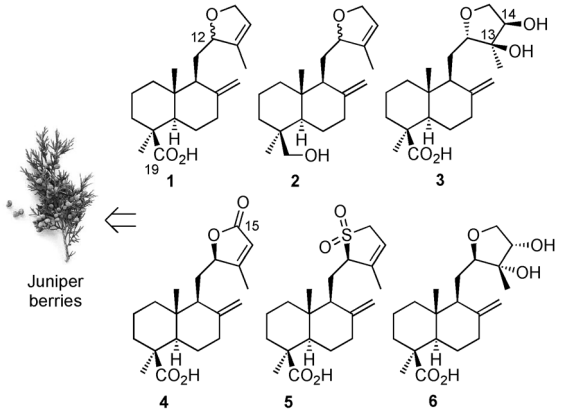
Total Synthesis

DOI: 10.1002/anie.201208412

Syntheses and Structural Confirmations of Members of a Heterocycle-Containing Family of Labdane Diterpenoids**

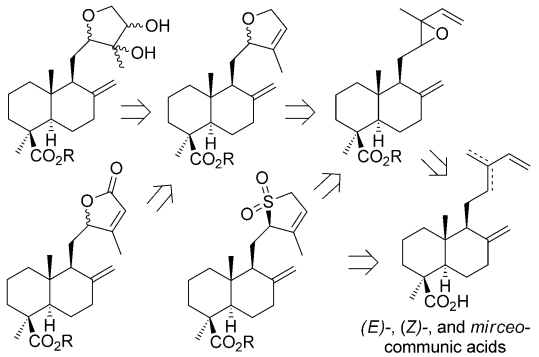
*Daniel J. Mack and Jon T. Njardarson**

Labdanes[1] are a large and structurally diverse class of diterpenoid natural products exhibiting a range of biological activities.[2] In the last few years, interesting new labdane natural products containing five membered heterocycles separated by a methylene unit from the *trans*-decalin core have been reported (**1**–**6**,[3] Scheme 1). These labdane natural products have never been synthesized and most of the structures have not been unambiguously assigned. For example, the C12 stereochemistry of **1** and **2** relative to the decalin core is not known. The relationship between **3** and **6** is particularly interesting, as they share an identical decalin core, but an enantiomeric relationship at C12–C14. Given our commitment to the synthesis of diterpenoid natural products,[4] contributions toward the synthesis of 2,5-dihydrofuran architectures,[5] and general interest in synthesizing new and unique collections of natural products for biological screening purposes, these targets seemed well suited.



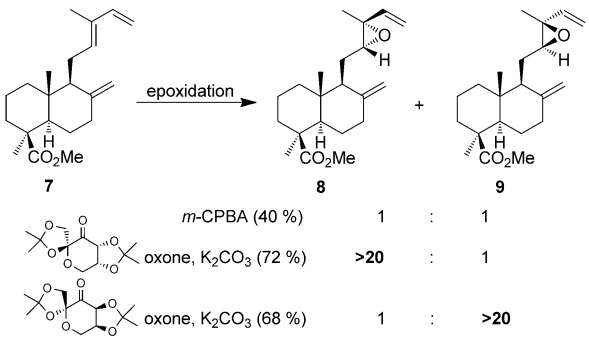
Scheme 1. Heterocycle-containing labdane natural product family.

We envisioned that the chiral decalin core of these target structures could be accessed in large quantities by extraction from juniper berries, and that our vinyl oxirane ring expansion reaction would be a good match for accessing the 2,5-dihydrofuran cores of **1** and **2**, which could then be further oxidized to lactone **4** and diols **3** and **6**.[6] A retrosynthetic analysis detailing these plans is shown in Scheme 2. The readily available and inexpensive starting materials for our synthesis would be the communic acids, which are typically isolated as a mixture of diene isomers (*E*-, *Z*-, and *mirceo*-communic acids) from the berries of *Juniperis communis*.[7] Other coniferous species also produce the communic acids in various ratios, but the common juniper berries can provide up to 57% by mass of the acids, thus making them an ideal source for our synthetic plans.[8]



Scheme 2. Retrosynthetic analysis.

