Organic LETTERS

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Expeditious Entry to the Chamigrane Endoperoxide Family of Natural Products

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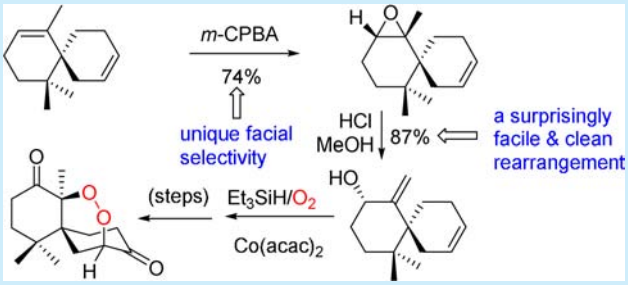
Supporting Information

ABSTRACT: Several members of the recently reported peroxy chamigrane family of natural products were synthesized via a distereoselective route with a novel facial-selective epoxidation of a spiroundecadiene, a facile epoxide rearrangement, and a Co(II)-mediated silylperoxidation as the key steps. Adaptation of the diastereoselective route to an enantioselective one is also illustrated.



The very recently reported[1] chamigrane/norchamigrane endoperoxides (exemplified in Figure 1) represent a new

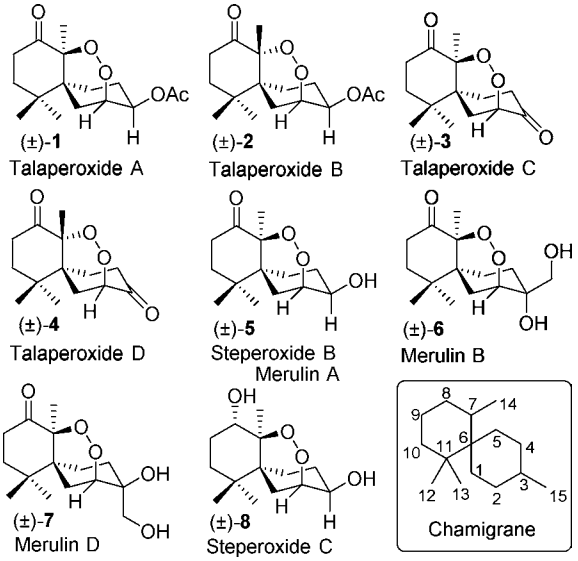


Figure 1. Structures for **1**−**8** in the literature along with the atom numbering of the parent core chamigrane (boxed).

family of natural products. These sesquiterpenoids were isolated from fungi *Steccherinum ochraceum*, *Xylocarpus granatum*, *Talaromyces flavus*, and *Pseudolagarobasidium acaciicola*, respectively. Their planar structures along with the relative configurations were established by extensive spectroscopic analyses and (in the cases of **1**, **2**, and **5**) single-crystal X-ray crystallography. With the aid of copper radiation, the absolute configurations for talaperoxides A and B as well as steperoxide B/merulin A (**1**, **2** and **5**) were successfully determined.[1d]

Preliminary biological tests have showed that some of the above-mentioned peroxy chamigranoids possess activities against human breast,[1b,d] colon,[1b] hepatoma,[1d] cervical,[1d] and prostatic[1d] cancer cell lines. The potential of these interesting compounds in biomedical studies along with their novel peroxy functionality-containing spiro/bridged/fused ring system prompted us to perform a synthetic study. Here are the primary results.

Although the molecular sizes of the peroxy chamigranoids seem unpretentious and thus tend to belie the difficulty of their synthesis, challenges do exist, mainly stemming from the construction of three contiguous[2] quaternary carbon centers embedded in multicyclic frameworks, especially in the presence of a troublesome peroxy functionality; many of our explorations were frustrated before finally a route was successful.

