Table I. Synthesis of Indoles via Palladium-Catalyzed Annulation of Alkynes (Eq 2)[a]

entry	R^1	R^2	R^3	alkyne equiv	procedure	base	PPh_3	time, h	% isolated yield[b]
1	H	*n*-Pr	*n*-Pr	5	A	K_2CO_3	+	16	70
2				5	B	K_2CO_3	-	24	80
3				2	B	K_2CO_3	-	24	64
4				1	B	K_2CO_3	-	24	50
5	Me			5	A	K_2CO_3	+	24	71
6	Ac			5	A	KOAc	-	24	91
7	Ts			5	A	KOAc	-	24	86
8	H	*t*-Bu	Me	5	A	Na_2CO_3	+	24	82
9		c-C_6H_{11}	Me	5	A	K_2CO_3	+	16	57
10		1-OH-c-C_6H_{10}	Et	2	A	Na_2CO_3	+	24	78
11				2	B	K_2CO_3	+	24	85
12				1	B	K_2CO_3	+	24	51
13		CMe_2OH	H_2C=CMe	2	A	KOAc	-	24	70
14				2	B	KOAc	-	12	67
15		Me_3Si	Me	5	A	Na_2CO_3	+	12	98
16		Me_3Si	CH_2OH	2	A	Na_2CO_3	+	24	60
17	Ac	Ph	Me	2	B	KOAc	-	16	75
18				1	B	KOAc	-	16	70
19		CH_2OH	Me	2	B	KOAc	-	16	60[c]
20	Ts	Ph	Ph	2	B	K_2CO_3	-	48	60

[a] All reactions were run by heating to 100 °C 5 mol % $Pd(OAc)_2$, aryl iodide (0.5 mmol), *n*-Bu_4NCl (0.5 mmol, procedure A) or LiCl (0.5 mmol, procedure B), base (2.5 mmol), alkyne (0.5, 1.0, or 2.5 mmol), DMF (10 mL), and where appropriate, 5 mol % PPh_3. [b] All products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral or elemental analytical data. [c] The product is 2-(acetoxymethyl)-3-methylindole.

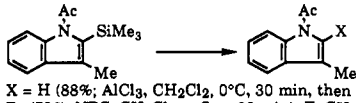
cedure A), but it was subsequently observed that LiCl (procedure B) was often more effective and reproducible. The number of equivalents of LiCl is critical. More than 1 equiv of LiCl sharply lowers the yield and appears to favor multiple insertion products.

This reaction is remarkably versatile as far as the aniline moiety is concerned. The nitrogen may be unsubstituted or bear groups as diverse as a methyl, acetyl, or tosyl group. Bromoanilines are generally unreactive, however.

A wide variety of internal alkynes have been successfully employed in this process. The more volatile the alkyne is, the greater the amount of alkyne that has been employed, although good yields can still be obtained by using lesser amounts (compare entries 2-4). The alkyne can bear alkyl, aryl, alkenyl, hydroxy, and silyl groups. Even bulky tertiary alkyl or trimethylsilyl groups are readily accommodated and indeed tend to afford the highest yields.

The annulation of unsymmetrical alkynes has proven to be highly regioselective, providing only the regioisomer shown in Table I. The more sterically bulky group ends up nearer the nitrogen atom in the indole product. This selectivity is consistent with previous work on the palladium-catalyzed hydroarylation of internal alkynes, although our reactions appear to be significantly more regioselective.[10] Even 1-phenyl-1-propyne (entries 17 and 18) and 1-cyclohexylpropyne (entry 9) afford only one regioisomer. Surprising regioselectivity is even observed in the reaction of *o*-iodoaniline and 2-pentyne, which produces a 2:1 mixture of regioisomers. Indeed, excellent regio- and chemoselectivity is observed with alkynes as diverse as 2-butyn-1-ol (entry 19) and 2,5-dimethyl-5-hexen-3-yn-2-ol (entries 13 and 14).

The facile annulation of silylalkynes broadens tremendously the scope of this synthetic process. Desilylation by acylation,[11] protonolysis, halogenation, or the Heck reaction provides a convenient entry into variously substituted indoles (eq 3).



