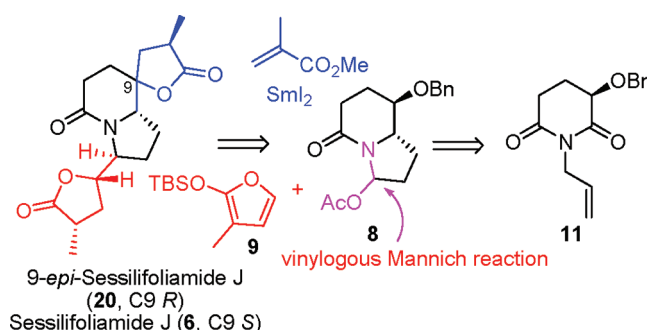


Concise Asymmetric Total Synthesis
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ABSTRACT



A 10-step asymmetric synthesis of 9-*epi*-sessilifoliamide J (**20**), together with sessilifoliamide J (**6**), has been accomplished from the key chiral building block **11** via a *threo*-selective vinylogous Mannich reaction and a Ley oxidation-SmI₂-mediated coupling lactonization. The absolute configuration of the natural sessilifoliamide J was established.

The extracts of roots and leaves of *Stemonaceae* plants have been used in traditional Chinese medicine as cough suppressants and domestic insecticides.¹ More than 100

alkaloids have been isolated from these plants.² Due to the challenging structures, these alkaloids have attracted much attention from many synthetic chemists, so that numerous ingenious total syntheses of stemona alkaloids,³ including (–)-stemoamide (**1**),⁴ (+)-croomine (**2**),⁵ (–)-stemone (**3**),⁶ (–)-tuberostemone (**4**),⁷ (–)-stemospirone (**5**),⁸

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(1) (a) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457–463. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *Phytochemistry* **1994**, *37*, 1205–1208.

(2) For a comprehensive review, see: Greger, H. *Planta Med.* **2006**, *72*, 99–113.

(3) For reviews on the synthetic studies, see: (a) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. d. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117–127. (b) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421–2435. (c) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. d. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908–1937.

(4) For recent synthesis of (–)-stemoamide, see: (a) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356–8357. (b) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295–4303. (c) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295–298. (d) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211–1214. (e) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287–3290. (f) Torssell, S.; Wangren, E.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 4246–4249. For a racemic synthesis, see: (g) Wang, Y.; Zhu, L.-L.; Zhang, Y.-Y.; Hong, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2787–2790.

(5) For synthesis of (+)-croomine, see: (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299–3300. (c) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990–6997.

(6) For synthesis of (–)-stemone, see: Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361–3364.

(7) For synthesis of (–)-tuberostemone, see: (a) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848–14849. (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225–235.

(8) For synthesis of (–)-stemospirone, see: (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721–2724.

(9) For synthesis of stereoisomers of stemona alkaloids, see: (a) Khim, S. K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7734–7736. (b) Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528–9531. (c) Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; De March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769–1772. (d) Hoye, A. T.; Wipf, P. *Org. Lett.* **2011**, *13*, 2634–2637.

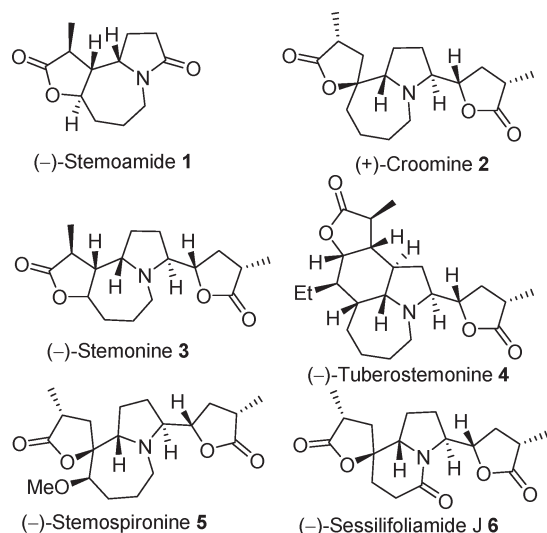


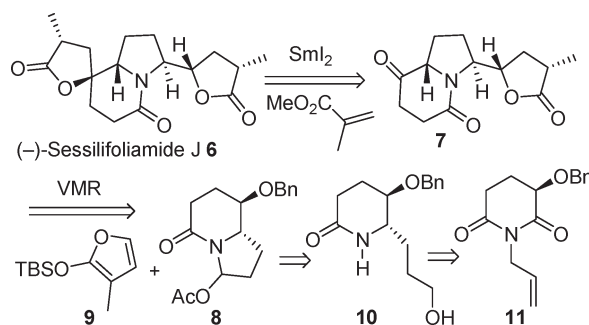
Figure 1. The structure of some stemona alkaloids.

