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Formal Total Synthesis of (+)-Cortistatins A and J

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Abstract: An efficient formal total synthesis of (+) cortistatins A and J has been accomplished, by exploiting a highly diastereoselective intramolecular [4+3] cycloaddition of epoxy enolsilanes as the key reaction to construct rings B and C of the cortistatins in one step.

In 2006 and 2007, Kobayashi and co-workers reported the isolation of a family of novel steroidal alkaloids named the cortistatins: unique, rearranged steroidal alkaloids possessing nitrogen heterocyclic substituents in their eastern quadrants, from the Indonesian marine sponge, *Corticium simplex*.[1] Studies revealed that cortistatin A (**1**, Figure 1) showed a powerful and

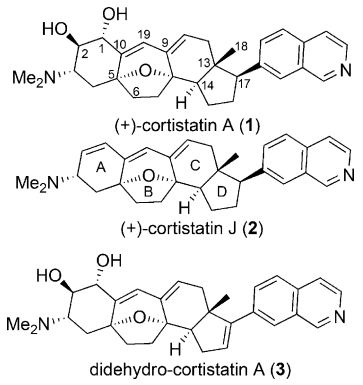

Figure 1. The most bioactive cortistatin congeners.

selective antiangiogenic activity ($IC_{50} = 1.8$ nM) against human umbilical vein endothelial cells (HUVECs).[1a] Cortistatin J (**2**, Figure 1) exhibited the next most potent antiproliferative activity against HUVECs at 8 nm.[1c] Recently, Valente and Baran patented **3** (Figure 1), the didehydro derivative of **1**, as an effective antiviral agent against human immunodeficiency virus (HIV) in infected cells (1 pm $< EC_{50} <$ 2 nM).[2] All of these biological activities make these natural products significant leads for further study.

Due to their promising bioactivities and therapeutic potential, unique architectures but low availability from natural sources, the cortistatins have attracted much attention from the organic chemistry community.[3] To date, six research groups have accomplished the synthesis of the cortistatins.[4] In addition, four formal syntheses, as well as many synthetic studies, have also been reported.[5,6] The oxygen-bridged ring B, the nucleus of all cortistatins, has been assembled by a range of methods,[4–6] including cycloisomerizations, ring-closing metatheses, ring expansions, cyclizations by radical, alkylation, cross-coupling, Michael and aldol reactions, as well as cycloadditions, many of which involve the furan nucleus.[4h,5d,6f–h] Following our first work on a partial structure,[6k] herein we report the asymmetric formal total synthesis of cortistatins A (**1**) and J (**2**), intercepting advanced intermediates in the Nicolaou–Chen total synthesis[4c–d] and the Yamashita–Hirama total synthesis.[4g] This approach featured a highly diastereoselective intramolecular [4+3] cycloaddition of epoxy enolsilanes with furan, a reaction developed in our group, to construct the key oxygen-bridged ring B concomitantly with ring C.[7,8]

Our synthesis of key cycloaddition precursor **11** commenced from the commercially available cyclopentanedione **4**, which is destined to be ring D of cortistatins A and J, and to serve as the chiral linker to unite the diene and the dienophile for the key intramolecular [4+3] cycloaddition. A number of reactions were examined to achieve the desymmetrizing reduction of cyclopentanedione **4**, including a CBS-reduction,[6k] but asymmetric transfer hydrogenation was ultimately found to be the most robust transformation for scale-up. Reduction using catalyst (*R*,*R*)-Ts-DENEB (**5**)[9] produced **6a** with consistently excellent *ee* and up to 95% yield of the two diastereomers (Table 1). Optimization of the reaction conditions by decreasing the reaction temperature eventually afforded **6a** in >99% *ee* and 77% reduction yield (Table 1, entry 3). In this manner, alcohol **6a** was prepared on a 15 to 42 g scale, with excellent *ee* and acceptable diastereoselectivity.

