ORGANIC LETTERS

2012
Vol. 14, No. 21
5492–5495

Total Synthesis of Alotaketal A

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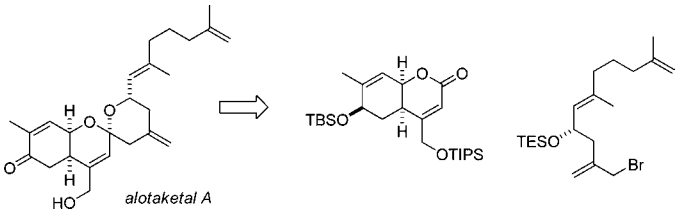
Received September 18, 2012

ABSTRACT



The total synthesis of the cAMP signaling pathway activator (−)-alotaketal A is reported. A convergent approach to the unusual alotane sesterterpenoid skeleton was employed, exploiting a remarkable LiDBB-mediated coupling of an (*R*)-carvone-derived δ-lactone with an allyl bromide side chain, followed by spiroacetalization.

The marine environment continues to provide an unrivalled array of novel, biologically prevalidated natural products, which offer an important source of lead compounds for the development of new chemotherapeutic agents and tools for chemical biology.[1] In search of such structures, recent screening of extracts of the marine sponge *Hamigera sp.*, collected off the coast of Papua New Guinea by Andersen and co-workers, led to the isolation of alotaketal A (**1**, Scheme 1). Structurally, this sesterterpenoid is characterized by its unprecedented "alotane" carbon skeleton, consisting of a hydrobenzopyranyl spiroacetal core appended with a geranyl side chain.[2] Notably, alotaketal A induces potent activation of the cAMP signaling pathway in HEK293 cells (EC_{50} = 18 nM), which given the importance of cAMP signaling to cellular function, bestows upon it potential utility as a small-molecule lead for further drug development as well as a potentially important probe for cell biology research.[3]

The closely related phorbaketals were subsequently isolated by Rho and co-workers from the Korean marine sponge *Phorbas sp.*,[4] and shown to exhibit low micromolar activity against a range of human cancer cell lines, and may find use for the treatment of osteoporosis.[5]

The recent first total synthesis of alotaketal A (**1**) by Yang and co-workers[6] served to verify the full configurational assignment of the alotaketals as suggested by Rho[3] and refined by Andersen.[7] As part of our ongoing interest in the synthesis of new bioactive marine natural products,[8] we now describe our own stereocontrolled total synthesis of alotaketal A (**1**), enabling access to synthetic material for further biological evaluation.

As outlined retrosynthetically in Scheme 1, our approach to alotaketal A (**1**) would exploit thermodynamic control in assembling the doubly anomerically stabilized spiroacetal upon deprotection of the C16 TES ether of **2**. Hemiacetal **2** would itself arise through addition of a suitably metalated derivative of side-chain allyl bromide **3** to the bicyclic lactone core **4**.[9] Allyl bromide **3** would be formed through elaboration of geraniol (**5**), including an asymmetric acetate aldol reaction to install the C16 stereocenter.

(1) (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144. (b) Dalby, S. M.; Paterson, I. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 777. (c) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.

(2) Forestieri, R.; Merchant, C. E.; de Voogd, N. J.; Matainaho, T.; Kieffer, T. J.; Andersen, R. J. *Org. Lett.* **2009**, *11*, 5166.

(3) (a) Pavan, B.; Biondi, C.; Dalpiaz, A. *Drug Discovery Today* **2009**, *14*, 982. (b) Beavo, J. A.; Brunton, L. L. *Nat. Rev. Mol. Cell. Biol.* **2002**, *3*, 710.

(4) Rho, J.-R.; Hwang, B. S.; Sim, C. J.; Joung, S.; Lee, H. Y.; Kim, H.-J. *Org. Lett.* **2009**, *11*, 5590.

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(7) Daoust, J.; Fontana, A.; Merchant, C. E.; de Voogd, N.; Patrick, B. O.; Kieffer, T. J.; Andersen, R. J. *Org. Lett.* **2010**, *12*, 3208.