and their diastereomers⁹ have been reported.¹⁰ Sessilifoliamide J (**6**) (Figure 1) is a new stemona alkaloid isolated in 2008 from the roots of *Stemona sessilifolia* (Miq.) Miq. (Stemonaceae).¹¹ Its structure and relative stereochemistry were established by single crystal X-ray crystallography analysis; however, the absolute configuration remained unknown. Different from all other known stemona alkaloids, (–)-sessilifoliamide J (**6**) contains a unique fused piperidin-2-one core. To date, no synthetic study toward sessilifoliamide J (**6**) has been reported. In continuation with our efforts in developing 3-hydroxyglutarimide-based synthetic methodology,^{12,13} we were engaged in the development of a novel strategy for the total synthesis of sessilifoliamide J. Preliminary results of this study are reported herein, which include the synthesis of 9-*epi*-sessilifoliamide J

(**20**) and the establishment of the absolute configuration of the natural product by characterization of minor diastereomer (–)-sessilifoliamide J (**6**).

Our retrosynthetic analysis for (3*S*,9*S*,9*aS*,11*R*,14*S*,16*S*)-**6** is displayed in Scheme 1. The spirolactone moiety was envisioned to be built via the SmI₂-mediated coupling of methacrylate with ketone **7**,^{14,15} while the other lactone ring by a vinylogous Mannich reaction (VMR)^{5b,c,16,17} on bicyclic *N,O*-acetal **8**. The indolizidinone core **8** was available from the chiral building block **11**^{13e–g} via the regio- and diastereoselective reductive alkylation.¹³

Scheme 1. Retrosynthetic Analysis of Sessilifoliamide J **6**



The synthesis started from a stepwise reductive alkylation¹³ of the known glutarimide derivative **11**,^{13e–g} readily available from D-glutamic acid in four steps with a 56% overall yield.^{13e} Treatment of a CH₂Cl₂ solution of **11** with a freshly prepared Grignard reagent **12** in THF at 0 °C, followed by BF₃·OEt₂-mediated reductive dehydroxylation of the resultant regio- and diastereomeric mixture of hemiaminal with Et₃SiH (–78 °C to rt),

(10) For selected recent racemic synthesis of other stemona alkaloids, see: (a) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197–199. (b) Zhao, Y.-M.; Gu, P.-M.; Tu, Y.-Q.; Fan, C.-A.; Zhang, Q.-W. *Org. Lett.* **2008**, *10*, 1763–1766. (c) Zhao, Y.-M.; Gu, P.-M.; Zhang, H.-J.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2009**, *74*, 3211–3213. (d) Chen, Z.-H.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, F.-M. *Org. Lett.* **2011**, *13*, 724–727. (e) Chen, Z.-H.; Zhang, Y.-Q.; Chen, Z.-M.; Tu, Y.-Q.; Zhang, F.-M. *Chem. Commun.* **2011**, *47*, 1836–1838.

(11) Hitotsuyanagi, Y.; Takeda, E.; Fukaya, H.; Takeya, K. *Tetrahedron Lett.* **2008**, *49*, 7376–7379.

(12) For an account, see: (a) Huang, P.-Q. *Synlett* **2006**, 1133–1149. For selected examples, see: (b) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927–1929. (c) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663–1667. (d) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001–6009. (e) Liu, L.-X.; Xiao, K.-J.; Huang, P.-Q. *Tetrahedron* **2009**, *65*, 3834–3841. (f) Yang, R.-F.; Huang, P.-Q. *Chem.—Eur. J.* **2010**, *16*, 10319–10322.

(13) (a) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality* **2005**, *17*, 595–599. (b) Wei, B.-G.; Chen, J.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 190–198. (c) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett.* **2006**, *8*, 1435–1438. (d) Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Huang, P.-Q. *Synlett* **2008**, 1189–1192. (e) Fu, R.; Du, Y.; Li, Z.-Y.; Xu, W.-X.; Huang, P.-Q. *Tetrahedron* **2009**, *65*, 9765–9771. (f) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230–4243. (g) Zhang, H.-K.; Li, X.; Huang, H.; Huang, P.-Q. *Sci. China Chem.* **2011**, *54*, 737–744 (available online from Springerlink).