After having secured the optically pure alcohol **6a**, which was protected as a silyl ether **7** in quantitative yield, enol triflation afforded **8** on a scale as large as 30 g (Scheme 1). Both Suzuki–Miyaura and Neigishi coupling reactions of **8** with **9a** or **9b** provided low yields of **10**. One problem encountered was the detrimental decomposition of **9a** under the reaction conditions. Finally, a Stille cross-coupling reaction with **9c**[10] afforded alkenylfuran **10** cleanly in 93% overall yield over two steps, which was reproducible on a >12 g scale. A cross-metathesis reaction with methyl vinyl ketone, mediated by the Hoveyda–Grubbs second-generation catalyst, yielded enone **11**, without concomitant ring-opening of the cyclopentene moiety (Scheme 1).[11]

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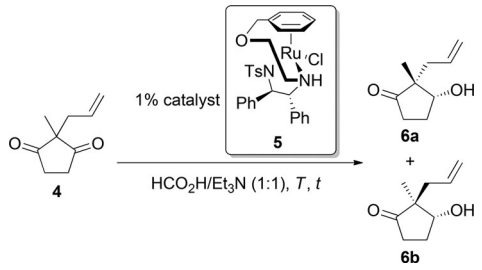
Table 1. Desymmetrizing reduction of **4**.[a]



Entry	Conditions	Yield [%][b] (**6a**+**6b**)	d.r.[c] (**6a**/**6b**)	*ee* [%][d] (**6a**)
1	15 °C, 10 h	93	3.8:1	98
2	0 °C, 24 h	95	4.2:1	>99
3	−5 °C, 72 h	94	4.6:1	>99

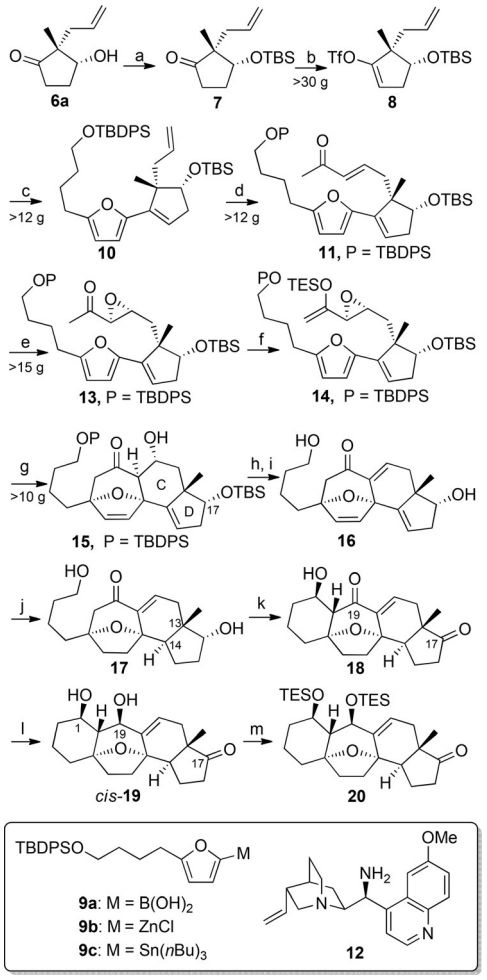
[a] Reactions on a 0.5 mmol scale. [b] Isolated yield of reduction. [c] d.r. determined by ^{1}H NMR spectroscopy of the crude products. [d] *ee* determined by chiral GC analysis.

Using epoxy enolsilanes as oxyallyl cation precursors in the intermolecular [4+3] cycloaddition with furan was first conceived by Ohno et al., although only a 12% yield for this reaction was reported at the time.[7a] However, because of the mild conditions to assemble the epoxy enolsilane precursors as well as to induce cycloaddition, we were interested in further developing the intramolecular version of this silyl triflate-catalyzed cycloaddition as a synthetic methodology.

