analytical sample was prepared by column chromatography. [h] $J$ values are given in hertz.

Table VI. Reactions of Senecioamide 18 with Carbonyl Compounds

| entry | electrophile | conditions (time)[a] | yield, % | products, % α (19) (erythro/threo) | γ (20) |
|---|---|---|---|---|---|
| 1 | PhCHO | A (10 s) | 95 | 70 (1/2.5) | 0 |
| 2 | PhCHO | A (15 min) | 78 | 80 (1/5) | 20 |
| 3 | PhCHO | B (16 h) | 72 | 0 | 100 |
| 4 | veratraldehyde | A (5 min)[b] | 84 | 88 (1/3) | 12 |
| 5 | veratraldehyde | B (5 h) | 75 | 0 | 100 |
| 6 | piperonal | A (5 min)[b] | 91 | 82 (threo only) | 18 |
| 7 | piperonal | B (5 h)[b] | 68 | 0 | 100 |
| 8 | PhCH=CHCHO | A (15 min) | 85 | 100 (threo only) | 0 |
| 9 | PhCH=CHCHO | B (16 h) | 60 | 100 (threo only) | 0 |
| 10 | pyridine-2-carboxaldehyde | A (15 min) | 73 | 100 (1/1) | 0 |
| 11 | pyridine-2-carboxaldehyde | B (16 h) | 55 | 100 (1/1) | 0 |
| 12 | pyridine-3-carboxaldehyde | A (1 h) | 79 | 100 (1/1.3) | 0 |
| 13 | pyridine-3-carboxaldehyde | B (16 h) | 78 | 15 (1/1) | 85 |
| 14 | pyridine-4-carboxaldehyde | A (15 min) | 80 | 100 (1/1.7) | 0 |
| 15 | pyridine-4-carboxaldehyde | B (16 h) | 60 | 100 (1/1) | 0 |
| 16 | cyclohexanone | A (5 min) | 91 | 94 | 6 |
| 17 | $Ph_2CO$ | A (5 min)[b] | 50 | 100 | 0 |
| 18 | *n*-PrCHO | A (5 min)[b] | 83 | 100 (1/2) | 0 |
| 19 | *n*-PrCHO | B (5 h)[b] | 78 | 13[c] | 87[d] |

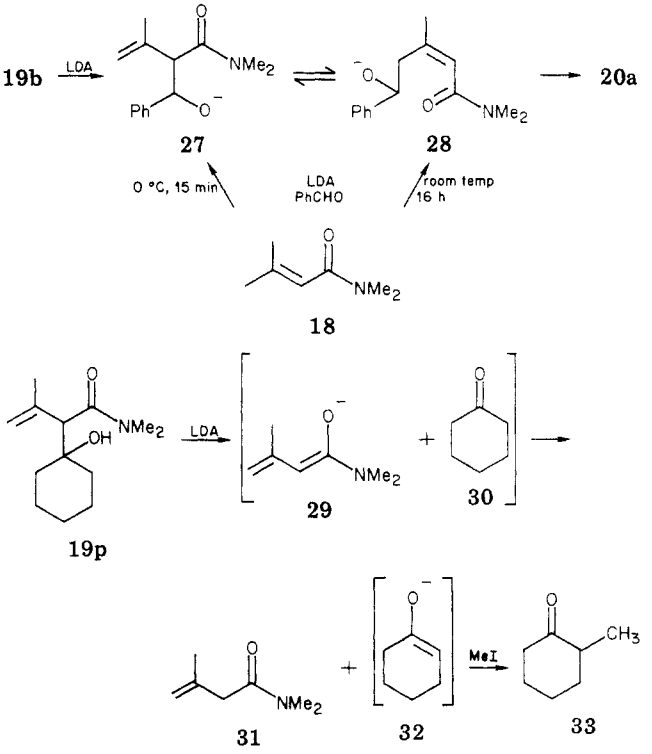
[a] See Experimental Section. [b] The aldehyde or ketone was added at −78 °C. [c] Diasteriomeric ratio was not determined. [d] γ-*E* isomer.

involved in the favored conformation **26** for the corresponding erythro isomer (**19g**). In agreement with expectation based on the anisotropic shielding effect of the pyridine ring, conformer **25** shows NMR absorption due to the methyl hydrogens of the isopropylidene group at higher field compared to that for conformer **26**. The stereochemical assignments of all isomeric pyridine aldehyde derived products are supported by the consistently lower melting points and higher chromatographic $R_f$ values of the erythro isomers compared to those of the threo isomers, properties which were generally observed for the corresponding diastereomeric pairs **19a,b**, **19c,d**, and **19e,f**.

The reaction of **18** with benzaldehyde was investigated in detail (Scheme IV), and it was shown that (1) the anion of the α product **27**, formed at −78 °C, underwent rearrangement to the corresponding γ species (**28**) under the conditions used for the formation of the γ product (**20a**) and (2) the anion **27**, generated separately from *threo*-**19b** at −78 °C, was similarly converted into the γ isomer (**20a**). Furthermore, it was observed that when a solution of the anion of the α product **19p**, formed at −78 °C, was treated with methyl iodide and allowed to warm to room temperature, 2-methylcyclohexanone (**33**) was obtained in addition to starting material and deconjugated amide **31**. These results demonstrate that the anion **27** is reversibly formed and that under longer reaction times and higher temperature it is tranformed irreversibly into the thermodynamically more stable **28**. The dissociation of the α anion of **19p** into separate components **29** and **30** is established by the isolation of **31** and **33** whose formation is explained by rapid proton exchange of **29** with the more acidic protons of cyclohexanone (**30**) at higher temperatures, yielding **31** and enolate **32**.

The contrasting behavior of the pyridine aldehydes compared to that of the other aromatic aldehydes in reaction with lithiated **18** (Table VI, entries 10–15) merits brief comment. Under conditions A which favor threo α products for aromatic aldehydes, the pyridine aldehydes yield the corresponding products with an erythro/threo ratio ≈ 1. Steric bulk factors being equal for the aromatic and the pyridine aldehydes, these results may reflect an unfavorable interaction between pyridine and amide nitrogen lone pairs in the preferred transition state leading to threo product. Under conditions B, the reaction of pyridine-3-carboxaldehyde clearly gives the γ-*Z* isomer as

