HETEROCYCLES, Vol. 72, 2007, pp. 167 - 174. © The Japan Institute of Heterocyclic Chemistry
Received, 11th December, 2006, Accepted, 1st February, 2007, Published online, 6th February, 2007. COM-06-S(K)42

STUDIES TOWARD THE TOTAL SYNTHESIS OF GRANDISINE A: SYNTHESIS OF 9-*epi*-GRANDISINE A

David J. Maloney[1] and Samuel J. Danishefsky[1,2,*]

[1]Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10021 and [2]Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027 (USA)

We dedicate this paper to the extraordinary and continuing accomplishments of Professor Yoshito Kishi.

Abstract – A concise synthesis of 9-*epi*-grandisine A is described, which makes use of a Lewis acid-promoted hetero-Diels-Alder reaction to construct the tricyclic skeleton. Attempts to obtain grandisine A through a late-stage controlled epimerization are also discussed.

Recently, several novel indolizidine alkaloids, grandisine A (**1**), B[1] and C–F,[2] were isolated by Carroll and co-workers from the leaves of the Australian rainforest tree, *Elaecarpus grandis*. In addition to their interesting structures, these compounds possess modest binding affinity (~1-75 μM) for the human δ-opioid receptor. Opioid receptors (μ, κ, δ) are G-protein coupled receptors, long known to be involved in the modulation of pain. Interestingly, activation of both the μ and κ-receptors by an agonist (i.e. morphine) causes a number of undesired side effects, including nausea, itching and reduced blood pressure. However, it has been shown in animal models that selective activation of the δ -receptor by agonists results in pain modulation without these adverse side effects.[3] Thus, higher affinity small molecule agents, perhaps based on the grandisine lead, which may selectively bind to the δ -receptor, could represent valuable avenues for exploration in the ongoing search for improved therapeutic agents for the management of pain.

Of this class of compounds, we were particularly interested in grandisine A (**1**), which presents all *cis*-hydrogens at C_7, C_8 and C_9 (Figure 1), resulting in a highly "cupped" tetracyclic structure. Carroll and co-workers had assigned the relative stereochemistry of **1** from a combination of coupling constants and ROESY correlations.[1] Interestingly, the relative stereochemistry of grandisine A differs from the other members of the grandisine family, in which C_7 and C_8 are *trans* with respect to C_9. We anticipated that a mission directed to the synthesis of the presumably internally hindered grandisine A would present a formidable synthetic challenge. The combination of this unique structural feature of grandisine A and its lead value en route to a potent and selective δ-opioid agonist rendered it an attractive target for total synthesis. Herein, we describe initial investigations toward the total synthesis of grandisine A. The approach makes use of a Lewis-acid promoted hetero-Diels-Alder (HDA) reaction, followed by an acid-catalyzed cyclization/dehydration sequence to construct the core scaffold of **1**. Moreover, our attempts at a late stage controlled epimerization of 9-*epi*-grandisine A are also discussed.

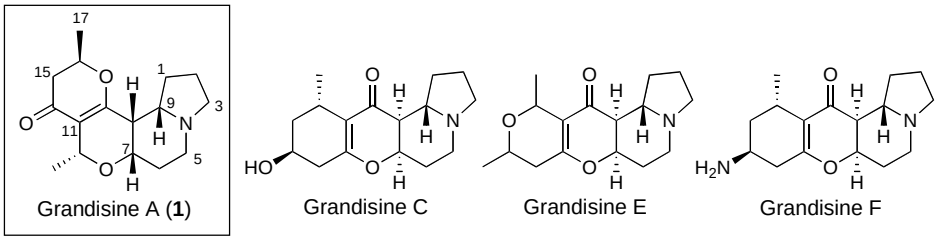
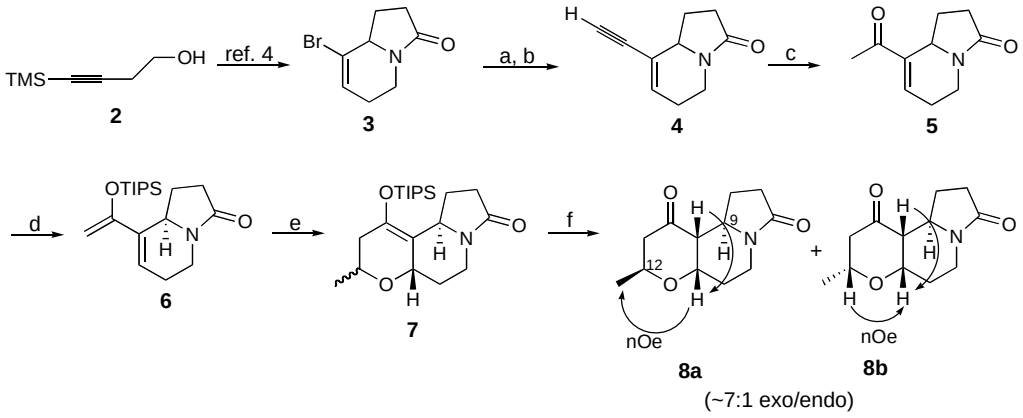