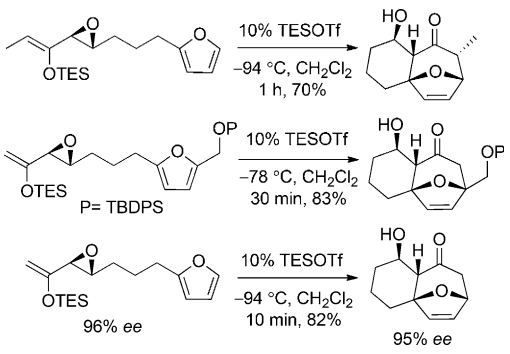
Our studies of this cycloaddition showed that it was both high-yielding and diastereoselective for the synthesis of carbobicyclic [5.4.0] systems (Scheme 2).[8a] Substituents at various positions are compatible, and the absolute stereochemistry of the epoxide determined the facial selectivity of the cycloaddition. We eventually discovered through computational studies that the high diastereoselectivity was because the cycloaddition did not in fact proceed from the putative oxyallyl cation as an intermediate, but rather, with the activated epoxide itself as the "dienophile".[12] Through a backside attack of the epoxide by the diene, the stereochemical information of the oxirane was almost perfectly translated to chirality in the cycloadduct (Scheme 3). The cycloadducts are amply functionalized, rigid polycyclic frameworks, which could potentially be further transformed and used in the synthesis of natural products.[6k]

For the synthesis of the cortistatins, establishing the correct epoxide stereochemistry was paramount to the success of the key cycloaddition step. The asymmetric epoxidation of the enone in the presence of the cyclopentene in **11** was accomplished employing Deng's cinchona-derived catalyst **12**, to generate epoxy ketone **13** as a single diastereomer in 96% yield.[13] Conversion of ketone **13** to its silyl enol ether yielded the requisite cycloaddition precursor **14**.

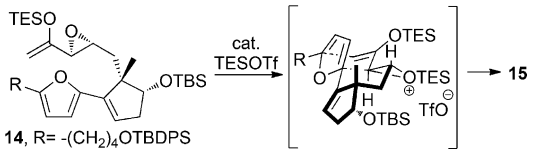
In our studies of the scope of the intramolecular [4+3] cycloaddition with epoxy enolsilanes as dienophiles, additional substituents about the furan, as well as at various positions of the epoxy enolsilane have been examined. However, epoxy enolsilane **14** was the most complex [4+3] cycloaddition precursor assembled to date, presenting the reaction within a context of a stereochemically defined tether that introduced addi-



Scheme 1. Scalable synthesis of **20**: a) TBSCl, imidazole, DMF, 25 °C, 100%; b) NaHMDS, −78 °C, THF, $PhNTf_2$; c) 3 mol% $[Pd(PPh_3)_4]$, LiCl, **9c**, THF, reflux, 93% over 2 steps; d) 5% Hoveyda–Grubbs 2nd-generation catalyst, methyl vinyl ketone, PhMe, 70 °C, 83%; e) 10% **12**, 20% TFA, PhMe, cumene hydroperoxide, 25 °C, 96%; f) LiHMDS, −78 °C, THF, then TESCl, 85%; g) 20% TESOTf, CH_2Cl_2, −78 °C, 87%; h) Florisil, PhMe, 80 °C, 90%; i) CSA, MeOH, 25 °C, 80%; j) 10% Crabtree's catalyst, CH_2Cl_2, H_2, 25 °C, 96%; k) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 84%; l) $Me_4N(OAc)_3BH$, MeCN/AcOH, −40 °C, 96%; m) TESCl, imidazole, DMAP, DMF, 25 °C, 97%. CSA = camphorsulfonic acid; DMAP = 4-dimethylaminopyridine; NaHMDS = sodium hexamethyl disilazide; TBSCl = tert-butyldimethylsilyl chloride; TESOTf = triethylsilyl trifluoromethanesulfonate; TFA = trifluoroacetic acid.



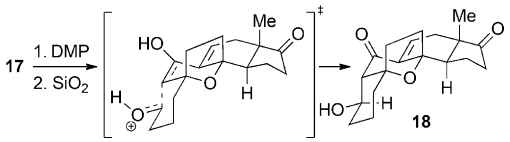
Scheme 2. Intramolecular [4+3] cycloadditions of epoxy enolsilanes.



Scheme 3. Mechanism of cycloaddition of **14**.

