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Synthesis of the KLMN Fragment of Gymnocin-A Using Oxiranyl Anion Convergent Methodology

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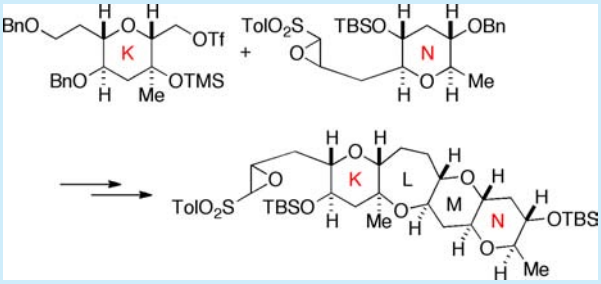
Supporting Information

ABSTRACT: Synthesis of the KLMN fragment of gymnocin-A has been achieved by a [*X* + 2 + *Y*]-type convergent strategy involving the coupling of a K-ring triflate and an N-ring epoxy sulfone. Fusions of the L ring and the M ring were carried out by intramolecular S_N2 substitution of a tertiary alcohol and reductive etherification to furnish the target molecule.



Marine dinoflagellates produce a number of complex bioactive molecules.[1] Gymnocin-A was isolated from a culture of red-tide dinoflagellate *Karenia mikimotoi*.[2] The structure of gymnocin-A (**1**) is characterized by a stunning array of 14 contiguous ether rings (Figure 1), the third longest marine polycyclic ether after brevisulcenal-F[3] and gymnocin-B[4] (17 and 15 contiguous rings, respectively). The potent cytotoxicity (IC_{50} = 1.3 μg/mL) against P388 mouse leukemia cells and the complex architecture make gymnocin-A an attractive target for synthetic chemists.[5] To date, only one total synthesis of gymnocin-A has been achieved by Tsukano and Sasaki using a Suzuki−Miyaura coupling strategy.[6] A structure−activity relationship study including truncated analogues was also reported by the same group.[7]

Construction of such a long ladder-like structure in a highly convergent manner is key in any total synthesis of marine polyether toxins.[8,9] We have recently reported a [*X* + 2 + *Y*]-type convergent strategy using an oxiranyl anion coupling, which integrates the construction of medium-ring ethers.[10−12] This unique methodology has prompted us to undertake a synthetic study of gymnocin-A, and here we report the synthesis of the KLMN fragment.

Retrosynthesis of the KLMN fragment **2** starts with disconnecting the C−O bond of the M ring. The unraveled seven-membered L ring could be constructed as a ring expansion reaction[13] of the six-membered ketone **3** (Scheme 1). This cyclic ketone would be accessible by intramolecular S_N2 substitution of bulky tertiary alcohol **4**, potentially a high-risk strategy to constructing the bicyclic ether containing an angular methyl group. Synthesis of **4** could be achieved by C−C bond formation between advanced building block K-ring triflate **5** and N-ring oxiranyl anion **6**, both of which would be prepared from 2-deoxy-D-ribose.

Synthesis of epoxy sulfone **16** began by tosylation and benzylation of methyl 2-deoxy-D-ribofuranoside (**7**) to give **8** (Scheme 2). Reduction of the tosylate with lithium triethylborohydride, followed by dithioacetalization, provided alcohol **10** in 91% yield over two steps. The resulting alcohol was converted to the unsaturated ester aldehyde **12** by reaction with ethyl propiolate followed by removal of the 1,3-dithiane. The SmI_2-mediated radical cyclization[14] of acyclic **12** afforded (3*S*,4*R*)- and (3*R*,4*S*)-hydroxy esters **13a** and **13b** in 71 and 22% yields, respectively. The secondary alcohol of the desired major isomer **13a** was protected with TBSOTf to afford ester **14**, which was also made by recycling the undesired (3*R*,4*S*)-isomer **13b** in a four-step process. The complete isomerization of the ester side chain of the undesired isomer was achieved by a retro-Michael/oxa-Michael reaction[15] after inversion of the C4 hydroxyl group.[16] Reduction of ester **14** with DIBALH and Horner−Wadsworth−Emmons (HWE) olefination of the resulting aldehyde with $TolSO_2CH_2P(O)(OEt)_2$ gave *trans*-vinylsulfone **15**. Subsequent epoxidation with *t*-BOOH/*t*-BuOK led to the desired *trans*-epoxy sulfone **16** as an 88:12 diastereomeric mixture.