(14) For key references and reviews on SmI₂, see: (a) Namy, J. L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5–7. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698. (c) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (d) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637.

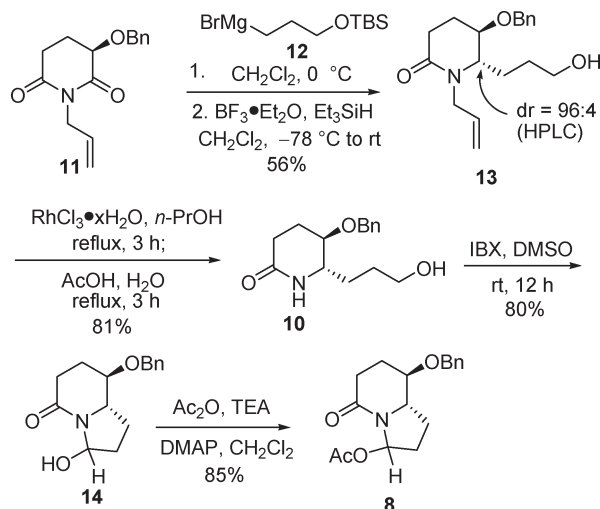
(15) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763–5764. (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624–625. (c) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669–1675. (d) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloys Compd.* **1993**, *192*, 197–199. (e) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900–6901. (f) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373–376. (g) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482–1483. (h) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371–2375. (i) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953–3962. (j) Fukuzawa, S.-i.; Miura, M.; Saitoh, T. *J. Org. Chem.* **2003**, *68*, 2042–2044.

(16) For reviews/accounts on vinylogous Mannich reactions, see: (a) Martin, S. F. *Pure Appl. Chem.* **1997**, *69*, 571–576. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972. (c) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242. (d) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904. See, also: (e) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070.

(17) For studies and examples on the use of VMR in the synthesis of stemona alkaloids, see: (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55–57. (b) Morimoto, Y.; Nishida, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 5773–5776. (c) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221–1222. (d) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641–7644. (e) Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445–3447.

afforded the concomitantly *O*-desilylated 2-piperidinone **13** in 56% yield over two steps, along with the C-6 adduct as a diastereomeric mixture in 12% yield (Scheme 2). The diastereomeric ratio of lactam **13** was determined to be 96:4 by HPLC analysis. Although we were unable to isolate the minor *cis*-diastereomer for a comparison,¹⁸ the stereochemistry of the major diastereomer was assigned as *trans* based on the observed small vicinal coupling constant between H-5 and H-6 ($J_{5,6} = 3.2$ Hz), and by analogy with the similar reductive alkylation reactions of glutarimide derivative **11**.^{13e–g} This assignment was confirmed by the X-ray analysis of compound **19** (*vide infra*). Treatment of **13** with 5 mol % of $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ in refluxing *n*-propanol for 3 h,¹⁹ followed by refluxing in a mixture of AcOH – H_2O ($v/v = 1/10$) for 3 h, gave the deprotected lactam **10** in 81% yield.

Scheme 2. Synthesis of Indolizidinone **8**



Oxidation of **10** with IBX in DMSO ²⁰ produced indolizidinone **14** in 80% yield, which was acetylated [DMAP (cat.), Ac_2O , NEt_3 , CH_2Cl_2] to give the *N,O*-acetal **8** as a 68:32 diastereomeric mixture (^1H NMR) in a combined yield of 85%. Because the subsequent vinylogous Mannich reaction would involve an *N*-acyliminium intermediate,²¹ which could be generated from either diastereomer of **8**, this diastereomeric mixture was used in the next step without further separation.