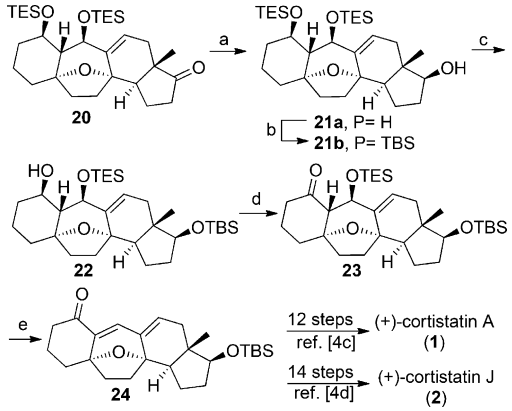
tional diastereoselectivity issues, as well as the nucleophilic reactivity of a proximate cyclopentene functional group. Gratifyingly, the key intramolecular [4+3] cycloaddition catalyzed by TESOTf proved to be versatile enough and compatible with all of the pre-existing functionalities, and afforded the desired cycloadduct **15** in 87% yield as a single diastereomer, a reaction which was carried out on as large as a 10 g scale. In this manner, we successfully completed the assembly of rings B, C, and D of the target molecule.

Catalytic hydrogenation of cycloadduct **15** led to the formation of a fully saturated product, but with the undesired *cis*-fused junction at the CD rings. To establish the *trans*-fused stereochemistry at C13–C14, the siloxy group at C17 must be deprotected. Therefore, dehydration of cycloadduct **15**, followed by desilylation with camphorsulphonic acid, provided **16** in 72% yield over two steps (Scheme 1). Catalytic hydrogenation of triene **16** was not chemoselective, and competitive reduction at the electron-deficient double bond was also observed. On the other hand, in the presence of Crabtree's catalyst, only the reduction of ring D and the dihydrofuran occurred to afford diol **17** in 96% yield. Bis-oxidation of **17** with Dess–Martin periodinane afforded the expected ketoaldehyde, which spontaneously underwent intramolecular aldol cyclization during chromatographic purification on silica gel, to afford **18** containing the full tetracyclic framework of the cortistatins in 84% overall yield. The stereoselectivity of the aldol cyclization could be rationalized as shown in Scheme 4.



Scheme 4. Aldol cyclization yielding **18**. DMP = Dess–Martin periodinane.

Whereas under the Luche conditions,[14] both the C17 and C19 carbonyl groups of **18** were reduced, a chemoselective reduction was achieved by a hydroxyl-directed triacetoxyborohydride reduction, affording 1,3-diol **19** in excellent yield, and as a single diastereomer, distinguishing the C17 carbonyl group for subsequent elaborations.[15] The stereochemistry of **19** was deduced through computer modelling of both the *cis*- and *trans*-diol diastereomers, which confirmed that the NOE between H_1 and H_{19} as observed would only be found in *cis*-**19** (see the Supporting Information). Bis-protection of *cis*-**19** with chlorotriethylsilane provided the key common intermediate **20** in 97% yield.



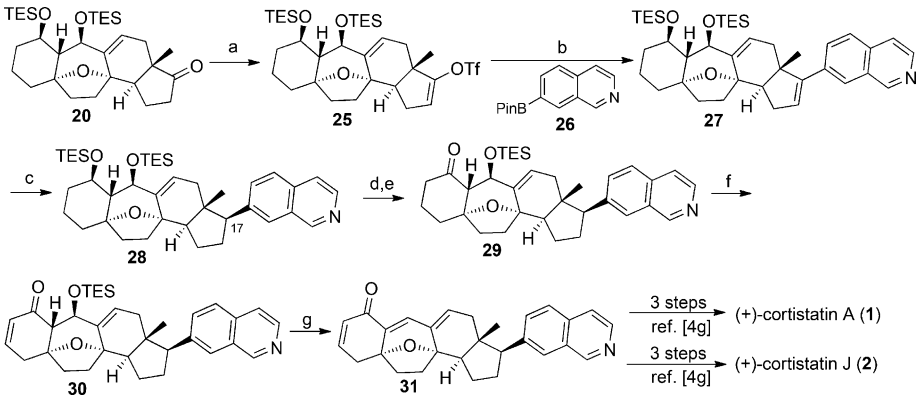
Scheme 5. Formal total synthesis of **1** and **2** intercepting **24** in the Nicolaou–Chen total synthesis: a) $NaBH_4$, MeOH, −78 °C, 100%; b) TBSCl, imidazole, DMAP, DMF, 25 °C, 86%; c) $Et_3N{\cdot}3HF$, THF, 25 °C, 96%; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 100%; e) TFA, CH_2Cl_2, reflux, 85%.

