Synthesis of Pyrethroid Amides via Epoxy Amide Cyclization[1]

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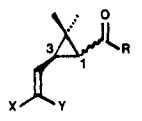
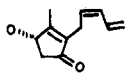
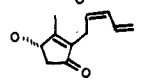
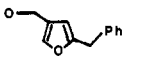
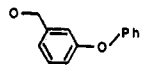
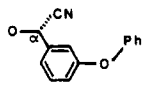
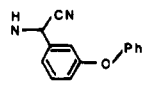
Two new syntheses of pyrethroid amides have been developed. In the first (Scheme II), unsaturated amide **8**, obtained by Claisen–Eschenmoser rearrangement of **7**, is converted into the unisolable epoxide **9** which upon treatment with LDA yields a mixture of *cis*- and *trans*-cyclopropane amides **10a** and **10b** in a ratio of 1:3. Dehydration of **10b** with $Ph_2S[OC(CF_3)_2Ph]_2$ (Martin's reagent) affords pyrethroid amide **12**—while the same reagent on **10a** yields only the bicyclic lactone **13**. In the second approach (Scheme IV), conjugate addition of 2-lithio-1,3-dithiane to senecioic acid provides **19** in an unexpected reaction which may have a broader synthetic application. Compound **19** is converted into **21** and thence into epoxide **22** which undergoes LDA-mediated cyclization to give *cis*- and *trans*-cyclopropane amides **23a** and **23b** in a ratio of 1:1. Oxidation of **23a** and **23b** separately to **24a** and **24b** followed by Wittig reaction provides the pyrethroid amides **25a** and **25b**, respectively. Compounds **8**, **10b**, and **12** showed insignificant insecticidal activity.

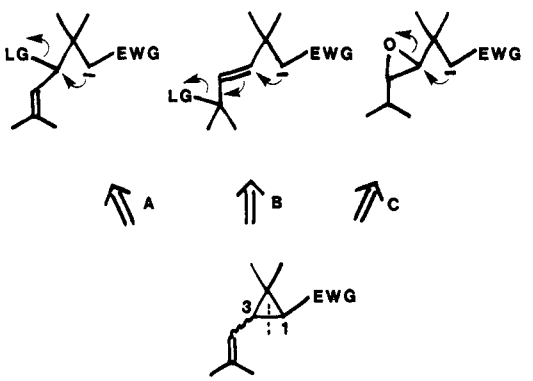
Pyrethrum, the dried powder of the daisy-like *Chrysanthemum* species has been used as an insecticide since ancient times. Soon after the structural elucidation of the active components, pyrethrin I (**1**) and II (**2**),[2] synthetic



		R	X	Y	C_1-C_3	Activity to Housefiles[8]
1	Pyrethrin I		Me	Me	trans	2
2	Pyrethrin II		CO_2Me	Me	trans	
3	Bioresmethrin (1R, 3S)		Me	Me	trans	100
4	Permethrin (1R,S; 3R,S)		Cl	Cl	trans	90
5	Decamethrin (1R, 3R, αS)		Br	Br	cis	1900
6			Me	Me	trans	inactive

analogues were prepared[2] which proved to be of superior activity compared to the natural substances but which, owing to poor photostability, were not extensively commercially developed. Systematic investigations by Elliot, Janes, and co-workers culminated in the late 1960's in the discovery of synthetic pyrethroids which showed remarkable environmental stability and bioactivity against a spectrum of insect types and yet low mammalian toxicity.[3] These discoveries triggered intense synthetic activity[4,5]

Scheme I



LG = Leaving group, EWG = Electron-withdrawing group

which resulted in the development of a new class of insecticides whose impact is already viewed[4] as having technical and economic significance comparable to that of the organophosphorus and carbamate insecticides. Its most prominent members bioresmethrin (**3**), permethrin (**4**), and decamethrin (**5**) are in large-scale commercial production and world-wide use.[6] The highly specific dependence of activity on absolute stereochemistry and the urgent need for new products to overcome already detected resistance[7] challenges the imagination of synthetic chemists

(1) Part of this work has appeared in preliminary form: Majewski, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 1343.

(2) Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 177, 201, 212, 236, 245, 390, 448.

(3) Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.

(4) For an excellent review, including reference to the patent literature, see: Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703.

(5) For recent work, see: Mulzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63. Torii, S.; Inokuchi, T.; Oi, R. *J. Org. Chem.* **1983**, *48*, 1944. DeVos, J. M.; Krief, A. *Tetrahedron Lett.* **1983**, *24*, 103. De Vos, M.; Krief, A. *J. Am. Chem. Soc.* **1982**, *104*, 4282. Ho, T. L.; Din, Z. U. *Synth. Commun.* **1982**, *12*, 257. Franck-Neumann, M.; Miesch, M. *Tetrahedron Lett.* **1982**, *23*, 1409. Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Ibid.* **1982**, *23*, 685. Franck-Newmann, M.; Martina, D.; Heitz, M. P. *Ibid.* **1982**, *23*, 3493. Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1982**, 2244. Genet, J.-P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, *23*, 5027. Johnson, W. M. P.; Holan, G. *Aust. J. Chem.* **1981**, *34*, 2461. Kutney, J. P.; Choudhurry, M. K.; Decesare, J. M.; Jacobs, H.; Singh, A. K.; Worth, B. R. *Can. J. Chem.* **1981**, *59*, 3162. Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 2743. Babin, D.; Fourneron, J. D.; Harwood, L. M.; Julia, M. *Tetrahedron* **1981**, *37*, 325. Hatch, C. E., III; Baum, J. S.; Takashima, T.; Kondo, K. *J. Org. Chem.* **1980**, *45*, 3281. Nesmeydnova, O. A.; Rudashevskaya, T. Y.; Dyachenko, A. L.; Savileva, S. F.; Nefedov, O. M. *Synthesis* **1980**, 296. Fitzimmons, B. J.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1979**, *101*, 6123.