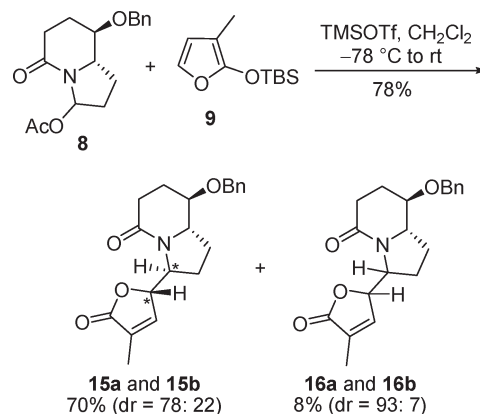
(18) For the 6-substituted piperidin-2-one derivatives of type **13**, the 5,6-*trans*-isomer generally exhibits a smaller vicinal coupling constant between H-5 and H-6 (e.g., $J_{5,6} = 1.5$ Hz;^{12d} 2.3 Hz;^{12f} 2.4 Hz^{13e}) than the *cis*-isomer does (e.g., $J_{5,6} = 4.5$ Hz;^{12e} 4.5 Hz^{12f}).

(19) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298–6300.

(20) (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945–7948. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(21) For recent reviews on the chemistry of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3871–3856. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (c) Royer, J. *Chem. Rev.* **2004**, *104*, 2311–2352. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541.

Scheme 3. Vinylogous Mannich Reaction of *N,O*-Acetal **8**



We next focused on the vinylogous Mannich reaction between 2-methylsilyloxyfuran **9** and *N,O*-acetal **8** (Scheme 3). Among the Lewis acids tested (TMSOTf , $\text{BF}_3 \cdot \text{OEt}_2$, InCl_3 , $\text{Bi}(\text{OTf})_3$, ZnCl_2 , Et_2AlCl), TMSOTf gave optimal results. Thus, by treating **8** (1.0 equiv) with **9** (1.5 equiv) and TMSOTf (1.0 equiv) in CH_2Cl_2 at -78 °C, and allowing the reaction to warm to room temperature and stir for 1 h, two fractions **15a/15b** and **16a/16b** were isolated. ^1H NMR analysis showed that the ratio of **15a/15b** was 78:22 and that of **16a/16b** was 93:7. The stereochemistry of the major diastereomer **15a** was determined to be *threo* at a latter stage (*vide infra*), whereas those of the minor isomer **15b**, **16a**, and **16b** were not determined. The observed *threo*-diastereoselection is in agreement with most vinylogous Mannich reactions involving cyclic iminium ion intermediates.^{16,17} A plausible Diels–Alder transition state^{17e} is displayed in Figure 2. Noteworthy is that the efficiency of the vinylogous Mannich reaction on our ring system using *N,O*-acetal **8** has been improved compared with the original one utilizing an α -amino acid as a precursor of the iminium ion intermediate.^{5b,c}

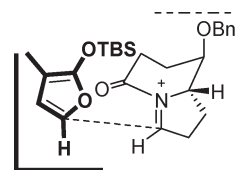


Figure 2. Proposed transition state for the *threo*-selective VMR of *N,O*-acetal **8** with 2-methylsilyloxyfuran **9**.

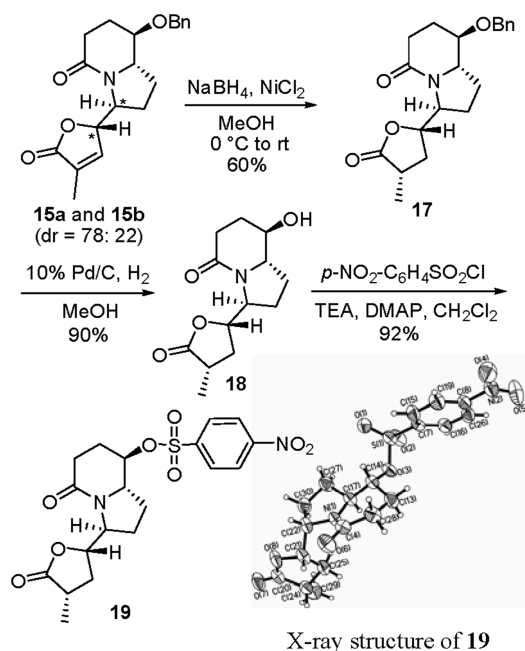
Reduction of the diastereomeric mixture **15** with $\text{NaBH}_4/\text{NiCl}_2$ ^{17b,c,22} in methanol gave compound **17** in 60% yield,

(22) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817–820.