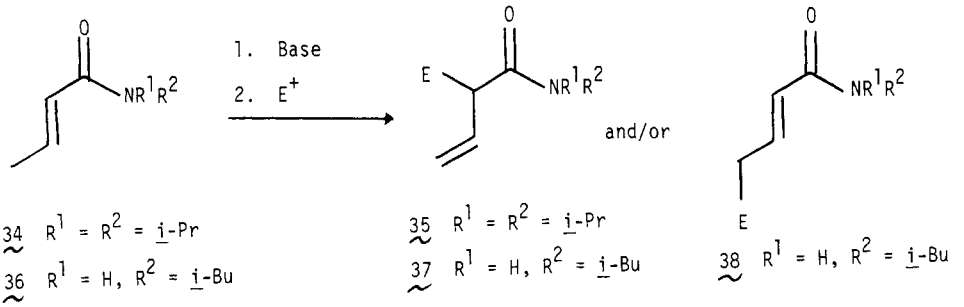
Scheme IV




the major product (entry 13), while the corresponding reactions with pyridine-2- and -4-carboxaldehydes provide the diastereomeric α product mixtures in somewhat decreased yields (entries 11, 15) compared to those observed under conditions A. This difference in behavior indicates a reluctance of the initally generated 2- and 4-pyridyl alkoxide α products to undergo retroaldol reaction compared to the corresponding reaction of the 3-pyridyl alkoxide. This may be a consequence of resonance effects which render greater stability to products resulting from nucleophilic attack on pyridine-2- and -4-carboxaldehydes compared to that of pyridine-3-carboxaldehyde.[36] The decrease in yields of α products in the former two cases

(36) Schofield, K. "Hetero-Aromatic Nitrogen Compounds"; Butterworths: London, 1967; p 311 ff.

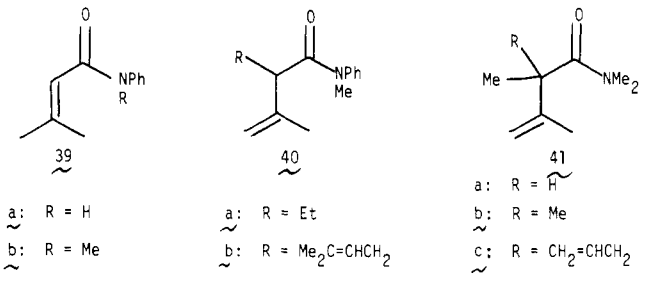
Scheme V




under conditions B compared to conditions A may be due to partial retroaldolization which allows the thus generated pyridine-2- and -4-carboxaldehydes to undergo a base-catalyzed Cannizzaro reaction, a reaction which is also known to be fast for these two aldehydes compared to pyridine-3-carboxaldehyde.[36]

**Alkylation of Metalated Crotonamides (Scheme V).** The alkylation of lithiated *N,N*-diisopropylcrotonamide (**34**) (Scheme V, Table VI) was less successful, requiring special procedures and workup owing to anion and product instabilities, respectively.[37] Nevertheless, moderate yields of $\alpha$ products **35** were obtained from reactions of **34** with MeI, $PhCH_2Br$, and PhCHO. On the other hand, good yields of mixtures of $\alpha$ and $\gamma$ products **37** and **38** were obtained from the condensation of dilithiated *N*-isobutylcrotonamide (**36**) with piperonyl bromide, *n*-hexadecanal, and piperonal. The $\gamma$ product **38a** is a member of the *Piper* group of alkaloids, isolated from *P. guineese* and named 3,4-dihydropiperlonguminine.[38] In all three cases studied, the low $\gamma$ regioselectivity could not be improved either by using thermodynamic control conditions or by addition of CuI, thus precluding efficient synthesis of **38a** and related alkaloids (see below).

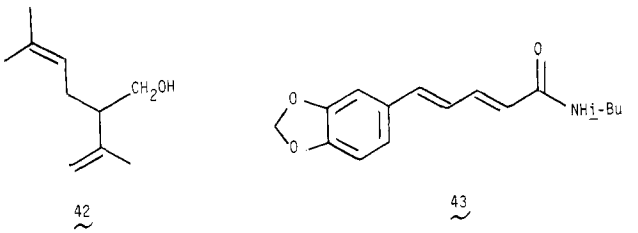
**N,$\alpha$- and $\alpha,\alpha$-Dialkylation.** Since tertiary amides offer advantages over secondary amides in some synthetic operations (e.g., see below), we subjected the dianion of *N*-phenylsenecioamide (**39**) to sequential one-pot ethylation and methylation. The deconjugated $\alpha$-ethyl-*N*-methyl amide **40a** was obtained in high yield, thus demonstrating the viability of this procedure.




A second alkylation of **41a** using LDA and the standard conditions could not be achieved. However, when lithium 2,2,6,6-tetramethylpiperidide (LiTMP)–TMEDA was used, alkylation proceeded smoothly with methyl iodide and allyl bromide to give high yields of the $\alpha,\alpha$-disubstituted products **41b** and **41c**, respectively.

**Synthesis of Lavandulol (42).** We have demonstrated the utility of the $\alpha$-regio- and *Z*-stereoselective prenylation reactions for the construction of terpenoid components such as (*Z,E*)-geranioic and (*Z,E*)-farnesoic amides (Table II, entries 18 and 20). That the $\alpha$-regioselective alkylation is also useful is shown by a short synthesis of lavandulol (**42**), an example of one of the classes of the irregular monoterpenoids.[39] Compound **40b**, obtained in excellent yield by $\alpha$-prenylation of *N*-methyl-*N*-phenylsenecioamide was reduced with lithium triethylborohydride, an excellent reagent introduced by Brown and co-workers[40] for the reduction of tertiary amides to primary alcohols, gave lavandulol directly in high yield.[41]

**Synthesis of Piperlonguminine (43).** The unsaturated amide functionality is the discerning feature of the *Piper* alkaloids[42] and the insecticidally active isobutylamides derived from plants of the Compositae and Rutaceae families.[43] A short route to the diene and triene isobutylamides using metalated, unsaturated amides appears to be thwarted by the observation that the model condensation of crotonamide **36** with *n*-hexadecanal (Table IV) proceeds with $\alpha$ regioselectivity even under thermodynamic control conditions. The reaction of **36** with piperonal leads to substantially greater amounts of $\gamma$ product **38c** ($\alpha/\gamma$ ratio of 2:1). Conversion of **38c** into the alkaloid piperlonguminine (**43**) was easily achieved by treatment




42 43

with mesyl chloride in pyridine. It is likely that other *Piper* alkaloids[42] and naturally occurring isobutylamides[43] and their analogues may be prepared via metalated unsaturated amides.

## Conclusions

We have demonstrated that metalated, $\beta,\beta$-disubstituted, unsaturated amides are useful synthons for C–C bond formation at the $\alpha$ and $\gamma$ sites (**44**). Predominant

(37) A further complication for **34** but not for **36** is the Michael addition of LDA since we have shown that this is a clean reaction for *N,N*-dimethylcrotonamide but not for *N*-methylcrotonamide.[29b]

(38) Dwuma-Badu, D.; Ayim, J. S. K.; Dabra, T. T.; El Sohly, H. N.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L., Jr. *Lloydia* **1976**, *39*, 60.