(6) In view of their increased insecticidal activity with decreasing temperature, the pyrethroids are particularly promising for controlling agricultural pests in Canada. For pertinent studies, see: Harris, C. R.; Turnbull, S. A. *Can. Entomol.* **1979**, *110*, 285. Harris, C. R.; Svec, H. J.; Chapman, R. A. *J. Econ. Entomol.* **1978**, *71*, 642, 692 and references cited therein.

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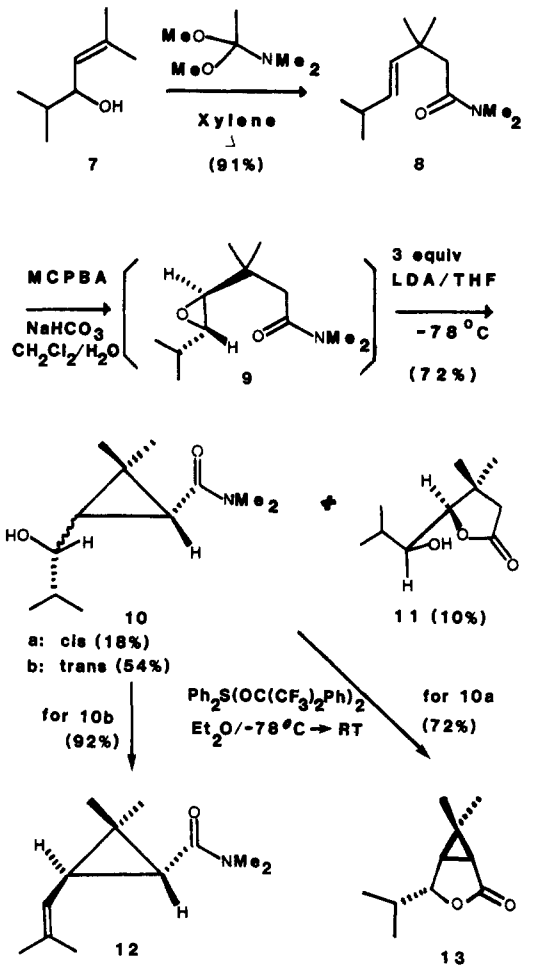
to devise not only enantioselective synthesis of pyrethroids but also new methods adaptable to commercial production.[8]

Perhaps the most important retrosynthetic disconnection for pyrethroid ring construction is the C_1–C_3 bond[4] as indicated for chrysanthemic ester (EWG = CO_2R) (Scheme I) which synthetically is based on intramolecular SN_2 (path A) or SN_2' (path B) mechanistic formulations. This approach generally leads to isomeric mixtures in which the *trans*-chrysanthemic esters predominate although several exceptions, providing the corresponding cis derivatives as major isomers, have been reported.[4,9] This has significance in view of the greater biological activity of the cis isomers, e.g., **5**. Synthetically equivalent to these two pathways is an epoxide-mediated ring closure (path C) of which two examples have been reported.[10,11]

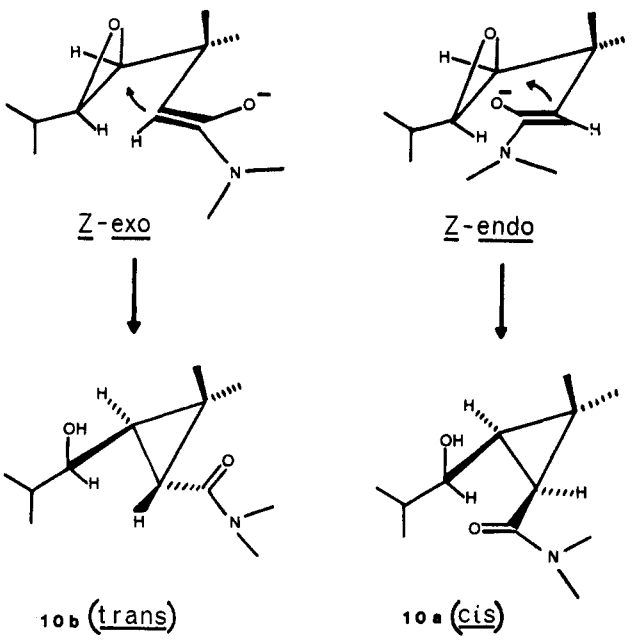
In view of the fact that almost all active pyrethroids are esters,[3] it is surprising that systematic structure activity studies of other functionalities at the same oxidation state (thioester, amide, thioamide) have been largely neglected. In the limited studies, a cyano amide (**6**) was found to be inactive, although a simple 2,2,3,3-tetramethylcyclopropanecarboxamide was found to have promising insecticidal properties.[12] Since ester cleavage is a significant pathway in the metabolic and environmental degradation of pyrethroids, such studies may provide ester analogues of biological interest. To stimulate interest in this area and to extend the utility of metalated amides in organic synthesis,[13] we developed two new routes to pyrethroid amides (Schemes II and IV) based on epoxy amide cyclization (Scheme I, path C, EWG = $CONR_2$), whose details are reported here.[1]

The readily available alcohol **7**, prepared by $LiAlH_4$ reduction rather than the reported $NaBH_4$ method,[10c] was subjected to Claisen–Eschenmoser rearrangement[14] to give the *E*-unsaturated amide **8** in high yield. Acid-catalyzed epoxidation (H_2O_2/HOAc) led exclusively to the hydroxy lactone **11**; however, a two-phase procedure using MCPBA[15] afforded the unstable epoxide **9** which could neither be characterized nor purified or distilled without undergoing cyclization to **11**. Therefore **9** was dried and treated with excess of LDA to give cyclopropane amides **10a** (18%) and **10b** (54%) and lactone **11** (10%), which were separated efficiently by preparative HPLC and characterized by ^1H NMR spectroscopy (see Experimental Section). Assuming *Z*-stereoselective deprotonation of **9**,[16] the trans diastereoselectivity may be attributed to the preference of the *Z*-exo intermediate over the *Z*-endo intermediate owing to the steric interactions between isopropyl and dimethylamino groups in the latter (Scheme III). The intermolecular counterpart of this reaction shows variation of *threo–erythro* diastereoselectivity as a function of epoxide- and N-substitution.[17] The regioselectivity (3-membered over 4-membered ring formation) cannot be well predicted on the basis of Baldwin's rules[18]

Scheme II



Scheme III



(7) MacDonald, R. S.; Surgeoner, G. A.; Solomon, K. R.; Harris, C. R. *Can. Entomol.* **1983**, *115*, 1555 and references cited therein.

