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Studies toward the Total Synthesis of Garsubellin A: A Concise Synthesis of the 18-*epi*-Tricyclic Core

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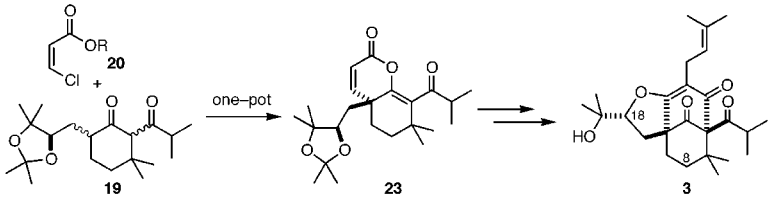
ABSTRACT



During studies directed toward the total synthesis of garsubellin A, a concise stereocontrolled synthesis of the 18-*epi*-tricyclic compound 3 was achieved. Key steps were a one-pot stereoselective construction of the bicyclic lactone 23 followed by a formal migration to the bicyclo-[3.3.1]nonane-1,3,5-trione and an intramolecular Wacker-type tetrahydrofuran ring formation.

There is an increasing demand for agents to treat neurodegenerative diseases, such as Alzheimer disease. Degeneration of cholinergic neurons is implicated in Alzheimer disease; thus compounds that can protect neurons or promote their survival (neurotrophic mimics) could provide promising pharmaceutical leads.[1] Garsubellin A (**1**, Figure 1), which

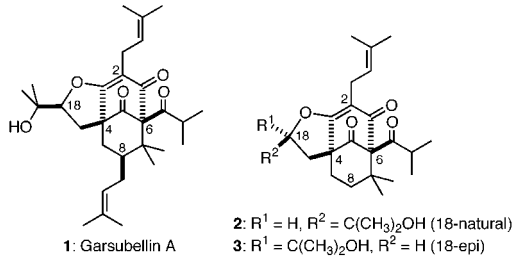


Figure 1. Garsubellin A (**1**) and our model (**2** and **3**)

was isolated by Fukuyama et al.,[2] potently induces choline acetyltransferase (ChAT), which is a key enzyme in the synthesis of the neurotransmitter acetylcholine. Structurally, garsubellin A is a polyprenylated phloroglucin derivative, characterized by a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-1,3,5-trione core fused to a tetrahydrofuran ring and appended by a prenyl side chain. Nicolaou et al. recently reported the synthesis of the bicyclic core, using a selenium-mediated cyclization.[3] We are interested in the structure and activity of garsubellin A, snd started a total synthesis project. Here, we describe our efforts, in model systems **2** and **3**, to construct the most advanced tricyclic core of garsubellin A.

Our initial retrosynthetic analysis is shown in Scheme 1. The prenyl group at the C-2 position should be introduced at the last stage via Stille coupling between tributylprenyltin (**5**) and vinyl iodide **4**. The tetrahydrofuran ring of **4** should be constructed via an intramolecular Wacker-type reaction of enone **6**. For key construction of the bicyclo[3.3.1]nonane-

(1) Cacabelos, R.; Lombardi, A.; Fernandez-Novoa, L.; Corzo, L.; Perez, P. Laredo, M.; Pichel, V.; Hernandez, A.; Varela, M.; Figueroa, J.; Prous, J.; Windisch, M. Vigo, C. *Drugs Today* **2000**, *36*, 415−499.

(2) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull*. **1997**, *45*, 947−949.

(3) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc*. **1999**, *121*, 4724−4725. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett*. **1999**, *1*, 807−810.

