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Total Synthesis and Structure Confirmation of Leptofuranin D

James A. Marshall* and Gregory M. Schaaf

Department of Chemistry, University of Virginia, P.O. Box 400319, Charlottesville, Virginia 22904

jam5x@virginia.edu

Received June 24, 2003

A convergent total synthesis of leptofuranin D is described. The linear polyketide C12−C24 segment was assembled through addition of a chiral allenylzinc reagent, derived from mesylate **12**, to the chiral aldehyde **11**. Directed hydrostannation of the adduct **13** followed by iodinolysis and Sonogashira coupling yielded the enyne **16**, which was converted to the methyl-substituted enye **20**, through hydrogenolysis of the derived bromide **19**. Hydrostannation of the terminal alkyne converted **21** to **22**, which was then treated with iodine to afford the vinyl iodide **23**. The dihydropyranone precursor **40** was prepared by addition of allenystannane **29** to aldehyde **27**. Partial hydrogenation of the derived propargylic alcohol then protection as the TBS ether afforded the (*Z*)-olefin **34**. Further homologation was effected through Witttig condensation of aldehyde **36** with the ylide derived from phosphonium bromide **37**. Selective deprotection of the primary TES ether of **38**, followed by conversion of alcohol **39** to iodide **40**, completed the synthesis of the C1−C11 segment. Suzuki coupling of boronate **41**, prepared from iodide **40**, with vinyl iodide **23** led to diene **42**, with the complete carbon skeleton of leptofuranin D. The synthesis was completed by oxidation of the unprotected alcohol of **42**, followed by global desilylation and exposure of the resulting tetrol to MnO_2.

Leptofuranins A−D were isolated in 1996 from the actinomycete strain *Streptomyces tanashiensis* (Figure 1).[1] They were found to inhibit the growth of normal human fibroblast cells while inducing apoptosis of human cervical cancer HeLa and osteosarcoma Saos-2 cells at nanogram per milliliter concentrations. The structures of these four closely related compounds, exclusive of stereochemistry, were assigned on the basis of the NMR spectra, which were quite similar to that of leptomycin B, an antifungal antibiotic isolated in 1983 from *Streptomyces* sp.[2] Subsequently, Kobayashi and co-workers completed a total synthesis of leptomycin B, thereby establishing the relative and absolute stereochemistry.[3] While the stereochemistry of no leptofuranin had been established prior to the present studies, their close structural similarity to leptomycin B was suggestive of close and possibly identical stereo structures, exclusive of the C22 tetrahydrofuran stereocenter. It should be noted that leptofuranins C and D were each isolated as nearly 1:1 mixtures of closely related and chromatographically inseparable stereoisomers. Their ^{1}H and ^{13}C NMR spectra revealed the presence of two "tautomers" in nearly equal amounts. This conclusion was verified by HPLC analysis. Interestingly, the two HPLC peaks coalesced at 60 °C leading to the conclusion that the two compounds were in rapid equilibrium, suggestive of a reversible 1,4-addition to an intermediate conjugated enal (Figure 2).

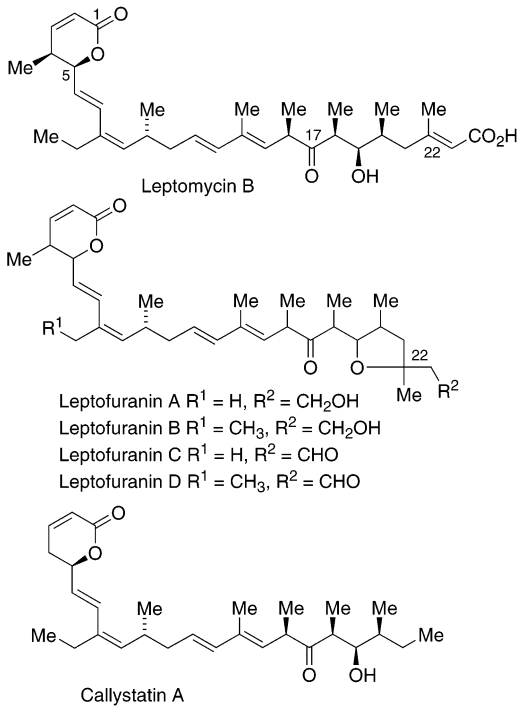


FIGURE 1. Leptomycin B, leptofuranins A−D, and callystatin A.