(8) For a recent symposium on synthesis and structure activity relationships, see: Elliott, M.; Janes, N. F. In "Advances in Pesticide Science"; Geissbühler, H., Ed.; Pergamon Press: Oxford, 1978; Part 2, p 166 and following papers in this publication.

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(11) For carbanionic epoxide-mediated ring closure reactions, see: Dececare, J. M.; Corbel, B.; Durst, T.; Blout, J. F. *Can. J. Chem.* **1981**, *59*, 1415 and extensive reference list therein.

(12) Elliot, M., Ed. "Synthetic Pyrethroids"; American Chemical Society: Washington, D.C., 1977; Symp. Ser. No. 42, pp 16, 67.

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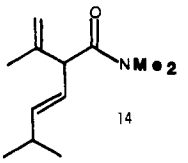
Table I. Attempted Dehydration of Amide Alcohols 10a and 10b

no.	amide alcohol	reagent	rxn condn	yield, % 14	12	13
1	**10b**	TsCl	DMF/DMAP 20 °C/2 h	60		
2	**10b**	NaH/CS_2, MeI	heat	50	3	
3	**10a**	$Et_3NSO_2NCO_2Me$	PhH/30 °C/ 15 min	69	23	
4	**10a**	TsCl	Py/0 °C/4 h	50		6
5	**10b**	$Et_3NSO_2NCO_2Me$	PhH/30 °C/ 2 h	77	6	

owing to inadequate theoretical basis and experimental documentation of such cases.[11,18]

As expected on the basis of (cyclopropylcarbinyl)carbenium ion behavior,[19] attempted dehydration of **10a** and **10b** led mainly to fragmentation to give the 3,4-*E*-diene amide **14** (Table I, entries 1 and 4).[20] The 2,4-*E*-stereochemistry is readily rationalized on the basis of a favorable bisected cyclopropyl conformation.[21] Although the Tchugaev pyrolytic cis-elimination method on **10b** gave a trace of the desired **12** (entry 2), a more encouraging result (23% of **12**) was obtained by using Burgess' triethylammonium *N*-carbomethoxysulfamate reagent (entry 3).[22,23] The desired dehydration **10b** → **12** (Scheme II) was achieved in high yield by using Martin's sulfurane, $Ph_2S[OC(CF_3)_2Ph]_2$,[24] at low temperatures in Et_2O solution. Unfortunately, but predictably,[10a] the *cis*-amide **10a** mainly underwent fragmentation to **14** (Table I, entry 3)



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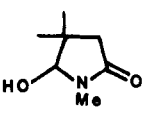
by using Burgess' reagent and in high yield (Scheme II) by using Martin's reagent. The close proximity of the amide carbonyl to a presumed super hot sulfurane leaving group[24] is a likely explanation for this result.

Detrimental points in the above synthesis (Scheme II) were the requirement of the elaborate sulfurane reagent for the dehydration step and the lack of adequate scope of the Claisen–Eschenmoser reaction for various N-substituted amide acetals. To circumvent these problems, a route was envisaged via the amide aldehyde **16** as the key intermediate which could be derived from the hemiaminal **15** and which could be elaborated by Peterson olefination into the ketene thioacetals **17**. The readily accessible **15**,[20,25] when treated with methyl (methylthio)methyl sulfoxide/Triton B, dimsyl sodium, methylenetriphenyl-



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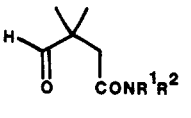
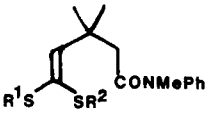


16



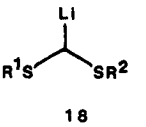
17

a: $R^1 + R^2 = -(CH_2)_3-$

b: $R^1 = R^2 = Et$

c: $R^1 + R^2 = -(CH_2)_3-$, S → O

d: $R^1 = R^2 = Et$, S → O



18

phosphorane, or the lithiodithianes **18a** and **18d**, led to regeneration of starting material in high yield.[20] The fact that the analogue of **15** lacking the two methyl groups was reported to undergo the Wittig reaction[25] leads to the conclusion that this substitution in **15** either disfavors equilibration to the open-chain form (**16**, R^1 = Me, R^2 = (–)) or prevents reaction by steric hindrance in the latter.

β,β-Disubstituted α,β-unsaturated carbonyl systems are generally poor Michael acceptors toward carbanionic species,[26] the outstanding exception being the organocopper reagents.[27] Therefore, it was somewhat surprising that the reaction of senecioic acid with 2-lithiodithiane gave, in good yield, the 1,4-addition product **19** (Scheme IV).[28] This result, which potentially has greater scope and synthetic value, allowed easy access to the desired aldehyde amide **21** by standard amidation followed by dethioketalization.[29] Ketene thioacetals **17a** and **17b** were prepared by condensation of **21** with **18a**[30] and **18b**,[31] respectively, in order to test intramolecular Michael reaction of amide enolate to ketene thioacetal acceptors. Although the formation of amide enolates from **17a** and **17b** by treatment with LDA or LTMP (THF/–78 °C) was established by D_2O-quench experiments, no evidence for their cyclization to cyclopropane derivative was obtained (recovery of starting material). The ketene thioacetal *S*-oxides **17c** and **17d**, prepared by $NaIO_4$ oxidation[32] of **17a** and **17b**, respectively, also failed to give cyclized products. These failures[20] are attributed to cyclopropyl ring strain factors causing an unfavorable equilibrium constant for the Michael reaction.

