Natural Product Synthesis

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Total Synthesis of the Hamigerans

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Abstract: *The first total synthesis of hamigerans D, G, L, and N–Q has been accomplished. A convergent approach was used to build the basic tricarbocyclic ring system bearing a 5-6-6 structure. A sequence of oxidative cleavage, homologation, and ring regeneration provided access to the 5-7-6 skeleton of hamigeran G. Based on the biogenetic hypothesis, elegant and highly efficient biomimetic transformations of hamigeran G into hamigerans D, N–Q, and L were achieved.*

Hamigerans belong to a family of halogenated natural products isolated from the poecilosclerid sponge *Hamigera tarangaensis* and were discovered by Cambie and co-workers in 2000 (Figure 1).[1] More recent investigation of the same sponge by Northcote and co-workers led to the isolation of several new hamigerans, particularly the nitrogenous congeners hamigeran D (**7**) and N–Q (**8**–**11**).[2] To date, over 30 hamigerans have been discovered and identified, and most of them show interesting biological activities. Notably, hamigeran B (**2**) completely inhibits replication of herpes and polio-virus in vitro without showing any significant cytotoxicity.[1] Hamigeran G (**6**) inhibits growth of the P388 tumor cell line as well as the HL-60 promyelocytic leukemia cell line (IC_{50} 8 μM).[2a] We have noticed that Hamigerans and gukulenins (Figure 1), a small group of marine tetraterpenoids from the Korean sponge *Phorbas gukulensis*, have similar structural features.[3] Gukulenins contain unusual bis(tropolone) fragments, and gukulenins A (**12**) and B (**13**) inhibit growth of human colon, renal, pharynx, and stomach cancer cell lines with nanomolar IC_{50} values.

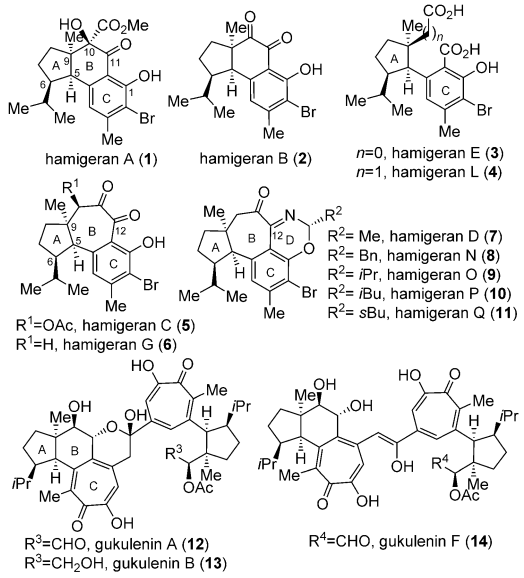
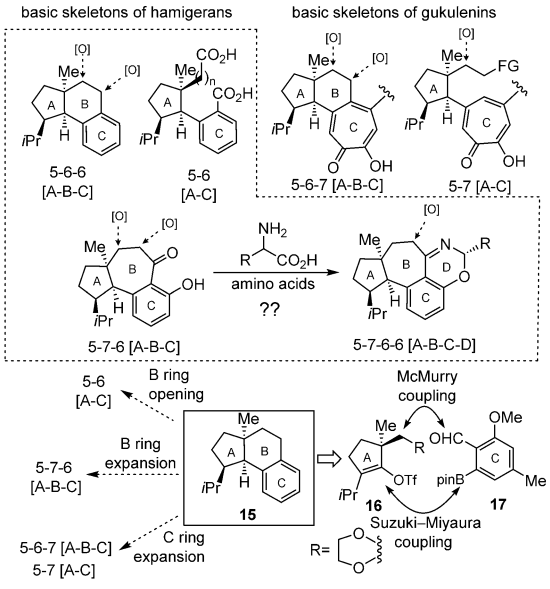


Figure 1. Hamigerans and gukulenins.

The unique structures and potent biological potential of hamigerans have attracted considerable attention from synthetic chemists.[4] Many synthetic studies have been reported, including those by the groups of Nicolaou,[5] Clive,[6] Trost,[7] Taber,[8] Stoltz,[9] Lau,[10] Jiang,[11] Miesch,[12] Xie and Zhou,[13] and others.[14] These synthetic endeavors have focused mainly on **2**, while to the best of our knowledge, the more challenging total syntheses of hamigerans and gukulenins containing seven-membered rings have not been reported. Herein we report the first total synthesis of hamigeran G (**6**) and its biomimetic transformation into hamigerans L (**4**), D (**7**), and N–Q (**8**–**11**).