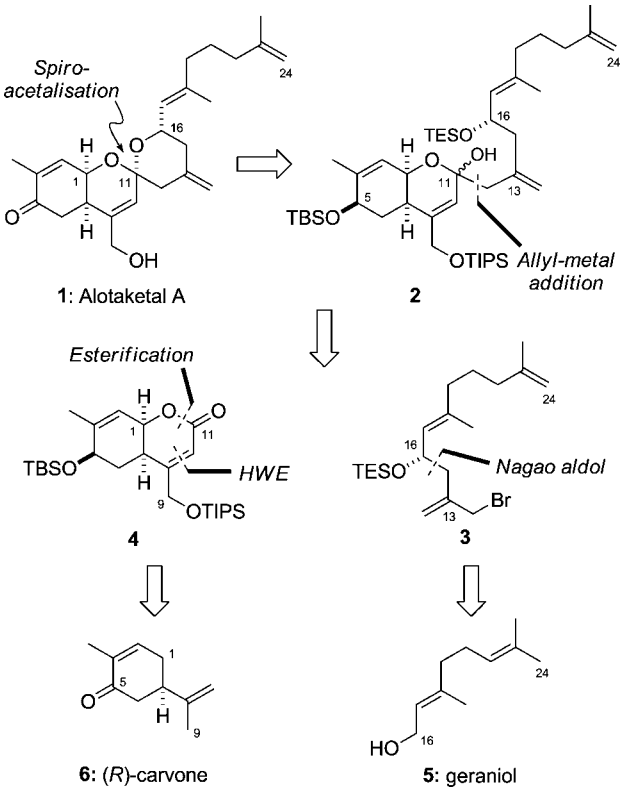
(8) (a) Paterson, I.; Maltas, P.; Dalby, S. M.; Lim, J. H.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 2749. (b) Paterson, I.; Naylor, G. J.; Gardner, N. M.; Guzmán, E.; Wright, A. E. *Chem. Asian J.* **2011**, *6*, 459. (c) Paterson, I.; Paquet, T.; Dalby, S. M. *Org. Lett.* **2011**, *13*, 4398.

(9) A similar generalized approach was employed by Yang and co-workers; see ref 6.

10.1021/ol302570k
Published on Web 10/24/2012

Lactone **4** meanwhile was considered to represent an oxidized (C1, C9) derivative of (*R*)-carvone (**6**), which might subsequently undergo esterification/intramolecular Horner–Wadsworth–Emmons lactonization.

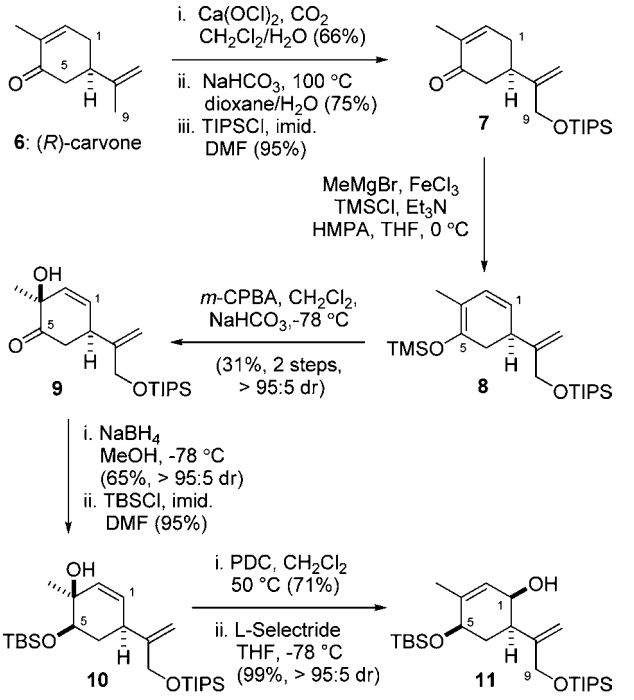
Scheme 1. Retrosynthetic Analysis of Alotaketal A



Initial attempts to incorporate the C1 and C9 oxygenation directly through a regioselective double allylic oxidation reaction of (*R*)-carvone (**6**), or its C5-TBS ether derivative, proved unrewarding.[10] In response, sequential introduction of both oxygens was carried out, commencing with regioselective allylic chlorination of (*R*)-carvone (**6**, Scheme 2).[11] Basic hydrolysis and silylation then provided the allylic ether **7** (47%, 3 steps).