The above discouraging results led to the development of an alternative cyclopropane ring construction, **21** → **22** → **23** (Scheme IV) which is a simple analogue of the first synthesis (Scheme II). Conversion of **21** into epoxide **22** was achieved in quantitative yield by using trimethylsulfonium iodide and solid KOH and Me_2SO.[34,35]

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(20) For details, see: Majewski, M. Ph.D. Thesis, University of Waterloo, 1982.
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(23) For a result of exclusive fragmentation observed in an ester analogous to the **10** → **14** conversion using the Burgess reagent, see ref 10c. For its successful use for sensitive dehydrations, see: Marino, J. P.; Ferro, M. P. *J. Org. Chem.* **1981**, *46*, 1912. Mulzer, J.; Brüntrup, G.; Hartz, G.; Kuhl, U.; Bkschek, U.; Böhrer, G. *Chem. Ber.* **1981**, *114*, 3701. Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945.
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(33) Other methods gave poorer yields: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353 (50–60%). Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845 (70–80%).
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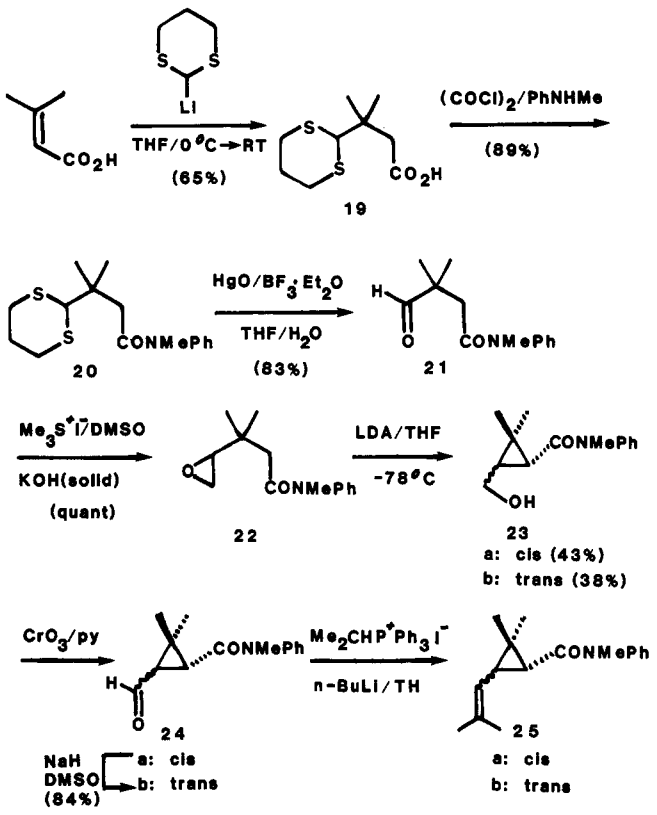
(35) An attempt to achieve an enantioselective synthesis of **22** by using an (–)-ephedrinium salt in a phase-transfer procedure failed. See: Hiyama, T.; Mishima, T.; Sawada, H.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 1626.

Scheme IV



Treatment of **22** with LDA followed by preparative HPLC gave the *cis*- and *trans*-cyclopropane amide alcohols **23a** (43%) and **23b** (38%). The lack of stereoselectivity compared to that observed for **10a** and **10b** suggests (vide supra) that steric factors from the isopropyl group play a significant role in the diastereoselectivity of the ring closure. Compounds **23a** and **23b** were separately oxidized[36] into the corresponding aldehydes **24a** and **24b** which were converted into the *cis*- and *trans*-pyrethroid amides **25a** and **25b** by using the method of Krief and co-workers.[37] Since the cis-aldehyde **24a** can be readily isomerized (NaH/Me_2SO) into the trans-aldehyde **24b**,[38] the formation of *trans*-pyrethroid amide **25b**, if desired, can be maximized.[39]

The bioactivity of pyrethroid amides **10b** and **12** and precursor **8** were evaluated against the onion maggot (adult) and cricket (first stage nymph) by procedures described in the literature.[6] None of these compounds showed significant insecticidal activity as compared to permethrin (**4**).

Conclusions

LDA-mediated cyclizations of epoxy amides **9** (Scheme II) and **22** (Scheme IV) lead to cyclopropane amides **10** and **23**, respectively. Unfortunately, for biological activity considerations, the formation of **10** is trans stereoselective. Compounds **10b** and **23** have been converted to pyrethroid amides **12** and **25**, respectively, completing short syntheses of these systems from readily available starting materials.

Contrary to generalizations concerning lack of conjugate addition reactivity of carbanions with β,β-disubstituted α,β-unsaturated carbonyl systems,[26] senecioic acid has been shown to undergo Michael reaction with 2-lithio-1,3-dithiane to give **20** (Scheme IV). This observation may have broader synthetic potential.

Experimental Section

General Methods. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. and Canadian Microanalytical Service Ltd. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. Infrared spectra were measured on a Beckman IR-10 instrument in chloroform unless otherwise specified. Nuclear magnetic resonance spectra were obtained by using a Varian T-60, Perkin-Elmer R-12, Bruker WP-80, or a Bruker WP-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard unless stated otherwise. Spectra listed are tabulated in the following order: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J, Hz), number of protons, assignment. Mass spectra were determined on a Varian MAT-CH 7 or a VG 7070F instrument. Gas–liquid chromatography was performed on a F&M Research Chromatograph with helium as a carrier and the following columns: A 6 ft × $^1/_8$ in. 10% SE-30; B 6 ft × $^1/_8$ in. OV-17. Preparative GLC was carried out on a Varian Autoprep A-700 instrument equipped with a Carbowax column. Thin-layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Merck silica gel of the size 70–230 mesh was used for column chromatography except where otherwise noted. High-pressure liquid chromatography was carried out on a Varian 5000 Liquid Chromatograph with a reverse-phase (C-18) column, and preparative HPLC on a Waters PREP-500 with a silica gel column. All solvents were dried and distilled before use; THF and diethyl ether were dried over sodium with benzophenone as an indicator and distilled just prior to use. All liquid reagents were dried over sodium hydride, calcium hydride, or molecular sieves 4A and distilled before use. The hexane solution of *n*-BuLi (Alfa, Aldrich) was titrated every few days by using the procedure of Gilman.[40] The phrase standard workup refers to drying of the organic phase with Na_2SO_4, filtration, and evaporation to dryness under reduced pressure.

