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Enantioselective Total Synthesis of (+)-Leucascandrolide A Macrolactone

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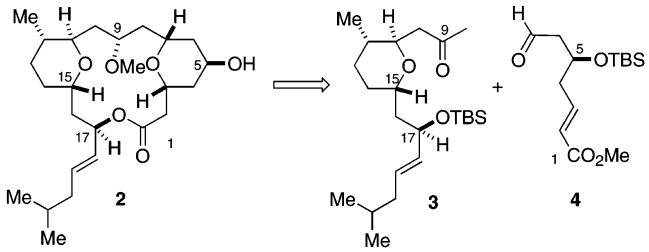
ABSTRACT



The enantioselective synthesis of the (+)-leucascandrolide A macrolactone has been achieved in 20 linear steps from 1,3-propanediol. The key steps in the synthesis are a reductive cleavage of bicyclic ketal 5 to establish the C15 stereogenic center and a diastereoselective aldol of the boron enolate of methyl ketone 3 to aldehyde 4 in preparation for a heteroconjugate addition for the introduction of the C3 stereocenter.

Leucascandrolide A (**1**) was isolated by Pietra and co-workers in 1996 from the calcareous sponge *Leucascandra caveolata* collected from the Coral Sea off the coast of New Caladonia.[1] The gross structure and relative stereochemistry were assigned on the basis of extensive two-dimensional NMR experiments, and the absolute configuration of the C5 stereocenter was assigned by Mosher ester analysis of the macrolactone. Leucascandrolide A displayed significant in vitro cytotoxicity (IC_{50} = 0.05 and 0.25 μg/mL with KB and P388 cells, respectively), as well as significant antifungal properties. Additional attempts to isolate leucascandrolide A from the sponge have proven unsuccessful,[2] and thus the full biological potential of the compound has not been established. Consequently, leucascandrolide A has attracted the interest of numerous synthetic groups;[3,4] the first total synthesis was reported by Leighton and co-workers in 2000.[5]

Our retrosynthetic analysis for the total synthesis of leucascandrolide A is illustrated in Scheme 1. Leucascandrolide A (**1**) would be derived from the macrolactone **2** by attachment of the oxazole-containing side chain at the C5 hydroxyl.[3,4] The key C7 stereocenter of the macrolactone would be established through a diasteroselective boron aldol between methyl ketone **3** and aldehyde **4**.[6] Methyl ketone **3** containing the *trans*-2,6-disubstituted-tetrahydropyran would be obtained from a stereoselective reductive cleavage of bridged ketal **5**.[7] The bridged ketal would be derived from a Horner−Wadsworth−Emmons reaction between aldehyde **6** (Scheme 3) and ketone phosphonate **7** (Scheme 2).

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−60.
(2) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347−353.
(3) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597−599.
(4) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242−3245. Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755−758. Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421. Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670−13671. Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812−6815. Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066−2067. Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Edit.* **2002**, *41*, 4098−4101. Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343. Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833−6849. Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934−3938.
(5) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894−12895.
(6) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788. Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893−10898.
(7) Kotsuki, H. *Synlett* **1992**, 97−106. Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595−4612. Bogaczyk, S.; Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 4352−4355.