(3)

X = H (88%; $AlCl_3$, CH_2Cl_2, 0°C, 30 min, then hydrolysis); Br (70%; NBS, CH_2Cl_2, reflux, 30 min); *E*- CH=$CHCO_2$Et (75%; 2 H_2C=$CHCO_2$Et, $Pd(OAc)_2$, DMF, 100°C, 2 days)

This indole synthesis presumably proceeds via (1) oxidative addition of the aryl iodide to Pd(0), (2) syn insertion of the alkyne into the arylpalladium bond, and (3) nitrogen displacement of the palladium in the resulting vinylpalladium intermediate, quite possibly by halide displacement to form a six-membered-ring, heteroatom-containing palladacycle and subsequent reductive elimination. Although there are previous examples of this last step,[7] the dramatic difference in our results and those reported earlier using a virtually identical complex **1** (eq 1)[8] is remarkable.

Acknowledgment. We gratefully acknowledge the National Institutes of Health for their generous financial support; Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Inc., for the palladium reagents; and NATO for a Collaborative Research Grant allowing valuable discussions with Professor Sandro Cacchi of the University of La Sapienza, Rome, Italy.

Supplementary Material Available: Description of procedures for annulation and all reactions described in eq 3 and experimental data, including IR, ^1H and ^{13}C NMR, and exact mass spectra and elemental analyses, for all products (6 pages). Ordering information is given on any current masthead page.

(10) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713.

(11) For the acylation of 3-silylindoles, see: Majchrzak, M. W.; Simchen, G. *Synthesis* **1986**, 956.

New Methodology for the Synthesis of Functionalized Indolizidine and Quinolizidine Ring Systems

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The widespread occurrence of indolizidine and quinolizidine systems across many families of alkaloids[1] warrants the further development of new and more efficient synthetic methodologies that can be targeted toward those members that reveal promising biological profiles.[2] We report a new strategy for the construction of these structural subunits. Our general scheme involves the reaction of 2-vinylazacycles **1** with the appropriate ketene, which generates zwitterionic intermediates **2** that undergo facile [3, 3] ring expansions[3] to give macrocyclic lactams **3** (eq 1).[4] This mode

(1) Indolizidine and quinolizidine alkaloids: Howard, A. S.; Michael, J. P. *Alkaloids*; **1986**, *28*, 183. Yohimbine and related alkaloids: Szantay, S.; Blasko, G.; Honty, K.; Dornyei, G. *Alkaloids* **1986**, *27*, 131.

(2) For certain antitumor alkaloids containing these structural subunits, see: Suffness, M.; Cordell, G. A. *Alkaloids* **1985**, *25*, 3.

(3) For a related process see: Baxter, E. W.; Labaree, D.; Ammon, Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682. Baxter, Labaree, D.; Chao, S.; Mariano, P. S. *J. Org. Chem.* **1989**, *54*, 2893. Chao, S.; Kunng, F. A.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 2708. Kunng, F. A.; Gu, J. M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262.

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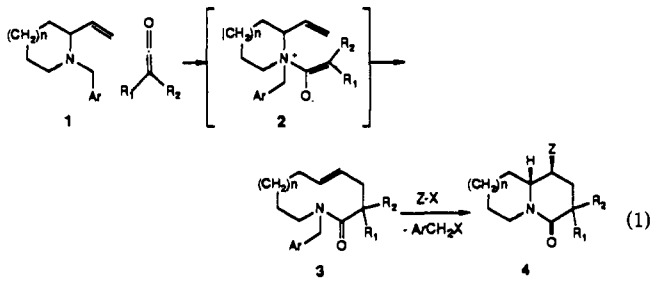
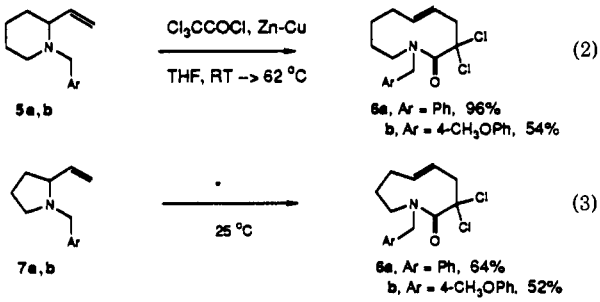


(1)

of reactivity for homoallylamines has not been documented[5] and constitutes a convenient regiocontrolled route to nine- and ten-membered-ring unsaturated lactams that are otherwise difficult to obtain.[6] Subsequent exposure of lactams **3** to certain electrophiles triggers a simultaneous transannular cyclization–debenzylation event[7] that affords the highly functionalized heterocycles **4**.