2,5-Dimethylhex-4-en-3-ol (7). To isobutyryl chloride (171.2 g, 1.6 mol) in dry CH_2Cl_2 (600 mL) at −78 °C was added tin tetrachloride (52.0 g, 0.2 mol), and isobutylene (182.0 g, 3.2 mol) was slowly bubbled through the mixture for 3 h. The resulting black mixture was stirred and allowed to warm to room temperature over 2 h and poured into ice–water (600 mL). Pyridine was added until the resulting exothermic reaction stopped. The yellow precipitate was collected by filtration and washed with CH_2Cl_2. The organic layers were combined and dried and the solvent was removed in vacuo to give a dark oil which was dissolved in DMF (400 mL). Anhydrous lithium chloride was added (81.0 g, 1.9 mol) and the whole was refluxed for 4 h. The product was collected by steam distillation and distilled to give 103.0 g (52%) of 2,5-dimethylhex-4-en-3-one: bp 48–52 °C (10 mm) [lit.[5c] bp 60–65 °C (20 mm)]; NMR ($CDCl_3$) δ 1.10 (d, J = 8.5), 1.90 (s, 3), 2.15 (s, 3), 2.70 (m, 1), 6.10 (m, 1).

This compound (3.18 g, 25 mmol) was dissolved in dry ether (20 mL) and added dropwise to a suspension of $LiAlH_4$ (0.50 g, 13 mmol) in dry ether (100 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, quenched with brine, and extracted with ether. Standard workup gave 2.88 g (90%) of compound **7** as a colorless oil: bp 60–64 °C (17 mm) [lit.[5c] bp 60–65 °C (18 mm)]; NMR ($CDCl_3$) δ 0.90 (m, 6), 1.50 (m, 1), 1.65 (m, 6), 2.00 (s, 1), 4.00 (m, 1), 5.20 (m, 1).

***N,N*,3,3,6-Pentamethylhept-4-enamide (8).** A mixture of 2,5-dimethylhex-4-en-3-ol (**7**) (12.8 g, 0.10 mol) and *N,N*-di-

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methylacetamide dimethyl acetal[41] (40.0 g, 0.30 mol) in dry xylene (150 mL) was refluxed for 4 h. Methanol was removed by distillation and the reflux continued for an additional 36 h. Removal of xylene followed by distillation, yielded 18.0 g (91%) of **8**: bp 75–80 °C (0.03 mm); IR ($CHCl_3$) ν(max) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (d, J = 6.8, 6), 1.19 (s, 6), 2.20 (m, 1), 2.31 (s, 2), 2.92 (s, 3), 2.99 (s, 3), 5.30 (dd, J_1 = 5, J_2 = 16, 1), 5.54 (d, J = 16, 1); MS, m/e (relative intensity) 197 (M^+, 12), 182 (21), 125 (100).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.10; H, 11.68; N, 7.11. Found: C, 73.22; H, 11.75; N, 7.14.

2-(1-Hydroxyisobutyl)-3,3,*N*,*N*-tetramethylcyclopropanecarboxamide (10). To a mixture of amide **8** (4.46 g, 22.6 mmol) in CH_2Cl_2 (250 mL) and aqueous $NaHCO_3$ (275 mL, 0.67 M) was added, with vigorous magnetic stirring, *m*-chloroperbenzoic acid (8.00 g, 46.0 mmol). Stirring was continued for 2 h (disappearance of **8** by TLC), Na_2SO_3 was added (6.30 g, 50.0 mmol), the layers were separated, and the organic phase was washed with saturated bicarbonate solution and subjected to standard workup. The oily product **9** was dried (by azeotropic removal of water using benzene), dissolved in THF (30 mL), and added to a solution of LDA (45 mmol) in THF (200 mL) at −78 °C. The solution was allowed to warm to room temperature over 8 h and quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with methylene chloride. Standard workup furnished a yellow oil (4.20 g) which was subjected to preparative HPLC (Waters PREP-500, SiO_2, AcOEt–hexane 1:1) to afford the following fractions.

Compound 11: 0.42 g (10%); bp 96–98 °C (0.02 mm); mp 63–64 °C (Et_2O–petroleum ether); IR ($CHCl_3$) ν(max) 3460, 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (d, J = 6.5, 3), 1.04 (d, J = 6.5, 3), 1.18 (s, 3), 1.30 (s, 3), 1.78 (s, 1), 2.00 (2 × sept, J_1 = 6.5, J_2 = 2.0, 1), 2.38, 2.40 (2 × s, 2), 3.65 (dd, J_1 = 2, J_2 = 7, 1), 4.00 (d, J = 7, 1); MS, m/e (relative intensity) 186 (M^+, 0.8), 114 (100), 99 (26), 73 (28), 72 (70).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.50; H, 9.68. Found: C, 64.60; H, 9.85.

Compound 10a: 0.87 g (18%); bp 105–107 °C (0.02 mm); IR ($CHCl_3$) ν(max) 3440, 1630 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 7.2, 3), 1.02 (d, J = 7.2, 3), 1.10 (dd, J_1 = 8, J_2 = 9, 1), 1.26 (s, 3), 1.28 (s, 3), 1.56 (d, J = 9, 1), 1.91 (2 × sept, J_1 = 7.2, J_2 = 4.5, 1), 2.75 (s, 1, OH), 2.94 (s, 3), 3.10 (s, 3), 4.11 (dd, J_1 = 4.5, J_2 = 8.0, 1); MS, m/e (relative intensity) 195 (M^+ − 18, 3), 170 (31), 140 (84), 128 (29), 72 (100).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.60; H, 10.80; N, 6.57. Found: C, 67.35; H, 11.08; N, 6.26.