Synthesis of the other coupling partner, K-ring triflate **5**, is shown in Scheme 3. Methyl 2-deoxy-D-ribofuranoside (**7**) was converted to unsaturated ester aldehyde **18** through a sequence including silylene protection of the 1,3-diol, dithioacetalization, oxa-Michael reaction with ethyl propiolate, and removal of the dithioacetal. SmI_2-mediated reductive cyclization of **18** on the rigid dioxasilinane ring proceeded stereoselectively to afford hydroxy ester **19** in 90% yield as a single diastereomer.

The ester was then reduced, and the resulting diol was protected as a dibenzyl ether (**20**). After removal of the silylene group and selective protection of the primary alcohol with a TBDPS group, the secondary alcohol was oxidized to give ketone **22**. Introduction of an axial methyl group with MeMgBr in Et_2O afforded the desired isomer **23** in 60% yield along with 39% of its epimer. Subsequent removal of the TBDPS group

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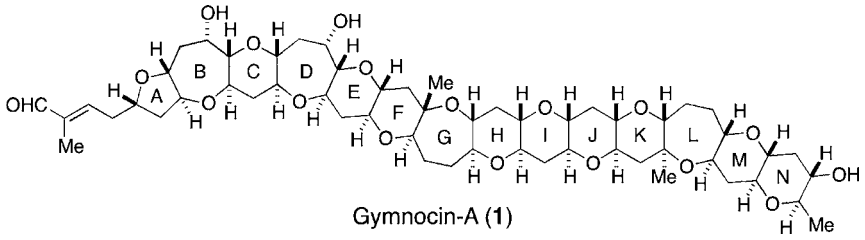
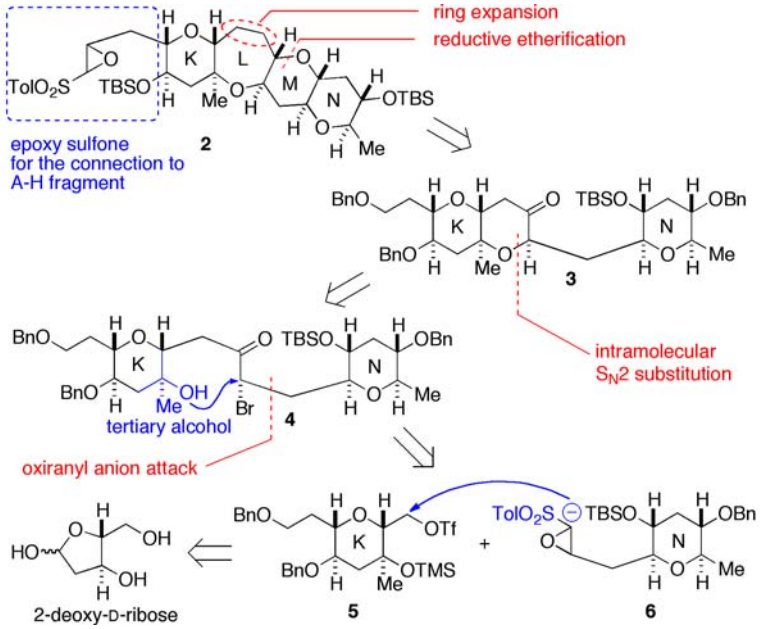
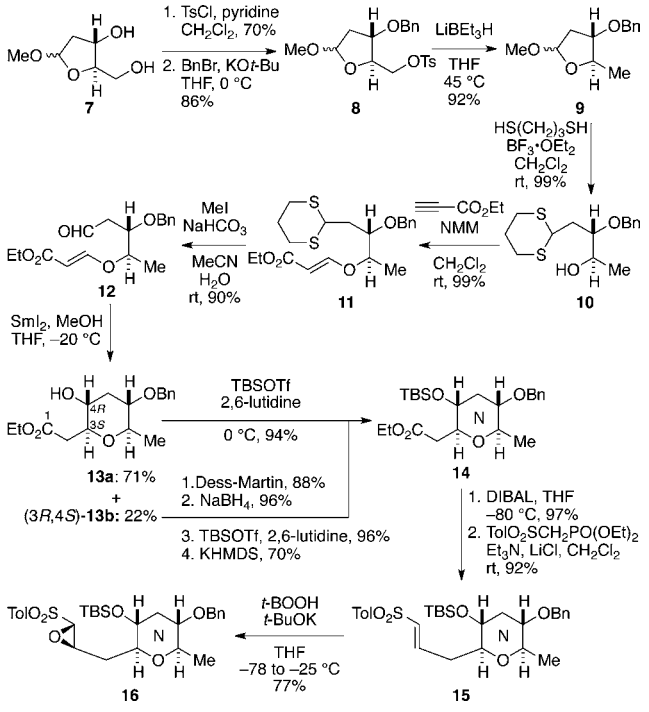