Following extraction of commercially available juniper berry powder, (*E*)-communic acid was separated from the other two olefin isomers and methylated (**7**). It is known that epoxidation of **7** selectively occurs at the trisubstituted olefin, although with poor facial selectivity (**8** and **9**, Scheme 3).[9]



Scheme 3. Reagent-controlled labdane diene epoxidation. *m*-CPBA = *meta*-chloroperoxybenzoic acid.

[*] Prof. J. T. Njardarson
Department of Chemistry and Biochemistry, University of Arizona
1306 E. University Blvd., Tucson, AZ 85721 (USA)
E-mail: njardars@email.arizona.edu
D. J. Mack
Department of Chemistry and Chemical Biology, Cornell University, Baker Laboratory, Ithaca, NY 14853-1301 (USA)

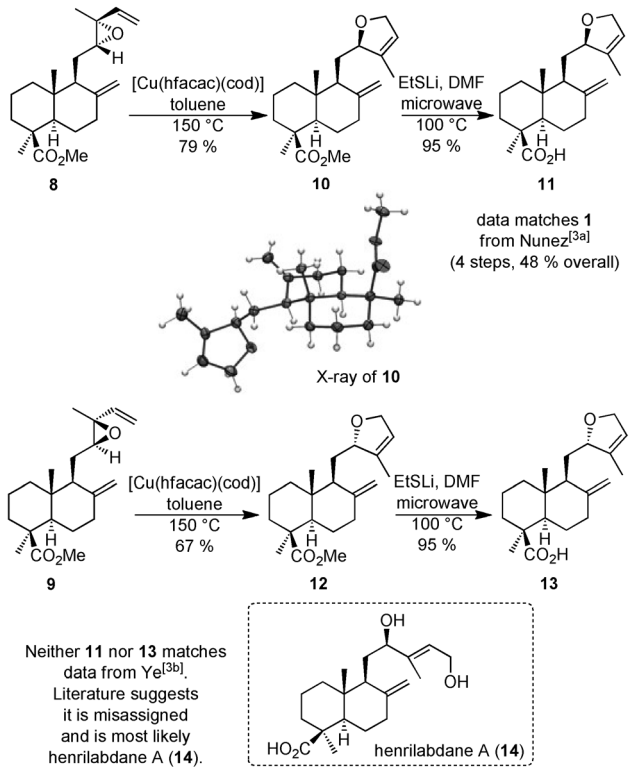
[**] We thank the NSF (CHE-0848324), NIH-NIGMS (RO1 GM086584) and the University of Arizona for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208412.

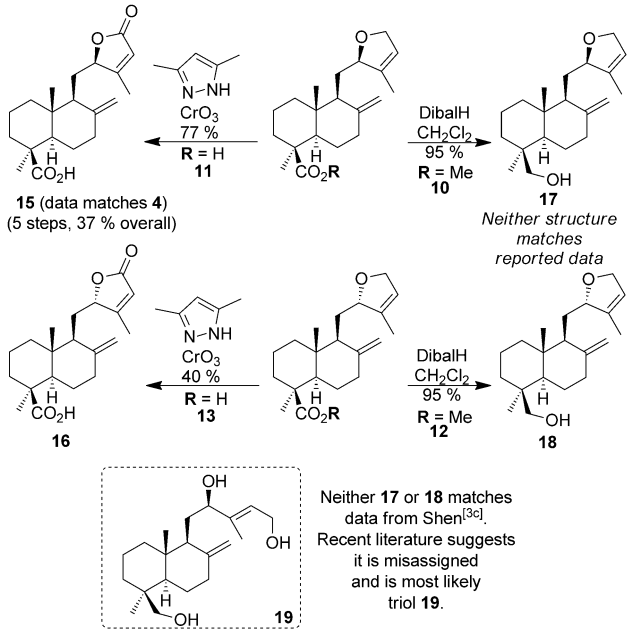
Given this poor facial selectivity and the fact that this key first step sets the important C12 stereochemistry of the natural products in this family, we set out to find a better solution. With no directing group available and the target olefin being trisubstituted, it seemed like the Shi epoxidation[10] would be our best chance of achieving a reagent-controlled oxidation. We were delighted to learn that Shi epoxidation of diene **7** using a natural D-fructose-derived chiral ketone selectively afforded epoxide **8** in high yield. Even more gratifying was the fact that this selectivity could be completely reversed, thus favoring **9**, by using the non-natural L-fructose-derived chiral ketone.[11] This was an important result, as it provided us with controlled routes to either **8** or **9**, which was integral to our mission of unambiguously assigning the stereochemistry of labdanes **1**–**6**.