Introduction of the C1 oxygenation would now be achieved through preparation and oxidation of the corresponding dienyl ether. Accordingly, regioselective enolization of enone **7** ($MeMgBr$, $FeCl_3$) and trapping with TMSCl provided silyl dienyl ether **8**,[12] which optimally was submitted crude to Rubottom oxidation with *m*-CPBA in CH_2Cl_2 at −78 °C.[13] Pleasingly, this provided α-hydroxy ketone **9** in a highly regio- and diastereoselective (> 95:5 dr) manner.[14–16] Subsequent diastereoselective reduction with $NaBH_4$ (> 95:5 dr) provided the corresponding diol, which was straightforwardly differentiated through TBS protection of the secondary C5 alcohol to provide **10**. Treatment of **10** with PDC in refluxing CH_2Cl_2 then induced smooth allylic transposition of the C3 tertiary alcohol to establish the requisite C1 oxygenation as the corresponding ketone.[17] Subsequent reduction with L-Selectride proceeded stereoselectively (> 95:5 dr) to finally provide the targeted, doubly oxidized carvone scaffold **11** for elaboration to the bicyclic δ-lactone core of alotaketal A (**4**).[14]

Scheme 2. Preparation of Oxidized Carvone Scaffold **11**



As shown in Scheme 3, this process commenced with regioselective oxidative cleavage of the less hindered/electron rich C8–C10 alkene of **11** under modified

(10) (a) Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 7, p 83. (b) CrO_3, SeO_2, $Mn(OAc)_3$, $Pd(OH)_2$ and $Rh_2(cap)_4$ based methods were all investigated.

(11) Hegde, S. G.; Vogel, M. K.; Saddlerqq, J.; Hrinyo, T.; Rockwell, N.; Haynes, R.; Oliver, M.; Wolinsky, J. *Tetrahedron Lett*. **1980**, *21*, 441.

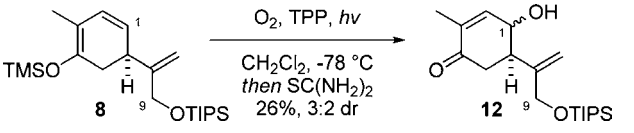
(12) (a) Krafft, M. E.; Holton, R. A. *J. Am. Chem. Soc*. **1984**, *106*, 7619. (b) Saraber, F. C. E.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; Groot, A. de *Tetrahedron* **2006**, *62*, 1726.

(13) Rubottom, G. M.; Vazques, M. A.; Pelegrina, D. R. *Tetrahedron Lett*. **1974**, *15*, 4319.

(14) Stereochemical determination was achieved through NOE-based NMR analysis. See Supporting Information for details.

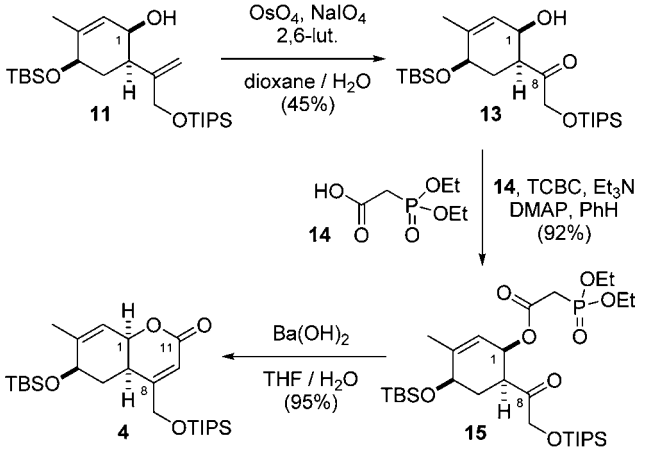
(15) The modest yield relates primarily to the formation of byproducts having incorporated an additional methyl group at C2 during the enolization step.