For example, generation of dichloroketene (DCK) over 3 h in the presence of *N*-benzyl-2-vinylpiperidine (**5a**)[8] at room temperature initially gave a zwitterionic species[9] which, upon gentle heating in THF, cleanly afforded hexahydroazec-5-en-2-one **6a**[10] in 96% yield (eq 2). Analogously, *N*-benzyl-2-vinyl-pyrrolidine



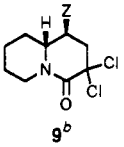
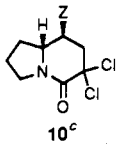
(2)

(3)

(**7a**)[8] provided hexahydroazon-5-en-2-one **8a**[10] in 64% yield following spontaneous rearrangement at room temperature (eq 3). In comparison, the 4-methoxybenzyl derivatives **5b** and **7b** afforded macrocyclic lactams **6b**[10] and **8b**[10] at room temperature in 54% and 52% yields, respectively.[11]

The room-temperature ^1H and ^{13}C NMR spectra for the ten-membered-ring lactams revealed the presence of two discrete conformers (2.7:1.0 ratio for **6a**), which began to coalesce at 80 °C.[12] It was not possible to extract the olefinic coupling constant; however, the *E* stereochemistry is inferred by the subsequent stereochemistry proven for the transannular cyclization products, vide supra. In contrast, the nine-membered-ring lactams **8a,b** exist as a single conformational species, as evidenced by their ^1H and ^{13}C NMR spectra. The structure of **8b** was confirmed by X-ray analysis,[13] which revealed an *E* configuration about the C-5, C-6, double bond and a cisoid arrangement around the planar amide bond. These conformational features contrast nicely with the X-ray structure for a structurally related hexahydroazon-5-en-2-one having a *Z* carbon–carbon double bond and a transoid amide array.[14]

Table I. Transannular Cyclizations of Macrocyclic Lactams **6a**, **8a**, and **8b** Using Electrophiles

substr	electrophile (equiv)	temp, °C (time, h)	product	yield,[a] %
6a	I_2 (2.0)	50 (8)	 **g**[b]	85
6a	PhSeBr (1.05)	25 (1.5)		84
8a	I_2 (2.0)	25 (3)	 **10**[c]	88
8a	PhSeBr (1.05)	25 (1.5)		79
8b	TMSI (1.5)	25 (4); H_2O		72

[a] Yields are reported for isolated materials purified by column chromatography using ethyl acetate/hexanes as the eluent. [b] **9a**, Z = I; **9b**, Z = SePh. [c] **10a**, Z = I; **10b**, Z = SePh; **10c**, Z = H.

In preliminary cyclization studies, macrocycles **6a** and **8a,b** were exposed to certain electrophiles[15] (CH_3CN, 25–50 °C) as shown in Table I. A single bicyclic product was obtained in all cases with complete regio- and stereocontrol. Lactam **6a** afforded the iodo- or phenylseleno-substituted quinolizidines **9a,b** in high yield whereas lactam **8a** gave the analogous indolizidines **10a,b** with equal efficiency. Unexpectedly, an attempt to remove the benzyl group from lactam **8b** [$(CH_3)_3SiI/CH_3CN$; H_2O] resulted in a proton-initiated cyclization, which afforded adduct **10c**. This behavior was not observed for the analogous ten-membered-ring lactam **6a** rather only N-debenzylation occurred.[16]