Most hamigerans contain 5-6-6 or 5-7-6 fused tricarbocyclic rings, also known as A-B-C rings (Scheme 1), which include a cyclopentane ring (A ring) with three stereogenic centers as well as a polysubstituted aromatic ring (C ring). Careful structural analysis has shown that the major structural differences among hamigerans are in the size and functionalization of the B ring. Oxidative cleavage of the B ring of the



Scheme 1. Structural and retrosynthetic analysis. FG = functional group.

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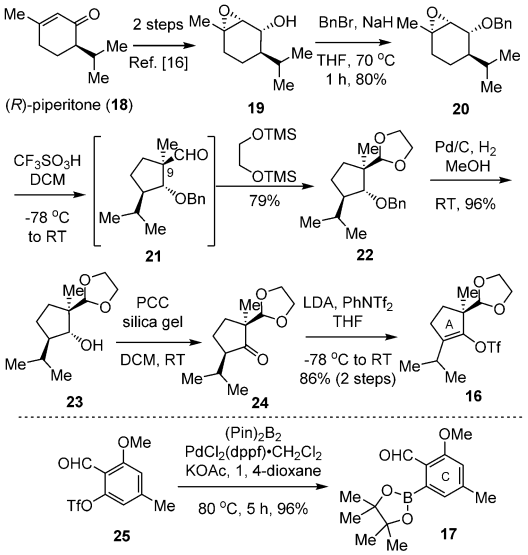
tricycle leads to formation of 5-6 structures (A-C rings), which are the basic skeletons of hamigerans E (**3**) and L (**4**). Northcote hypothesized that condensing **6** with various amino acids should generate **7** and **8**–**11**, which contain a benzoxazine ring (D ring).[2b] Gukulenins and hamigerans share a similar basic skeleton (A-B rings) and differ primarily in the aromatic tropolone C ring.

Based on this structural analysis, we postulated that hamigerans and gukulenins could be synthesized from the same intermediate **15** with the basic 5-6-6 structure (A-B-C ring; Scheme 1). Appropriate ring-opening or ring-expansion reactions could regulate the size of the B or C ring, thus affording related natural products. Based on this hypothesis, we cleaved **15** to give the fragments **16** (A ring) and **17** (C ring), and used Suzuki–Miyaura cross-coupling and McMurry coupling to construct the central B ring.

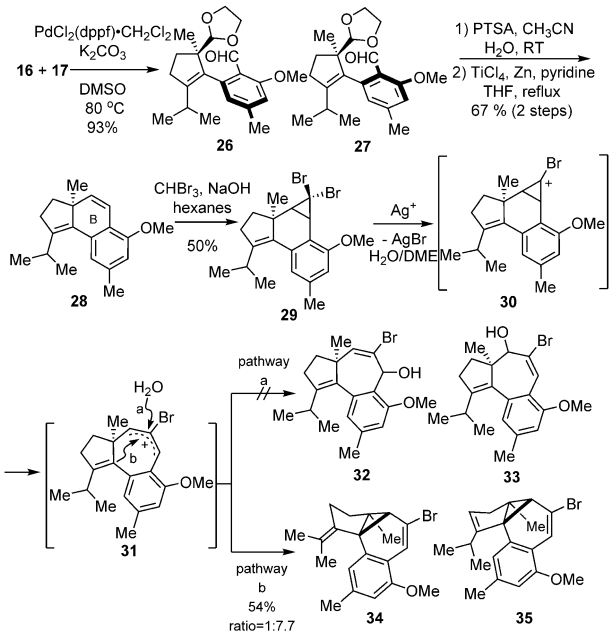
Our synthesis commenced with the syntheses of the coupling fragments vinyl triflate **16** and arylboronate **17** (Scheme 2). The starting material was (*R*)-piperitone (**18**),