(16) Direct installation of the C1 oxygenation from silyl dienyl ether **9** was also investigated through photooxidation with singlet oxygen. Optimally, irradiation of a solution of **8** in CH_2Cl_2 at −78 °C under an oxygen atmosphere using a TPP sensitizer provided, after reductive workup of the C1 peroxide with thiourea, the targeted keto-alcohol **12** in low yield (26%) with much diminished diastereoselectivity (3:2 dr). Use of the nitrosobenzene oxygen equivalent proved similarly unfruitful in this case; Tian, G.-Q.; Yang, J.; Rosa-Perez, K. *Org. Lett*. **2010**, *12*, 5072.



Johnson–Lemieux conditions.[18] Yamaguchi esterification of the ensuing alcohol **13** with phosphonate **14** then provided keto-phosphonate **15**, set for HWE ring closure. In the event, treatment with $Ba(OH)_2$ in wet THF delivered bicyclic δ-lactone **4** in excellent yield (95%).[19]

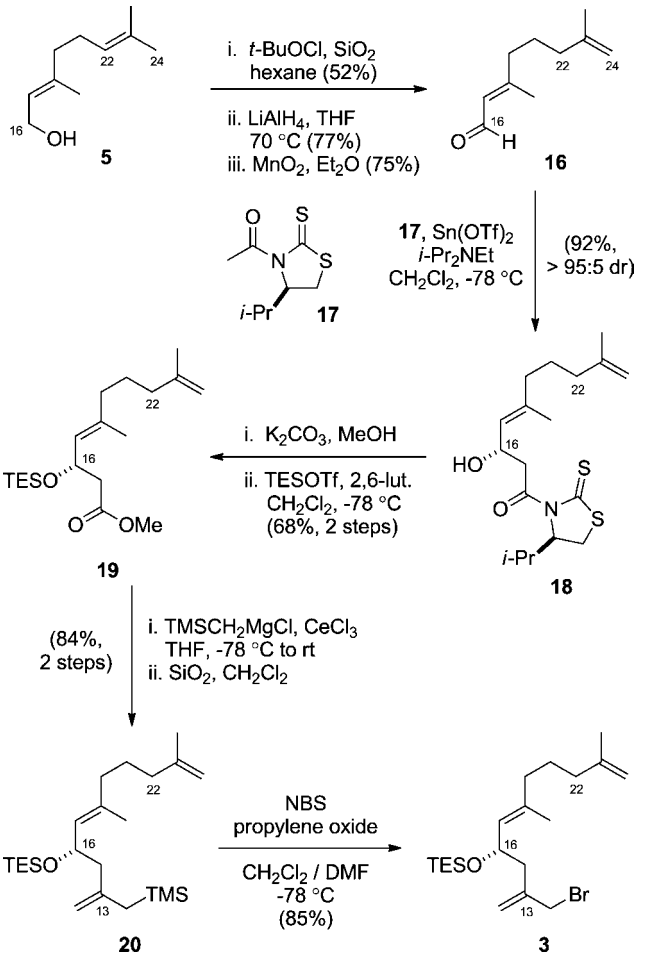
Scheme 3. Completion of the Bicyclic Lactone Core **4**



The synthesis of the side-chain coupling partner, allyl bromide **3**, commenced with regioselective allylic chlorination of geraniol with *t*-BuOCl (Scheme 4). This provided a secondary allylic chloride, which was reduced with $LiAlH_4$ in refluxing THF to effect overall isomerization to the terminal alkene.[20] Allylic oxidation with MnO_2 then provided aldehyde **16** in readiness for a Nagao acetate aldol reaction to install the C16 stereocenter.[21] In the event, exposure of **16** to the tin(II) enolate of thioimide **17** at −78 °C afforded the desired aldol adduct **18** in excellent yield and diastereoselectivity (92%, >95:5 dr). Methanolytic cleavage of the auxiliary (K_2CO_3, MeOH) followed by silyl protection then provided methyl ester **19** (68%, 2 steps). Elaboration of methyl ester **19** to allyl bromide **3** was carried out by way of the corresponding allyl silane **20**. Accordingly, addition of two equivalents of freshly prepared $TMSCH_2MgCl$ to **19** provided the corresponding tertiary alcohol, which underwent smooth, acid-mediated Petersen elimination upon prolonged (15 h) stirring over silica gel to give allyl silane **20**.[22] Finally, brief (30 min), low temperature (−78 °C) exposure of **20** to NBS in the presence of propylene oxide led to smooth bromination of the allyl silane without accompanying reaction of the C23–C24 alkene.