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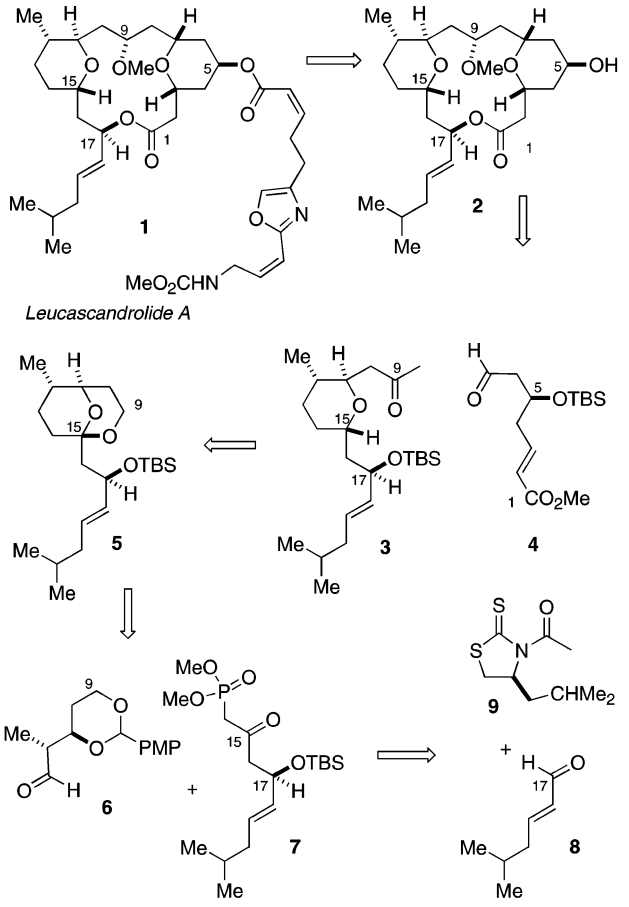
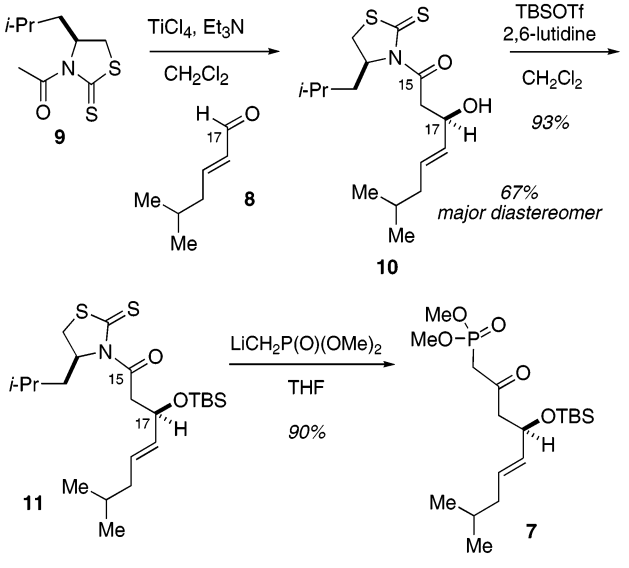
Scheme 1. Retrosynthesis of Leucascandrolide A (**1**)



Aldehyde **6** could be obtained easily through the well-established Brown crotylation[8] of 3-*p*-methoxybenzyloxypropanal. The phosphonate fragment **7** could be derived through a thiazolidinethione acetate aldol between the α,β unsaturated aldehyde **8** and acetyl thiazolidinethione **9**.

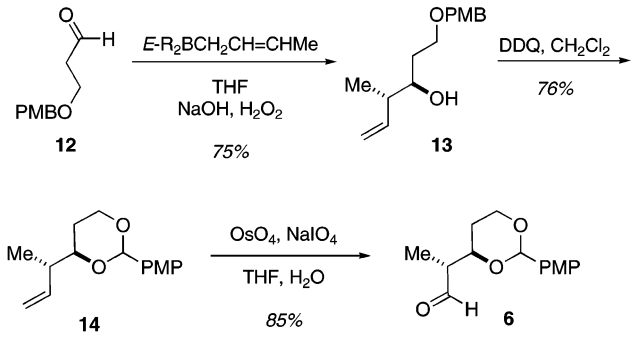
Scheme 2. Preparation of β-Ketophosphonate **7**



Synthesis of the β-keto phosphonate **7** was completed as outlined in Scheme 2. Addition of the titanium enolate of acetyl thiazolidinethione **9** to aldehyde **8** gave **10** in high yield as a 93:7 mixture of diastereomers.[9] The diastereomeric aldol adducts were readily separated[10] by flash chromatography and the major diastereomer was obtained in 67% purified yield. Subsequent protection of the alcohol as a silyl ether delivered TBS ether **11** in 93% yield. The thiazolidinethione auxiliary was directly displaced with the anion of methyl dimethylphosphonate providing the desired phosphonate **7** in excellent yield.

The aldehyde required for the Horner−Wadsworth−Emmons reaction with phosphonate **7** was constructed as illustrated in Scheme 3. The known aldehyde **12** is easily

Scheme 3. Preparation of Aldehyde **6**



accessible in 2 steps from 1,3-propanediol. Treatment of aldehyde **12** according to the Brown protocol afforded alcohol **13**. Exposure of PMB ether **13** to DDQ in dichloromethane under anhydrous conditions provided the 1,3-PMP acetal, and subsequent oxidative cleavage of the terminal olefin delivered the desired aldehyde **6**.[11]

The synthesis of the remaining C1−C7 fragment **4** (Scheme 4) began with the alkylation of TBS-protected glycolate **15** with allyl iodide to give **16** (>98:2 dr).[12] Reductive removal of the chiral auxiliary and a cross metathesis[13] of the resultant alcohol **17** with methyl acrylate using Grubb's second generation catalyst provided the α,β unsaturated ester **18** in good yield. Alcohol **17** was oxidized to aldehyde **19** followed by a one-carbon homologation via methoxymethylene Wittig and treatment with mercuric(II) acetate resulting in the desired aldehyde **4**.