Recently, we reported a total synthesis of callystatin A, a close relative of the leptofuranins.[4] It was of interest to apply some of the methodology developed in that

(1) Hayakawa, Y.; Sohda, K.-Y.; Furihata, K.; Kuzuyama, T.; Shin-Ya, K.; Seto, H. *J. Antibiot.* **1996**, 974.
(2) Hayakawa, Y.; Sohda, K.-Y.; Seto, H. *J. Antibiot.* **1996**, 980.
(3) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291.
(4) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751.

10.1021/jo0348930 CCC: $25.00
Published on Web 08/23/2003

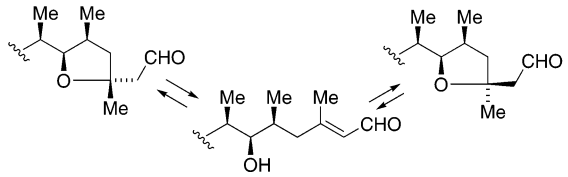


FIGURE 2. Epimerization pathway for leptofuranin C and leptofuranin D.

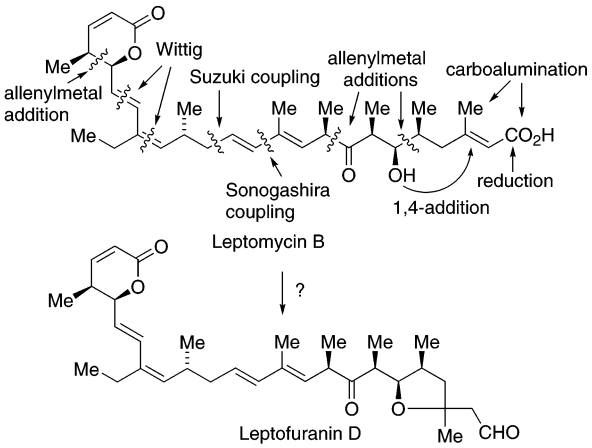
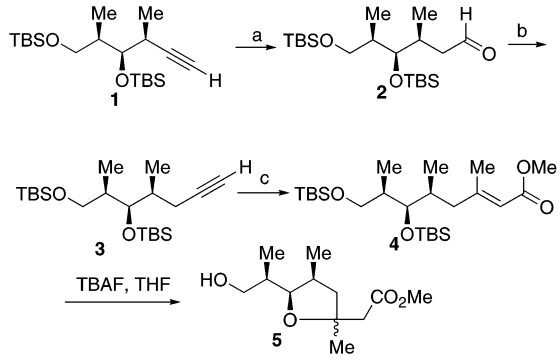


FIGURE 3. Principal bond-forming reactions for the synthesis of leptomycin B and leptofuranin D.

synthesis to the leptofuranins to establish the stereochemistry and eventually provide samples for evaluation of antitumor activity. Our initial efforts were directed at leptomycin B and leptofuranin D. We assumed that, apart from C22, the two are stereochemically identical. Synthetic leptofuranin D would expectedly be formed as a nearly 1:1 mixture of stereoisomers at C22, in accord with the natural material. The essence of our plan is diagrammed in Figure 3. Accordingly, successive allenylmetal additions to aldehyde intermediates would provide the means for introducing most of the stereocenters with concomitant C−C bond formation.[5] Additional C−C bonds would be formed through Pd(0)-catalyzed couplings and Wittig reactions. The β-methyl acrylic acid terminus of leptomycin B lends itself to construction by carboalumination of a terminal acetylene. Finally, assuming a stereochemical congruence, leptomycin B could be converted to leptofuranin D through internal 1,4-addition and reduction.