Figure 1. Structure of gymnocin-A (**1**).

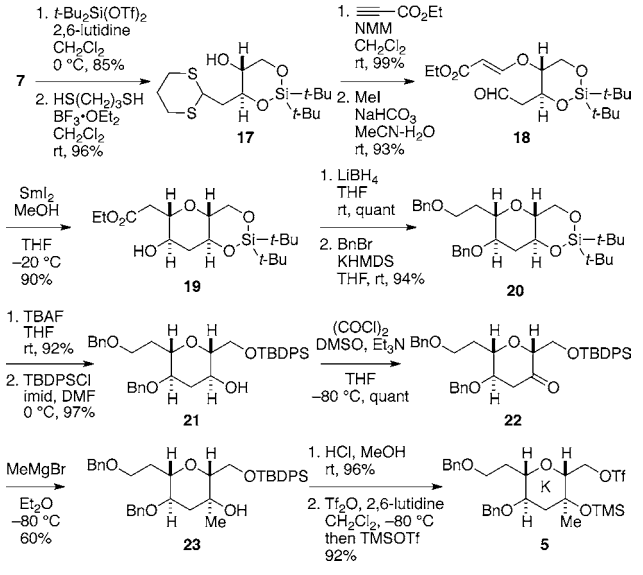
Scheme 1. Retrosynthetic Analysis of the KLMN Fragment 2



Scheme 2. Preparation of the N-Ring Epoxy Sulfone 16



Scheme 3. Preparation of the K-Ring Triflate 5



followed by a one-pot triflation−trimethylsilylation of the resulting diol afforded the desired K-ring triflate **5**.

Union of the K-ring triflate **5** and the N-ring epoxy sulfone **16** was achieved by oxiranyl anion alkylation (Scheme 4). A mixture of **5** and **16** was treated with *n*-BuLi in the presence of HMPA at −100 °C to provide the product **24** in 67% yield (76% conversion based on the recovered triflate). The reaction at −80 °C resulted in a significant drop in yield to 19% because

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Scheme 4. Reaction of the N-Ring Epoxy Sulfone 16 with the K-Ring Triflate 5