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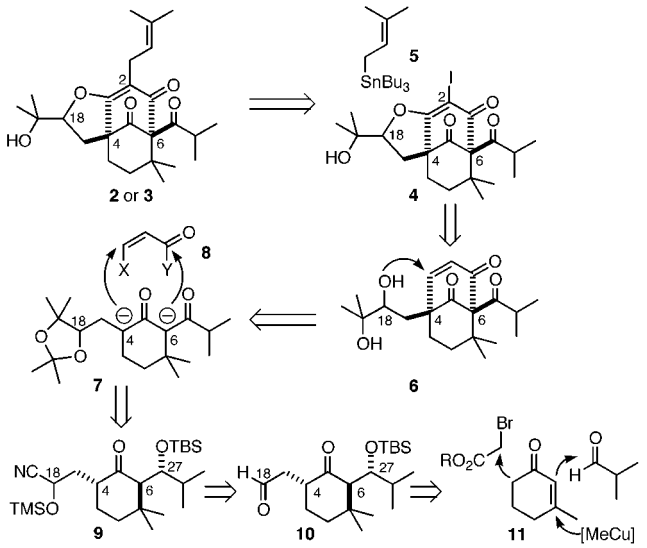
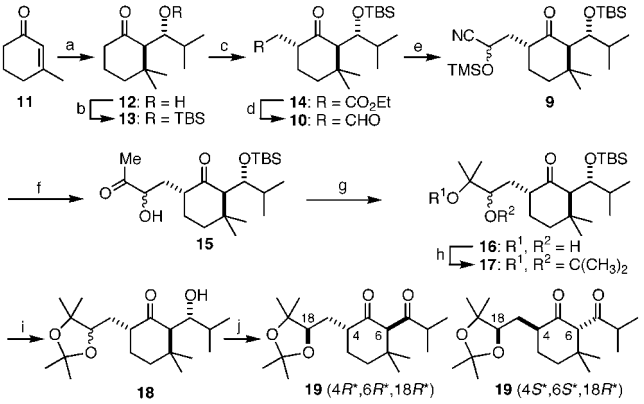
Scheme 1. Retrosynthetic Strategy



1,3,5-trione core of **6**, we planned a one-pot Michael addition−elimination (bond-formation at C-4) followed by a Dieckmann ester condensation (bond-formation at C-6) between nucleophile **7** and electrophile **8**. The face-selectivity of the electrophile entry to **7** might be controlled by the stereochemistry of C-18; however, it could not be predicted at this stage. We planned to construct the secondary alcohol at C-18 via a cyanosilylation of aldehyde **10** to extend this synthetic approach to a catalytic enantioselective synthesis of garsubellin A.[4,5] Eventually, the relative stereochemistry between C-18 and C-4, -6, and -27 was not a major concern because the stereochemistry of the latter three carbons disappeared at the later stage. Aldehyde **10** should be rapidly synthesized via a Michael−aldol reaction and a regioselective alkylation of 3-methylcyclohexen-2-one (**11**).

The initial stage of the synthesis is shown in Scheme 2. Catalytic conjugate addition of methylcuprate to enone **11** followed by a kinetic trap of the resulting magnesium enolate with isobutyraldehyde gave *threo*-isomer **12** as the sole stereoisomer.[6] After protection of the alcohol with a TBS group, the kinetically formed potassium enolate of **13** was alkylated with ethyl bromoacetate through an axial attack to

Scheme 2[a]



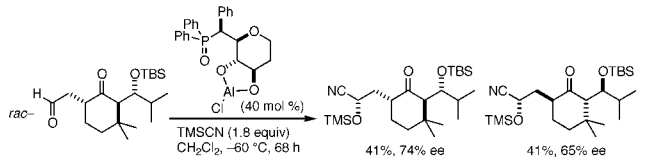
[a] Conditions: (a) 1. CuI (0.07 equiv), MeMgBr, Me_2S-THF; 2. isobutyraldehyde, 55%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 59%; (c) 1. KHMDS, THF; 2. $BrCH_2CO_2Et$, HMPA, 85%; (d) DIBAL-H, CH_2Cl_2, 88%; (e) TMSCN, Et_3N (cat.), CH_2Cl_2; (f) CuCN/MeLi = 1/3, Et_2O; H^+, 55% (2 steps); (g) MeMgBr, Et_2O, 83%; (h) dimethoxyacetone, PPTS, DMF, 80%; (i) $BF_3{\cdot}OEt_2$, $CHCl_3$; (j) Dess−Martin periodinane, CH_2Cl_2, 80% (2 steps).