The quinolizidines **9a,b** were found to have an equatorial iodo or phenylseleno substituent, as indicated by the diaxial coupling between the bridgehead and the adjacent methine protons (**9a**, J = 9.9 Hz; **9b**, J = 10.2 Hz). The structure for **9a** was confirmed by X-ray analysis.[13] The trans-fused bicyclic array in **9a,b** would logically arise from anti addition of the electrophile and nitrogen lone pair across an *E* double bond in the precursor **6a**. The regiochemistry in the indolizidine cycloadducts **10a–c** was assigned by comparison of the amide carbonyl IR stretches (**9a**, 1672 cm^{-1} vs **10a**, 1670 cm^{-1}; **9b**, 1674 cm^{-1} vs **10b** 1678 cm^{-1}).[17] The

(4) For the reaction of 2-alkenylthianes, unsaturated cyclic thio ketals, and 2-alkenylpyrans with dichloroketene, see: (a) Johnson, B. D.; Czyzewska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693. (b) Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840. (c) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860. (d) Rosini, G.; Spineti, G. G.; Forest, E.; Pradella, G. *J. Org. Chem.* **1981**, *46*, 2228.

(5) The ring expansion of 2-vinylpiperidines and 2-vinylpyrrolidines via [2, 3] sigmatropic shifts is well documented: (a) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831. (b) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185. (c) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.

(6) Previous syntheses of nine-membered-ring unsaturated lactams involves Beckmann ring expansion starting from substituted cyclooct-4-en-1-ones; however, mixtures of regioisomers are obtained (refs 8 and 14).

(7) For transannular cyclizations of eight- and nine-membered-ring amines and amides, see: Wilson, S. R.; Sawicki, R. A. *J. Heterocycl. Chem.* **1982**, *19*, 81; *J. Org. Chem.* **1979**, *44*, 287, 330. Mariano, P. S.; Osborn, M. E.; Dunaway-Mariano, D.; Gunn, B. C.; Pettersen, R. C. *J. Org. Chem.* **1977**, *42*, 2903.

(8) Compound **5a** has been prepared previously.[5a] A general route to **5a,b** and **7a,b** starting from pipicolinic acid or proline was implemented by using well-known procedures: (i) LAH, THF; (ii) ArCOCl, NaOH, H_2O, Et_2O; (iii) Swern–Moffatt; (iv) $Ph_3P{=}CH_2$, $PhCH_3$; (v) LAH, THF. Overall yields for the five steps ranged from 50% to 60%.

(9) Evidence for this intermediate (from **5a**) was obtained by ^1H and ^{13}C NMR.

(10) All new compounds have been fully characterized by ^1H and ^{13}C NMR and IR spectroscopies and either elemental analysis or high-resolution mass spectroscopy.

(11) The lower yields for these systems was attributed to byproducts arising from premature cleavage of the 4-methoxybenzyl group from the intermediate zwitterionic species.

(12) These two species are believed to be geometrical isomers about the planar amide array. For a discussion on the conformational properties of analogous ten-membered-ring lactones see: Reference 4c.

(13) Full details on the X-ray crystallographic data for compounds **8b** and **9a** are provided in the supplementary material.

(14) Olsen, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323.

(15) Cyclization of benzyl-protected 5-hexen-2-ol derivatives using iodine has been documented: Rychonovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3964. Amidoselenation of unsaturated amides: Toshimitsu, A.; Tereo, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724, and references cited therein.

(16) Attempts to provide the unsubstituted quinolizidine **9** (Z = H) or indolizidine **10c** by exposing **6b** or **8b** to mercury salts followed by treatments with $NaBH_4$ were unsuccessful.[7]

(17) The electronic effect arising from the geminal dichloride substituents shifts the carbonyl IR stretch ~25 cm^{-1}. Reductive cleavage[18] of the chlorine atoms from **9a** and **10c** afforded lactams with C=O stretches at 1646 and 1645 cm^{-1}, respectively.[7]

stereochemistry for **10a,b** was assigned by the diaxial coupling observed between the bridgehead and the neighboring methine proton (**10a**, J = 10.7 Hz; **10b**, J = 10.8 Hz).