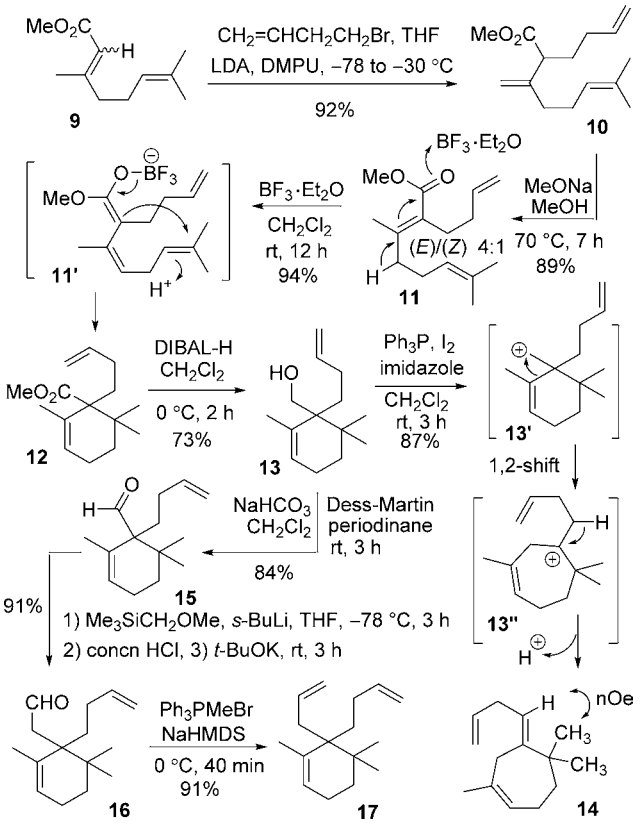
The eventual approach emerged (Scheme 1) with elaboration of methyl geranate into cyclohexene carboxylate **12** via alkylation, isomerization, and cyclization following similar transformations reported[3] by Weyerstahl.[4] Reduction of **12** with DIBAL-H afforded alcohol **13** smoothly, but the attempts to acquire the corresponding iodide (a potentially suitable precursor for chain extension) led to ring-expansion product **14**. After many potentially applicable alternatives were tested, the chain elongation finally was most satisfactorily achieved by conversion of **13** into aldehyde **15** followed by one-carbon homologation and olefination to give triene **17**.

A ring-closing metathesis was then performed on **17** (Scheme 2) to deliver norchamigrene (±)-**20**. Exposure of this diene to *m*-CPBA led to the very unstable epoxide (±)-**21** as a single diastereomer.[5] Subsequent attempts to install a

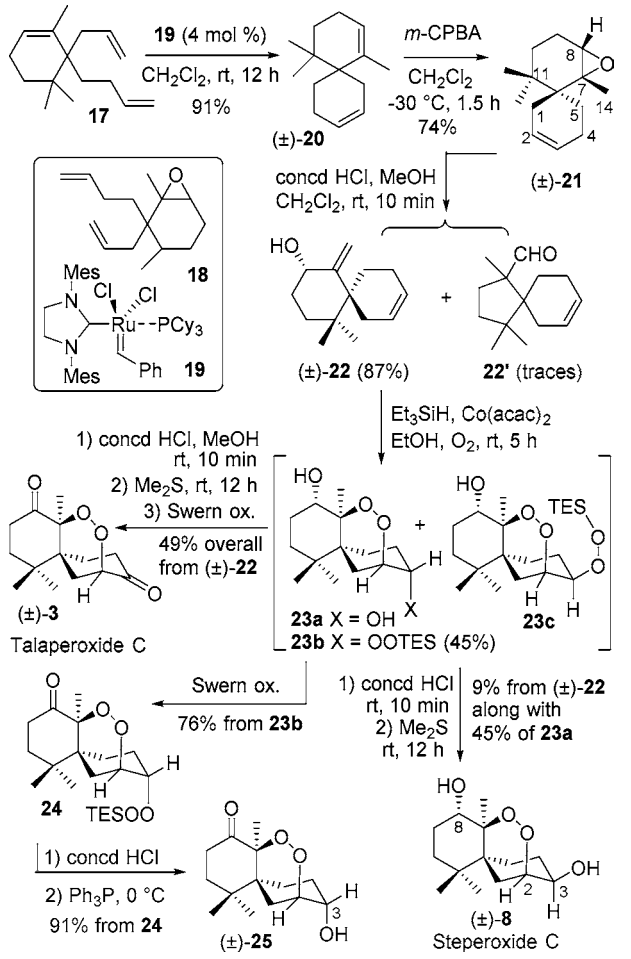
Received: December 15, 2014
Published: January 12, 2015