give the *trans*-isomer **14** with complete selectivity. The ester group was selectively reduced using DIBAL-H, and aldehyde **10** was obtained in four steps from **11**. Cyanosilylation of **10** in the presence of a catalytic amount of Et_3N[7] gave cyanohydrin **9** as a mixture of diastereomers (1.3:1), which was converted to methyl ketone **15**[8] using a higher order cuprate prepared from CuCN and MeLi in a 1:3 ratio.[9] Selective methylation of the methyl ketone gave diol **16**, which was protected as an acetonide to give **17**. Deprotection of the TBS group with $BF_3{\cdot}OEt_2$[10] and oxidation of the resulting alcohol gave diketone **19** as a diastereo-mixture (1.3:1).[11]

Having established a facile synthetic route to **19**, the key bicyclic core construction was studied intensively.[12] To determine the feasibility of this idea, we first attempted a step-by-step reaction (Scheme 3). After deprotonation of **19** (4*R**,6*R**,18*R**) with KO^{t}Bu, the corresponding enolate was treated with electrophile **20**.[13] The resulting major product was **21** (ca. 50%), which was formed through a Michael addition−elimination reaction at C-4 (garsubellin numbering), together with Claisen condensation product **22** (10%). These results indicated that the steric factor, not the pK_a value

(4) We developed general enantioselective catalysts for cyanosilylation of aldehydes: (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (b) Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405−2409.

(5) Preliminary results indicated the feasibility of this idea (see the following scheme). Absolute configurations of the cyanohydrins are temporarily assigned from the preceding examples (ref 4b).



(6) Other isomers emerged through a retro aldol−aldol sequence, if the reaction temperature was raised to slightly over −70 °C or if there was a long reaction time (>1 h). For an organocuprate conjugate addition−*threo*-selective aldol reaction, see: Heng, K. K.; Smith R. A. J. *Tetrahedron* **1979**, *35*, 425−435.

(7) Cyanosilylation promoted by a Lewis acid catalyst (Et_2AlCl) failed. For Lewis base-catalyzed cyanosilylation of aldehydes, see: (a) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *49*, 4929−4932. (b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537−540.

(8) The diastereomers of **15** or **19** could be separated by column chromatography. We continued the synthesis as a diatereo-mixture, because the stereochemistry of C-4, -6, and -27 disappeared at the later stage.

(9) Reactions using a normal higher order cuprate (CuCN/MeLi = 1/2) gave unpredictable results. On the other hand, reactions performed under the conditions described in the text were completely reproducible.

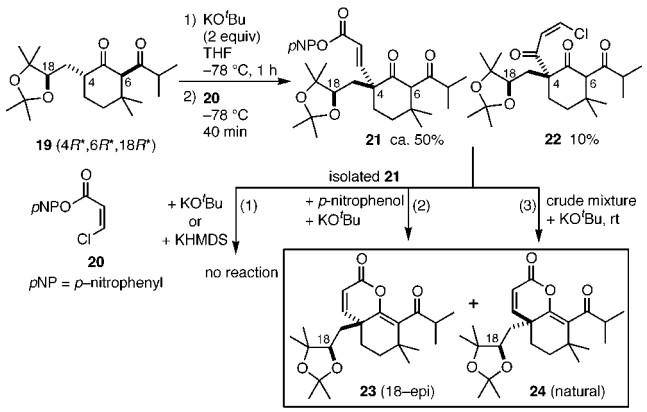
(10) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295−299.

(11) The relative configuration was determined by X-ray analysis.

(12) These preliminary studies were conducted with the diastereomerically pure compound.

(13) **20** was prepared from the corresponding carboxylic acid: Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1993**, *49*, 5225−5236.