Compound 10b: 2.61 g (54%); mp 64–65 °C (Et_2O–petroleum ether); IR ($CHCl_3$) ν(max) 3440, 1630 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, J = 7.0, 3), 1.02 (d, J = 7, 3), 1.08 (s, 3), 1.38 (s, 3), 1.44 (d, J = 6, 1), 1.58 (dd, J_1 = 6, J_2 = 10, 1), 1.64 (s, 1, OH), 1.84 (2 × sept, J_1 = 7, J_2 = 7, 1), 2.96 (s, 3), 3.06 (s, 3), 3.01 (m, 1); MS, m/e (relative intensity) 213 (M^+, 0.3), 140 (100), 112 (13), 95 (21), 72 (99).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.60; H, 10.80; N, 6.57. Found: C, 67.28; H, 10.97; N, 6.26.

***trans*-*N*,*N*-Dimethylchrysanthemamide (12). Using Burgess' Reagent.** Compound **10b** (0.340 g, 1.6 mmol) was dissolved in anhydrous benzene (5 mL) and added dropwise to a solution of $Et_3N^+SO_2N^-CO_2Me$[22] (0.405 g, 1.70 mmol) in benzene (5 mL). The mixture was stirred for 15 min at 30 °C and evaporated to dryness. Column chromatography (hexane–EtOAc 1:1) afforded two fractions.

(3*E*)-2-Isopropenyl-*N*,*N*,5-trimethylhex-3-enamide (14): 0.215 g (69%); bp 88–92 °C (0.01 mm); IR ($CHCl_3$) ν(max) 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (d, J = 7.5, 6), 1.80 (s, 3), 2.30 (m, 1), 2.97 (s, 3), 3.00 (s, 3), 3.78 (d, J = 8, 1), 4.80 (m, 2), 5.40 (dd, J_1 = 5.1, J_2 = 16, 1), 5.71 (dd, J_1 = 8, J_2 = 16, 1); MS, m/e (relative intensity) 195 (M^+, 17), 81 (12), 72 (100).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.85; H, 10.77; N, 7.18. Found: C, 73.81; H, 10.69; N, 7.25.

***trans*-*N*,*N*-Dimethylchrysanthemamide (12)**: 0.72 g (23%); bp 120–125 °C (0.02 mm); IR ($CHCl_3$) ν(max) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 3), 1.18 (s, 3), 1.40 (d, J = 5.8, 1), 1.70 (s, 6), 2.10 (dd, J_1 = 9.0, J_2 = 5.8, 1), 3.02 (s, 6), 4.90 (d, m, J = 9, 1); MS, m/e (relative intensity) 195 (M^+, 52), 179 (36), 123 (100), 122 (28).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.85; H, 10.77; N, 7.18. Found: C, 73.87; H, 11.04; N, 7.11.

Using Martin's Reagent. (***Note***: Martin's reagent is extremely hygroscopic and requires handling in a dry box under argon). Compound **10b** (0.213 g, 1 mmol) was added to Ph_2S-$[OC(CF_3)_2Ph]_2$[24] (0.762 g, 1.0 mmol) dissolved in dry Et_2O (10 mL) at −78 °C under argon. The mixture was stirred for 1 h at −78 °C and allowed to warm to room temperature. Water was added (3 mL) and the mixture was extracted with CH_2Cl_2. The organic layer was washed with 6 N aqueous NaOH and the crude product was purified by column chromatography (neutral Al_2O_3, activity 1, hexane–EtOAc) yielding 0.180 g (92%) of **12** which was shown to be identical (melting point, mixture melting point, IR, NMR) with the sample obtained above.

From *trans*-Chrysanthemic Acid. A sample of *trans*-chrysanthemic acid (0.1 g, 0.6 mmol) was dissolved in benzene (3 mL), $SOCl_2$ (1 mL) was added, and the solution was stirred for 1 h at room temperature, cooled to 0 °C, and treated with gaseous dimethylamine (5 min). Addition of water followed by extraction with Et_2O afforded 0.098 g (84%) of **12**, shown to be identical (melting point, mixture melting point, IR, NMR, MS) with a sample obtained above.

Bicyclic Lactone 13. Using Burgess' Reagent. Compound **10a** (0.213 g, 1.0 mmol) in anhydrous benzene (3 mL) was added to a solution of Burgess' reagent[22] (0.262 g, 1.1 mmol) in benzene (5 mL). The mixture was stirred for 2 h at 30 °C. GLC analysis indicated one major product and two minor products in a ratio of 85:6:9. Workup and column chromatography as described in the preparation of **12** afforded **14** (0.151 g, 77%), which was characterized by comparison with the sample as obtained above. The middle component was identified as **13** by GLC retention time comparison with authentic material obtained below.

Using Martin's Reagent. Compound **10a** (0.458 g, 2.15 mmol) was added to a solution of Martin's reagent[24] (1.469 g, 2.18 mmol) in Et_2O (15 mL) at −78 °C under argon. The mixture was stirred for 1 h at −78 °C, warmed to room temperature, stirred for 0.5 h, and quenched with brine (2 mL). Extraction with CH_2Cl_2 afforded a yellow oil which was purified by column chromatography (hexane–EtOAc) yielding 0.150 g of starting material (**10a**) and 0.259 g (72%) of 2-isopropyl-4-oxo-6,6-dimethyl-3-oxabicyclo[3.1.0]hexane (**13**) as a colorless oil: bp 90–95 °C (0.01 mm); IR ($CHCl_3$) ν(max) 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, J = 7.5, 6), 1.18 (s, 6), 1.25 (d, J = 7.0, 1), 1.90 (dd, J_1 = 7, J_2 = 8, 1), 1.92 (m, 1), 4.11 (dd, J_1 = 8, J_2 = 3, 1); MS, m/e (relative intensity) 168 (M^+, 14), 138 (24), 126 (62), 125 (65), 109 (73), 96 (87), 41 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.71.