The assembly of the three key fragments began by execution of a Horner−Wadsworth−Emmons coupling

(8) Brown, H. C.; Bhat, R. S.; Liao, Y.; Khanna, V. V. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923.

(9) González, Á; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949−8952. Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032.

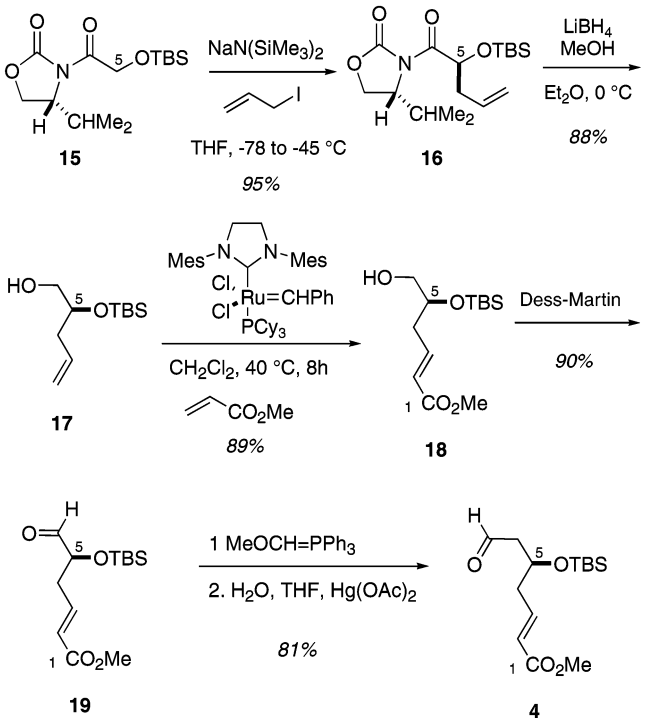
(10) *N*-Acylthiazolidinethiones are bright yellow, resulting in the ability to follow the chromatography visually as the two yellow bands pass down the column.

(11) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478−479.

(12) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167.

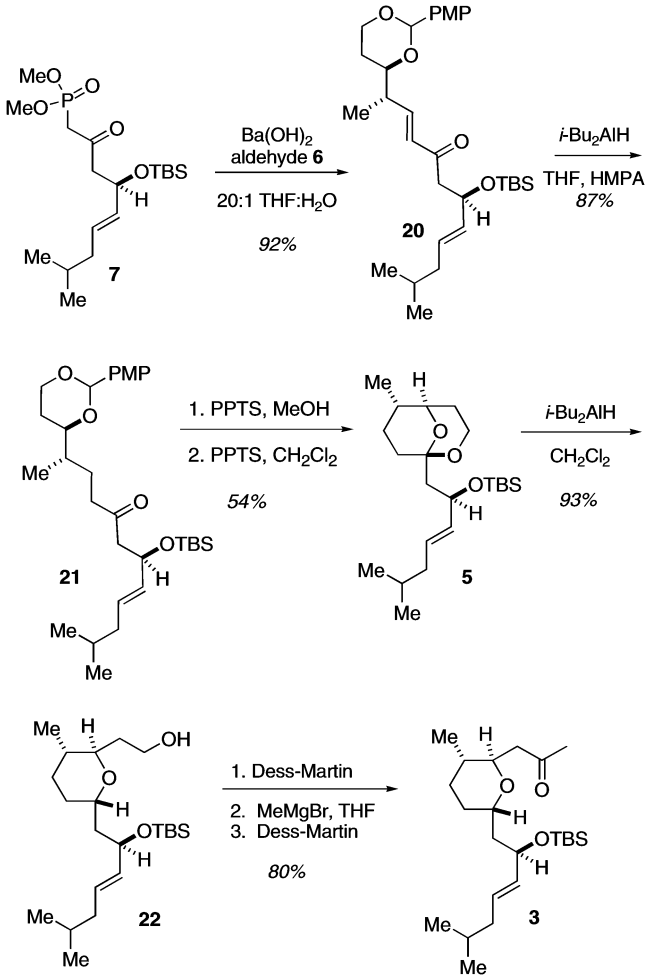
(13) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784.