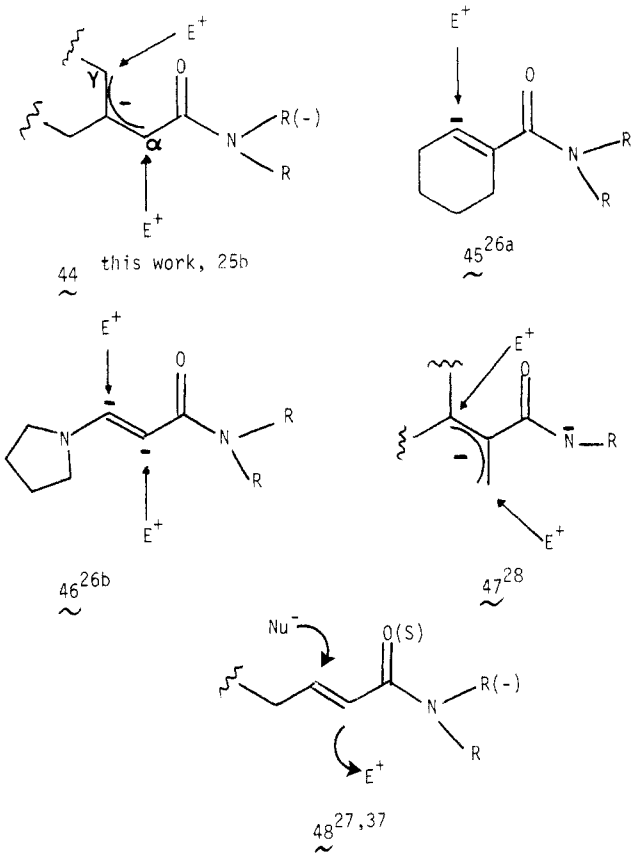
(39) Review: Thomas, A. F. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 2, pp 43–49. Recent synthesis: Bertrand, M.; Gil, G.; Viala, J. *Tetrahedron Lett.* **1977**, *1785*.

(40) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(41) The two-step reductive procedure which we reported previously[1] for the conversion of **40b** into **42** (60–73% overall yield) was subsequently found to be poorly reproducible and is therefore not recommended.

(42) Review: Atal, C. K.; Dhar, K. L.; Singh, J. *Lloydia* **1975**, *38*, 256. Recent isolation work: Smith, R. M. *Tetrahedron* **1979**, *35*, 437; Gupta, O. P.; Gupta, S. C.; Dhar, K. L.; Atal, C. K. *Phytochemistry* **1978**, *17*, 601; Addae-Mensah, I.; Torto, F. G.; Dimonyeka, C. I.; Baxter, I.; Sanders, J. K. M. *Ibid.* **1977**, *16*, 757.

(43) Jacobson, M. In "Naturally Occurring Insecticides"; Jacobson, M., Crosby, D. G., Eds.; Marcel Dekker: New York, 1971, p 137.




γ-alkylation, achieved via cuprated amide dienolates, has advantages in scope and greater regio- and stereoselectivity over the corresponding reaction of unsaturated acid dienolates.[21b,c,55] Our methodology allows the efficient preparation of stereochemically pure geranioic and farnesoic amide derivatives (**17d,f**) and, less significantly, the synthesis of irregular monoterpene systems **42** and amide alkaloids **38a** and **43**. In general, lithiated β,β-unsaturated amide dienolates are conveniently generated (0 °C to room temperature), are stable to self-condensation and 1,2- or 1,4-addition,[37] and undergo smooth α-alkylation in high yield. These properties recommend their complementary synthetic use with the alkylation of unsaturated nitriles[17] and esters,[18a] providing the amide functionality is compatible with further synthetic operations. Finally, the scope of the amide alkylation reaction is broadened by the availability of amide into acid, ester, aldehyde, ketone, amine,[44] and, most recently, thioamide[27] conversions.

Other recently developed methodologies for C–C bond formation using carbanions derived from unsaturated amides **45–48** attest to the increasing versatility of these intermediates in organic synthesis.

## Experimental Section

**General Methods.** Microanalyses were pefromed by A. B. Gygli, Baron Consulting Co., Heterocyclic Chemical Corp., and Guelph Chemical Laboratories Ltd. Melting points were determined on Mel-Temp and Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were measured on a Beckman IR-10 and Perkin-Elmer 180 instruments. Nuclear magnetic resonance spectra were recorded on Varian T-60, Perkin-Elmer R-12B, and Brucker WP-80 spectrometers in deuteriochloroform solution with $Me_4Si$ as an internal standard. Mass spectra were obtained on an ACI MS-30 double-beam, double-focussing spectrometer. Thin-layer and preparative layer chromatography were carried out by using Merck Precoated silica gel sheets 60-F-254 and with Merck silica gel GF-254 (Type G), respectively. Column chromatography was performed by using silica gel 60 (70–230 mesh). All chromatographic supplies were obtained from Brinkmann (Canada) LTD. Analytical gas–liquid chromatography (GLC) was effected on Varian Aerograph 1520 (6 ft × $^1/_8$ in. Ultrabond column) and F&M 810 (6 ft × $^1/_4$ in., 10% SE-30 column) chromatographs. Preparative GLC was carried out on a Varian Autoprep A-700 instrument equipped with a Carbowax column. THF and ether were dried over sodium with benzophenone as indicator and distilled immediately before use. *n*-Butyllithium, as a solution in hexane, diisopropylamine, tetramethylethylenediamine (TMEDA), and 2,2,6,6-tetramethylpiperidine were purchased from Aldrich Chemical Co. Diisopropylamine and TMEDA were distilled from sodium hydride and calcium hydride, respectively, and stored over 5A molecular sieves. Cuprous iodide, purchased from Fischer Scientific Co., was used without purification. All reactions were carried out under high-purity Linde nitrogen; reagents were injected through septum caps by using syringes. When used below, the phrase "standard workup" signifies that a given organic solution was quenched with water or 2 N HCl solution, dried ($Na_2SO_4$), and evaporated to dryness in vacuo.

**Preparation of Unsaturated Amides 4, 5, 12, 15, 18, 34, 36, and 39a. (Diethylphosphonoacetyl)-*o*-toluidide.** This compound was prepared by a modification of a literature method.[45] A mixture of chloroacetyl *o*-toluidide[46] (9.2 g, 50 mmol) and freshly distilled triethyl phosphite (8.4 g, 50 mmol) was stirred at 135 °C (oil bath temperature) for 5 h. The reaction mixture was allowed to cool to room temperature, and the crude product was recrystallized from ether to give the product: 10.5 g (70%); mp 77–78 °C; IR ($CHCl_3$) 3260, 1680, 1220, 1165, 1035 $cm^{-1}$; NMR ($CDCl_3$) δ 1.33 (t, 6 H, $J$ = 7 Hz), 2.30 (s, 3 H), 3.03 (d, 2 H, $J$ = 20 Hz), 4.13 (q, 2 H, $J$ = 7 Hz), 4.28 (d, 2 H, $J$ = 7 Hz), 7.0–7.4 (m, 3 H), 7.9 (m, 1 H), 8.7 (br s, 1 H). Anal. Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.53; H, 7.02; N, 4.88.