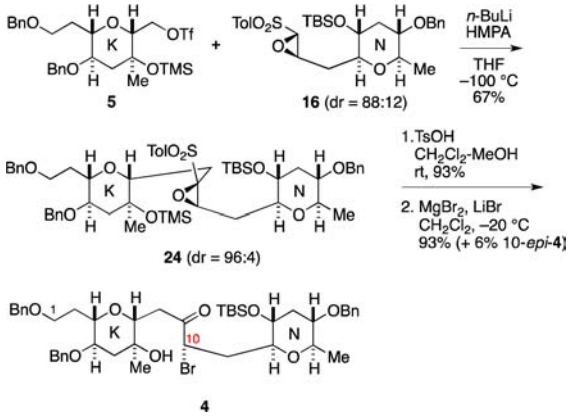
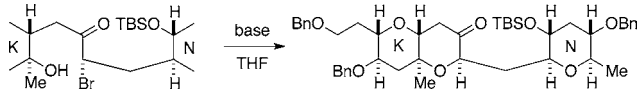


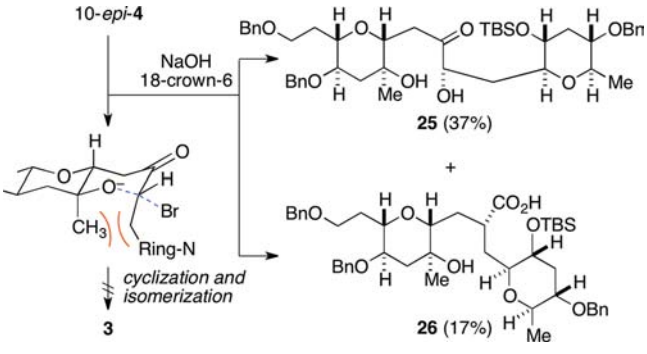
Table 1. Reaction Conditions for Base-Mediated Cyclization of 4 to 3



entry	base	additive	temp (°C)	time (h)	yield (%)
1	NaH		−10	3	37
2[a]	TMG		25	24	4
3	KHMDS		0	1	20
4	1 M aq NaOH		0	24	44
5	0.4 M n-Bu_4NOH in MeOH		−40	1	60
6	1 M aq NaOH	15-crown-5	0	24	81
7	1 M aq NaOH	18-crown-6	0	8	88

[a] CH_2Cl_2 was used as a solvent.

Scheme 5. Attempting the Cyclization Reaction Using 10-*epi*-4



of the instability of the oxiranyl anion at this temperature. Removal of the TMS group of **24** followed by bromination with $MgBr_2$ afforded bromoketone **4** (93%) along with a small amount of the minor isomer 10-*epi*-**4** (6%).

Ring fusion of **4** by intramolecular S_N2 reaction to bicyclic ether **3** containing an angular methyl group is a challenging task as the reaction sites are an unfavorable combination of a bulky tertiary alcohol and a secondary alkyl bromide, as dictated by the Williamson ether synthesis. We have previously reported that NaH is suitable for S_N2 cyclization in a similar system with a tertiary alcohol.[12a] The cyclization of **4** under the same conditions as before, however, resulted in the formation of **3** in only 37% yield (Table 1, entry 1). Several other conditions with NaH were tried but failed to give satisfactory yields. The low yield prompted us to re-examine other bases. When KHMDS and tetramethylguanidine (TMG) were used, the reactions were sluggish and gave even lower yields (entries 2 and 3). Cyclization using a weaker base such as hydroxide was then attempted to minimize decomposition of the substrate. Reaction with 1 M aqueous NaOH in THF afforded **3** as the sole product in 44% yield, along with 51% recovery of the bromoketone starting material (entry 4). The low reactivity may be due to the poor solubility of NaOH in THF. Addition of tetra-*n*-butylammonium hydroxide enhanced the reaction rate, but the yield was still moderate (entry 5). We found that addition of a crown ether greatly improved the yield (entry 6) and that 18-crown-6 is the best additive for the NaOH-mediated S_N2 cyclization to afford the desired product in 88% yield (entry 7).

Cyclization using NaOH and 18-crown-6 was also examined for the minor bromoketone isomer (10-*epi*-**4**). However, the desired product **3** was not obtained; instead, intermolecular substitution with hydroxide and a Favorskii rearrangement occurred to give **25** and **26**, respectively (Scheme 5). Ether ring formation is prevented by the steric repulsion between the axial methyl group and the N-ring moiety in the chairlike transition state. The marked difference of reactivity between the major isomer **4** and the minor isomer 10-*epi*-**4** can be attributed to their C10-configurations being *S* and *R*, respectively.