Figure 1. Grandisine A, C, E and F

Studies directed to the synthesis of grandisine A (**1**) commenced with bromoindolizidine **3**,[4] itself prepared by known methods in 6 steps (47% overall yield) from commercially available 4-trimethylsilyl-3-butyn-1-ol (**2**). Sonogashira coupling[5] of **3** with TMS-acetylene under standard conditions, followed by base-mediated silyl deprotection, afforded the desired product **4** (76%, 2 steps). Formation of the enone **5** was accomplished in high yield via $Hg(OAc)_2$ catalyzed hydration of the alkyne followed by basic workup. With enone **5** in hand, our attentions turned to the key hetero-Diels-Alder cycloaddition. Our initial investigations of this reaction utilized a TBS-siloxy diene (formed from **5**, using TBSOTf, 2,6-lutidine). Following an extensive survey of reaction conditions, we identified BF_3•OEt_2 in CH_2Cl_2 at –78 °C as the optimal system.[6] Indeed, most other Lewis acids and solvents examined yielded mainly Mukaiyama aldol[7] product, or resulted in no reaction. However, even under our optimal system, we observed significant amounts of hydrolyzed starting material (~25%) and Mukaiyama aldol product (~20%) in addition to the desired HDA adduct (51%, 2.5:1 *exo*:*endo*). We thus turned to the TIPS-siloxy diene **6**, in the hope that it might be more robust toward

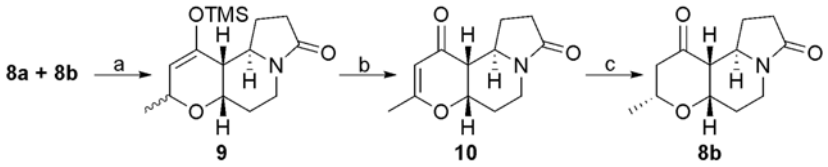
hydrolysis and that it also would favor the desired cycloaddition pathway over the competing Mukaiyama aldol pathway.[8] To our delight, exposure of **6** to our optimal HDA conditions (*vide supra*) gave the desired product (from the standpoint of the C_7-C_9 relationship), albeit as a mixture of *exo*:*endo* isomers. Subsequent deprotection of the TIPS enol ether using acetic acid buffered TBAF furnished the tricyclic compounds **8a** and **8b** as a ~7:1 mixture of isomers. Following 2D NMR analysis (COSY and NOESY) of the cycloadducts, it became apparent that the HDA cycloaddition had strongly favored the undesired *exo* isomer. However, although the HDA cycloaddition occurred primarily from the undesired face, the subsequent protonation of the enol ether did afford the desired C_7–C_8 *cis*-ring junction. Interestingly, the product obtained from the HDA reaction and subsequent protonation of the enol ether represents the required relative stereochemistry for grandisines C, E and F, as shown in Figure 1. Despite the stereochemical outcome of the HDA reaction, the facile construction of this advanced tricyclic intermediate encouraged us to proceed with the synthesis, in the hopes of correcting the stereochemistry of C_{12} and C_9 at a later juncture.