**(Cyclohexylideneacetyl)-*o*-toluidide (5).** This compound was obtained in 80% yield by the Witting reaction of (diethylphosphonacetyl)-*o*-toluidide with cyclohexanone according to a literature procedure;[47] mp 104–105 °C ($Et_2O$) (lit.[48] mp 105–106 °C).

All amides described below were prepared from the requisite acid chlorides and amines by the standard procedure.

***N,N*-Dimethylcyclohexylideneacetamide (4).** This amide was obtained in 70% yield; bp 98–102 °C (0.7 mm) [lit.[49] bp 118–122 °C (0.2 mm)].

***N,N*-Diisopropylsenecioamide (12).** This amide was prepared in 34% yield; bp 60–62 °C (0.2 mm). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.13; H, 11.58; N, 7.62.

***N*-Methylsenecioamide (15).** This amide was secured in 54% yield; mp 78–79 °C ($Et_2O$) [lit.[50] bp 145–146 °C (10 mm)].

***N,N*-Dimethylsenecioamide (18).** This amide was obtained in 94% yield; bp 50–52 °C (0.3 mm) [lit.[51] bp 28–30 °C (0.5–1.5 mm)].

***N,N*-Diisopropylcrotonamide (34).** This amide was prepared in 53% yield; bp 70 °C (1 mm). Anal. Calcd for $C_{10}H_{19}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.13; H, 11.58; N, 7.62.

***N*-Isobutylcrotonamide (36).** This amide was prepared in 82% yield; mp 67–68 °C ($Et_2O$). Anal. Calcd for $C_8H_{15}NO$: C, 67.60; H, 10.56; N, 9.86. Found: C, 67.48; H, 10.42; N, 9.89.

***N*-Phenylsenecioamide (39a).** This compound was obtained

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in 80% yield; mp 129–130 °C (lit.[52] mp 129–130 °C).

***N*-Methyl-*N*-phenylsenecioamide (39b).** This compound was obtained in 82% yield; bp 95–99 °C (0.6 mm) [lit.[53] bp 145–146 °C (13 mm)].

**Typical Procedures for Alkylation of Amides 4, 5, 12, 15, 34, 36. Alkylation of Lithiated Amides and 14. Procedure A.** A stirred solution of diisopropylamine (111 mg, 1.1 mmol) and compound **4** (167 mg, 1 mmol) in THF (5 mL) cooled in an ice–salt bath was treated with a solution of *n*-BuLi (1.5 M; 0.7 mL, 1.1 mmol) by the syringe-injection technique. The solution was stirred at room temperature for 1 h and then warmed to 30–35 °C for 0.5 h. The resulting yellow solution was cooled to 0 °C and methyl iodide (0.08 mL, 1.2 mmol) was injected. The reaction mixture was stirred at room temperature for 4 h, quenched with water, and processed in the normal manner to give, after chromatography (petroleum ether–ether, 80:20), 105 mg (58%) of compound **6a**, whose physical and spectral properties are recorded in Table I.

**Alkylation of Dilithiated Amides 5 and 15. Procedure B.** To a stirred solution of **5** (450 mg, 2 mmol) and TMEDA (6 mL, 4 mmol) in diethyl ether (5 mL) at room temperature was added a solution of *n*-BuLi (4.5 mmol). After 1.5 h, the yellow solution was treated with ethyl bromide (0.20 mL, 2.5 mmol), and stirring was continued for 1 h. The resulting colorless reaction mixture was quenched with water. Normal workup gave a colorless solid which was recrystallized to give pure product **7b**, shose physical and spectral data are given in Table I.

**Procedure C.** A solution of *n*-BuLi (2 mmol) was injected by syringe into a stirred, ice-cooled solution of **15** (113 mg, 1 mmol) and TMEDA (0.3 mL, 2 mmol) in THF (5 mL). The solution was stirred at room temperature for 2 h, cooled to 0 °C, and treated with methyl iodide (0.06 mL, 1 mmol). The reaction mixture was quenched by pouring it onto an ice–water sludge containing 2 N HCl. Normal workup followed by distillation afforded pure **16a** (see Table III for physical and spectral data).

**Alkylation of Cuprated–Lithiated and Dicuprated Amides 15.** The dilithiated species generated according to procedure C were treated with either 1 or 2 equiv of CuI and then alkylated with the appropriate electrophile. *It was found that identical results were observed in both cases for a variety of electrophiles.* Since the workup was more convenient (less inorganic precipitate) when 1 equiv of CuI was used, this set of conditions was generally adopted.

**Procedure D.** The yellow solution of the dilithiated species generated as described in procedure C from compound **15** (560 mg, 5 mmol) was cooled to −78 °C and treated with CuI (960 mg, 5 mmol). The yellow-orange heterogeneous mixture was stirred vigorously at −78 °C for 1 h. (Some reaction mixtures were gray, but this effect, unlike the observations on dicuprated dienolates of unsaturated acids,[21b] did not affect the yields.) Methyl iodide (0.32 mL, 5 mmol) was injected, resulting in a reddish brown or dark gray mixture which was allowed to warm to room temperature overnight. The black mixture was acidified (2 N HCl), $CH_2Cl_2$ was added, and the two-phase system was filtered through Celite to remove inorganic salts. The filtrate was separated, and the aqueous layer was extracted with several portions of $CH_2Cl_2$. The combined organic extract was treated by normal workup procedures to give 540 mg (80%) of a clean, colorless oil which showed the $\alpha$(**16a**)/$\gamma$(**17a**) and $\gamma$-*Z*/$\gamma$-*E*(**17a**) ratios listed in entry 12 of Table II. Separation of **16a** and **17a** was achieved by column chromatography (PhH–EtOAc–$CH_2Cl_2$, 1:2:2). $\gamma$-*Z* and $\gamma$-*E* isomer separation for **17a** was not possible; assignment of the ratio is based on benzene-induced solvent shift studies (see below).

**Alkylation of Crotonamides 34 and 36. Preparation of Compound 35c.** A cooled (ice–salt bath) solution of LDA (4 mmol) in THF (5–10 mL) was treated with neat amide **34** (683 mg, 4 mmol) under vigorous stirring. After further stirring at room temperature for 0.5 h, the yellow solution was cooled to −78 °C, and freshly distilled benzaldehyde (430 mg, 4 mmol) was introduced by dropwise addition. The temperature was allowed to rise to −5 °C (bath temperature) during 1 h, and the reaction mixture was quenched with ice-cold dilute HCl and worked up in the normal manner to yield, after chromatography ($Et_2O$–petroleum ether, 20:80), 464 mg (42%) of crystalline **35c**, whose physical and spectral properties are given in Table VI.