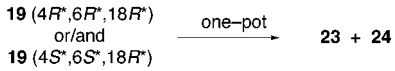
Scheme 3. Preliminary Results of the Cyclization Reaction



of α-protons, determined the position of the deprotonation, and sterically less hindered C-4 was selectively deprotonated.[14] Isolated **21** was then treated with a second base (KO^{t}Bu or KHMDS); however, no cyclization occurred, probably due to the *trans* geometry of the carbon−carbon double bond (Scheme 3, (1)). On the other hand, when the crude mixture was treated with KO^{t}Bu, cyclized compounds **23** + **24**[15] were obtained, albeit in low yield (20%) (Scheme 3, (3)). Although **23** + **24** (*O*-acylated compounds) were not the compounds we initially expected (i.e., *C*-6-acylated compound), there was a great possibility of accessing the desired bicyclic system from these compounds. We rationalized the partial success of the cyclization as follows: because of the side reaction of the Claisen condensation, the crude mixture should contain a *p*-nitrophenol, which could perform a conjugate addition to the α,*β*-unsaturated ester part of **21** (+ diastereomer) in the presence of a base in the cyclization step. This should make the activated ester accessible to the nucleophilic oxygen atom, and *O*-acylation followed by elimination of the *p*-nitrophenoxide should give unsaturated lactones **23** + **24**. Consistent with this rationale, **23** was obtained in ca. 20% yield from isolated **21**, when *p*-nitrophenol was added to the reaction mixture of the cyclization step (Scheme 3, (2)).

These promising results prompted us to investigate the possibility of one-pot cyclization from **19** (Table 1). Detecting the formation of **21** on TLC after the first step, KO^{t}Bu was then added and the reaction temperature was allowed to rise to room temperature (entry 1). This one-pot procedure gave the target bicyclic compounds in 15% yield, which was only slightly worse than the two-step procedure. Tracing the reaction by TLC indicated that the low yield of **23** + **24** should be attributed to the first Michael addition−elimination step, possibly due to the high nucleophilicity of the potassium enolate. Therefore, we planned to convert the initially formed potassium enolate to a milder nucleophile by transmetalation. Although transmetalation to the zinc enolate with $ZnCl_2$ did not give the initial product **21**, the lithium enolate formed through the transmetalation with LiBr gave a clean conversion to **21**.[16] This time, however, the second cyclization step became problematic due to the lower nucleophilicity of the lithium enolate at C-6 compared to the potassium enolate, even in the presence of DMAP as an activating reagent of the electrophile (entry 2). To improve the nucleophilicity of the C-6 lithium enolate for the cyclization, we added 12-crown-4 and the yield of **23** + **24** improved to 40% (entry 3). Transmetalation with $LiClO_4$, instead of LiBr, gave **23** + **24** in a much higher yield of 76% (entry 4). Although predominant isomer **23** was the unnatural one (18-epi), this one-pot cyclization is useful for the synthesis of the epi-form.[17] This reaction was also applicable to the other diastereomer **19** (4*S**,6*S**,18*R**), and **23** + **24** were obtained in 63% yield with a ratio of 5:1, again with **23** as the major isomer (entry 5).[18] Finally, even using a mixture (1.3:1) of **19** (4*R**,6*R**,18*R**) and **19** (4*S**,6*S**,18*R**), **23** + **24** were obtained in 71% yield (**23**:**24** = 11:1), which greatly simplified the synthetic route.