With chiral epoxides **8** and **9** in hand, we were able to utilize our copper-catalyzed ring-expansion method to afford 2,5-dihydrofurans **10** and **12** in high yields (Scheme 4). Having recently demonstrated that [Cu^{I}(hfacac)] (hfacac = hexafluoroacetylacetonate) is the active catalyst in this reaction,[12] we used [Cu(hfacac)(cod)] as a catalyst for the ring expansion.[13] X-ray analysis[14] of crystals obtained from **10** unambiguously confirmed its structure. Thiolate deprotection then afforded acids **11** and **13** in only four steps and 48% overall yield from (*E*)-communic acid. Dihydrofuran **1** was reported to be isolated from the leaves of *Mikaniea sp. nov.*, collected in Brazil.[3a] It was also reportedly isolated from the seeds of *Platycladus orientalis*, collected in south central China.[3b] The seeds are used as a hemostatic agent and cough expectorant in traditional Chinese medicine, and have been shown to aid inebriated mice with memory retention.[15] Stereochemistry at C12 was left unassigned in both reports. A comparison with the literature revealed that dihydrofuran acid **11** matched the reported spectral data,[3a] which in turn allowed C12 to be assigned and the absolute stereochemistry confirmed. The data for the same proposed structure (**1**) from the Ye[3b] group did not match the spectral data for **11** or **13**. An extensive survey of the labdane literature and close inspection of the data strongly suggests that structure proposed by the Ye group is most likely henrilabdane A (**14**).[16]

We next set out to synthesize and confirm the structures of labdanes **2** and **4**, which we envisioned could be accessed in a single step from dihydrofurans **11** and **13**. Lactone **4** was isolated from the bark of *Thuja standishii* in Wakayama Prefecture in Japan.[3e–g] The lactone showed anti-tumor activity against a mouse-skin carcinogenesis assay. The stereochemistry at C12 was assigned based on a negative Cotton effect in the circular dichroism spectra.[17] Exposing dihydrofurans **11** and **13** to chromium(VI) oxide in the presence of 3,5-dimethylpyrazole selectively oxidized the C15 methylene, thus yielding unsaturated lactones **15** and **16** (Scheme 5). Interestingly, oxidation of dihydrofuran **13** was much less effective than for **11**. Spectral and physical data for lactone **15** perfectly matched the data for lactone **4**. Primary alcohol labdane **2** was isolated from *Fritillaria anhuiensis*, which is a plant commonly found in mountainous regions and used in traditional Chinese medicine as a cough suppressant.[3c] Treatment of **11** and **13** with diisobutylaluminum hydride cleanly afforded alcohols **17** and **18**, neither of which matched the reported natural product isolation data for **2**. We



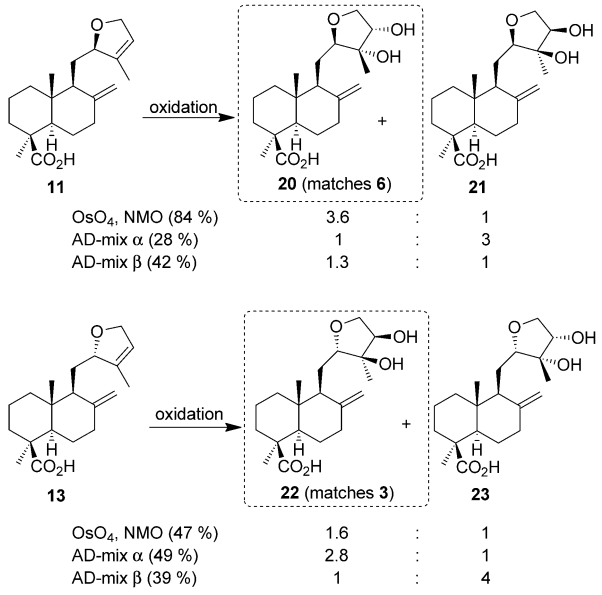
Scheme 4. Synthesis and structural confirmation of dihydrofuran labdane.



