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Synthesis of *cis*- and *trans*-2,5-Disubstituted Tetrahydrofurans by a Tandem Dihydroxylation-S_N2 Cyclization Sequence

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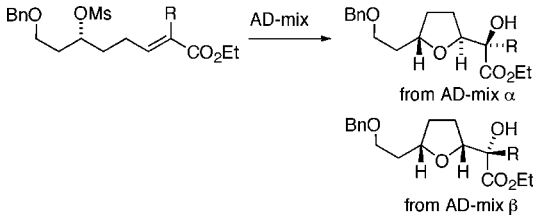
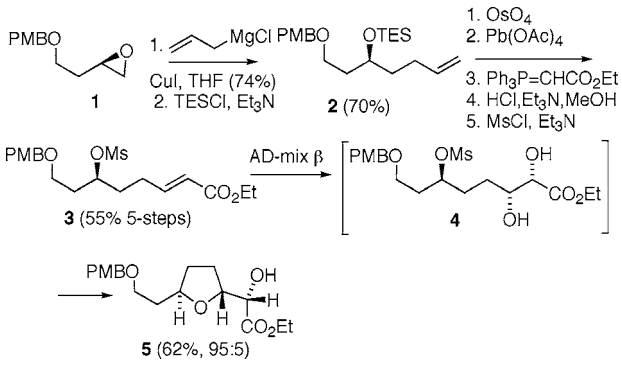
ABSTRACT



Dihydroxylation of δ- and ϵ-mesyloxy α,β-unsaturated esters proceeds with in situ cyclization to afford 2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofurans.

In connection with a projected synthesis of certain macrocyclic polyketide marine natural products of the amphidinolide family,[1] we examined the sequence outlined in Scheme 1 for the preparation of the tetrahydrofuran **5**.[2]

Scheme 1



Toward that end, we treated the unsaturated mesylate **3** with the Sharpless AD-mix β reagent, expecting to isolate the diol **4**, which would then be subjected to base treatment. However, this latter step proved unnecessary as the cyclization took place in situ to afford hydroxy ester **5** as the major isolable product. Evidently the basic medium of the dihydroxylation reaction was sufficient to effect the cyclization step. In view of the widespread occurrence of 2,5-disubstituted tetrahydrofurans in bioactive natural products such as Annonaceous acetogenins[3] and polyether antibiotics,[4] as well as the aforementioned amphidinolides, we decided to survey

(1) Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.* **1991**, *44*, 1259.

(2) Schaaf, G. M. PhD Thesis, University of Virginia, August, 2004.

(3) (a) Isolation: Oberlies, N. J.; Chang, C.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102. (b) Reviews: Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359. Hoppe R.; Scharf, H.-D. *Synthesis* **1995**, 1447. Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97. (d) Casiraghi, G.; Zanardi, F.; Battistina, L.; Rassu, G.; Appendino, G. *Chemtracts*: *Org. Chem.* **1998**, *11*, 803. Total synthesis: (e) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (f) Naito, H.; Kawahara, E.; Maruta, K.; Naeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. (g). Sinha, S.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. (h) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (i) Sinha, S. C.; Sinha, A.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014 (j) Emde, U.; Koert, U. *Tetrahedron Lett.* **1999**, *40*, 5979. (k) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771.

(4) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

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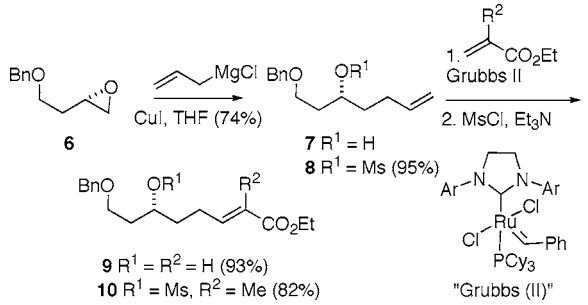
other applications of this cascade sequence in order to probe its generality.

We initiated these studies with the unsaturated alcohol **7**, prepared from epoxide **6**[5] of *95*% enantiopurity (see Suporting Information) and allylmagnesium chloride/CuI in THF (Scheme 2). Our first modification was to improve access

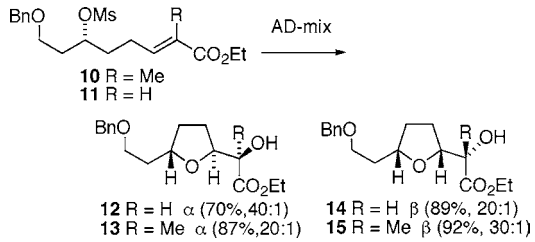
Scheme 2



to conjugated ester substrates for the cascade sequence. This was achieved through use of an efficient Grubbs cross metathesis reaction of olefin **7** with ethyl acrylate to afford hydroxy ester **9**.[6] A methyl homologue **10** was prepared directly through cross metathesis of unsaturated mesylate **8** with ethyl methacrylate.