Table 1. Optimization of Cyclization Reaction



entry	**19**	conditions	**23** + **24**/%[a]
1	4*R**,6*R**,18*R**	1. KO^{t}Bu (2 equiv), −78 °C, 1 h 2. **20** (3 equiv), −78 °C, 1 h 3. KO^{t}Bu (2.1 equiv), −78 °C to rt, 16 h	15
2	4*R**,6*R**,18*R**	1. KO^{t}Bu (2.1 equiv), −78 °C, 1 h 2. LiBr (2.5 equiv), −78 °C, 1 h 3. **20** (1.5 equiv), −78 °C to rt 4. DMAP (3 equiv), −78 °C to rt, 16 h	16
3	4*R**,6*R**,18*R**	1. KO^{t}Bu (2.1 equiv) −78 °C, 1 h 2. LiBr (3 equiv), −78 °C, 1 h 3. **20** (3 equiv), −78 °C, 3 h 4. DMAP (6 equiv), 12-crown-4, (6 equiv) −78 °C to rt, 36 h	40
4	4*R**,6*R**,18*R**	1. KO^{t}Bu (3 equiv), −78 °C, 100 min 2. $LiClO_4$ (4.5 equiv), −78 °C, 50 min 3. **20** (2 equiv), −78 °C, 5.5 h 4. DMAP (5 equiv), 12-crown-4 (6 equiv), −78 °C to rt, 30 h	76 (25:1)[b]
5	4*S**,6*S**,18*R**	same as entry 4	63 (5:1)[b]
6	4*R**,6*R**,18*R** + 4*S**,6*S**,18*R**	same as entry 4	71 (11:1)[b]

[a] Isolated yield after purification. [b] Ratio of **23**:**24**.

With lactone **23** at hand, the next task was to convert the lactone to the [3.3.1] bicyclic system (Scheme 4). The results described above suggested that it was necessary to use a softer electrophile, such as an aldehyde, instead of a hard

(14) The possibility that the reaction proceeded through a dianion could be excluded because the reaction using 1.2 equiv of KO^{t}Bu under the optimized conditions (see below) gave **23** + **24** in 43% yield.

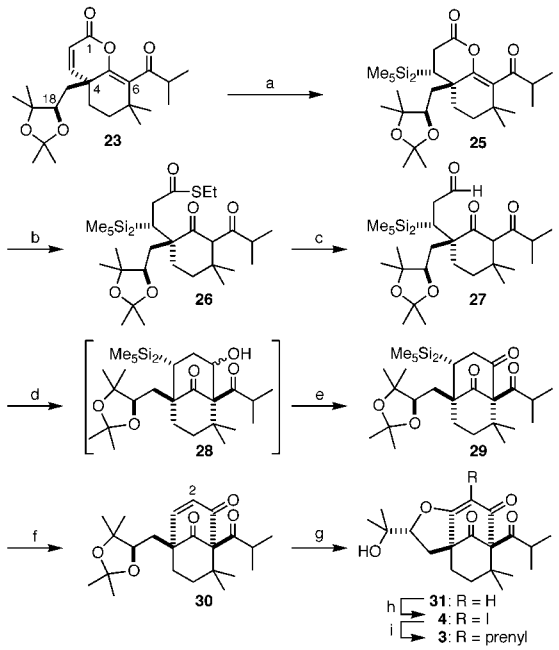
(15) The structure of **23** was unequivocally determined by X-ray crystallography. See Supporting Information for details.

(16) Direct formation of the lithium enolate with LiO^{t}Bu failed due to the lower basicity of the base.

(17) Preliminary studies to reverse the stereoselectivity of this one-pot cyclization revealed that employing a cyclic carbonate for the protecting group of the diol instead of the acetonide gave an ca. 1:1 mixture of diastereomers. Although the origin of the high stereoselectivity in the case of acetonide-protected **19** is not clear, coordination of the 18-oxygen atom to the lithium atom of the enolate might fix the substrate conformation to block the entry of the electrophile from the *β*-side.

(18) These results indicated that the observed high stereoselectivity was derived from the C-18 configuration.