Scheme 5. Synthesis and structural confirmation of lactone **4** and alcohol **2**. DibalH = diisobutylaluminium hydride.

propose that **2** is also a wrongly assigned structure, and that it is instead triol **19**, as the published data for **2** matches with recent data reported for **19**.[18] Our own conversion experiments[19] of epoxide **8** into **19** strongly support this new structural assignment.

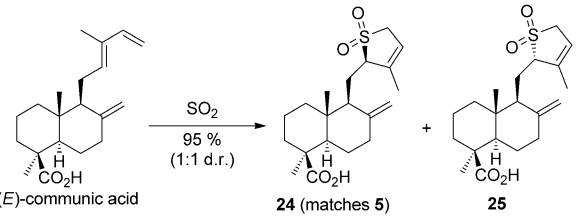
Labdanes **3** and **6** were isolated a few years ago from *Platycladus orientalis*.[3d] The seeds of this important plant have been used in traditional Chinese medicine to cure a range of different ailments. Labdane diols **3** and **6** are also intriguing, as they are enantiomeric at C12–C14. Furthermore, diol **3** is the only one in this heterocyclic labdane series reported to date to have a 12*S* configuration. We were convinced that these two natural products could be accessed in a single dihydroxylation step from **11** and **13**, and that the bulky side-chain appended to the dihydrofuran would effectively block one face of the olefin and direct the dihydroxylation to the desired diols **20** and **22**. This proved to be the case, as treatment of **11** with catalytic OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide (NMO) afforded diol **20** as the main product, albeit with modest selectivity (3.6:1, Scheme 6). After chromatographic separation of the two



Scheme 6. Substrate-controlled dihydrofuran dihydroxylations.

isomers, it was revealed that *anti*-diol **20** perfectly matched the data reported for natural diol **6**. When the dihydrofuran diastereomer **13** was subjected to the same dihydroxylation conditions, the yields were inferior[20] and the diol selectivity dropped to 1.6:1, favoring diol **22**. Again, dihydrofuran **13** produces inferior results compared to dihydrofuran **11**. Clearly, the conformation of (12*S*)-dihydrofuran **13** opens the door for unproductive pathways for both the chromium and osmium oxidants. We were pleased to learn that labdane diol **22** matched the reported data for diol **3**.[21] Inspired by the excellent reagent control in the Shi epoxidation of diene **7**, we wondered if similar levels of control could be achieved for this oxidation task by using the Sharpless asymmetric dihydroxylation method.[22] The results were mixed and suggested that the Sharpless oxidation was not well matched for dihydrofurans **11** and **13**. It is worth noting that there are surprisingly few examples of the use of the Sharpless asymmetric dihydroxylation to dihydroxylate cyclic trisubstituted olefins, and the reported examples follow the proposed mnemonic. Using this model, we would expect AD-mix α to favor formation of diols **21** and **22**, whereas AD-mix β should favor diols **20** and **23**. The Sharpless asymmetric dihydroxylation oxidation for labdanes **11** and **13** not only affords the expected diols with poor selectivity (4:1 is the best result), but the reactions are slow (requiring days) and suffer from low conversions. The modest facial control in our case can be explained by placing the large olefin substituent (dihydrofuran side-chain) in what Sharpless refers to as the "attractive" southwest quadrant.[23]