**Preparation of Compounds 37a and 38a.** *N*-Isobutylcrotonamide (**36**, 1 equiv) was treated with LDA (2 equiv) and piperonyl bromide (2 equiv) according to procedure A. A standard workup gave crude product which was resolved by column chromatography (silica gel; eluent $CH_2Cl_2$–acetone, 2:1) into $\alpha$ and $\gamma$ products **37a** and **38a**, whose physical and spectral properties are described in Table IV.

**Correlation of $\alpha$-Alkylated Products 7a–d with Saturated Amides 9a–d. Hydrogenation of 7a–d.** A solution of 250 mg (1 mmol) of compound **7a** in 25 mL of ethanol containing 25 mg of palladium on charcoal was reduced in a Paar apparatus to yield 231 mg (95%) of solid which upon recrystallization from EtOH–$H_2O$ gave colorless crystals of **9a**: mp 138–139 °C; IR ($CHCl_3$) 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.03–2.33 (m, including 1.23, d, $J$ = 7 Hz, and 2.28, s, 18 H), 6.87–7.30 (m, 4 H), 7.88 (br s, 1 H); mass spectrum, $m/e$ 245 ($M^+$). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.54; H, 9.03; N, 5.60. Found: C, 78.56; H, 9.03; N, 5.62.

Compounds **7b–d** were likewise hydrogenated to give the following products.

**9b**: mp 165–166 °C (EtOH–$H_2O$); 95% yield; IR ($CHCl_3$) 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.0–2.05 (m, 17 H), 2.28 (s, 3 H), 6.93–7.28 (m, 4 H), 7.92 (br s, 1 H); mass spectrum, $m/e$ 259 ($M^+$). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.59; H, 9.62; N, 5.22. Found: C, 78.57; H, 9.67; N, 5.25.

**9c**: mp 126–128 °C (EtOH–$H_2O$); 90% yield; IR ($CHCl_3$) 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.77–1.98 (br m, 18 H), 2.28 (s, 3 H), 6.93–7.30 (m, 4 H), 7.87 (br s, 1 H); mass spectrum, $m/e$ 273 ($M^+$). Anal. Calcd for $C_{18}H_{27}NO$: C, 79.01; H, 9.82; N, 5.37. Found: C, 79.01; H, 9.80; N, 5.27.

**9d**: mp 137–138 °C (EtOH–$H_2O$); 90% yield; IR ($CHCl_3$) 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.03–2.17 (br m, 15 H), 2.23 (s, 3 H), 2.93 (d, 2 H, $J$ = 7 Hz), 6.95–7.37 (m, 9 H), 7.83 (br s, 1 H); mass spectrum, $m/e$ 321 ($M^+$). Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.53; N, 4.35. Found: C, 82.10; H, 8.43; N, 4.30.

**Preparation of 8.** Hydrogenation of compound **5** as described above for **7a** gave after recrystallization from EtOH–$H_2O$ a 95% yield of **8**: mp 145–146 °C; NMR ($CDCl_3$) $\delta$ 0.78–1.97 (m, 11 H), 2.08–2.38 (m, 2 H), 2.27 (s, 3 H), 6.98–7.33 (m, 4 H), 7.82 (br s, 1 H); mass spectrum, $m/e$ 231 ($M^+$). Anal. Calcd for $C_{15}H_{21}NO$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.40; H, 9.77; N, 6.43.

**Alkylation of Compound 8.** A solution of *n*-BuLi (2.45 M in hexane, 4.5 mmol) was injected into a stirred solution of **8** (465 mg, 2 mmol) and TMEDA (6 mL, 4 mmol) in anhydrous ether (5 mL) at room temperature under nitrogen. After the mixture was stirred for 1.5 h, methyl iodide (0.16 mL, 2.5 mmol) was added. The yellow color was discharged to give an almost colorless solution which was stirred for 1 h and quenched with water. A normal workup gave 419 mg (85%) of crude product. Recrystallization from EtOH–$H_2O$ gave colorless crystals of **9a** (mp 138–139 °C) which was shown to be identical (melting point, mixture melting point, TLC, IR, NMR) with a sample obtained by reduction of **7a** as described above.

Similarly, alkylation of **8** with ethyl bromide, allyl bromide, and benzyl bromide gave **9b** (75%), **9c** [after hydrogenation (Pd/C) of the intermediate $\alpha$-allyl product: mp 85–86 °C, 23% yield overall], and **9d** (30%), respectively. These products were shown to be identical by criteria used for **9a** above with samples obtained by reduction of **7b–d**.

**Hydride Transfer Reaction of 5 with Benzaldehyde.** Amide **5** (458 mg, 2 mmol) in a mixture of dry ether (20 mL) and TMEDA (0.5 mL, 4 mmol) under a nitrogen atmosphere was treated with *n*-BuLi (4 mmol) in hexane solution at 0 °C. The mixture was stirred for 0.5 h and treated with benzaldehyde (0.42 mL, 4 mmol). The ice bath was removed, and stirring was continued for 0.5 h. A standard workup gave 705 mg of crude material which upon chromatography (silica gel, $Et_2O$–hexane eluent) gave 81 mg (38%) of benzyl alcohol (identified by GLC and NMR), 206 mg (45%) of starting amide **5**, and 253 mg (38%) of compound **10**: mp 121–122 °C (EtOH); IR ($CHCl_3$) 1688, 1640 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.60 (m, 4 H), 2.20 (m, 4 H), 2.35 (s, 3 H) 5.05 (s, 1 H), 5.90 (br s, 1 H), 7.0–8.2 (m, 9 H); mass spectrum, $m/e$ (relative intensity) 333 ($M^+$, 3), 228 (24), 107 (48), 105 (100). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 78.93; H, 7.02; N, 4.27.

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**Alkylation of Cuprated-Lithiated Dienolate of *N*-Methylsenecioamide (15) with 3,3-Dimethylallyl Bromide.** By use of the general procedure D described above, the reaction of **15** with 3,3-dimethylallyl bromide gave an oil [95% yield, bp 99–110 °C (0.25 mm)] which was chromatographed (silica gel; PhH–EtOAc, 1:10) to yield the following fractions in order of elution: fraction 1, $\alpha$-product **16d** (12%) which was shown to be identical (IR, NMR, GLC) with that obtained from the corresponding reaction of the dilithiated dienolate of **15**; fraction 2, $\gamma$-*Z* product **17d** (50%) which was characterizaed by IR, NMR, and mass spectra (Table III); fraction 3, a mixture of $\gamma$-*E* (**21**, 16%) and $S_N2'$ (**22**, 17%) isomers and rearranged $\alpha$ product **24** (5%).