With an efficient and scalable route to tetracyclic **20** available, we proceeded to the synthesis of the Nicolaou–Chen intermediate **24** (Scheme 5). Reduction of ketone **20** with sodium borohydride afforded β-alcohol **21a** in quantitative yield and as a single diastereomer. Quantitative protection with TBSCl, followed by selective deprotection of the less hindered of the triethylsiloxy groups, yielded alcohol **22** in 96% yield. Oxidation of **22** with Dess–Martin periodinane under buffered conditions afforded ketone **23**, which was subjected to treatment with trifluoroacetic acid to effect β-elimination to afford **24** in 16.0% overall yield and in 19 steps by the longest linear route. This synthetic sample of **24** exhibited identical spectroscopic data (^1H NMR, ^{13}C NMR, IR, MS and optical activity) compared with those reported. According to the Nicolaou–Chen synthesis, intermediate **24** can be converted to cortistatins A (**1**) and J (**2**) by a 12- and 14-step sequence, respectively.[4c,d]

Although the cortistatins could be obtained via **24**, evidently this was a rather early intermediate, as more than 10 steps are still required to complete the total synthesis of the natural products. Therefore, we pursued a more efficient approach to an advanced, isoquinoline-substituted synthetic intermediate, the Yamashita–Hirama intermediate **31**, which would constitute a more rapid access to both cortistatins A and J (Scheme 6).

Ketone **20** was converted to vinyl triflate **25** in 95% yield by using NaHMDS and $PhNTf_2$. Suzuki–Miyaura coupling between **30** and pinacolboronate **26** afforded isoquinoline **27** in 85% yield.

The conversion of **27** to **28** required a chemoselective reduction of the cyclopentene over the cyclohexene moiety. Notably, the corresponding transformation in several previous literature syntheses was the penultimate step of the total synthesis, that is, reduction of **3**→**1** (Figure 1), which suffered either from low conversion/yield and/or chemoselectivity.[4a,c–e] However, the desired chemo- and stereoselective reduction was accomplished by catalytic hydrogenation of **27** to give **28** as a single diastereomer in 84% yield, with no over-reduction. The stereo-



Scheme 6. Asymmetric formal synthesis of **1** and **2** based on the Yamashita–Hirama total synthesis: a) NaHMDS, −78 °C, THF, $PhNTf_2$, 95%; b) 10 mol% $[Pd(PPh_3)_4]$, K_2CO_3, **26**, THF, reflux, 85%; c) 10% Pd/C, MeOH, H_2, 25 °C, 40 h, 84%; d) $Et_3N{\cdot}3HF$, THF, 25 °C, 93%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 85%; f) LDA, THF, *N*-*tert*-butylphenylsulfinimidoyl chloride, −78 °C, 80%; g) TFA, DCE, 70 °C, 79%. DCE = 1,2-dichloroethane; LDA = lithium diisopropylamide.

chemistry of **28** was assigned based on the NOE spectra, and ultimately confirmed by the successful synthesis of the known target compound **31**. As before, chemoselective deprotection of the less hindered TES ether, followed by oxidation, produced ketone **29**. Following a similar protocol in the Yamashita–Hirama synthesis, a Mukaiyama oxidation of ketone **39** afforded enone **30** in 80% yield.[16] Warming in the presence of TFA in 1,2-dichloroethane induced elimination to produce target trienone **31.** Our compound **31** exhibited comparable spectroscopic data (^1H NMR, ^{13}C NMR, IR, MS, and optical activity) with those reported by the Yamashita–Hirama group.[4g] The transformation of trienone **31** into both cortistatins A (**1**) and J (**2**) has been realized in three additional steps.[4g] Thus we have also successfully synthesized **31** in 21 steps and 7.7% overall yield from commercially available **4**, and have achieved the asymmetric formal total synthesis of cortistatins A (**1**) and J (**2**) by intercepting the Yamashita–Hirama synthetic route.