Scheme 2. Preparation of the two coupling components. DCM = dichloromethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, LDA = lithium diisopropylamide, PCC = pyridinium chlorochromate, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

which contains an isopropyl group,[15] and was efficiently converted into the epoxide **19** through a previously described two-step procedure.[16] Protecting the hydroxy group of **19** as benzyl ether gave the compound **20**, after which ring contraction was achieved using acid-promoted semipinacol rearrangement, thus generating the cyclopentane A ring.[17] Extensive screening of reaction conditions using various Lewis and Brønsted acids showed that the reaction could be promoted using a catalytic amount (10 mol%) of trifluoromethanesulfonic acid, thus providing the aldehyde **21**, having a quaternary carbon atom (C9), as a single diastereomer. Adding 1,2-bis(trimethylsiloxy)ethane to the reaction mixture directly protected the aldehyde group as a dioxolane, thus affording **22** in 79% yield over two steps. Removal of the benzyl group and subsequent PCC oxidation furnished the ketone **24**, which was efficiently converted into **16**. The aryltriflate **25** was derived from 2,6-dimethoxy-4-methylbenzaldehyde in two steps[19] and then transformed into the pinacol boronate **17** by Miyaura's protocol[18] involving palladium-catalyzed borylation with bis(pinacolato)diboron.

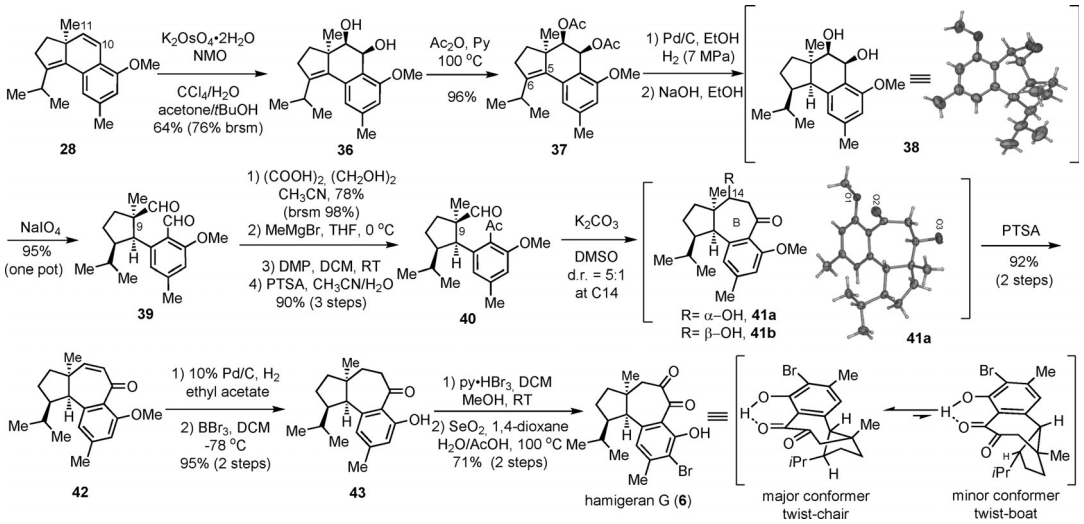
With both coupling components in hand, we explored the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction (Scheme 3).[20] Treating **16** and **17** with $PdCl_2(dppf)\cdot CH_2Cl_2$ in



Scheme 3. Attempt at the B ring expansion. DME = 1,2-dimethoxyethane, DMSO = dimethylsulfoxide.

the presence of K_2CO_3 in DMSO produced the desired coupling products **26** and **27** as a mixture of two rotamers in excellent yield. Removal of the ketal groups of both rotamers generated dialdehyde intermediates, which were converted, by McMurry coupling, into the cyclized compound **28** in 67% yield over two steps. The compound **28** contains the basic 5-6-6 tricarbocyclic skeleton and was considered to be a common intermediate for the divergent synthesis of hamigerans. We speculated that olefin cyclopropanation on the B ring and subsequent ring opening would form a molecule with a 5-7-6 structure. Reacting **28** with dibromocarbene smoothly delivered the *gem*-dibromocyclopropane **29** in 50% yield, and subsequent treatment with $AgNO_3$, AgOAc, or other silver salts led to electrophilic ring opening in **29,** thus generating **30** and then the allylic carbocation **31**. We reasoned that this carbocation could be intermolecularly trapped by water to form the hydroxylated products **32** or **33** (Scheme 3; pathway a). Instead, the undesired compounds **34** and **35** were produced by an intramolecular reaction with the electron-rich olefin (Scheme 3; pathway b).[21]