(23) Although the direct conversion of **15** to **18** by hydrogenolysis (Pd/C , H_2 , MeOH) afforded a higher yield, compound **18** could not be separated from other stereoisomers.

along with three other diastereomers (dr = 9:30:61) in 20% yield.²³ On the basis of these results, the diastereoselectivity in the hydrogenation of *threo*-**15a** was estimated to be at least 10:1, which is in accordance with literature precedent for similar systems.^{5b,c,9c,10e,17b,c} *O*-Debenzylation of the major diastereomer **17** under catalytic hydrogenolytic conditions [10% Pd/C, H₂, MeOH] produced alcohol **18** in 90% yield. To determine the stereochemistry of **18**, its tosylate derivative **19** was prepared. Single crystal X-ray analysis revealed that **19** possessed the structure shown in Scheme 4. Thus the relative stereochemistries of **17** and **18** were confirmed, and the major diastereomer (**15a**) obtained from the vinylogous Mannich reaction was established as *threo*.

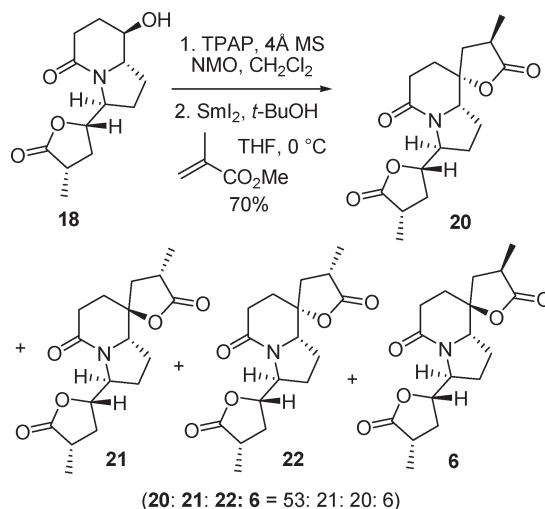
Scheme 4. Synthesis of Alcohol **18**



Now, we were in a position to install the spiro lactone moiety. Swern oxidation²⁴ followed by SmI₂-mediated coupling gave eight diastereomers, which implied that partial epimerization at C-9a might have occurred during Swern oxidation. However, when the Ley oxidation²⁵ was used, only four isomers were observed, in a ratio of 53:21:20:6 (Scheme 5). Extensive NMR experimentation (see Supporting Information) indicated that the major component had the structure assigned as 9-*epi*-sessilifoliolamide J (**20**), the minor component **6** was the natural product, and the other diastereomers had the structures assigned as **21** and **22**, respectively. The stereochemical outcome of the SmI₂-mediated lactonization reaction is attributable to the approach of methyl acrylate from the more accessible convex face of the ketyl radical intermediate, initially formed from the ketone and SmI₂. Optical

rotation data {synthetic **6**: [α]_D²⁰ –71 (c 0.15, CHCl₃); sessilifoliolamide J (**6**):¹¹ [α]_D²⁶ –73 (c 0.13, CHCl₃)} and spectral data for the synthetic product (**6**) are in good agreement with those reported for the natural product.¹¹ Thus the absolute configuration of the natural (–)-sessilifoliolamide J (**6**) is 3*S*,9*S*,9*aS*,11*R*,14*S*,16*S*.

Scheme 5. Final Synthesis of 9-*epi* and (–)-Sessilifoliolamide J



To the best of our knowledge, among various synthetic approaches for the synthesis of stemona alkaloids, this is the first example utilizing the SmI₂-mediated coupling to install the spiro lactone moiety.

In summary, we have demonstrated that the chiral building block **11** can serve as a powerful platform for the rapid assembly of the tetracyclic skeletal framework of sessilifoliolamide J. Using this novel strategy, the first asymmetric synthesis of 9-*epi*-sessilifoliolamide J (**20**) has been achieved in only 10 steps with a 4.3% overall yield. Meanwhile sessilifoliolamide J (**6**) was obtained as a minor diastereomer, which allowed the establishment of the absolute configuration of the natural sessilifoliolamide J as 3*S*,9*S*,9*aS*,11*R*,14*S*,16*S*. Considering the complexity of the molecule with six chiral centers, our asymmetric approach is remarkably concise. Work is currently in progress in our laboratories for improving the selectivity in the asymmetric total synthesis of sessilifoliolamide J, and the results will be reported in due course.

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Supporting Information Available. Full experimental procedures; ¹H and ¹³C NMR spectra of all new compounds; NOESY spectra of compounds **20**–**22**; X-ray crystallographic data (CIF) of compound **19**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(24) Mancuso, A. J.; Swern, D. *Synthesis* **1992**, 165–185.
(25) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.