Scheme 1. a) TMS-acetylene (3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.1 equiv), NEt_3 (4 equiv), DMF, 50 °C, 3 h, 76% b) 2 N KOH MeOH, MeOH, 25 °C, 100% c) $Hg(OAc)_2$ (0.1 equiv), H_2SO_4 (1.1 equiv), AcOH, 25 °C, 95% d) TIPSOTf (1.5 equiv), 2,6-lutidine, CH_2Cl_2, 4Å mol. sieves, 0 °C→25 °C, 91% e) **6**, CH_2Cl_2, –78 °C then acetaldehyde (10 equiv), BF_3•OEt_2 (2 equiv), CH_2Cl_2, –78 °C f) TBAF (1.1 equiv), AcOH (1.5 equiv), THF, 0 °C→25 °C, 79-88% (2 steps).

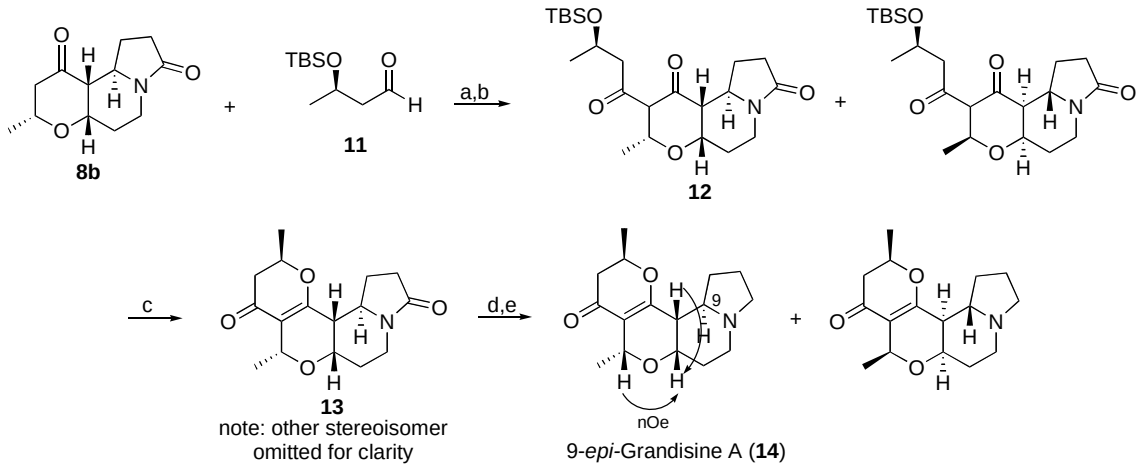
As suggested in Scheme 2, we envisioned that the configuration of the C_{12} methyl group of **8a** could be inverted by conversion to enone **10,** followed by hydrogenation from the less hindered β-face. In the event, the TMS enol ether (**9**) was generated smoothly through the action of LiHMDS and TMSCl, as depicted in Scheme 2. Our initial attempts to form enone **10** through a Saegusa-Ito oxidation

($Pd(OAc)_2$ (1.1 equiv), MeCN)[9] led to significant hydrolysis of the TMS-enol ether. Attempts to buffer the reaction conditions with $NaHCO_3$ led to partial epimerization of the resulting enone. A more robust TES enol ether afforded minimal hydrolysis but the reaction did not proceed in MeCN. By changing the solvent to DMSO and using the catalytic variant ($Pd(OAc)_2$ (0.1 equiv), O_2),[10] we were able to observe product formation; however, the isolated yield suffered considerably due to the water solubility of the product. Fortunately, the employment of conditions reported by Shibasaki and co-workers ($Pd_2(dba)_3$ (0.1 equiv), diallycarbonate (2.0 equiv), MeCN)[11] resulted in the clean conversion of **9** to the desired enone **10**, with minimal hydrolysis. Gratifyingly, hydrogenation with Pd/C and H_2 gave the desired product **8b** exclusively by ^{1}H NMR. One advantage of this route is that both products of the HDA can be carried through to give exclusively **8b**; thus, the distribution of *exo*/*endo* isomers arising from the cycloaddition is ultimately inconsequential.



Scheme 2. a) LiHMDS (1.3 equiv), TMSCl (2.0 equiv), THF, –78 °C b) $Pd_2(dba)_3$ (0.1 equiv), diallylcarbonate (2.0 equiv), MeCN, 25 °C, 70% (2 steps) c) 10% Pd/C, H_2 (1 atm), THF, 94%.