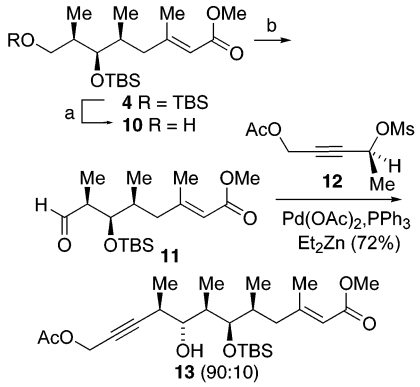
Our synthesis commenced with the known stereotriad **1**, the product of a chiral allenyltin addition to (*R*)-3-OTBS-2-methylpropanal (Scheme 1).[6] Hydroboration−oxidation of the alkyne terminus led to aldehye **2**, which was converted to alkyne **3** through treatment with the Ohira diazo phosphonate reagent.[7] Water-accelerated carboalumination of this alkyne, under conditions developed by Wipf, followed by addition of methyl chloroformate afforded the conjugated ester **4** in 64% yield.[8] In the absence of water this reaction proceeded in less than 50% yield. As a preview of an end-game strategy we treated **4** with TBAF whereupon the tetrahydrofuran **5** was produced as a 57:43 mixture of diastereomers.

SCHEME 1[a]



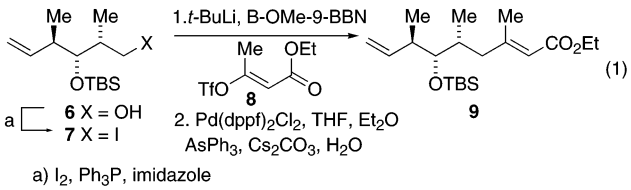
[a] Reagents and conditions: (a) Cy_2BH then NaOH, H_2O_2 (95%); (b) $MeCOC(N_2)PO(OMe)_2$, K_2CO_3 (75%, 2 steps); (c) Cp_2ZrCl_2, $AlMe_3$, H_2O then $ClCO_2Me$ (64%).

SCHEME 2[a]



[a] Reagents and conditions: (a) PPTS, MeOH (91%); (b) Swern oxidation (97%).

We also examined an alternative route to the terminal acrylic acid segment on a model substrate through application of a Suzuki coupling (eq 1).[9] For this



(1)

sequence, the iodide **7** was lithiated in the presence of B-MeO-9-BBN to form the boronate intermediate in situ. Addition of the vinyl triflate **8** and a Pd(0) catalyst afforded the coupled product **9**, but in only 25% yield.

Returning to the main sequence, the primary TBS ether of intermediate **4** was selectively hydrolyzed through exposure to PPTS in methanol−THF. Swern oxidation of the derived alcohol **10** afforded aldehyde **11** in 97% yield.[10] Addition of the allenylzinc reagent, generated in situ from the (*S*)-propargylic mesylate **12**, gave the anti adduct **13** as a 90:10 mixture of diastereomers in 72% yield.[6]

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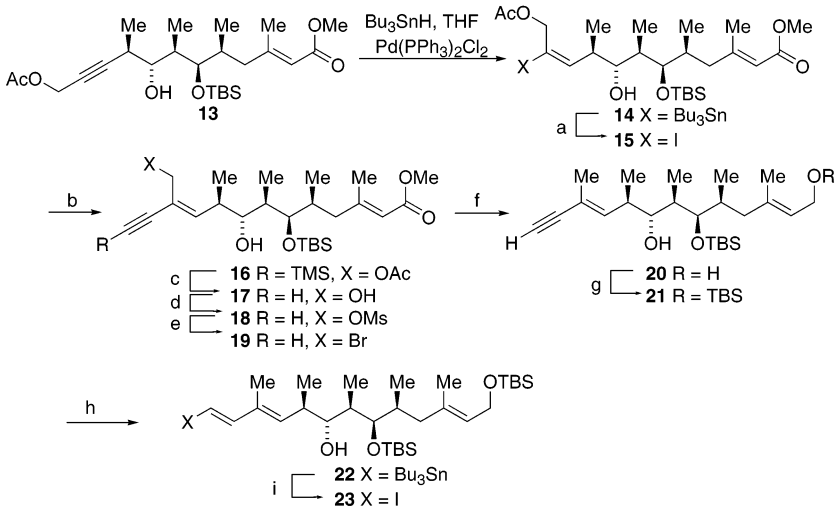
(6) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.
(7) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(8) Lim, S.; Wipf, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.
(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Chemler, S. R.; Travner, D.; Danishefsky, S. J. *Angew Chem., Int. Ed.* **2001**, *40*, 4545.
(10) Omurka, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