3-Methyl-3-(1,3-dithian-2-yl)butanoic Acid (19). A solution of 1,3-dithiane (12.0 g, 0.1 mol) in THF (100 mL) at 0 °C was treated with *n*-BuLi solution (0.1 mol). The solution was stirred for 0.5 h at 0 °C and a solution of senecioic acid (5 g, 0.05 mol) in a small amount of THF was added. The mixture was stirred for 20 h at room temperature and quenched with water (200 mL), 3 N aqueous NaOH was added (20 mL), and the solution was extracted (EtOAc). Standard workup afforded unreacted 1,3-dithiane (6.0 g, 50%), which was purified by crystallization (EtOH) and sublimation. The water layer was acidified with concentrated HCl, saturated with NaCl, and extracted with EtOAc. Standard workup gave an oil which was distilled to afford 3.2 g of a colorless oil, bp 40–50 °C (0.1 mm), which consisted mainly of unreacted senecioic acid. The residue solidified and was recrystallized from Et_2O–hexane yielding 7.15 g (65%) of **19**: mp 113–114 °C (EtOH–Et_2O); IR ($CHCl_3$) ν(max) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 6), 2.0 (m, 2), 2.60 (s, 2), 2.9 (m, 4), 4.38 (s, 1); MS, m/e (relative intensity) 220 (M^+, 11), 119 (100).

Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.09; H, 7.27. Found: C, 49.00; H, 7.38.

***N*,3-Dimethyl-*N*-phenyl-3-(1,3-dithian-2-yl)butanamide (20).** To a solution of acid **19** (2.8 g, 12.7 mmol) in benzene (30 mL) was added oxalyl chloride (2.8 mL, 32 mmol) and the mixture was stirred overnight. The solvent was removed in vacuo and the residual oil was dissolved in benzene (50 mL). To the resulting solution, a mixture of triethylamine (1.9 mL, 13 mmol) and *N*-methylaniline (1.5 mL, 13 mmol), was added dropwise and the

(41) Hanessian, S.; Moralioglu, E. *Can. J. Chem.* **1972**, *50*, 223.

black solution was stirred for 2 h. Triethylamine hydrochloride was collected by filtration and the filtrate was washed with 2 N aqueous HCl and saturated Na_2CO_3 solutions, dried, and evaporated in vacuo to afford 4.5 g of an oil. Distillation gave 3.5 g (89%) of **20**: bp 120–125 °C (0.1 mm); IR ($CHCl_3$) ν(max) 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 6), 2.0 (m, 2), 2.3 (s, 2), 2.9 (m, 4), 3.26 (s, 3), 4.8 (s, 1), 7.3 (m, 5); MS, *m/e* (relative intensity) 309 (M^+, 21), 161 (18), 159 (100), 149 (85), 119 (85).

Anal. Calcd for $C_{16}H_{23}NOS_2$: C, 62.14; H, 7.44; N, 4.53. Found: C, 61.92; H, 7.65; N, 4.40.

***N*,3-Dimethyl-*N*-phenyl-3-formylbutanamide (21).** The amide **20** was dethioketalized according to a literature method.[29] To a mixture of red HgO (5.3 g, 24 mmol) and $BF_3{\cdot}Et_2O$ (3 mL, 24 mmol) in 15% aqueous THF (50 mL) under N_2 was added dropwise with stirring a solution of amide **20** (6.18 g, 20 mmol) in THF (10 mL). After stirring for 30 min at room temperature, the reaction was processed under the following crucial conditions. Anhydrous Na_2SO_4 was added followed by Et_2O (150 mL) under vigorous stirring. The precipitate was collected by filtration and washed with EtOAc, and the filtrate was washed with saturated aqueous Na_2CO_3 solution. After evaporation of the solvent, distillation yielded 3.64 g (83%) of **21**: bp 110–112 °C (0.2 mm); mp 44–45 °C (Et_2O–hexane); IR ($CHCl_3$) ν(max) 1720, 1648 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (s, 6), 2.38 (s, 2), 3.24 (s, 3), 7.3 (m, 5), 9.65 (s, 1); MS, *m/e* (relative intensity) 219 (M^+, 1), 191 (26), 134 (11), 107 (100).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.12; H, 7.85; N, 6.28.

Attempted Cyclizations of 17a–d. Amides **17a–d** (1 mmol) were added to LDA (2 mmol) or LiTMP (2 mmol) in THF (10 mL) at −78 °C. The mixtures were allowed to warm to room temperature over 8–12 h, quenched with water, and worked up in the standard way. In all cases, the starting materials were regenerated (85–95%). When 5 equiv of LDA or LiTMP were used, mixtures of five to seven products resulted.

***N*,3,3-Trimethyl-*N*-phenyl-4,5-epoxypentanamide (22).** A solution of aldehyde **21** (0.109 g, 0.5 mmol) in Me_2SO (2 mL) was treated with KOH (2 pellets) and $Me_3S^+ I^-$ (1 mmol, 0.204 g) and the mixture was stirred at room temperature for 12 h. Water (20 mL) was added and the mixture was extracted with EtOAc. The organic layer was washed with successive portions of saturated aqueous K_2CO_3 solution and water and worked up in the standard manner to give 0.110 g (92%) of **22** as a colorless oil: NMR ($CDCl_3$) δ 0.95 (s, 6), 2.5–3.0 (m, 5), 3.25 (s, 3), 7.3 (m, 5). Since attempted distillation resulted in decomposition, this product was used directly as described below.