Having corrected the stereochemistry at C_{12}, we next turned our attention to the completion of the grandisine A core structure, with the hope of accomplishing a late stage epimerization at C_9 to complete the synthesis. One of the more difficult transformations of the synthesis was expected to be the aldol reaction of **8b** with aldehyde **11**[12] (prepared from commercially available ethyl-(*R*)-3-hydroxybutyrate). Possible complications of this transformation might include β-elimination and the formation of *bis*-aldol products, resulting from the undesired enolization of the amide moiety. Ultimately we found that *in situ* formation of the zinc enolate with $ZnCl_2$ and careful warming of the reaction mixture from –78 °C to –50 °C resulted in formation of the desired β-hydroxy ketone in 40-65% overall yield (60-86% BRSM). Unfortunately, full consumption of the starting material was never realized, as efforts to drive the reaction to completion by increasing the temperature or equivalents of reactants led to significant decomposition (*vide supra*).



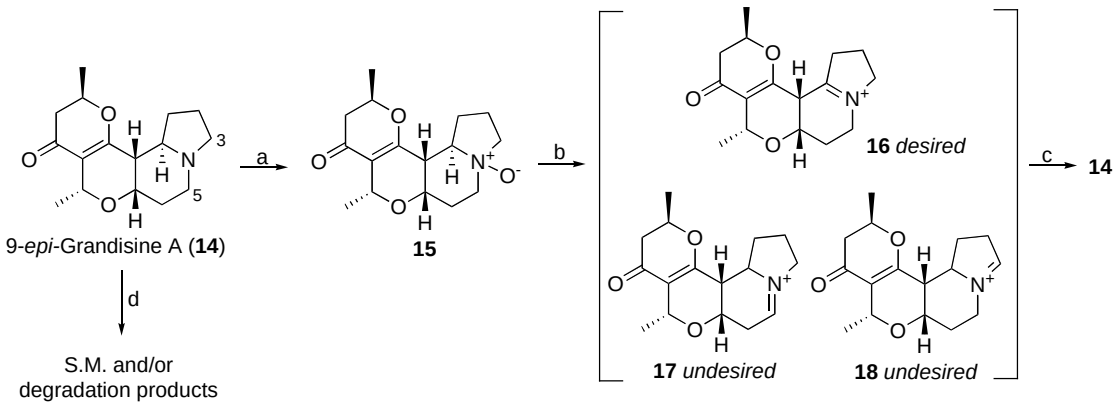
Scheme 3. a) LiHMDS (1.3 equiv), $ZnCl_2$ (2.0 equiv), (*R*)-3-(*tert*-butyldimethylsiloxy)butanal (**11**) (1.5 equiv), THF, –78 ºC→ –50 ºC, 40-65% overall, 60-86% BRSM b) Dess-Martin periodinane (1.4 equiv), CH_2Cl_2, 0 ºC→25 ºC, 84% c) cat. *p*TsOH•H_2O, 4Å mol. sieves, toluene, 90 ºC, 80% d) Lawesson's reagent (0.5 equiv), toluene, 25 ºC→60 ºC, 85% e) Raney nickel, EtOH, 40 ºC, 100%, HPLC separation yields a 1:1 mixture of stereoisomers.

Additionally, it should be noted that given that **8b** is racemic and aldehyde **11** is introduced as a single enantiomer, the resulting product is a mixture of diastereomers as shown in Scheme 3. Although this solution is not ideal, the remote nature of the stereocenter at C_{16} makes this methyl group difficult to introduce with stereoselectivity in the racemic series. Since the diastereomeric products could not be readily separated by column chromatography at this stage, the mixture was carried through to a later stage of the synthesis. Thus, Dess-Martin oxidation of the β-hydroxy ketone arising from the aldol provided the desired 1,3-diketone **12** in 84% yield. This intermediate was then subjected to acid-catalyzed cyclization with concomitant dehydration using *p*TsOH in toluene at 90 ºC, to furnish the desired dihydropyrone **13** in 80% yield.