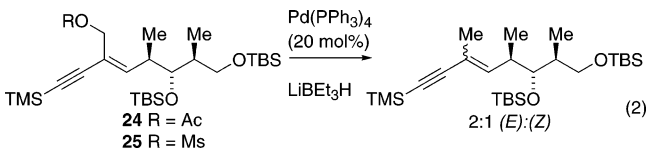
SCHEME 3[a]



[a] Reagents and conditions: (a) I_2, CH_2Cl_2 (82%, 2 steps); (b) TMSC≡CH, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (87%); (c) NaOH, MeOH−THF (90%); (d) MsCl, Et_3N, CH_2Cl_2; (e) LiBr, 2-butanone; (f) $LiBEt_3H$, THF (78%, 3 steps); (g) TBSCl, Im, CH_2Cl_2 (82%); (h) Bu_3SnH, $Pd(PPh_3)_2Cl_2$,THF; (i) I_2, CH_2Cl_2 (82%, 2 steps).

Final construction of the C12−C24 polypropionate array utilized a sequence that was developed both for this segment and for a comparable segment of callystatin A.[11] Accordingly, Pd(0)-catalyzed hydrostannation of the propargylic acetate **13** with Bu_3SnH afforded vinylstannane **14** regioselectively in high yield (Scheme 3). The derived vinyl iodide **15** underwent efficient Sonogashira coupling with TMS acetylene leading to the enyne **16**.[12] Reduction of the acetoxy methyl group of this intermediate was effected in a 3-step process culminating in the hydrogenolysis of allylic bromide **19** with $LiBEt_3H$ in 78% overall yield.

In some preliminary model studies, we attempted to effect the hydrogenolysis of allylic acetate **24** via π-allyl palladium intermediates under conditions that would preserve the terminal acrylic ester grouping, and thereby avoid a later reoxidation to the acid moiety of leptomycin B. However, our efforts were not rewarded. Treatment of acetate **24** with $Pd(PPh_3)_4$ followed by triethylammonium formate gave only recovered acetate.[13] The use of $LiBEt_3H$ in combination with $Pd(PPh_3)_4$ resulted in reduction of the acetate to afford the alcohol.[14] When the allylic mesylate **25** was treated with $Pd(PPh_3)_4$ followed by $LiBEt_3H$, a 2:1 mixture of the (*E*)- and (*Z*)-hydrogenolysis products was isolated (eq 2).



(2)

As the $LiBEt_3H$ hydrogenolysis of the allylic bromide also reduced the terminal acrylic ester of **19**, we elected to protect the resulting primary allylic alcohol as the TBS ether **21**, a decision we were to later regret. Completion of the C12−C24 segment was effected by hydrostannation of the terminal alkyne **21** and iodinolysis of the resulting vinylstannane **22** to afford the (*E*)-vinyl iodide **23** in 82% yield (Scheme 3).

The second major segment for our proposed synthesis of leptomycin B and leptofuranin D was the C1−C11 dihydropyrone precursor **34**. Its preparation started from the mono PMB ether **26** of ethylene glycol (Scheme 4). Oxidation to aldehyde **27** followed by $MgBr_2$-promoted propargylation of aldehyde **27** with chiral (acetoxymethyl)allenyl stannane **28**[5] produced adduct **30** as a 66:34 mixture of diastereomers. Fortunately, the related allenyl stannane analogue **29** afforded propargyl adduct **31** as a more manageable 83:17 mixture of syn and anti adducts in 85% yield. This mixture could be separated by chromatography on silica gel affording the pure syn isomer in 68% yield. The hydroxymethyl derivative of the latter adduct was obtained through lithiation of the terminal alkyne and addition of paraformaldehyde. The resulting diol **32** was converted to bis-TBS ether **33**, which was cleanly reduced to (*Z*)-alkene **34** with H_2 over Pd on $BaSO_4$ poisoned with quinoline.[15] Cleavage of the PMB ether with DDQ and Swern oxidation of alcohol **35** afforded aldehyde **36** in high yield. Homologation of aldehyde **36** was effected through condensation with the Wittig reagent **37**, previously employed in our synthesis of callystatin A, to afford diene **38**.[4] Selective cleavage of the primary TES ether with methanolic PPTS and treatment of alcohol **39** with I_2, Ph_3P, and imidazole effected conversion to iodide **40**.[16]