**Rearranged $\alpha$ Product 24.** The structure of this product was proved by chemical correlation with the $\alpha$ product **16d** as follows. Compound **16d** (1 equiv) in THF (10 mL) was treated with *n*-BuLi (1.5 equiv) at room temperature, and the mixture was stirred for 3 h. A standard workup yielded **24**: 100% yield; mp 63–64 °C; identical GLC retention time (Ultrabond 10% SE-30) with a sample of **24** obtained from the reaction mixture.

Hydrogenation of **24** and **16d** over Pd/C in MeOH under STP conditions gave quantitatively the same tetrahydro derivative [**23**; mp 64–66 °C (EtOH–$H_2O$)] as established by spectral (IR, NMR) and GLC comparison. Anal. Calcd for $C_{11}H_{23}NO$: C, 71.24; H, 12.41; N, 7.56. Found: C, 71.16; H, 12.62; N, 7.61.

**$\gamma$-*E* (21) and $S_N2'$ (22) Products.** Further chromatography of the mixture of **21**, **22**, and **24** gave a sample containing only **21** and **22**. Separation was achieved by preparative GLC on Carbowax.

**$\gamma$-$S_N2'$ Product 22**: oil; IR ($CHCl_3$) 1630 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.03 (s, 6 H), 2.08 (s, 2 H), 2.13 (d, 3 H, $J$ = 1 Hz), 2.81 (d, 3 H, $J$ = 5 Hz), 4.80 (dd, 2 H, $J$ = 1, 4 Hz), 5.4–6.2 (m, 3 H). The benzene-induced solvent shift parameters $\delta_{(Z)\text{-Me}}$ ($C_6D_6$) (=2.13 ppm) and $\delta_{CH_2}$ ($C_6D_6$) (=2.00 ppm) were consistent with the *E* stereochemical assignment. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.50; N, 7.41. Found: C, 72.60; H, 10.69; N, 7.47.

**$\gamma$-*E* Product 21**: oil; IR ($CHCl_3$) 1635 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.60 (s, 3 H), 1.68 (s, 3 H), 2.15 (m, 7 H), 2.83 (d, 3 H, $J$ = 5 Hz), 5.05 (m, 1 H), 5.35 (m, 1 H), 5.50 (s, 1 H). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.50; N, 7.41. Found: C, 73.04; H, 10.80; N, 7.19.

**Control Experiments. Stability of $\alpha$ Product 16c to Rearrangement into $\gamma$ Product 17c.** Compund **16c** (210 mg, 1.4 mmol) dissolved in a mixture of THF (10 mL) and TMEDA (0.3 mL, 2 mmol) was treated with a solution of *n*-BuLi (2.8 mmol) at room temperature and the mixture was stirred for 24 h. A standard workup gave a product which was shown to be identical (NMR, GLC) with starting material (100% recovery).

**Stability of Lithiated and Cuprated $\gamma$-*Z* Product 17d to Isomerization into the Corresponding $\gamma$-*E* Product.** Product **17d** (93 mg, 0.5 mmol) dissolved in a mixture of THF (10 mL) and TMEDA (0.08 mL, 0.5 mmol) was treated with a solution of *n*-BuLi (0.5 mmol) and the mixture allowed to stir at room temperature for 0.5 h. A standard workup gave unreacted **17d** (95%, GLC pure).

In a second experiment, the solution of lithiated **17d** prepared as above was cooled to −78 °C and, after being stirred for 15 min, was treated with CuI (90 mg, 0.5 mmol). The reaction mixture was allowed to warm slowly to room temperature and processed in the standard manner to give unchanged **17d** (97%, GLC pure).

**Cope Rearrangement of Compound 16c.** The $\alpha$-allylsenecioamide **16c** (153 mg, 1 mmol) was thermolyzed at 190–200 °C under nitrogen for 18 h. A normal workup afforded 15% of starting material and 75% of $\gamma$-product **17c** (*Z*/*E* ratio of 1:1 by GLC).

**Assignment of *Z*/*E* Stereochemistry to $\gamma$ Products 14 and 17.** In general agreement with results observed for $\alpha,\beta$-unsaturated ketones,[33] *N*-methylsenecioamide (**15**) shows the following benzene-induced solvent shifts for the (*E*)- and (*Z*)-$\beta$-Me signals: $\delta_{(E)\text{-Me}}$ ($CDCl_3$) 1.85, $\delta_{(E)\text{-Me}}$ ($C_6D_6$) 1.60, $\delta_{(Z)\text{-Me}}$ ($CDCl_3$) 2.13, $\delta_{(Z)\text{-Me}}$ ($C_6D_6$) 2.23. Similar solvent shifts [$\Delta\delta_{(E)\text{-Me}}$ ($CDCl_3$–$C_6D_6$) $\simeq$ 0.25 ppm (upfield) and $\Delta\delta_{(Z)\text{-Me}}$ ($CDCl_3$–$C_6D_6$) $\simeq$ 0.10 ppm (downfield)] were observed in comparisons of $\beta$-Me signals of products **14** and **17** either as *Z*/*E* mixtures or as the respective pure components, e.g.: (*Z*)-**17a**, $\delta_{(E)\text{-Me}}$ ($CDCl_3$) 1.81, $\delta_{(E)\text{-Me}}$ ($C_6D_6$) 1.58; (*E*)-**17a**, $\delta_{Z\text{-Me}}$ ($CDCl_3$) 2.15, $\delta_{(Z)\text{-Me}}$ ($C_6D_6$) 2.24.

**Reaction of Senecioamide 18 with Carbonyl Compounds (Table VI). Typical Conditions A.** To a stirred solution of the anion of *N*,*N*-dimethylsenecioamide (**18**, 82 mmol) prepared as described in procedure A above at −5 °C was added dropwise a solution of freshly distilled benzaldehyde (82 mmol) in THF (200 mL). The mixture was vigorously stirred for 5 min and quenched with a saturated solution of ammonium chloride (1 mL). A standard workup followed by fractional crystallization of the crude product from ether gave the pure threo isomer **19b** (10.50 g). The mother liquor was evaporated to dryness, and the residue was chromatographed (silica gel, $CH_2Cl_2$–hexane eluent) to give in order of elution the $\gamma$ product **20a** (2.50 g) and the erythro isomer **19a** (2.50 g). The physical and spectroscopic properties of all products are given in Table V.

**Typical Conditions B.** A stirred solution of the anion of compound **18** (82 mmol) prepared as above was treated with benzaldehyde (82 mmol) at −5 °C, and the mixture was allowed to warm to room temperature overnight. A standard workup followed by recrystallization gave the $\gamma$ product **20a** (13.55 g) whose physical and spectral data are given in Table V.