Scheme 4. Synthesis of Aldehyde **4**



between ketophosphonate **7** and aldehyde **6** under Paterson's conditions with barium hydroxide to deliver enone **20** in excellent yield.[14] At this point, it was necessary to selectively reduce the enone double bond. While $NaBH_4-NiCl_2$ cleanly reduced the enone,[15] varying amounts (10−20%) of reduction of the C18−C19 isolated olefin always accompanied enone reduction. After a brief survey of conditions, it was found that the enone double bond could be selectively reduced with *i*-Bu_2AlH in THF in the presence of HMPA to give the saturated ketone **21** in 87% yield with no evidence of over reduction of the ketone.[16] Attempts to directly access the bridged ketal **5** from **21** under acid catalysis resulted in significant decomposition. Therefore, a two-step protocol was adopted, wherein the PMP benzylidine was first treated with PPTS in methanol to give the mixed methyl ketal. Upon further treatment with PPTS in dichloromethane, methanol was lost to provide the desired bicyclic ketal **5**. Treatment of **5** with *i*-Bu_2AlH under the conditions described by Kotsuki smoothly delivered the tetrahydropyran **22** in 93% yield presumably through the intramolecular delivery of hydride by coordination of *i*-Bu_2AlH to the ketal oxygen.[6] Unfortunately, the desired 2,6-*trans* tetrahydropyran was inseparable from its 2,6-*cis* isomer and their ratio could not be directly determined by ^1H NMR. Both isomers **22** were converted to methyl ketone **3** through a three-step oxidation, methyl Grignard addition, and oxidation sequence. Inspection of the ^1H NMR of ketone **3** indicated a ratio of 15:1 in favor of the desired trans isomer. Thus, the internal delivery of the coordinated reducing agent in the reduction of **5** provided the desired *trans* 2,6-tetrahydropyran as a 15:1 mixture of diastereomers.

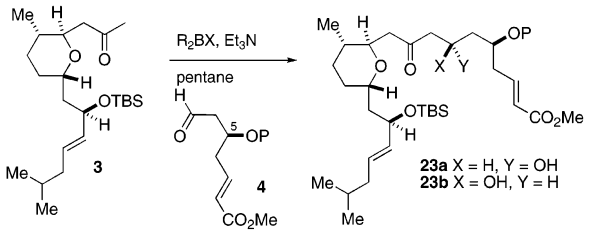
Scheme 5. Completion of Methyl Ketone **3**



With both methyl ketone **3** and aldehyde **4** in hand, it was possible to explore the assembly of the two subunits through a double diastereoselective aldol reaction. On the basis of precedent from studies by Evans[6] and examples from our own synthesis of spongistatin,[17] as well as other recent examples,[18] we anticipated a highly selective aldol reaction by virtue of the direction of the β-alkoxy group of the methyl ketone. In the event, formation of the dicyclohexyl boryl enolate of ketone **3** (Cy_2BCl, Et_3N, pentane, 0 °C) followed by addition of aldehyde **4** (−78 °C, 3 h) resulted in a yield of 82% of the aldol adducts, but in a disappointing 68:32 ratio of **23a**:**23b** (see Table 1).

(14) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774−776.
(15) Abe, N.; Fujisaki, F.; Sumoto, K.; Miyano, S. *Chem. Pharm. Bull.* **1991**, *39*, 1167−1170.
(16) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537−540.
(17) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; MacAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661−5663. Crimmins, M. T.; Katz, J. D.; Captain, L. F.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949−952.
(18) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481−484. Diaz, L. C.; Bao, R. Z.; de Sousa, M. A.; Zukeman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325−4327.