Coupling of the two major fragments **23** and **40** was achieved by Suzuki methodology via boronate **41**, which

(11) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2002**, *4*, 3931.
(12) Cf.: (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.4. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
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(14) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4380.
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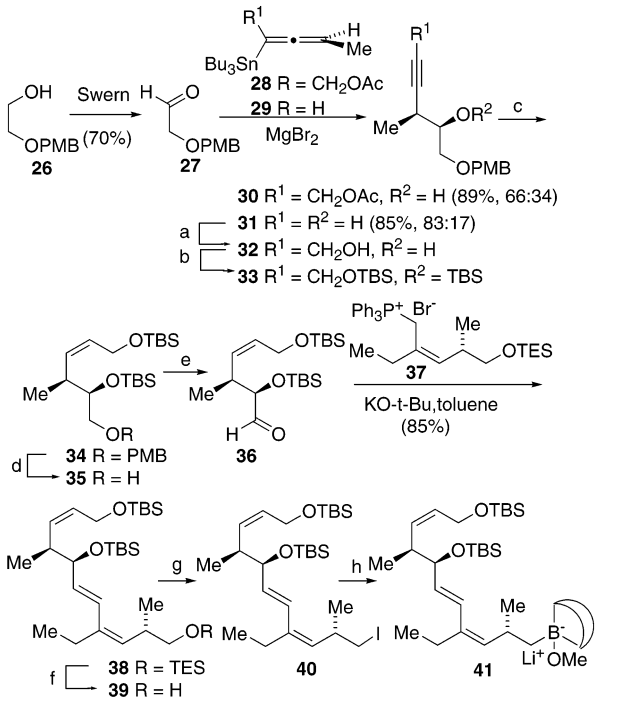
SCHEME 4[a]



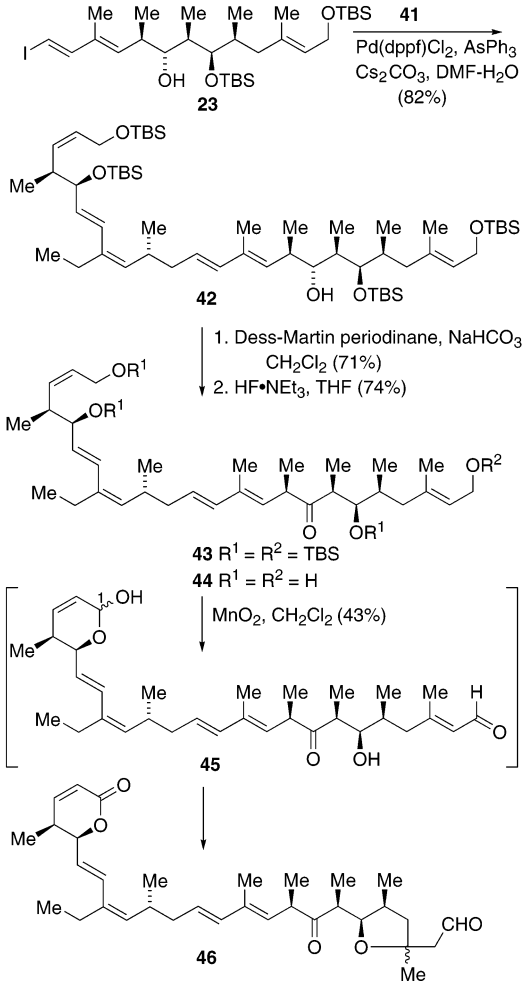
[a] Reagents and conditions: (a) BuLi, $(CH_2O)_n$, THF; (b) TBSOTf, 2,6-lut, CH_2Cl_2 (83%, 2 steps); (c) H_2/5% Pd−$BaSO_4$, quinoline, toluene (90%); (d) DDQ, CH_2Cl_2, pH 7 (91%); (e) Swern oxidation (98%); (f) PPTS, MeOH−THF (74%); (g) I_2, PPh_3, Im (94%); (h) *t*-BuLi, Et_2O, B-MeO-9-BBN, −78 °C.