In summary, we have completed two solutions to the asymmetric formal syntheses of cortistatins A and J, by intercepting the Nicolaou–Chen intermediate **24**, and the Yamashita–Hirama intermediate **31**, in 19 and 21 steps, respectively. This enantioselective synthetic route is efficient, and provides both cortistatin A and J from commercially available starting materials via **31** in the highest yields to date. The key features of our enantioselective route are: 1) the application of the asymmetric transfer hydrogenation of **4** to establish the chiral framework of ring D of the cortistatins on a multigram scale; 2) the successful application of a controlled, diastereoselective intramolecular [4+3] cycloaddition of an optically pure epoxy enolsilane with a furan to construct rings B and C of the cortistatins in one step.[17] The successful application of this [4+3] cycloaddition reaction in the context of a complex framework demonstrates its synthetic utility in the preparation of stereochemically defined polycyclic compounds, and compatibility with a range of functional groups. Its further application to the synthetic design of routes to other natural and bioactive compounds will be reported in due course.

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Keywords: alkaloids · [4+3] cycloaddition · cortistatins · natural products · total synthesis

[1] a) S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku, M. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149; b) Y. Watanabe, S. Aoki, D. Tanabe, A. Setiawan, M. Kobayashi, *Tetrahedron* **2007**, *63*, 4074–4079; c) S. Aoki, Y. Watanabe, D. Tanabe, A. Setiawan, M. Arai, M. Kobayashi, *Tetrahedron Lett.* **2007**, *48*, 4485–4488.

[2] a) G. Mousseau, M. A. Clementz, W. N. Bakeman, N. Nagarsheth, M. Cameron, J. Shi, P. Baran, R. Fromentin, N. Chomont, S. T. Valente, *Cell Host Microbe* **2012**, *12*, 97–108; b) S. Valente, P. S. Baran, WO2012096934A2, **2012**.

[3] For reviews on the synthesis of the cortistatins, see: a) A. R. H. Narayan, E. M. Simmons, R. Sarpong, *Eur. J. Org. Chem.* **2010**, 3553–3567; b) D. Y. K. Chen, C. C. Tseng, *Org. Biomol. Chem.* **2010**, *8*, 2900–2911; c) C. F. Nising, S. Brase, *Angew. Chem. Int. Ed.* **2008**, *47*, 9389–9391; *Angew. Chem.* **2008**, *120*, 9529–9531.

[4] a) R. A. Shenvi, C. A. Guerrero, J. Shi, C. C. Li, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243; b) J. Shi, G. Manolikakes, C. H. Yeh, C. A. Guerrero, R. A. Shenvi, H. Shigehisa, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 8014–8027; c) K. C. Nicolaou, Y. P. Sun, X. S. Peng, D. Polet, D. Y. Chen, *Angew. Chem. Int. Ed.* **2008**, *47*, 7310–7313; *Angew. Chem.* **2008**, *120*, 7420–7423; d) K. C. Nicolaou, X. S. Peng, Y. P. Sun, D. Polet, B. Zou, C. S. Lim, D. Y. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 10587–10597; e) H. M. Lee, C. Nieto-Oberhuber, M. D. Shair, *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866; f) A. N. Flyer, C. Si, A. G. Myers, *Nat. Chem.* **2010**, *2*, 886–892; g) S. Yamashita, K. Iso, K. Kitajima, M. Himuro, M. Hirama, *J. Org. Chem.* **2011**, *76*, 2408–2425; h) M. G. Nilson, R. L. Funk, *J. Am. Chem. Soc.* **2011**, *133*, 12451–12453.