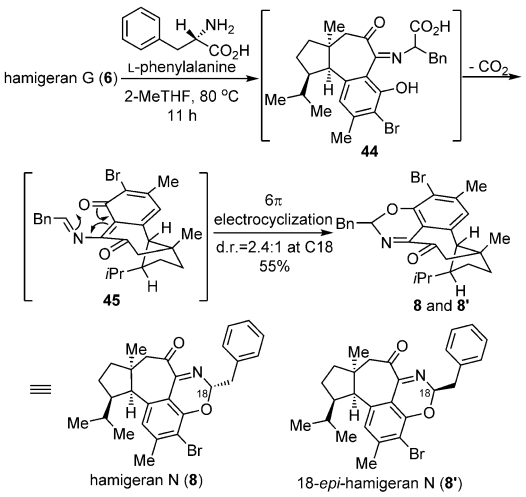
Therefore we revised our strategy for generating the seven-membered B ring, thus opting for a sequence of oxidative cleavage, homologation, and ring regeneration (Scheme 4). The C10=C11 bond in the B ring of **28** was



Scheme 4. Total synthesis of **6**. X-ray structures are shown. Thermal ellipsoids shown at 50% probability.[24] DMP = Dess–Martin periodinane, NMO = 4-methyl-morpholin-4-oxide, PTSA = *p*-toluenesulfonic acid, Py = pyridine.

selectively dihydroxylated and the resulting diol was protected as acetates, thus affording **37**. High-pressure hydrogenation of the tetrasubstituted olefin (C5=C6) and hydrolysis of the acetates gave the desired product **38** as a single diastereomer with *cis*-fused stereochemistry, which was confirmed by X-ray analysis. Oxidative cleavage of the diol in **38** using sodium periodate produced the dialdehyde **39**, in which the aldehyde at C9 could be selectively protected as a ketal. One-carbon homologation of the resulting monoaldehyde was achieved through methylmagnesium bromide addition followed by Dess–Martin oxidation, thus yielding the compound **40** after removal of the ketal group. Intramolecular aldol reaction under basic conditions generated a β-hydroxy ketone (**41a** and **41b**, d.r. = 5:1) with a seven-membered B ring. The relative stereochemistry of **41a** was confirmed by X-ray analysis. PTSA-mediated dehydration of **41a** and **41b** smoothly provided the enone **42**. Hydrogenation of this enone followed by methoxy group removal using BBr_3 afforded the ketone **43** in 95% yield over two steps.[22] Various brominating reagents were tested for their ability to achieve regioselective *o*-bromination of the phenol **43**, including NBS/iPr_2NH, tetrabutylammonium tribromide, and pyrrolidone hydrotribromide. Pyridinium tribromide (py·HBr_3) was found to work best, thus providing the monobrominated product in excellent yield. Finally, selenium dioxide oxidation in the presence of catalytic acetic acid[23,10,14a] led to introduction of the 1,2-diketone moiety, thus completing the total synthesis of **6**. ^1H and ^{13}C NMR spectra as well as HRMS data for synthetic (−)-**6** were in agreement with published data for the natural product.[2a] Hamigeran G (**6**) was found to exist as an equilibrium mixture of twist-chair and twist-boat conformers, fully consistent with observations by Northcote and co-workers.[2a]

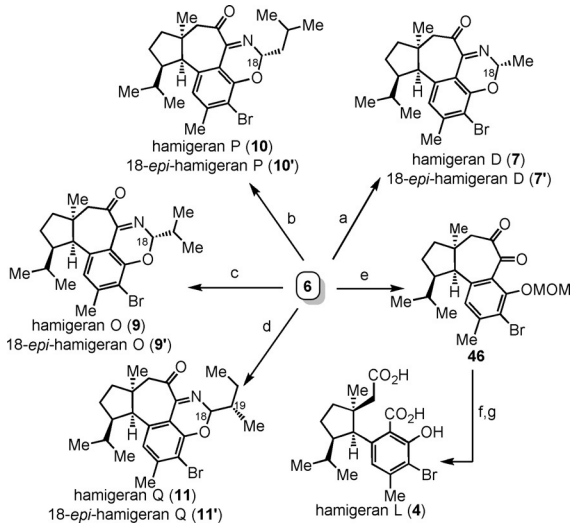
Naturally occurring **7** and N–Q (**8**–**11**), as well as their 18-*epi* isomers contain the basic skeleton (A-B-C ring) of **6** with an unusual benzoxazine D ring. Northcote and co-workers proposed that these molecules could be viewed as hybrids of amino acids and **6**.[2b] To test this hypothesis, we investigated the reactivity of **6** with various amino acids. As predicted, heating a solution of **6** with L-phenylalanine in 2-methyltetrahydrofuran at 80 °C generated **8** and its 18-*epi* isomer in a ratio of 2.4:1 in 55% yield (Scheme 5). We proposed that



Scheme 5. Biomimetic transformation of **6** into **8** and its 18-*epi* isomer.

condensing **6** with L-phenylalanine gave the imine intermediate **44**, which underwent tautomerization and a key decarboxylation to generate **45** with higher oxidation state. Subsequent 6π electrocyclization of **45** generated the benzoxazine D ring and furnished the desired products.