was prepared from iodide **40** in situ with *t*-BuLi and B-MeO-9-BBN.[9] The most effective catalyst for the coupling reaction was derived from $Pd(dppf)Cl_2$ and $AsPh_3$, which gave rise to the fully elaborated leptofuranin carbon segment **42** in 82% yield (Scheme 5). Oxidation of the unprotected alcohol of **42** led to ketone **43** and subsequent desilylation with $HF{\cdot}NEt_3$ produced tetrol **44** in 74% yield. The desilylation reaction was quite slow, requiring 6 days for completion. Attempts to shorten the reaction time by increasing the temperature caused decomposition of the starting material.

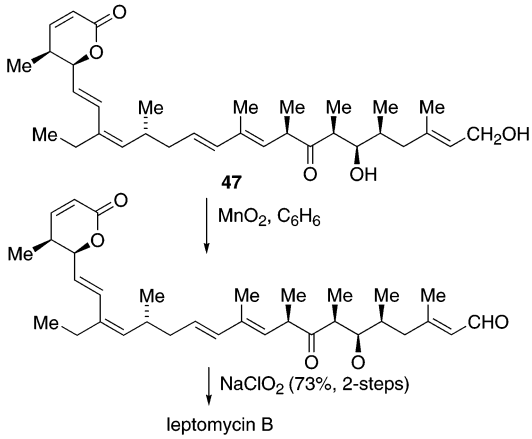
For the final stage of the synthesis we planned to effect selective oxidation of the allylic alcohols with MnO_2. It was expected that such treatment would give rise to a transient bis-enal intermediate in which the C1 aldehyde would cyclize to the lactol **45** and be further oxidized to the lactone.[4] In fact, treatment of the tetrol with excess MnO_2 in CH_2Cl_2 resulted in slow conversion to multiple intermediate products which gradually converged to a major product. This product, a nearly 1:1 mixture of inseparable isomers, was not the expected enal, but rather the internal 1,4-adduct **46** of enal **45**. This mixture proved identical to leptofuranin D by comparison of the ^1H NMR spectrum and optical rotation with the reported values.[2]

TLC analysis of the oxidation in progress showed the near simultaneous formation of multiple spots. These were slowly replaced by a single spot. Thus it appears likely that both primary allylic alcohols are oxidized at comparable rates and each is intercepted by proximal hydroxyl groups leading to four diastereomeric intermediates and finally two inseparable products, after oxidation of the lactol moiety to lactone **46**. Interestingly, Kobayashi employed an MnO_2 oxidation of allylic alcohol **47** in his synthesis of leptomycin B without competing 1,4-addition of the C19 hydroxyl group to the enal product (Scheme 6).[3] That reaction was carried out in benzene as solvent. Unfortunately, tetrol **44** was only sparingly soluble in benzene so this option could not be explored. While the foregoing synthesis confirms the stereochemistry of leptofuranin D, the route in its present form is

SCHEME 5



SCHEME 6



not feasible for leptomycin B. Presumably an early stage protecting group modification for the C24 alcohol function of the eventual oxidation substrate **44** (e.g. **43**, R^2 = PMB) would solve the problem. However, we prefer to examine an alternative strategy that does not result in the reduction of the terminal acrylic ester grouping of **19**, or a close relative. The results of those investigations will be reported in due course.

Acknowledgment. Support for these studies was provided by Grant R01 CA090383 from the U.S. National Cancer Institute.

Supporting Information Available: Experimental procedures and selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0348930