DOI: 10.1021/ol503603t
Org. Lett. 2015, 17, 592−595

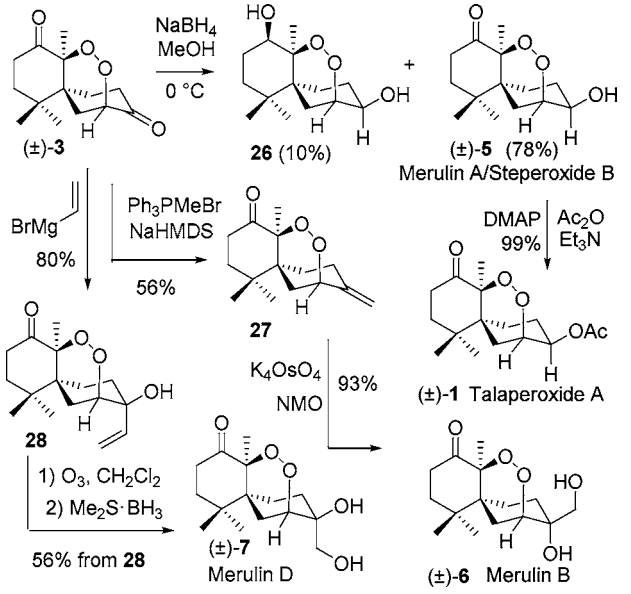
Scheme 1



Scheme 2



Scheme 3



hydroperoxyl group onto (±)-**21** by PMA (phosphomolybdic acid)-mediated perhydrolysis[6] as initially planned was unsuccessful, leading predominantly to unexpected (±)-**22** and **22**′ in a nearly 1:1 ratio. However, exposure of (±)-**22** to O_2/$Co(acac)_2$/Et_3SiH[7] very gratifyingly provided a mixture of **23a**−**c**,[8] providing the first entry (to our knowledge) to the target ring system.

As access to adequate amounts of (±)-**22** was a prerequisite for continuation of the synthesis, we next examined the isomerization[9] of (±)-**21** to (±)-**22** under different conditions. The results were very pleasing because the desired transformation could be satisfactorily achieved without recourse to any expensive reagents and/or tedious operation. Thus, by adding a solution of concd HCl in MeOH to a solution of (±)-**21** in CH_2Cl_2, the desired allylic alcohol **22** was formed in 87% yield together with only negligible amounts of aldehyde **22**′.

The secured supply of (±)-**22** enabled us to examine the Co-mediated peroxidation more closely. It was then found that direct hydrolysis of the mixture of **23b**,**c** (difficult to separate from each other) followed by Me_2S reduction could afford (±)-**8** (steperoxide C) along with its C-3 epimer **23a**. Alternatively, a Swern oxidation of isolated **23b** (the major component of the peroxidation, 45% from (±)-**22**) led to ketone **24**, which upon removal of the TES group and reduction of the −OOH group gave (±)-**25** (C-3 *epi*-steperoxide B/merulin A) in 91% yield. If the hydrolyzed crude mixture of **23a**−**c** was directly subjected to Me_2S reduction and Swern oxidation, (±)-**3** (talaperoxide C) could be obtained in 49% overall yield (from (±)-**22**).