Notably, our methodology provides a new a regiocontrolled route into nine- and ten-membered-ring unsaturated lactams via a charge accelerated variant of the aza Claisen rearrangement starting from simple monocyclic precursors. Furthermore, the regio- and stereocontrolled introduction of new heteroatom functionality into bicyclic compounds from macrocyclic precursors provides a variety of opportunities for the elaboration of additional functionality.[18] Application of this methodology to the synthesis of bioactive compounds is currently being pursued.

Acknowledgment. This work was supported by funds from Utah State University and the Donors of the Petroleum Research Fund, administered by the American Chemical Society. The X-ray structural information was obtained by Dr. Atta Ariff, Department of Chemistry, University of Utah.

Supplementary Material Available: Synthetic procedures and analytical data for **6a**, **6b**, **8a**, **8b**, **9b**, and **10a-c** and listings of crystallographic details, ORTEP, bond distances, bond angles, torsion angles, and positional and displacement parameters for **8b** and **9a** (25 pages); listing of observed and calculated structure factors for **8b** and **9a** (11 pages). Ordering information is given on any current masthead page.

(18) For purposes of future synthetic applications, both chlorine atoms can be readily cleaved from the macrocyclic lactams **6a** and **8a** by using Zn/Ag: Heathcock, C. H.; Clark, R. D. *J. Org. Chem.* **1972**, *38*, 3658.

Antineoplastic Agents. 220. Synthesis of Natural (-)-Dolastatin 15[1]

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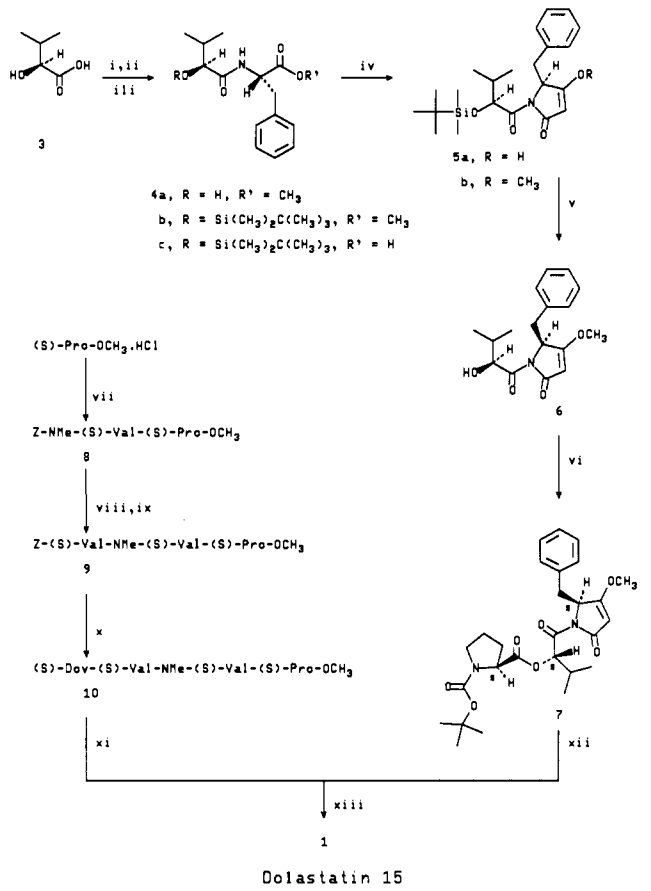
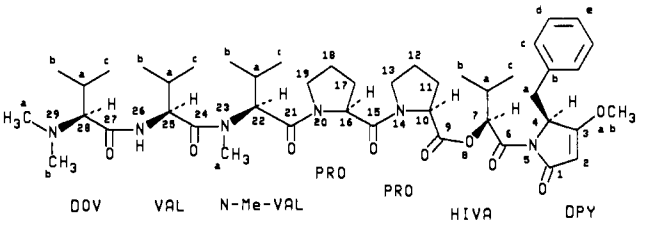
The discovery and synthesis[2] of potentially useful antineoplastic peptides comprise one of the most essential and promising approaches to new types of anticancer drugs. Of special interest here are the dolastatins,[2d,g,3] an unprecedented series of linear and cyclic antineoplastic and/or cytostatic peptides isolated from the Indian Ocean sea hare *Dolabella auricularia*.[3] Presently dolastatins 10[2d,3e] and 15 (**1**)[3a] represent the two most important members. While dolastatin 10 has recently yielded to total synthesis,[2d] the corollary problem of deducing the absolute configuration (seven chiral centers) of dolastatin 15 (**1**) and devising a total synthesis has remained urgent. We now report the absolute configuration of dolastatin 15 (**1**) and total synthesis of the correct natural (-)-isomer from among 128 possibilities.