**Conversion of $\alpha$ Products 19a,b into $\gamma$ Product 20a.** A stirred solution of LDA (1 mmol) in THF (10 mL) cooled to 0 °C was treated with a solution of the crude diastereomeric mixture of the $\alpha$-product **19a,b** (233 mg, 1 mmol) in THF (2 mL). The mixture was stirred at room temperature for 20 h and worked up in the standard manner to give crude material (206 mg) which upon chromatography (silica gel, $CH_2Cl_2$–hexane (1:4) eluent) gave the following fractions: 52 mg of a mixture of deconjugated amide **31** [NMR ($CDCl_3$) $\delta$ 1.90 (s, 3 H), 3.0 (s, 6 H), 3.12 (s, 2 H), 4.85 (m, 2 H)], benzaldehyde, benzyl alcohol (identified by GC), 30 mg (13%) of the $\alpha$ product mixture **19a,b**, 102 mg (44%) of the $\gamma$ product **20a**.

A qualitatively similar result was obtained when the reaction mixture from typical conditions A was allowed to stir at room temperature overnight.

**Retroaldolization of $\alpha$ Product 19p. Formation of 2-Methylcyclohexanone (33).** To a stirred solution of LDA (1.5 mmol) in THF (15 mL) was added a solution of compound **19p** (326 mg, 1.45 mmol) in THF (5 mL). Methyl iodide (1 mL, 1.6 mmol) was then injected, and the mixture was stirred and allowed to warm to room temperature overnight. A standard workup gave crude product (290 mg) which was shown to consist of starting amide **19p** (80%) and a mixture (20%) of deconjugated amide **31** and 2-methylcyclohexanone (**33**), identified by GC and NMR comparison with authentic materials.

**Dialkylation. Preparation of *N*-Methyl-*N*-phenyl-2-isopropenylbutyramide (40a).** To a stirred solution of LDA (40 mmol) in THF (20 mL) cooled in an ice–salt bath was added a solution of *N*-phenylsenecioamide (**39a**; 3.30 g, 20 mmol) in THF (5 mL). The solution was stirred at room temperature for 1.5 h during which time it developed a deep orange color. It was cooled to 0 °C, and ethyl bromide (3.18 mL, 20 mmol) was added over 15 min. After being stirred at room temperature for 1.5 h, the resulting yellow reaction mixture was again cooled to 0 °C and treated with methyl iodide (1.2 mL, 20 mmol). The yellow color was discharged, and a colorless precipitate appeared. Stirring overnight at room temperature followed by a normal workup gave crude material which upon chromatography afforded 3.58 g (86%) of **40a** as a colorless oil: bp 110–115 °C (1.5 mm); IR (neat) 1660 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.79 (t, 3 H, $J$ = 7 Hz), 1.62 (br s, 3 H), 1.70 (m, 2 H), 2.90 (t, 1 H, $J$ = 7 Hz), 3.27 (s, 3 H), 4.56, 4.75 (2 br s, 2 H), 7.32 (m, 5 H); mass spectrum, $m/e$ 217 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.69; H, 8.48; N, 6.50.

**Preparation of *N*,*N*,2,2,3-Pentamethyl-3-butenamide (41b).** To a vigorously stirred solution of 2,2,6,6-tetramethylpiperidine (0.60 mL, 5 mmol) and TMEDA (0.76 mL, 5 mmol) in THF (20 mL) cooled to −20 °C was slowly added a solution of *n*-BuLi (2.5 M in hexane; 2.0 mL, 5 mmol). After being stirred at this temperature for 10 min, a solution of compound **41a** (0.705 g, 5 mmol) in THF was added dropwise, and the solution was stirred at room temperature for 0.5 h and then at 50 °C for 10 min to ensure complete anion formation. It was then cooled to −20 °C and treated with methyl iodide (0.48 mL, 8 mmol). The reaction mixture was stirred at room temperature for 3 h and processed in the normal manner to give crude material which upon dis-

tillation gave 0.684 g (88%) of pure **41b**: bp 63 °C (1.5 mm); IR (neat) 1635 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.35 (s, 6 H), 1.71 (s, 3 H), 2.98 (s, 6 H), 4.90 (s, 2 H); mass spectrum, *m/e* 155 ($M^+$). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.23; H, 10.81; N, 9.23.

**Preparation of *N*,*N*,2,5-Tetramethyl-2-isopropenyl-4-hexenamide (41c).** By use of the same scale (5 mmol) and workup conditions similar to those described for the preparation of **41b** there was obtained 0.840 g (80%) of product **41c**: bp 100–102 °C (0.1 mm); IR (neat) 1635 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.28 (s, 3 H), 1.61 (s, 6 H), 1.70 (s, 3 H), 2.40 (br d, 2 H), 3.0 (s, 6 H), 4.72–5.22 (m, 3 H); mass spectrum, *m/e* 209 ($M^+$). Anal. Calcd for $C_{13}H_{23}NO$: C, 74.56; H, 11.07; N, 6.69. Found: C, 74.03; H, 10.87; N, 6.78.

**Synthesis of Lavandulol (42). *N*,5-Dimethyl-*N*-phenyl-2-isopropenyl-4-hexenamide (40b).** Compound **40b** was prepared in 93% yield according to typical procedure A and showed bp 104–106 °C (0.06 mm); IR ($CHCl_3$) 1660 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.60 (m, 9 H), 2.40 (m, 2 H), 2.95 (m, 1 H), 3.25 (s, 3 H), 4.60 (m, 2 H), 5.0 (m, 1 H), 7.20 (m, 5 H); mass spectrum, *m/e* (relative intensity) 257 ($M^+$, 16), 107 (100). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.38; H, 8.95; N, 5.45. Found: C, 79.42; H, 9.12; N, 5.31.

**Lavandulol (42).** A solution of compound **40b** (514 mg, 2 mmol) in THF (10 mL) was slowly added to a THF solution of lithium triethylborohydride (5 mL, 4.4 mmol) cooled to 0 °C. The mixture was allowed to warm to room temperature, and stirring was continued for 18 h. After addition of water (3 mL) and aqueous 3 N HCl (4 mL), the reaction mixture was evaporated to dryness in vacuo, and the residue was extracted with ether. The extract was dried ($Na_2SO_4$) and evaporated to dryness to give 283 mg (93%) of lavandulol (**42**) as a sweet-smelling oil: bp 38–40 °C (0.05 mm) [lit.[54] bp 85–94 °C (12 mm)]; IR ($CCl_4$) 3420, 1640, 885 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.60 (m, 9 H), 1.82 (s, 1 H, $D_2O$ exch), 2.10 (m, 2 H), 2.40 (m, 1 H), 3.50 (d, 2 H, $J$ = 6 Hz), 4.80 (m, 2 H), 5.10 (m, 1 H); mass spectrum, *m/e* (relative intensity) 154 ($M^+$, 4), 127 (60), 83 (41), 69 (100).