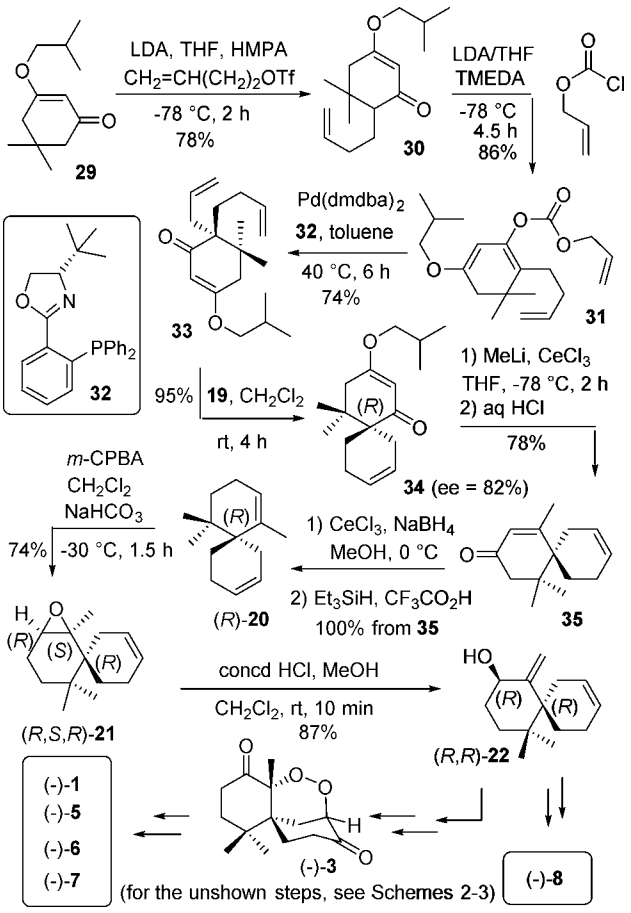
Carefully controlled reduction of **3** with $NaBH_4$/MeOH at 0 °C (Scheme 3) yielded steperoxide B (±)-**5** in 78% yield, along with 10% of **26**. Acetylation of isolated **5** resulted in talaperoxide A (±)-**1**. Alternatively, treatment of (±)-**3** with Ph_3PMeBr/NaHMDS led to exocyclic alkene **27** in 56% yield, which could be further converted into merulin B (±)-**6** by a standard dihydroxylation. Upon exposure of (±)-**3** to CH_2=

DOI: 10.1021/ol503603t
Org. Lett. 2015, 17, 592−595

CHMgBr, the vinyl group added exclusively from the unobstructed face, leading to **28** in 80% yield. Ozonolysis of alkene **28** followed by sequential reduction the intermediate ozonide and the aldehyde with Me_2S and $Me_2S{\cdot}BH_3$, respectively, led to merulin D (±)-**7**.

The above results showed that the absolute configurations of the end products peroxy chamigranoids were decided by the configuration of the spiro stereogenic center; the corresponding optically active compounds would be also attainable if optically active **20** was used. Stoltz and co-workers have developed a straightforward access to such species in their synthesis[10a] of α-chamigrene. Employing that elegant method[10c] for constructing the enantioenriched spiro-stereogenic center, we next synthesized (*R*)-**20** as shown in Scheme 4.

Scheme 4



Conversion of **29** all the way to **35** was achieved in a fashion similar to that reported by Stoltz, but with slight modification; the alkylation of **29** was done with a triflate instead of an iodide as in the original protocol[10a] because the latter led to very low yields despite prolonged time and higher temperatures. The quaternary center-generation step was then carried out in the presence of $Pd(dmdba)_2$ with **32**[11] as the chiral ligand. The resulting **33** was converted first into spirocycle **34** and then **35** in a fashion similar to that in the literature.