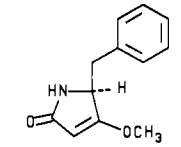
Scheme I[a]



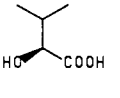
[a] (i) Phe-OMe, diethyl phosphorocyanidate (DEPC), NMM, CH_2Cl_2; (ii) TBDMS chloride, imidazole, DMF; (iii) 1 N NaOH, CH_3OH-H_2O-H_2O; (iv) Meldrum's ester, 4-DMAP, $C_6F_5O_2CCF_3$, CH_2Cl_2; CH_3OH, ΔH; K_2CO_3, $(CH_3O)_2SO_2$, THF; (v) HF-pyridine; (vi) Boc-(*S*)-Pro, DCCI, 4-pyrrolidinopyridine, CH_2Cl_2; (vii) Z-NMe-(*S*)-Val, DEPC, TEA, DME; (viii) H_2, 10% Pd/C, EtOAc-CH_3OH, HCl-ether; (ix) Z-(*S*)-Val, $(CH_3)_3CCOCl$, NMM, $CHCl_3$; (x) (*S*)-Dov-OPfp, H_2, 10% Pd/C, dioxane; (xi) NaOH, dioxane, H_2O, HCl; (xii) TFA, CH_2Cl_2; (xiii) DEPC, TEA, DME, 0 °C → room temperature. Satisfactory elemental and spectral analyses were obtained for each new substance.



1, Dolastatin 15



2, Dolapyrrolidone (Dpy)



3, Hiva

The structure of dolastatin 15,[3a] elucidated via extensive 2D NMR and high resolution mass spectral techniques, was found

* To whom correspondence should be addressed.

(1) Part 219: Pettit, G. R.; Herald, C. L.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, M. H.; Cerny, R. L.; Rutzler, K. *J. Org. Chem.*, submitted.

(2) Cf.: (a) Li, W. R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659-7672. (b) Ewing, W. R.; Harris, B. D.; Li, W. R.; Joullié, M. M. *Tetrahedron Lett.* **1989**, *30*, 3757-3760. (c) Holzapfel, C. W.; van Zyl, W. J. *Tetrahedron* **1990**, *46*, 649-660. (d) Pettit, G. R.; Singh, S. B.; Hogan, F. M.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463. (e) Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *29*, 4407-4408. (f) Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *29*, 3057-3060. (g) Pettit, G. R.; Kamano, Y.; Holzapfel, C. W.; van Zyl, W. J.; Tuinman, A. A.; Herald, C. L.; Baczynskyj, L.; Schmidt, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 7581-7582.

(3) (a) Pettit, G. R.; Kamano, Y.; Dufresne, C.; Cerny, R. L.; Herald, C. L.; Schmidt, J. M. *J. Org. Chem.* **1989**, *54*, 6005. (b) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Dufresne, C.; Bates, R. G.; Schmidt, J. M.; Cerny, R. L.; Kizu, H. *J. Org. Chem.* **1990**, *55*, 2989-2990. (c) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Dufresne, C.; Cerny, R. L.; Herald, D. L.; Schmidt, J. M.; Kizu, H. *J. Am. Chem. Soc.* **1989**, *111*, 5015-5017. (d) Pettit, G. R.; Kamano, Y.; Kizu, H.; Dufresne, C.; Herald, C. L.; Bontems, R. J.; Schmidt, J. M.; Boettner, F. E.; Nieman, R. A. *Heterocycles* **1989**, *28*, 553-558. (e) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883-6885.

0002-7863/91/1513-6692$02.50/0