**Synthesis of Piperlonguminine (43).** The $\gamma$-hydroxy amide **38c** (291 mg, 1 mmol) in pyridine (4 mL) was treated with methanesulfonyl chloride (1.5 mL, 2 mmol), and the reaction mixture was stirred at room temperature overnight. A normal workup provided 230 mg (84%) of piperlonguminine (**43**): mp 167–168 °C (lit.[38] mp 166–168 °C); IR ($CHCl_3$) 1645, 1615 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.0 (d, 6 H, $J$ = 6 Hz), 1.9 (m, 1 H), 3.3 (m, 2 H), 6.1 (s, 2 H), 6.15 (d, 1 H, $J$ = 15 Hz), 6.7–7.1 (m, 4 H), 7.53 (dd, 1 H, $J$ = 7, 15 Hz), 7.60 (dd, 1 H, $J$ = 7, 14 Hz).

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**Registry No.** **4**, 65378-67-8; **5**, 67986-39-4; **6a**, 67986-40-7; **6b**, 67986-41-8; **6c**, 76756-71-3; **6d**, 67986-42-9; **6e**, 67986-43-0; **6f**, 76756-72-4; *threo*-**6g**, 67986-51-0; *erythro*-**6g**, 67986-44-1; **6h**, 67986-45-2; **6i**, 67986-46-3; **7a**, 67986-47-4; **7b**, 76756-73-5; **7c**, 76756-74-6; **7d**, 67986-49-6; *threo*-**7e**, 67986-52-1; *erythro*-**7e**, 67986-50-9; **8**, 40748-54-7; **9a**, 76756-75-7; **9b**, 76756-76-8; **9c**, 76756-77-9; **9d**, 76756-78-0; **10**, 76756-79-1; **12**, 15745-04-7; **13a**, 76756-80-4; **13b**, 76756-81-5; **13c**, 76756-82-6; **13d**, 76756-83-7; **13e**, 76756-84-8; **14a**, 76756-85-9; (*E*)-**14b**, 76756-86-0; (*Z*)-**14b**, 76756-87-1; (*E*)-**14c**, 76756-88-2; (*Z*)-**14c**, 76756-89-3; (*E*)-**14d**, 76756-90-6; (*Z*)-**14d**, 76756-91-7; **15**, 1189-04-4; **16a**, 76756-92-8; **16b**, 76756-93-9; **16c**, 76756-94-0; **16d**, 76756-95-1; **16e**, 76756-96-2; (*E*)-**16f**, 76756-97-3; (*E*)-**17a**, 76756-98-4; (*Z*)-**17a**, 76756-99-5; (*E*)-**17b**, 76757-00-1; (*Z*)-**17b**, 76757-01-2; (*E*)-**17c**, 76757-02-3; (*Z*)-**17c**, 76757-03-4; (*E*)-**17d**, 76757-04-5; (*Z*)-**17d**, 76757-05-6; (*E*)-**17e**, 76757-06-7; (*Z*)-**17e**, 76757-07-8; (*E*,*E*)-**17f**, 75757-08-9; (*Z*,*E*)-**17f**, 76757-09-0; **18**, 42902-94-3; **19a**, 76757-10-3; **19b**, 76757-11-4; **19c**, 76757-12-5; **19d**, 76757-13-6; **19e**, 76757-14-7; **19f**, 76757-15-8; **19g**, 76757-16-9; **19h**, 76757-17-0; **19i**, 76757-18-1; **19j**, 76757-19-2; **19k**, 76757-20-5; **19l**, 76757-21-6; **19m**, 76757-22-7; **19n**, 76757-23-8; **19o**, 76757-24-9; **19p**, 76757-25-0; **19q**, 76757-26-1; **20a**, 76757-27-2; **20b**, 76757-28-3; **20c**, 76757-29-4; **20d**, 76757-30-7; **22**, 76757-31-8; **24**, 76757-32-9; **31**, 19435-60-0; **33**, 583-60-8; **34**, 56209-39-3; **35a**, 24560-67-6; **35b**, 76757-33-0; **35c** (isomer 1), 76757-34-1; **35c** (isomer 2), 76757-35-2; **36**, 71256-94-5; **37a**, 76757-36-3; **37b** (isomer 1), 76757-37-4; **37b** (isomer 2), 76757-38-5; **37c** (isomer 1), 76757-39-6; **37c** (isomer 2), 76757-40-9; **38a**, 76757-41-0; **38b**, 76757-42-1; **38c**, 76757-43-2; **39a**, 13209-80-8; **39b**, 20886-47-9; **40a**, 76757-44-3; **40b**, 67986-78-1; **41a**, 67986-53-2; **41b**, 76757-45-4; **41c**, 76757-46-5; **42**, 498-16-8; **43**, 5950-12-9; ethyl bromide, 74-96-4; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; benzaldehyde, 100-52-7; 3,3-dimethylallyl bromide, 870-63-3; (diethylphosphonoacetyl)-*o*-toluidide, 40748-62-7; veratraldehyde, 120-14-9; piperonal, 120-57-0; pyridine-2-carboxaldehyde, 1120-60-4; pyridine-3-carboxaldehyde, 500-22-1; pyridine-4-carboxaldehyde, 872-85-5; cyclohexanone, 108-94-1; MeI, 74-88-4; *i*-PrI, 75-30-9; $MeC(Cl)=CHCH_2Cl$, 926-57-8; PhSeBr, 34837-55-3; (*Z*)-$CH_2=CHC(Me)_2CH_2C(Me)=CHCON(i\text{-}Pr)_2$, 68473-06-3; (*E*)-$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2Br$, 6138-90-5; $PhCH=CHCHO$, 104-55-2; $Ph_2CO$, 119-61-9; *n*-PrCHO, 123-72-8.

(54) Brack, K.; Schinz, H. *Helv. Chim. Acta* **1951**, *34*, 2009.

(55) **Note Added in Proof.** For a further comprehensive study of dicuprated dienolates of unsaturated carboxylic acids, see: Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239.

(56) **Note Added in Proof.** In comparison, the aldol condensation of $\alpha$-metalated thioamides is highly diastereoselective: Tamara, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806.

(57) **Note Added in Proof.** Savu and Katzenellenbogen[55] have observed that addition of 0.1 equiv of CuI to the dilithiated dienolate of tiglic acid is sufficient to effect 90% $\gamma$-alkylation. They also observed that $CuBr\cdot SMe_2$ gives higher $\gamma$-regioselectivity than CuI. We have found that the use of 1 or 2 equiv of $CuBr\cdot SMe_2$ [or $CuI\cdot P(OEt)_3$] on the dienolate of **15** does not significantly change the $\alpha/\gamma$ alkylation ratio from that observed with CuI. Majewski, M.; Snieckus, V., unpublished results.