Subsequent removal of the carbonyl group in **35** was realized via $NaBH_4/CeCl_3$ (Luche) reduction followed by deoxygenation with Et_3SiH/CF_3CO_2H.[12] Although many similar protocols using other acids (such as $BF_3{\cdot}Et_2O$ and AcOH) were also known, in the particular system involved in this work CF_3CO_2H gave the best result. Compared with the thioketalization−desulfurization procedure in the original report, the present sequence for transforming **35** into (*R*)-**20** is experimentally more convenient and better yielding.

Using the optically active **20** as the substrate, the remaining steps were performed as described in the racemic synthesis to deliver the antipodes of natural **1**, **3**, **5**, **6**, **7**, and **8** in the same yields as reported for their racemic counterparts. All of them showed spectroscopic data consistent with those reported for the corresponding natural products. Comparison of the signs for the optical rotations for the latter five compounds with those for their natural counterparts also unambiguously proved that the absolute configurations for the natural **3**, **6**, **7**, and **8** are indeed as depicted in Figure 1.

In brief, the peroxy bridge-containing ring system of the chamigrane endoperoxide family of natural products is synthetically accessed for the first time (to our knowledge). The (in a sense) protecting-group-free[13] route to talaperoxides A and C, merulins A, B, and D, as well as steperoxide C[14] developed in this work featured the use of a novel facial selective epoxidation of a spirocyclic diene, a clean rearrangement of the epoxide to allylol, and a Co(II)-mediated silylperoxidation as the key steps. The absence[15] of any heteroatoms or additional stereogenic centers in the spirocyclic diene to differentiate the two faces of the reacting C−C double bond in the epoxidation and the optimal results observed with HCl/MeOH[16] (among cheapest reagents) are particularly noteworthy. The highly selective clean ring expansion leading to the seven-membered triene **14** is also of interest, though not exploited in this work. With the aid of the Stoltz's method (with modifications), the diastereoselective route can also be rendered enantioselective. Finally, the facility of the key steps perhaps also lends some support for the hypothesis of the biosynthetic[1d] routes of these endoperoxides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data/scanned spectra for products (new compounds), and chiral HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21372248, 21172247, 21032002) and the Chinese Academy of Sciences.

■ REFERENCES

(1) (a) Liu, D.-A.; Dong, Z.-J.; Wang, F.; Liu, J.-K. *Tetrahedron Lett.* **2010**, *51*, 3152−3153. (b) Chokpaiboon, S.; Sommit, D.; Teerawatananond, T.; Muangsin, N.; Bunyapaiboonsri, T.; Pudhom, K. *J. Nat. Prod.* **2010**, *73*, 1005−1007. (c) Liu, D.-Z.; Luo, M.-H. *Fitoterapia* **2010**, *81*, 1205−1207. (d) Li, H.; Huang, H.; Shao, C.; Huang, H.; Jiang, J.; Zhu, X.; Liu, Y.; Liu, L.; Lu, Y.; Li, M.; Lin, Y.; She, Z. *J. Nat. Prod.* **2011**, *74*, 1230−1235. (e) Chokpaiboon, S.; Sommit, D.; Bunyapaiboonsri, T.; Matsubara, K.; Pudhom, K. *J. Nat.*

DOI: 10.1021/ol503603t
Org. Lett. 2015, 17, 592−595

Prod. **2011**, *74*, 2290−2294. (f) Wibowo, M.; Prachyawarakorn, V.; Aree, T.; Wiyakrutta, S.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Eur. J. Org. Chem.* **2014**, 3976−3980. For use of merulin A for the treatment of African sleeping sickness, see: (g) Navarro, G.; Chokpaiboon, S.; De Muylder, G.; Bray, W. M.; Nisam, S. C.; McKerrow, J. H.; Pudhom, K.; Linington, R. G. *PLoS One* **2012**, *7*, e46172. and (h) Linington, R.; Navarro, G.; Pudhom, K.; McKerrow, J. WO 2013019686 A2 (CAN 158:302292).