In preparation for the fusion of ring M, the six-membered ketone **3** was homologated with trimethylsilyldiazomethane to give the seven-membered ketone **27** in 91% yield (Scheme 6). Methyl acetalization and reductive etherification provided tetracyclic polyether **28**, with the construction of the full KLMN ring system. After debenzylation and protection of the resulting triol with TBSOTf, the primary silyl ether was selectively removed under acidic conditions. Dess-Martin oxidation of alcohol **29** to the aldehyde, followed by a HWE reaction, provided *trans*-vinyl sulfone **30**. The synthesis of the KLMN fragment **2** was completed by epoxidation of the vinyl sulfone with *t*-BuOOH/*t*-BuOK. This epoxy sulfone will be reacted with a triflate of the H-ring terminal fragment, the synthesis of which is in progress.

In conclusion, we have synthesized the KLMN fragment (**2**) of gymnocin-A from the N-ring epoxy sulfone **16** and the K-ring triflate **5**, which were prepared from 2-deoxy-D-ribose using a SmI_2-mediated reductive cyclization. Assembly of the two building blocks was achieved using our [*X* + 2 + *Y*]-type convergent strategy, where the fused cyclic ether bearing an angular methyl group was constructed by intramolecular S_N2 cyclization of a tertiary alcohol. Further studies toward the total synthesis of gymnocin-A are continuing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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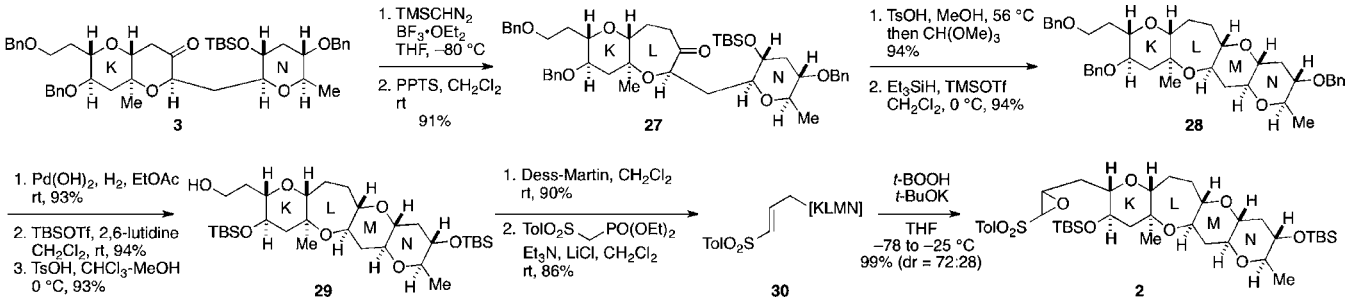
Scheme 6. Completion of the KLMN Fragment 2 Synthesis



Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kornprobst, J.-M. *Encyclopedia of Marine Natural Products*; Wiley-Blackwell: Weinheim, Germany, 2010; Vols. *1*–3. (b) Shimizu, Y. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. *1*. (c) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685–1698. (d) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (e) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293–314. (f) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228–242. (g) Daranas, A. H.; Norte, M.; Fernández, J. J. *Toxicon* **2001**, *39*, 1101–1132. (h) Steidinger, K. A.; Landsberg, J. H.; Flewelling, L. J.; Kirkpatrick, B. A. In *Ocean and Human Health: Risks and Remedies from the Sea*; Walsh, P. J., Smith, S. L., Fleming, L. E., Solo-Gabriele, H. M., Gerwick, W. H., Eds.; Academic Press: Burlington, MA, 2008; Chapter 13 (Toxic Dinoflagellates), pp 239–256.