The remaining challenges for the completion of the synthesis of grandisine A would be the reduction of the amide and the controlled epimerization of the C_9 stereocenter. Given the presence of the enone moiety in the molecule, we anticipated that direct hydride- or borane- mediated reduction of the amide to the amine would be difficult to achieve. Thus, the amide was selectively converted to the thioamide in the presence of the ketone, through the use of Lawesson's reagent (0.5 equiv) in toluene at 25 °C→60 °C. When these conditions were not carefully adhered to, substantial amounts of the thioketone-thioamide were observed. Completion of the 9-*epi*-grandisine A synthesis was accomplished via Raney nickel mediated desulfurization, which proceeded in quantitative yield. At this stage, the two stereoisomers arising from the aldol reaction could be separated through normal

phase HPLC purification, and analysis using ^{1}H, ^{13}C and 2D NMR experiments (COSY and NOESY) provided support for the assignment of stereochemistry of 9-*epi*-grandisine A.[13]

With **14** in hand, we sought to explore the possibility of effecting the inversion of the C_9 stereocenter, in the hopes of reaching the natural product itself. Given the "cupped" nature of the natural product, we envisioned that if the desired iminium ion between C_9 and the nitrogen could be formed (*cf.* **16**), then the ensuing hydride delivery should occur from the desired convex face. Toward this end, we turned to the Potier-modified[14] Polonovski reaction[15] to effect this transformation (Scheme 4). As such, treatment of 9-*epi*-grandisine A (**14**) with *m*-CPBA led to clean conversion to the desired *N*-oxide (**15**), which was then treated with trifluoroacetic anhydride (TFAA), followed by exposure to a hydride source ($NaCNBH_3$ or $NaB(OAc)_3H$). Unfortunately, only starting material was recovered from this reaction sequence.



Scheme 4. a) 100% *m*-CPBA (1.1 equiv), CH_2Cl_2, 0 °C, b) TFAA (2.0 equiv), CH_2Cl_2, –20 °C→25 °C c) $NaCNBH_3$ or $NaB(OAc)_3H$, MeOH, 0 °C ~20-30% d) 1) $Hg(OAc)_2$ (10 equiv), 5% AcOH, 100 °C or 2) $Hg(OAc)_2$:EDTA (1:1) (3.0 equiv), 33% aq. EtOH, reflux.

This result suggests that imine formation is likely occurring via deprotonation at either C_5 or C_3 to afford intermediates **17** or **18**, respectively. Formation of either of these iminium ion intermediates would clearly represent an unproductive pathway, as hydride delivery would lead to the re-generation of starting material. Several variations to this reaction were investigated; however, all resulted in relatively low recovery (~30%) of starting material as the only isolated product. Although discouraging, this observation is not without precedent, as often the Polonovski-Potier reaction proceeds from the less-substituted position, unless other factors, such as extended conjugation, are involved. Upon the failure of the Polonovski-Potier method, we next investigated the possibility of using mercury-based reagents, such as $Hg(OAc)_2$[16] or $Hg(OAc)_2$:EDTA,[17] to promote formation of the correct

iminium ion. Unfortunately, these efforts led to either recovered starting material or degradation products.

In conclusion, the results disclosed herein provide important perspective which might well form a basis for the completion of a total synthesis of grandisine A. Further studies toward this end are currently ongoing and their results will be described in due course.

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health (Grant CA103823). We are especially thankful to Dr. Emile Velthuisen for helpful discussions and Rebecca Lambert for editorial assistance.