(2) For examples for synthesis of three or more contiguous quaternary centers, see: (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473−477. (b) Taber, D. F.; Sikkander, M. I.; Storck, P. H. *J. Org. Chem.* **2007**, *72*, 4098−4101. (c) Srikrishna, A.; Ramachary, D. B. *Indian J. Chem.* **2005**, *44B*, 751−761. (d) Srikrishna, A.; Anebouselvy, K. *Indian J. Chem.* **2005**, *44B*, 1029−1039. (e) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425−7426. (f) Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517−519. (g) Srikrishna, A.; Yelamaggad, C. V.; Kumar, P. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2877−2881. (h) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716. (i) van der Waals, A.; Keese, R. *J. Chem. Soc., Chem. Commun.* **1992**, 570−571. (j) Weyerstahl, P.; Brendel, J. *Liebigs Ann. Chem.* **1992**, 669−679. (k) Corey, E. J.; Kang, M.-c.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649−651.

(3) (a) Weyerstahl, P.; Schneider, K. *Liebigs Ann. Chem.* **1992**, 1049−1053. (b) Weyerstahl, P.; Buchmann, B.; Marschall-Weyerstahl, H. *Liebigs Ann. Chem.* **1988**, 507−523.

(4) It should be noted that although similar cyclization forming a tertiary rather than quaternary carbon is very common, no quaternary cases other than ref 3 can be found, presumably due to much increased steric congestion. Because the mechanism for this cyclization (ref 3) was never shown, a plausible (not experimentally proven) rationalization is incorporated in Scheme 1 to facilitate understanding. Several other acids (such as $SnCl_4$, Et_2AlCl, $ZnBr_2$, $La(OTf)_3$, and $Sc(OTf)_3$) were also tested in the cyclization. However, none of them was as good as $BF_3{\cdot}Et_2O$. It is also noteworthy that in this work the cyclization was completed under much milder conditions using much less $BF_3{\cdot}Et_2O$ without heating.

(5) In contrast, *m*-CPBA epoxidation of **17** led to an inseparable 1.5:1 mixture of two diastereomers of **18** (leading to an inseparable diastereomeric mixture of **21** after RCM). A clue to the unexpected stereoselectivity of epoxidation of **20** can be found from the molecular model: when both cyclohexene rings are in a semichair conformation without having the C-14 "crushed" into the π-bond space over the C-2/C-3, the face of the C-7/C-8 double bond *cis* to C-1 is blocked by the *quasi*-axial CH_3 at C-11, leaving only the face *cis* to the C-5 open to *m*-CPBA attack.

(6) (a) Li, Y.; Hao, H.-D.; Zhang, Q.; Wu, Y.-K. *Org. Lett.* **2009**, *11*, 2691−2694. (b) Hao, H.-D.; Li, Y.; Han, W.-B.; Wu, Y.-K. *Org. Lett.* **2011**, *13*, 4212−4215. (c) Hao, H.-D.; Wittlin, S.; Wu, Y.-K. *Chem. — Eur. J.* **2013**, *19*, 7605−7619.

(7) For the original report for the Co(II)-TES-mediated perxidation, see: (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573−576. For applications, see, e.g.: (b) Barnych, B.; Vatèle, J.-M. *Org. Lett.* **2012**, *14*, 564−567. (c) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron* **2001**, *57*, 5979−5989. (d) Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525−536. (e) Tokuyasu, T.; Kunikawa, S.; Abe, M.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Begum, K.; Wataya, Y. *J. Org. Chem.* **2003**, *68*, 7361−7367. (f) Gemma, S.; Marti, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719−5722. (g) O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569−4571. For other radical trapping $^3O_2$ to make peroxy bonds, see: (h) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449−2469. (i) Kim, J.; Li, H. B.; Rosenthal, A. S.; Sang, D.; Shapiro, T. A.; Bachi, M. D.; Ponser, G. H. *Tetrahedron* **2006**, *62*, 4120−4127. For a recent example of using Mn(III)-mediated peroxidation in an elegant total synthesis, see: (j) Hu, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2014**, *135*, 5287−5290.