[5] a) S. Yamashita, K. Iso, M. Hirama, *Org. Lett.* **2008**, *10*, 3413–3415; b) S. Yamashita, K. Kitajima, K. Iso, M. Hirama, *Tetrahedron Lett.* **2009**, *50*, 3277–3279; c) E. M. Simmons, A. R. Hardin-Narayan, X. Guo, R. Sarpong, *Tetrahedron* **2010**, *66*, 4696–4700; d) L. Fang, Y. Chen, J. Huang, L. Liu, J. Quan, C. C. Li, Z. Yang, *J. Org. Chem.* **2011**, *76*, 2479–2487.

[6] a) M. Dai, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6610–6612; b) M. Dai, Z. Wang, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6613–6616; c) L. Kurti, B. Czako, E. J. Corey, *Org. Lett.* **2008**, *10*, 5247–5250; d) E. M. Simmons, A. R. Hardin, X. Guo, R. Sarpong, *Angew. Chem. Int. Ed.* **2008**, *47*, 6650–6653; *Angew. Chem.* **2008**, *120*, 6752–6755; e) N. Kotoku, Y. Sumii, T. Hayashi, M. Kobayashi, *Tetrahedron Lett.* **2008**, *49*, 7078–7081; f) D. T. Craft, B. W. Gung, *Tetrahedron Lett.* **2008**, *49*, 5931–5934; g) P. Magnus, R. Littich, *Org. Lett.* **2009**, *11*, 3938–3941; h) F. Yu, G. Li, P. Gao, H. Gong, Y. Liu, Y. Wu, B. Cheng, H. Zhai, *Org. Lett.* **2010**, *12*, 5135–5137; i) J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2009**, *11*, 5394–5397; j) C. Baumgartner, S. Ma, Q. Liu, B. M. Stoltz, *Org. Biomol. Chem.* **2010**, *8*, 2915–2917; k) L. L. Liu, P. Chiu, *Chem. Commun.* **2011**, *47*, 3416–3417; l) N. Kotoku, Y. Sumii, M. Kobayashi, *Org. Lett.* **2011**, *13*, 3514–3517; m) Z. Wang, M. J. Dai, P. K. Park, S. J. Danishefsky, *Tetrahedron* **2011**, *67*, 10249–10260.

[7] For the intermolecular [4+3] cycloaddition of epoxy enolsilanes, see: a) M. Ohno, K. Mori, T. Hattori, S. Eguchi, *J. Org. Chem.* **1990**, *55*, 6086–

6091; b) B. Lo, S. Lam, W. T. Wong, P. Chiu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12120 – 12123; *Angew. Chem.* **2012**, *124*, 12286 – 12289; c) S. Lam, B. Lo, W. T. Wong, P. Chiu, *Asian J. Org. Chem.* **2012**, *1*, 30 – 33; d) B. Lo, P. Chiu, *Org Lett.* **2011**, *13*, 864 – 967.

[8] For the intramolecular [4+3] cycloaddition of epoxy enolsilanes, see: a) W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W. T. Wong, P. Chiu, *J. Am. Chem. Soc.* **2009**, *131*, 4556 – 4557.

[9] a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521 – 2522; b) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960 – 14963.

[10] M. Yamamoto, H. Munakata, K. Kishikawa, S. Kohmoto, K. Yamada, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2366 – 2370.

[11] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.

[12] E. H. Krenske, S. Lam, J. P. L. Ng, B. Lo, S. K. Lam, P. Chiu, K. N. Houk, *Angew. Chem. Int. Ed.* **2015**, *54*, 7422 – 7425; *Angew. Chem.* **2015**, *127*, 7530 – 7533.

[13] X. J. Lu, Y. Liu, B. F. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134 – 8135.

[14] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226 – 2227.

[15] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560 – 3578.

[16] T. Mukaiyama, J. Matsuo, H. Kitagawa, *Chem. Lett.* **2000**, 1250 – 1251.

[17] It should be noted that a [4+3] cycloaddition approach was also used effectively by Funk to achieve a highly concise, racemic total synthesis of **2**, see ref. [4h].

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