REFERENCES AND NOTES

1. A. R. Carroll, G. Arumugan, R. J. Quinn, J. Redburn, G. Guymer, and P. Grimshaw, *J. Org. Chem.,* 2005, **70**, 1889.
2. P. L. Katavic, D. A. Venables, P. I. Forster, G. Guymer, and A. R. Carroll, *J. Nat. Prod.,* 2006, **69**, 1295.
3. M. Williams, E. A. Kowaluk, and S. P. Arneric, *J. Med. Chem.,* 1999, **42**, 1481.
4. C. Flann, T. C. Malone, and L. E. Overman, *J. Am. Chem. Soc.,* 1987, **109**, 6097.
5. a) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.,* 1975, 4467. b) M. Toyota, C. Komori, and M. Ihara, *J. Org. Chem.,* 2000, **65**, 7110.
6. a) S. Danishefsky, E. Larson, D. Askin, and N. Kato, *J. Am. Chem. Soc.,* 1985, **107**, 1246. (b) S. J. Danishefsky, W. H. Pearson, and D. F. Harvey, *J. Am. Chem. Soc.,* 1984, **106**, 2455. c) S. J. Danishefsky, W. H. Pearson, and D. Harvey, *J. Am. Chem. Soc.,* 1984, **106**, 2456. d) S. Danishefsky, E. R. Larson, and D. Askin, *J. Am. Chem. Soc.,* 1982, **104**, 6457. e) E. R. Larson and S. Danishefsky, *J. Am. Chem. Soc.,* 1982, **104**, 6458. f) E. R. Larson and S. Danishefsky, *Tetrahedron Lett.,* 1982, **23**, 1975. g) S. Danishefsky, J. F. Kerwin, and S. Kobayashi, *J. Am. Chem. Soc.,* 1982, **104**, 358. h) S. Danishefsky, N. Kato, D. Askin, and J. F. Kerwin, *J. Am. Chem. Soc.,* 1982, **104**, 360.
7. a) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.,* 1974, **96**, 7503. b) T. Mukaiyama, K. Narasaka, and K. Banno, *Chem. Lett.,* 1973, 1011.
8. a) M. T. Mujica, M. M. Afonso, A. Galindo, and J. A. Palenzuela, *Tetrahedron,* 1996, **52**, 2167. b) S. J. Danishefsky, K-H. Chao, and G. Schulte, *J. Org. Chem.,* 1985, **50**, 4650.
9. Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.,* 1978, **43**, 1011.
10. R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, and D. Zheng, *Tetrahedron Lett.,* 1995, **36**,

2423.

11. T. Ohshima, Y. Xu, R. Takita, S. Shimizu, D. Zhong, and M. Shibasaki, *J. Am. Chem. Soc.,* 2002, **124**, 14546.
12. a) L. Ferrie, P. Capdevielle, and J. Cossy, *Synlett,* 2005, 1933. b) I. Paterson, R. Britton, K. Ashton, H. Knust, and J. Stafford, *Proc. Natl. Acad. Sci. U.S.A.,* 2004, **101**, 11986. c) P. Perlmutter, W. Selajerern, and F. Vounatsos, *Org. Biomol. Chem.,* 2004, **2**, 2220.
13. 9-*epi*-Grandisine A: ^{1}H NMR (d_6-benzene, 500 MHz, relative to TMS) δ 4.72 (1H, qd, *J* = 1.1 Hz, 6.3 Hz), 3.70 (1H, m), 3.35 (1H, q, *J* = 2.6 Hz), 2.92 (1H, t, *J* = 8.4 Hz), 2.72 (1H, dd, *J* = 2.0 Hz, 5.2 Hz), 2.45 (1H, m), 2.23 (1H, m), 1.98 (4H, m), 1.80 (3H, d, *J* = 6.3 Hz), 1.69 (5H, m), 1.46 (1H, m), 0.88 (3H, d, *J* = 6.3 Hz) ppm. ^{13}C NMR (d_6-benzene, 500 MHz, relative to TMS) δ 190.03, 170.77, 116.08, 74.84, 70.53, 69.77, 63.51, 54.28, 48.06, 45.99, 43.46, 31.20, 30.40, 22.81, 21.60, 20.64 ppm. mass spectrum (electrospray ionization), *m/z* 278.2 $(M + H)^+$, *m/z* theoretical 278.2 $(M + H)^+$.
14. M. Polonovski, *Bull. Soc. Chim.,* 1927, 1190.
15. a) A. Cave, C. Kan-Fan, P. Potier, and J. Le Men, *Tetrahedron,* 1967, **23**, 4681. b) T. Tamminen, R. Jokela, B. Tirkkonen, and M. Lounasmaa, *Tetrahedron,* 1989, **45**, 2683. c) M. Lounasmaa and E. Karvinen, *Tetrahedron*, 1991, **47**, 6371.
16. a) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.,* 1955, **77**, 439. b) N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.,* 1956**, 78**, 1984. c) N. J. Leonard and D. F. Morrow, *J. Am. Chem. Soc.,* 1958, **80**, 371.
17. a) T. Fujii, M. Ohba, and N. Sasaki, *Heterocycles,* 1984, **22**, 1805. b) T. Fujii, M. Ohba, and N. Sasaki, *Chem. Pharm. Bull.,* 1989, **37**, 2822.