We then showed that **6** can serve as a common biogenetic precursor for synthesizing **7**, **9**–**11**, and their 18-*epi* isomers by reacting **6** with appropriate amino acids as described above for L-phenylalanine (Scheme 6). We predict that this strategy will allow preparation of benzoxazine-containing hamigerans and their derivatives, some of which may be isolated from natural sources in the future. In addition, we were able to transform **6** into hamigeran L (**4**) through a three-step



Scheme 6. Divergent synthesis of hamigerans. Reagents and conditions: a) D-alanine, 2-Me-THF, 80°C, d.r. = 1.6:1 at C18, 50%(78% brsm); b) DL-leucine, 2-Me-THF, 80°C, d.r. = 1.4:1 at C18, 60% (65% brsm); c) L-valine, 2-MeTHF, 80°C, d.r. = 3.9:1 at C18, 43%(57% brsm); d) L-isoleucine, 2-MeTHF, 80°C, d.r. = 1.8:1 at C18, 56% (60% brsm); e) MOMCl, K_2CO_3, DMF, 0°C; f) H_2O_2, NaOH, 1,4-dioxane, 0°C; g) HCl, H_2SO_4, THF, RT, 34% (3 steps). brsm = based on recovered starting material, DMF = *N*,*N*-dimethylformamide, MOM = methoxymethyl.

sequence involving phenol group protection, oxidative cleavage of the diketone, and deprotection.

In summary, we have accomplished the first total synthesis of hamigerans L (**4**), G (**6**), D (**7**), and N–Q (**8**–**11**). A convergent synthetic strategy was developed based on the versatile common intermediate **28**. Our results suggest that benzoxazine-containing **7** and **8**–**11** may derive from naturally occurring amino acids and **6**. We believe that this biomimetic approach should enable the synthesis of a variety of hamigerans and their derivatives, thus facilitating biological studies of these promising natural products. We are currently studying the total synthesis of the gukulenins.