(2) Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829–5832.

(3) Hamamoto, Y.; Tachibana, K.; Holland, P. T.; Shi, F.; Beuzenberg, V.; Itoh, Y.; Satake, M. *J. Am. Chem. Soc.* **2012**, *134*, 4963–4968.

(4) Satake, M.; Tanaka, Y.; Ishikura, Y.; Oshima, Y.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **2005**, *46*, 3537–3540.

(5) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 4430–4432.

(6) (a) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294. (b) Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326–4335.

(7) Tsukano, C.; Sasaki, M. *Tetrahedron Lett.* **2006**, *47*, 6803–6807.

(8) For total synthesis reviews, see: (a) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314–4347. (b) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182–7225. (c) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401–426. (d) Isobe, M.; Hamajima, A. *Nat. Prod. Rep.* **2010**, *27*, 1204–1226. For recent total synthesis, see: (e) Ebine, M.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2275–2278. (f) Crimmins, M. T.; Zuccarello, J. L.; Ellis, J. M.; McDougall, P. J.; Haile, P. A.; Parrish, J. D.; Emmitte, K. A. *Org. Lett.* **2009**, *11*, 489–492. (g) Takamura, H.; Kikuchi, S.; Nakamura, Y.; Yamagami, Y.; Kishi, T.; Kadota, I.; Yamamoto, Y. *Org. Lett.* **2009**, *11*, 2531–2534. (h) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382–4385. (i) Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 3208–3216. (j) Yamashita, S.; Ishihara, Y.; Morita, H.; Uchiyama, J.; Takeuchi, K.; Inoue, M.; Hirama, M. *J. Nat. Prod.* **2011**, *74*, 357–364. (k) Kuranaga, T.; Ohtani, N.; Tsutsumi, R.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2011**, *13*, 696–699. (l) Fuwa, H.; Ishigai, K.; Hashizume, K.; Sasaki, M. *J. Am. Chem. Soc.* **2012**, *134*, 11984–11987.

(9) For a review of the convergent synthesis of polycyclic ethers, see: (a) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379–4405. For recent convergent fragment synthesis examples, see: (b) Yamashita, S.; Uematsu, R.; Hirama, M. *Tetrahedron* **2011**, *67*, 6616–6626. (c) Oishi, T.; Hasegawa, F.; Torikai, K.; Konoki, K.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 3599–3602. (d) Tsubone, K.; Hashizume, K.; Fuwa, H.; Sasaki, M. *Tetrahedron* **2011**, *67*, 6600–6615. (e) Nicolaou, K. C.; Baker, T. M.; Nakamura, T. *J. Am. Chem. Soc.* **2011**, *133*, 220–226. (f) Takamura, H.; Abe, T.; Nishiuma, N.; Fujiwara, R.; Tsukeshiba, T.; Kadota, I. *Tetrahedron* **2012**, *68*, 2245–2260.

(10) For reviews on oxiranyl anions, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3326. (b) Mori, Y. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1997; Vol. *17*, pp 183–211. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642. (d) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942.

(11) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158–8159.

(12) (a) Sakai, T.; Sugimoto, A.; Mori, Y. *Org. Lett.* **2011**, *13*, 5850–5853. (b) Sakai, T.; Sugimoto, A.; Tatematsu, H.; Mori, Y. *J. Org. Chem.* **2012**, *77*, 11177–11191.

(13) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619–4622. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119–124. (c) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917–12932. (d) Sakai, T.; Ito, S.; Furuta, H.; Kawahara, Y.; Mori, Y. *Org. Lett.* **2012**, *14*, 4564–4567.

(14) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811–2814. (b) Nakata, T. *Chem. Soc. Rev.* **2010**, *39*, 1955–1972.

(15) (a) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063–1066. (b) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177–6179. (c) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570–4583.

(16) DBU-mediated C3 isomerization of the ketone product of the Dess-Martin oxidation of **13b** resulted in a low yield due to *β*-elimination of benzyl alcohol.

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