With both key fragments, bicyclic lactone **4** and allyl bromide **3** in hand, the pivotal coupling reaction for the

Scheme 4. Synthesis of Allyl Bromide **3**



total synthesis of alotaketal A (**1**) could be investigated. Initial model studies, involving the addition of various metalated derivatives of methallyl bromide to **4**, revealed that while lithiated derivatives (*t*-BuLi/*n*-BuLi) failed to undergo any productive reaction, the corresponding Grignard (Mg) and zinc (Zn, Cp_2TiCl_2)[23] derivatives were highly competent allyl donors. Translating these results to allyl bromide **3** proved problematic however, with difficulties encountered in forming the requisite allyl metal derivatives of **3**, which then could not be coaxed into undergoing productive reaction with **4**.[24] Ultimately, it was found that addition of an excess of LiDBB[25] (ca. 5 equiv, titrated until color persisted) to a mixture of lactone **4** and allyl bromide **3** (1.2 equiv) in THF at −78 °C led to rapid (<5 min)

(17) (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (b) Luzzio, F. A. *Org. React.* **1998**, *53*, 1.

(18) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

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(21) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211.

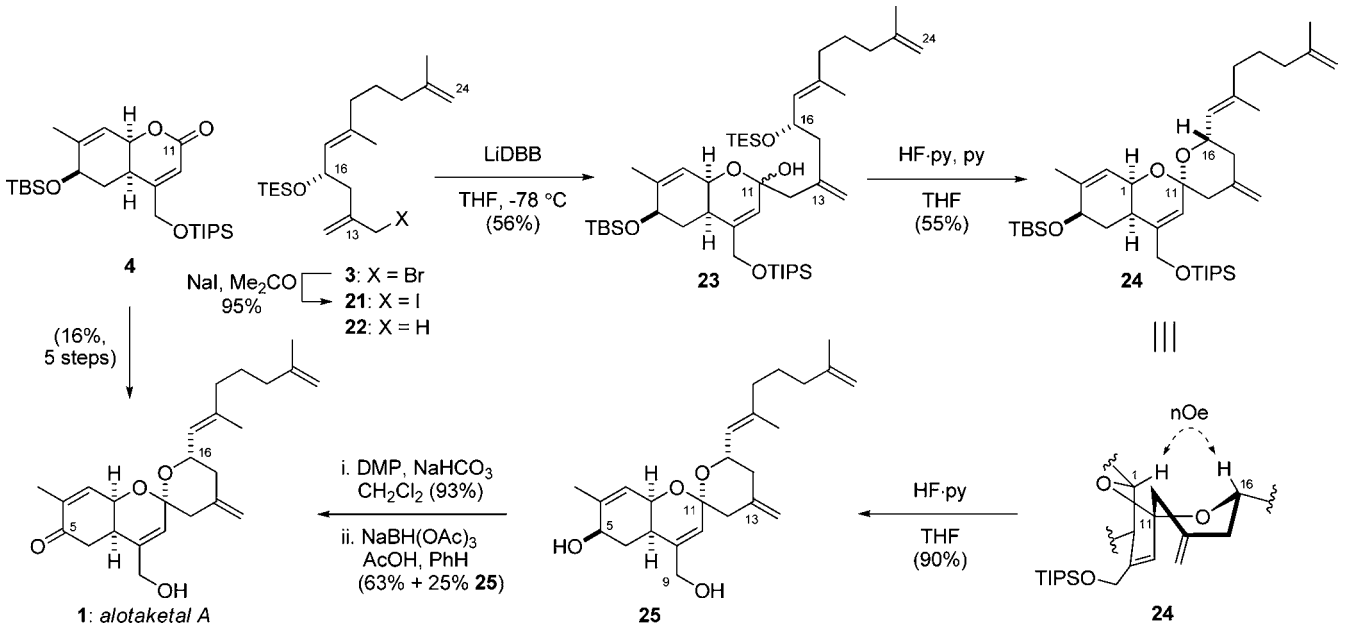
(22) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.