Scheme 4[a]



[a] Conditions: (a) Me_5Si_2Li, THF−HMPA, 91%; (b) Me_2AlSEt, CH_2Cl_2, 96%; (c) Et_3SiH, Pd/C, CH_2Cl_2; (d) K_2CO_3, MeOH; (e) Dess−Martin periodinane, CH_2Cl_2, 98% (3 steps); (f) 1. *m*CPBA, CH_2Cl_2; 2. TBAF, THF, 77%; (g) Na_2PdCl_4 (40 mol %), TBHP, AcOH−H_2O, 69%; (h) I_2, CAN, CH_3CN, 84%; (i) $PdCl_2$(dppf), tributylprenyltin, DMF, 39%.

activated ester to achieve the desired carbon (C-6)−carbon (C-1) bond formation. Considering the geometric instability of an enal derived from **23**, we first masked the carbon−carbon double bond of the unsaturated lactone by introducing a silicon atom. This transformation should facilitate the desired cyclization because of the increased flexibility of the electrophile to reach the C-6 nucleophilic center. Furthermore, the silicon−carbon bond should be stable enough to tolerate several conversions, and it should be possible to regenerate an olefin via Tamao oxidation[19] and elimination, when necessary. After intensive effort,[20] we determined that the pentamethyldisilyl group[21] was best for our purpose. Thus, pentamethyldisilyllithium reacted with **23** in a 1,4-fashion to give **25** in 91% yield. Lactone **25** was next converted to thiol ester **26** using an aluminum thiolate;[22] then **26** was reduced under Fukuyama conditions[23] to aldehyde **27**. Successive treatment of **27** with a base (K_2CO_3/MeOH) and Dess−Martin periodinane gave **29** containing a bicyclo-[3.3.1]nonane-1,5-dione structure (98% from **26**). β-Silyl ketone **29** was then converted to enone **30** in one pot through a modified Tamao-type oxidation[24] followed by β-elimination.

Having established the synthesis of the bicyclic core, the stage was set for the construction of the tetrahydrofuran ring and introduction of the prenyl group at C-2 to complete the synthesis. These manipulations were achieved in three steps (Scheme 4). When **30** was subjected to Wacker oxidation conditions,[25] deprotection of the acetonide first occurred, followed by an intramolecular Wacker-type reaction, giving tricyclic compound **31** in 69% yield. Oxidative vinyl iodide formation[26,27] followed by Stille coupling with tributylprenyltin[28] completed the synthesis of 18-*epi*-8-deprenylgarsubellin A (**3**).

In summary, we developed a concise stereocontrolled synthetic route for a model compound that contains the tricyclic core of garsubellin A. The chemistry described in this paper should be very useful, not only for the total synthesis of garsubellin A but also for related natural compounds.[29] Efforts toward a total synthesis of garsubellin A are currently ongoing.

Acknowledgment. Financial support was provided by RFTF of the Japan Society for the Promotion of Science.

Supporting Information Available: Experimental procedures and characterization of new compounds, including X-ray data (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

(20) We tried dimethylphenylsilyl, (diethylamino)diphenylsilyl, and dimethyl(*o*-methoxy)phenylsilyl groups, in addition to the pentamethyldisilyl group. The former two silyl groups could be introduced to **23** by conjugate addition in high yields (>90%); however, later conversions were unsuccessful. The third one (Lee, T. W.; Corey, E. J. *Org. Lett*. **2001**, *3*, 3337−3339) did not produce the conjugate adduct to **23**.

(21) (a) Krohn, K.; Khanbabaee, K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 99−100. (b) Barret, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem*. **1999**, *64*, 6005−6018.

(22) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem*. **1977**, *42*, 3960−3961.

(23) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc*. **1990**, *112*, 7050−7051.

(24) Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett* **1995**, 941−942. Reaction under normal Tamao-oxidation conditions failed, possibly due to the instability of the intermediate alcohol under basic conditions.

(25) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett*. **1980**, 257−260.

(26) Zhang, F. J.; Li, Y. L. *Synthesis* **1993**, 565−567.

(27) The structure of **4** was unequivocally determined by X-ray crystallography. See the Supporting Information for details.

(28) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Org. Synth*. **1992**, *71*, 118−124.

(29) For examples, see: (a) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853−857. (b) Shan, M. D.; Hu, L. H.; Chen, Z. L. *J. Nat. Prod*. **2001**, *64*, 127−130.