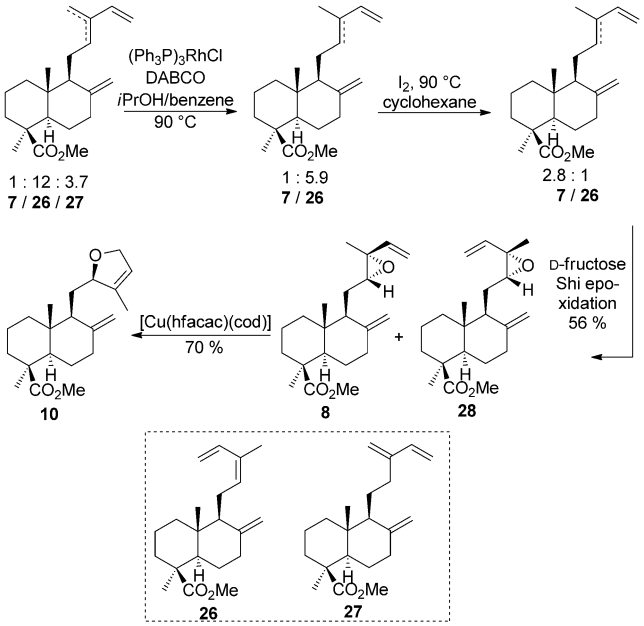
Labdane **5** is intriguing, as it is reported to be the first diterpenoid isolated that contains a sulfonyl group.[3 h] It was isolated from *Fritillaria anhuiensis* and shown to strongly attenuate nitric oxide production in a macrophage cell line. At first, we envisioned converting vinyl oxiranes **8** and **9** into their corresponding vinyl thiiranes and then using our copper-catalyzed ring expansion method[24] to form the dihydrothiophenes, which would then be oxidized to the target sulfones. Before launching these efforts, we wondered if the natural product (**5**) could be made in a single step from (*E*)-communic acid by treating it with sulfur dioxide (Scheme 7).[25] The proposed [4+1] cheletropic reaction proceeded near quantitatively, affording cyclic sulfones **24**



Scheme 7. One-step synthesis of dihydrothiofuran diterpenoid **5**.

and **25** in a 1:1 ratio. These two isomers were readily separable and the data for **24** was shown to match the published data for **5**.

In using communic acids as a starting material, one main challenge is how to handle highly fluctuating ratios of diene mixtures (*E*-, *Z*- and *mirceo*-) in the juniper berries, coupled with the fact that these three dienes require a challenging chromatographic separation to get each component pure. In thinking about how to tackle this unsolved inconvenience, we decided to explore whether the methyl ester mixture (**7**, **26**, and **27**) of these dienes, which are readily available from the crude extract, could be isomerized into a mixture containing primarily the thermodynamically most stable (*E*)-communic acid (Scheme 8). After screening several iridium,[26] ruthenium,[27] and palladium[28] catalysts, we learned that the Wilkinson[29] catalyst in an *iso*-propyl alcohol/benzene mixture isomerized the *mirceo*-ester component (**27**) into a mixture of *E*/*Z*-methyl communates. With one diene component out of the way, we then tackled the task of converting as much



Scheme 8. Labdane diene isomerization.

of the diene *Z* isomer into the corresponding *E* isomer. The best conditions we have thus far identified involve heating the diene mixture with iodine in cyclohexane.[30] This works quite well, as we are able to convert an unfavorable 1:5.9 mixture (14% of **7**) into a favorable 2.8:1 mixture (74% of **7**). We then asked if the asymmetric Shi epoxidation would epoxidize this diene mixture from the same face. If successful, this would alleviate the need for chromatographic separations, as a single dihydrofuran product (**10**) would be formed after ring expansion. We were delighted to learn that this is indeed the case, with vinyl oxiranes **8** and **28** being formed as single products with the same C12 configuration.[31] Our proposal was realized when this mixture (**8** and **26**) was ring expanded to form 2,5-dihydrofuran **10** as the only product. These new isomerization insights, coupled with the substrate control of the Shi epoxidation and our ring expansion reaction, alleviate any need for challenging chromatographic separation of the three communic acid diene components and thus pave the way for a scalable route to this new heterocyclic labdane family.

In summary, by the marriage of an excellent starting material from a natural source with our copper catalyzed ring expansion reaction and substrate control of the powerful asymmetric Shi oxidation protocol, we were able to complete the first syntheses of the labdane natural products **1**–**6** in five steps or less and in high overall yields. Furthermore, our synthetically flexible routes allowed confirmation of the stereochemistry of these natural products and structural reassignment of a diterpene that was proposed to have structure **2**. Our labdane olefin isomerization studies should prove broadly useful to researchers interested in using communic acids as starting materials. The control and efficiency of these routes has put us in a great position for creating a diverse new natural product collection to study. Biological evaluation of the compounds presented herein, and analogs thereof, are currently underway.