Acknowledgments

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[1] a) K. D. Wellington, R. C. Cambie, P. S. Rutledge, P. R. Bergquist, *J. Nat. Prod.* **2000**, *63*, 79; b) R. C. Cambie, C. E. F. Rickard, P. S. Rutledge, K. D. Wellington, *Acta Crystallogr. Sect. A* **2001**, *57*, 958.
[2] a) P. T. Northcote, A. J. Singh, J. D. Dattelbaum, J. J. Field, Z. Smart, E. F. Woolly, J. M. Barber, R. Heathcott, J. H. Miller, *Org. Biomol. Chem.* **2013**, *11*, 8041; b) P. T. Northcote, J. D. Dattelbaum, A. J. Singh, J. J. Field, J. H. Miller, *J. Org. Chem.* **2015**, *80*, 304.
[3] a) S. Y. Park, H. Choi, H. Hwang, H. Kang, J.-R. Rho, *J. Nat. Prod.* **2010**, *73*, 734; b) J.-e. Jeon, L. Liao, H. Kim, C. J. Sim, D.-C. Oh, K.-B. Oh, J. Shin, *J. Nat. Prod.* **2013**, *76*, 1679; for synthetic studies of gukulenins, see: c) R. Kats-Kagan, S. B. Herzon, *Org. Lett.* **2015**, *17*, 2030.
[4] For reviews of synthetic studies of hamigerans, see: a) M. Harmata, *Strategies Tactics Org. Synth.* **2013**, *37*, 203; b) D. L. J. Clive, J. Wang, *Org. Prep. Proced. Int.* **2005**, *37*, 1.
[5] a) K. C. Nicolaou, D. Gray, J. Tae, *Angew. Chem. Int. Ed.* **2001**, *40*, 3675; *Angew. Chem.* **2001**, *113*, 3787; b) K. C. Nicolaou, D. Gray, J. Tae, *Angew. Chem. Int. Ed.* **2001**, *40*, 3679; *Angew. Chem.* **2001**, *113*, 3791; c) K. C. Nicolaou, D. Gray, J. Tae, *J. Am. Chem. Soc.* **2004**, *126*, 613.
[6] a) D. L. J. Clive, J. Wang, *Angew. Chem. Int. Ed.* **2003**, *42*, 3406; *Angew. Chem.* **2003**, *115*, 3528; b) D. L. J. Clive, J. Wang, *Tetrahedron Lett.* **2003**, *44*, 7731; c) D. L. J. Clive, J. Wang, *J. Org. Chem.* **2004**, *69*, 2773.
[7] a) B. M. Trost, C. Pissot-Soldermann, I. Chen, G. M. Schroeder, *J. Am. Chem. Soc.* **2004**, *126*, 4480; b) B. M. Trost, C. Pissot-Soldermann, I. Chen, *Chem. Eur. J.* **2005**, *11*, 951.
[8] D. F. Taber, W. Tian, *J. Org. Chem.* **2008**, *73*, 7560.
[9] B. M. Stoltz, H. Mukherjee, N. T. McDougal, S. C. Virgil, *Org. Lett.* **2011**, *13*, 825.
[10] S. Y. W. Lau, *Org. Lett.* **2011**, *13*, 347.
[11] B. Jiang, M. Li, P. Xing, Z. Huang, *Org. Lett.* **2013**, *15*, 871.
[12] M. Miesch, L. Miesch, T. Welsch, V. Rietsch, *Chem. Eur. J.* **2009**, *15*, 4394.
[13] H. Lin, L. Xiao, M. Zhou, H. Yu, J. Xie, Q. Zhou, *Org. Lett.* **2016**, *18*, 1434.
[14] For the construction of the core skeleton of hamigerans, see: a) G. Mehta, H. M. Shinde, *Tetrahedron Lett.* **2003**, *44*, 7049; b) J. P. Castells, E. Arnáiz, J. Blanco-Urgoiti, D. Abdi, G. Domínguez, *J. Organomet. Chem.* **2008**, *693*, 2431; c) C. J. Lovely, C. E. Madu, *Org. Lett.* **2007**, *9*, 4697; d) M. Harmata, P. Zheng, P. R. Schreiner, A. Navarro-Vázquez, *Angew. Chem. Int. Ed.* **2006**, *45*, 1966; *Angew. Chem.* **2006**, *118*, 2000; e) M. Harmata, Z. Cai, *Org. Lett.* **2010**, *12*, 5668; f) D. L. Wright, J. B. Sperry, *Tetrahedron Lett.* **2005**, *46*, 411.
[15] The commercial available (*R*)-piperitone has an *ee* value of 85.3% (ChiralCel OJ-H, 99:1 hexanes/isopropyl alcohol, 1 mL min^{-1}, 230 nm).
[16] Á. Cantín, C. Lull, J. Primo, M. A. Miranda, E. Primo-Yúfera, *Tetrahedron: Asymmetry* **2001**, *12*, 677.
[17] For a review of semipinacol rearrangement, see: a) Z.-L. Song, C.-A. Fan, Y.-Q. Tu, *Chem. Rev.* **2011**, *111*, 7523; for rearrangements of α-hydroxy epoxides, see: b) C.-A. Fan, X.-D. Hu, Y.-Q. Tu, B.-M. Wang, Z.-L. Song, *Chem. Eur. J.* **2003**, *9*, 4301; c) D.-R. Li, W.-J. Xia, Y.-Q. Tu, F.-M. Zhang, L. Shi, *Chem. Commun.* **2003**, 798; d) K. Maruoka, T. Ooi, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 6431; e) K. Suda, T. Kikkawa, S.-i. Nakajima, T. Takanami, *J. Am. Chem. Soc.* **2004**, *126*, 9554.
[18] a) T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508; b) T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron* **2001**, *57*, 9813.
[19] X. Bugaut, E. Roulland, *Eur. J. Org. Chem.* **2012**, 908.
[20] N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.

[21] a) P. E. Riley, R. E. Davis, N. T. Allison, W. M. Jones, *J. Am. Chem. Soc.* **1980**, *102*, 2458; b) A. V. Vorogushin, W. D. Wulff, H.-J. Hansen, *Org. Lett.* **2001**, *3*, 2641; c) T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2011**, *133*, 418; d) T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2013**, *135*, 3243.

[22] The ketone **43** exists as an equilibrium mixture of two conformers at a ratio of 1.9:1.

[23] N. Rabjohn, *Org. React.* **1976**, *24*, 261.

[24] CCDC 1469961 (**38**) and 1469997 (**41a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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