(23) (a) Fleury, L.; Ashfeld, B. *Org. Lett.* **2009**, *11*, 5670. (b) Ding, Y.; Zhao, G. *Tetrahedron Lett.* **1992**, *33*, 8117.

(24) The allyl Grignard and allyl zinc derivatives of **3** were prepared from iodide **21**, neither of which underwent addition to lactone **4**. The corresponding allyl lithium species could be prepared from bromide **3** (*t*-BuLi), although in line with model studies this, and the organocerium derivative ($CeCl_3$) also failed in adding to lactone **4**. Unreacted **4** and dehalogenated **22** were returned in each case. Similar observations were made by Yang and co-workers; see ref 6.

(25) (a) Freeman, P. K.; Hutchinson, L. L. *Tetrahedron Lett.* **1976**, *17*, 1849. (b) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

Scheme 5. Total Synthesis of Alotaketal A (**1**)



consumption of lactone **4** and formation of the targeted hemiacetal **23**, which was isolated as a single (presumably stabilized) anomer in 56% yield (Scheme 5). The mode of addition proved critical to the success of the reaction, where addition of lactone **4** to the preformed organolithium derivative of **3** led only to recovery of debrominated **22** without formation of **23**.[26]

Spiroacetalisation of the rather acid-sensitive hemiacetal **23** was then accomplished through removal of the C16 TES-ether upon treatment with buffered HF·py, which provided **24** as a single diastereomer, in addition to ca. 15% of a chromatographically separable C12–C13 alkene isomer. That the newly formed C11 spiroacetal (δ_C = 96.8 ppm) adopted the correct, anomerically stabilized configuration was confirmed by a diagnostic NOE enhancement observed from H16 to H1, also observed for the natural product.[14]

Completion of the total synthesis of alotaketal A required deprotection and adjustment of the C5 oxidation state. Since selective deprotection of the C5 TBS-ether proved elusive, removal of both silyl ethers was carried out using HF·py. While access to diol **25** could be effected directly from **23** (HF·py), increased amounts (ca. 30%) of the undesired and now chromatographically inseparable C12–C13 alkene isomer were encountered in doing so. Double oxidation of **25** cleanly provided the corresponding keto-aldehyde, which finally underwent selective reduction of the C9 aldehyde with $NaBH(OAc)_3$ to deliver alotaketal A (**1**, 63%) together with some over-reduced **25** (25%) which could be further recycled.

Synthetic alotaketal A exhibited spectral characteristics ($^1H/^{13}C$ NMR, IR, HRMS) identical in all respects to that reported for the natural sample,[2] together with the measured specific rotation ($[\alpha]_D^{20} = -63.6$ (*c* 0.11, MeOH), lit: $[\alpha]_D^{20} = -38.9$ (c 0.01, MeOH), thus confirming the integrity of the total synthesis.

In summary, we have completed the total synthesis of alotaketal A in 0.5% yield over 17 steps. This convergent approach, utilizing readily available carvone and geraniol to construct the novel alotane skeleton, should also be appropriate for preparing the phorbaketals,[4] and amenable to the generation of a range of non-natural analogs for SAR studies and further biological evaluation.

Acknowledgment. We thank the EPSRC National Mass Spectrometry Service (Swansea) for mass spectra and Clare College, Cambridge (Fellowship to S.M.D.).

Supporting Information Available. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) The success of this procedure is in marked contrast to that using *t*-BuLi and might point to either the formation of a subtly different organometallic species or an alternate reaction mechanism leading to **23**. For a related case, see: Meyers, A. I.; Rawson, D. J. *Tetrahedron Lett.* **1991**, *32*, 2095.

The authors declare no competing financial interest.