Received: October 18, 2012
Published online: December 18, 2012

Keywords: labdanes · olefin isomerization · ring expansion · total synthesis · vinyl oxiranes

[1] a) R. J. Peters, *Nat. Prod. Rep.* **2010**, *27*, 1521 – 1530; b) L. M. T. Frija, R. F. M. Frade, C. A. M. Afonso, *Chem. Rev.* **2011**, *111*, 4418 – 4452.
[2] a) M. Singh, M. Pal, R. P. Sharma, *Planta Med.* **1999**, *65*, 2 – 8; b) I. Chinou, *Curr. Med. Chem.* **2005**, *12*, 1295 – 1317.
[3] a) C. V. Nunez, M. C. Amendola, J. Henrique, G. Lago, N. F. Roque, *Biochem. Soc. Trans.* **2004**, *32*, 233 – 237; b) X.-Y. Ren, Y. Ye, *J. Asian Nat. Prod. Res.* **2006**, *8*, 677 – 682; c) L. Kang, J.-X. Zhou, Z.-W. Shen, *Acta Pharm. Sin.* **2007**, *42*, 58 – 60; d) Y.-Z. Wang, C.-P. Tang, C.-Q. Ke, H.-C. Weiss, E.-R. Gesing, Y. Ye, *Phytochemistry* **2008**, *69*, 518 – 526; e) M. Iwamoto, H. Ohtsu, H. Tokuda, H. Nishino, S. Matsunaga, R. Tanaka, *Bioorg. Med. Chem.* **2001**, *9*, 1911 – 1921; f) Y.-C. Li, Y.-H. Kuo, *Chem. Pharm. Bull.* **2002**, *50*, 498 – 500; g) T. Minami, M. Iwamoto, H. Ohtsu, H. Ohishi, R. Tanaka, A. Yoshitake, *Planta Med.* **2002**, *68*, 742 – 745; h) Q.-Y. Shou, Q. Tan, Z.-W. Shen, *Tetrahedron Lett.* **2009**, *50*, 4185 – 4187.
[4] a) N. A. McGrath, C. A. Lee, H. Araki, M. Brichacek, J. T. Njardarson, *Angew. Chem.* **2008**, *120*, 9592 – 9595; *Angew. Chem. Int. Ed.* **2008**, *47*, 9450 – 9453; b) J. G. M. Morton, L. D. Kwon, J. D. Freeman, J. T. Njardarson, *Tetrahedron Lett.* **2009**, *50*, 1684 – 1686; c) J. G. M. Morton, L. D. Kwon, J. D. Freeman, J. T. Njardarson, *Synlett* **2009**, 23 – 27; d) J. G. M. Morton, C. Dragichi, L. D. Kwon, J. T. Njardarson, *Org. Lett.* **2009**, *11*, 4492 – 4495; e) N. A. McGrath, E. S. Bartlett, S. Sittihan, J. T. Njardarson, *Angew. Chem.* **2009**, *121*, 8695 – 8698; *Angew. Chem. Int. Ed.* **2009**, *48*, 8543 – 8546; f) N. A. McGrath, J. R. Binner, G. Markopoulos, M. Brichacek, J. T. Njardarson, *Chem. Commun.* **2011**, *47*, 209 – 211.
[5] a) L. A. Batory, C. E. McInnis, J. T. Njardarson, *J. Am. Chem. Soc.* **2006**, *128*, 16054 – 16055; b) M. Brichacek, J. T. Njardarson, *Angew. Chem.* **2010**, *122*, 1692 – 1695; *Angew. Chem. Int. Ed.* **2010**, *49*, 1648 – 1651; c) M. Brichacek, L. A. Batory, N. A. McGrath, J. T. Njardarson, *Tetrahedron* **2010**, *66*, 4832 – 4840.
[6] For a recent example of the marriage of chiral natural decalin cores with a method for accessing a family of natural products, see: D. D. Dixon, J. W. Lockner, Q. Zhou, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 8432 – 8435.
[7] J. De Pascual Teresa, A. San Feliciano, A. F. Barrero, *An. Quim.* **1973**, *69*, 1065 – 1067; For a review on the use of communic acids as starting materials in synthesis, see: A. F. Barrero, M. M. Herrador, P. Arteaga, J. F. Arteaga, A. F. Arteaga, *Molecules* **2012**, *17*, 1448 – 1467.
[8] A. F. Barrero, S. Arseniyadis, J. F. Quilez del Moral, M. M. Herrador, M. Valdivia, D. Jimenez, *J. Org. Chem.* **2002**, *67*, 2501 – 2508.
[9] A. F. Barrero, Q. M. Rafael, J. C. Altarejos, *Tetrahedron* **1991**, *47*, 4441 – 4456.
[10] Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488 – 496.
[11] M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377 – 5379.
[12] D. J. Mack, J. T. Njardarson, *Chem. Sci.* **2012**, *3*, 3321 – 3325.
[13] [Cu(hfacac)(cod)] produced a faster ring expansion and a product that was cleaner and higher in yield than [Cu(hfacac)$_2$].
[14] Sue Roberts is gratefully acknowledged for collecting and analyzing data for the crystal structure of dihydrofuran **10**. CCDC 906543 contains the supplementary crystallographic data