2-(Hydroxymethyl)-*N*,3,3-trimethyl-*N*-phenylcyclopropanecarboxamide (23). Epoxide **22** (1.165 g, 5 mmol) was added to a solution of LDA (15 mmol) in THF (20 mL) at −78 °C. The mixture was allowed to warm to room temperature over 8–12 h and was quenched with saturated aqueous NH_4Cl solution and acidified with 2 N HCl. Extraction with AcOEt and chromatography (Waters PREP-500, EtOAc:hexane 4:1) afforded unidentified forerun (0.220 g) and the following.

Compound 23a: 0.503 g (43%); bp 150 °C (0.03 mm (Kugelrohr)); IR ($CHCl_3$) ν(max) 3420, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (s, 3), 1.15 (s, 3), 1.20 (m, 2), 3.27 (s, 3), 3.7 (m, 1), 3.9 (m, 2), 7.3 (m, 5); MS, *m/e* (relative intensity) 233 (M^+, 5), 202 (62), 134 (17), 107 (100).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.76; H, 8.29; N, 6.02.

Compound 23b: 0.440 g (38%); mp 108–109 °C (Et_2O); IR ($CHCl_3$) ν(max) 3460, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3), 1.07 (d, J = 6,1), 1.24 (s, 3), 1.6 (m, 1), 1.8 (m, 1), 3.32 (s, 3), 3.5 (m, 2), 7.3 (m, 5); MS, *m/e* (relative intensity) 233 (M^+, 4), 202 (100), 107 (62).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.18; N, 6.04.

***cis*-2-Formyl-*N*,3,3-trimethyl-*N*-phenylcyclopropanecarboxamide (24a).** A literature procedure[36] was adopted. To a mixture of dry CrO_3 (0.40 g, 4 mmol) and pyridine (0.7 mL, 8.0 mmol) in CH_2Cl_2 (10 mL) was added Celite (0.5 g) and **23a** (0.150 g, 0.64 mmol). After stirring for 0.5 h, Et_2O (100 mL) was added and the resulting dark mixture was filtered through a short column of Florisil containing a layer of Celite to give 0.117 g (79%) of **24a** bp 180–185 °C (0.015 mm); IR ($CHCl_3$) ν(max) 1692, 1645 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3), 1.47 (m, 1), 1.6 (s, 3), 1.9 (d, J = 8, 1), 3.31 (s, 3), 7.30 (m, 5), 9.85 (d, J = 6.4, 1); MS, *m/e* (relative intensity) 231 (M^+, 9), 202 (56), 107 (100), 97 (81), 69 (23).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91; H, 7.62; N, 6.26.

***trans*-2-Formyl-*N*,3,3-trimethyl-*N*-phenylcyclopropanecarboxamide (24b).** Compound **23b** was oxidized according to the conditions described for the preparation of **24a**. From 0.20 g (0.86 mmol) of **23b** there was obtained 0.175 g (88%) of **24b**: bp 170–175 °C (0.01 mm); IR ($CHCl_3$) ν(max) 1700, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (s, 3), 1.32 (s, 3), 2.12 (d, J = 6, 1), 2.64 (dd, J_1 = 6, J_2 = 3.3, 1), 3.31 (s, 3), 7.3 (m, 5), 9.54 (d, J = 3.3, 1); MS, *m/e* (relative intensity) 231 (M^+, 15), 202 (65), 107 (90), 97 (100), 77 (36).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.46; N, 6.16.

Isomerization of 24a into 24b. Compound **24a** (0.231 g, 1 mmol) was dissolved in Me_2SO (2 mL) and NaH (0.036 g, 1.5 mmol) was added. The mixture was stirred for 12 h at room temperature and diluted with water (20 mL), and the resulting mixture was extracted with EtOAc to give 0.193 g (83%) of **24b**, identical (IR, NMR) with a sample prepared above.

***cis*-*N*-Methyl-*N*-phenylchrysanthemamide (25a).** A suspension of triphenylisopropylphosphonium iodide[42] (3 mmol, 1.314 g) in THF (15 mL) at −78 °C was treated with *n*-BuLi solution (3 mmol). The mixture was allowed to warm to 0 °C, stirred for 0.5 h, and cooled to −78 °C. Aldehyde **24a** (0.578 g, 2.5 mmol) was added, the reaction mixture was allowed to warm to room temperature over 4 h was treated with water, and the whole was extracted with Et_2O. Standard workup followed by column chromatography (EtOAc–hexane 1:4) afforded 0.483 (75%) of **25a**: bp 175 °C (0.01 mm); IR ($CHCl_3$) ν(max) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3), 1.28 (s, 3), 1.34 (d, J = 9, 1), 1.55 (m, 1), 1.66 (d, J = 1, 3), 1.78 (d, J = 1, 3), 3.25 (s, 3), 5.61 (2 × sept, J_1 = 1, J_2 = 8.5, 1), 7.3 (m, 5); MS, *m/e* (relative intensity) 257 (M^+, 25), 242 (17), 134 (33), 123 (100), 107 (49).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.05; H, 9.17; N, 5.48.

***trans*-*N*-Methyl-*N*-phenylchrysanthemamide (25b).** Compound **24b** was subjected to the reaction conditions, workup, and purification used for the conversion of **24a** into **25a**. From 0.231 g (1 mmol) of **24b** there was obtained 0.208 g (81%) of **25b**: bp 181–184 °C (0.01 mm); IR ($CHCl_3$) ν(max) 1645 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (s, 3), 1.06 (d, J = 5.3, 1), 1.24 (s, 3), 1.65 (d, J = 1, 3), 1.71 (d, J = 1, 3), 2.20 (dd, J_1 = 5.3, J_2 = 8, 1), 3.30 (s, 3), 4.7 (2 × sept, J_1 = 1; J_2 = 8, 1), 7.3 (m, 5); MS, *m/e* (relative intensity) 257 (M^+, 23), 242 (14), 134 (31), 127 (100), 107 (43).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.01; H, 9.27; N, 5.48.

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