(8) Use of $Co(thd)_2$ (cf., e.g., ref 7b) instead of $Co(acac)_2$ led to very low yields of peroxy products (<6%), while no reaction occurred with $Mn(acac)_3$ or $CuCl_2$.

(9) For previous studies on the rearrangement of epoxides into allylic alcohols, cf. e.g.: (a) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1598−1600. (b) Terao, S.; Shiraishi, M.; Kato, K. *Synthesis* **1979**, 467−468. (c) Bermejo, F.; Sandoval, C. *J. Org. Chem.* **2004**, *69*, 5275−5280. (d) Raptis, C.; Garcia, H.; Stratakis, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3133−3136. (e) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699. (f) Crandall, J. K.; Crawley, L. C. *Org. Synth.* **1973**, *53*, 17−21. (g) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1075−1708. (h) Arata, K.; Tanabe, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 299−303. (i) Deagostino, A.; Tivola, P. B.; Prandi, C.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2856−2860. (j) Weidmann, V.; Schaffrath, M.; Zorn, H.; Rehbein, J.; Maison, W. *Beilstein J. Org. Chem.* **2013**, *9*, 2233−2241.

(10) (a) White, D. E.; Stewart, I. C.; Seashore-Ludlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668−4686. (b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810−812. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. (d) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924−6927. For syntheses of other chamigrane related spiro-rings, cf. also: (e) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1913−1821. (f) Ireland, R. E.; Dow, W. C.; Dodfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001−1013. (g) Niwa, H.; Yoshida, Y.; Hasegawa, T.; Yamada, K. *Chem. Lett.* **1985**, *14*, 1687−1688. (h) Iwata, C.; Akiyama, T.; Miyashita, K. *Chem. Lett.* **1988**, *36*, 2872−2877. (i) Niwa, H.; Yoshida, Y.; Hasegawa, T.; Yamada, K. *Tetrahedron* **1991**, *47*, 2155−2162. (j) Chen, Y.-J.; Wang, C.-Y.; Lin, W.-Y. *Tetrahedron* **1996**, *52*, 13181−13188. (k) Fraga, B. M. *Nat. Prod. Rep.* **2004**, *21*, 669−693 (a review). (l) Srikrishna, A.; Lakshmi, B. V.; Mathews, M. *Tetrahedron Lett.* **2006**, *47*, 2103−2106. (m) Taber, D. F.; Sikkander, M. I.; Storck, P. H. *J. Org. Chem.* **2007**, *72*, 4098−4101. (n) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165−193 (a review). (o) Hsu, D.-S.; Juo, B.-C. *Tetrahedron Lett.* **2013**, *54*, 1751−1753. (p) Zhu, J.-L.; Huang, P.-W.; You, R.-Y.; Lee, F.-Y.; Tsao, S.-W.; Chen, I.-C. *Synthesis* **2011**, 715−722.

(11) The best chiral ligand developed by Stoltz et al. (ref 10a,b) was not commercially available. Therefore, the second best one **32** was chosen for this work, the antipode of **32**, though it was unavailable in the catalogs.

(12) (a) Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Tetrahedron Lett.* **2013**, *54*, 1612−1615. (b) Egi, M.; Umemura, M.; Akai, S. *J. Org. Chem.* **2013**, *77*, 7092−7097. (c) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, *34*, 2955−2958.

(13) The TES here was installed as part of the radical reaction, not like those from TESCl, which at their introduction step were entirely meant for protections in later steps.

(14) For ORTEP drawings and CCDC numbers for **1**, **5**, **8**, and **25**, see the Supporting Information.

(15) If there is a heteroatom or another substituent in either ring of the spirocycle, one would expect some differentiation of the two faces of the reacting C−C double bond.

(16) Similar rearrangements with comparable selectivity were normally achieved using more expensive reagents and/or involving more complicated systems (cf. ref 9).

DOI: 10.1021/ol503603t
Org. Lett. 2015, 17, 592−595