for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[15] N. Nishiyama, Y.-L. Wang, H. Saito, *Biol. Pharm. Bull.* **1995**, *18*, 1498 – 1503.
[16] C.-J. Li, D.-M. Zhang, Y.-M. Luo, S.-S. Yu, Y. Li, Y. Lu, *Phytochemistry* **2008**, *69*, 2867 – 2874.
[17] J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadare, J. H. Fried, *Tetrahedron Lett.* **1972**, *13*, 791 – 794.
[18] X. Gan, L. Ma, Q. Chen, Q. Chen, Q. Yu, L. Hu, *Planta Med.* **2009**, *75*, 1344 – 1348.
[19] Treatment of epoxide **8** with $[Pd_2(dba)_3]$ in acetic acid (D. R. Deardorff, D. C. Myles, K. D. MacFerrin, *Tetrahedron Lett.* **1985**, *26*, 5615 – 5618), followed by treatment of the resulting product with diisobutylaluminum hydride afforded triol **19**. Our spectral data for **19** in CD_3OD matched the misassigned ^{13}C NMR data reported in Ref. [3c] and the ^{13}C NMR data (in $CDCl_3/CD_3OD$) reported in Ref. [18].
[20] In the dihydroxylation of dihydrofuran **13** we observe competing dihydroxylation of the decalin *exo*-olefin. No competing oxidation pathways are observed for **11**.
[21] ROESY-NMR spectra were obtained for the four diol diastereomers (**20**–**23**) and the crosspeaks were correlated with assignments.
[22] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 – 2547.
[23] It is worth noting that this is the opposite facial selectivity to what Sharpless reports for 1-methyl cyclohexene.
[24] E. Rogers, H. Araki, L. A. Batory, C. E. McInnis, J. T. Njardarson, *J. Am. Chem. Soc.* **2007**, *129*, 2768 – 2769.
[25] B. Deguin, P. Vogel, *J. Am. Chem. Soc.* **1992**, *114*, 9210 – 9211.
[26] S. G. Nelson, C. J. Bungard, K. Wang, *J. Am. Chem. Soc.* **2003**, *125*, 13000 – 13001.
[27] D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592 – 9593.
[28] D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998 – 8009.
[29] E. J. Corey, J. W. Suggs, *J. Org. Chem.* **1973**, *38*, 3224 – 3224.
[30] a) P. E. Sonnet, *Tetrahedron* **1980**, *36*, 557 – 604; b) S. Karim, E. R. Parmee, E. J. Thomas, *Tetrahedron Lett.* **1991**, *32*, 2269 – 2272.
[31] As expected, the *Z* isomer epoxidizes slower than the *E* isomer.