Table 1. Aldol Additions of Boron Enolates of Ketone **3**



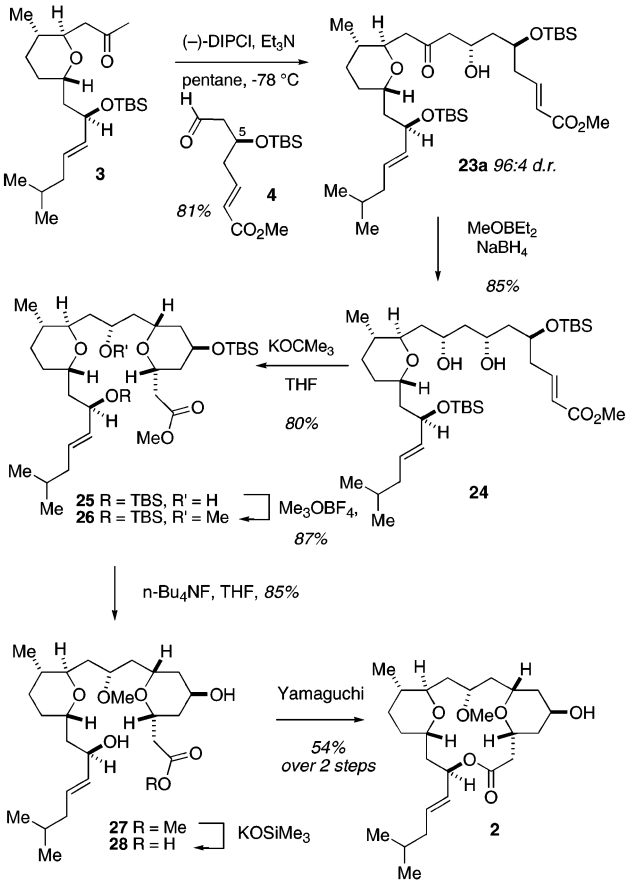
conditions	P	ratio **23a**:**23b**	yield, %
Cy_2BCl, Et_3N, pentane, −78 °C	TBS	68:32	82
Cy_2BCl, Et_3N, pentane, −100 °C	TBS	68:32	88
Bu_2BOTf, DIEA, Et_2O, −78 °C	TBS	25:75	87
Cy_2BCl, Et_3N, pentane, −78 °C	PMB	75:25	74
(−)-DIPCl, Et_3N, pentane, −78 °C	TBS	96:4	81

Attempts to improve the selectivity by lowering the reaction temperature and by altering the protecting group of the β-alkoxy group (TBS to PMB) of the aldehyde met with no significant change in the diastereoselectivity. Since De Brabander[19] had noted improvements in a similar aldol addition by changing from the dicyclohexylboryl enolate to dibutyl or diethylboryl enolate, the dibutylboryl enolate of **3** was tested. Surprisingly, a reversal of the selectivity to 25:75 favoring the 1,5-syn adduct **23b** was observed.

Since the dicyclohexylboryl enolate resulted in an aldol addition favoring the desired 1,5 anti adduct **23a**, it seemed reasonable that the use of the chiral dialkylboron chloride, (−)-DIPCl,[19] might improve the selectivity. Indeed, enolization of ketone **3** ((−)-DIPCl, Et_3N, pentane, 0 °C), followed by addition of aldehyde **4** (−78 °C), resulted in a highly diastereoselective aldol reaction favoring the 1,5 anti adduct **23a** (81%, 96:4; **23a**:**23b**).

With all the carbons installed, the β-hydroxy ketone **23a** was readily reduced to the *syn*-1,3-diol **24** by the action of diethylmethoxyborane and sodium borohydride.[20] 2,6-*cis*-Disubstituted-tetrahydropyran **25** (12:1 dr) was then obtained via a hetero-Michael addition when unsaturated ester **24** was exposed to catalytic *t*-BuOK in THF. The C9 alcohol was then converted to methyl ether **26** by treatment with Meerwein's salt and 4-methyl-2,6-di-*tert*-butylpyridine. Both *tert*-butyldimethyl silyl groups were removed with TBAF, and the methyl ester was hydrolyzed with potassium trimethylsilanolate to give acid **28**.[4] Finally, regioselective macrolactonization under Yamaguchi conditions[21] provided macrocycle **2**, which was identical in all respects with published spectral data and optical rotation.[4]

Scheme 6. Synthesis of Leucascandrolide A Macrolactone **2**



The synthesis of the leucascandrolide A macrolactone **2** has been accomplished in a highly convergent 20 linear steps from propanediol. The synthesis is highlighted by a diastereoselective reductive opening of a bicyclic ketal and a hetero-Michael addition to construct the two tetrahydropyrans, and a (−)-DIPCl-mediated diastereoselective aldol addition to establish the C7 stereocenter.

Acknowledgment. We thank the National Institutes of Health (NCI, CA63572) for generous financial support.

Supporting Information Available: Spectral data (^{1}H and ^{13}C NMR) of macrolactone **2** as well as full experimental details for the synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581−8584.

(20) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9.