The mesylate derivative **11** of alcohol **9** was subjected to dihydroxylation with the Sharpless AD-mix α reagent, whereupon the *trans*,*syn* tetrahydrofuran **12** was obtained in high yield with excellent diastereoselectivity (Scheme 3).[7]

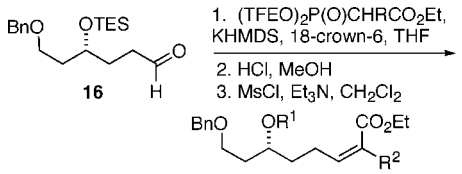
Scheme 3



The methyl homologue **10** was likewise converted to the tetrahydrofuran **13**.[8] The *cis*,*syn* isomer **14** was produced from mesylate **11** through use of the AD-mix *β* reagent, which also effected conversion of mesylate **10** to the homologue **15**. In each case barely detectable amounts of isomeric tetrahydrofurans could be detected in the NMR spectra of the products or by TLC analysis. The stereochemistry of these tetrahydrofuran products was surmised from the well-established steric preference of the AD-mix reagents and the presumed S_N2 nature of the cyclization reaction.[9]

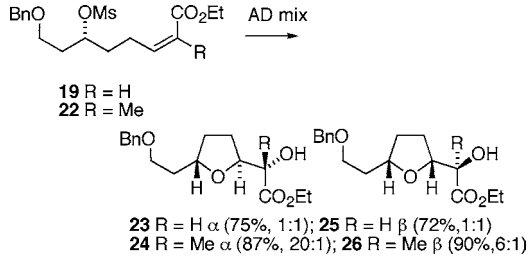
Aldehyde **16** was prepared by a slight modification of the sequence outlined in Scheme 1 (see Supporting Information). Condensation with the Still−Gennari trifluoroethyl phosphonoacetate and propionate reagents effected conversion to the (*Z*)-conjugated esters **17** and **20** (Scheme 4).[10]

Scheme 4



The unsaturated mesylate derivative **19** was subjected to the AD-mix α and *β* reagents to yield the tetrahydrofurans **23** and **25** (Scheme 5). Both reagents afforded essentially

Scheme 5



identical 1:1 mixtures of diastereomers. Evidently, dihydroxylation of the (*Z*)-unsaturated ester **19** is nonselective. The 2-methyl homologue **22** proved more amenable. Dihydroxylation with the AD-mix α reagent afforded the *trans*,*anti* tetrahydrofuran **24** as the major component of a 20:1 mixture of diastereomers and the *cis*,*anti* isomer **26** as the major component of a 6:1 mixture of diastereomers from the reaction with AD-mix *β*.

We also examined sequences leading to the 3-hydroxy tetrahydrofurans **32**−**35** (Scheme 7). One of the conjugated

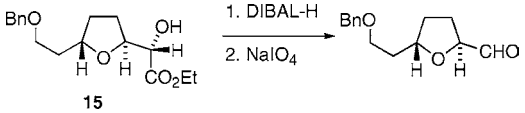
(5) Epoxide **6** was obtained through Jacobsen kinetic resolution of the racemate. Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.

(6) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003,** *125*, 11360.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

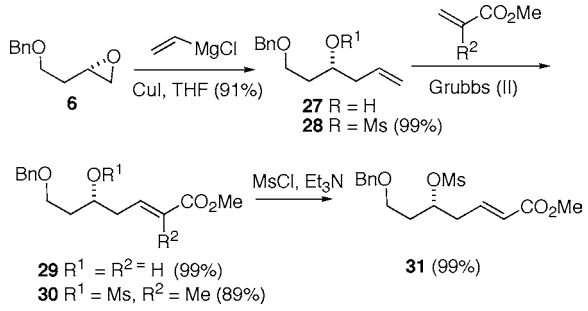
(8) The stereochemistry of the dihydroxylation reaction was ascertained through dihydroxylation of the TBS ether anlog of mesylate **10** with AD-mix α and conversion of the derived diol to the *O*-methyl mandelate derivative (see Supporting Information).

(9) As an added proof that the cyclization leads to a tetrahydrofuran rather than a tetrahydropyran, we carried out the following conversion of hydroxy ester **15**:



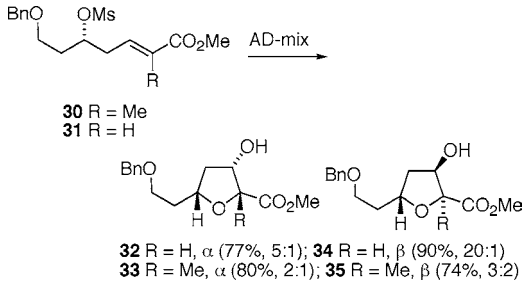
(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4404.

Scheme 6



esters (**31**) required for these studies was prepared from the alcohol **27** by cross metathesis with methyl acrylate and subsequent mesylation (Scheme 6). Similar treatment of the mesylate **28** and methyl methacrylate afforded the homologous ester mesylate **30**.

Scheme 7



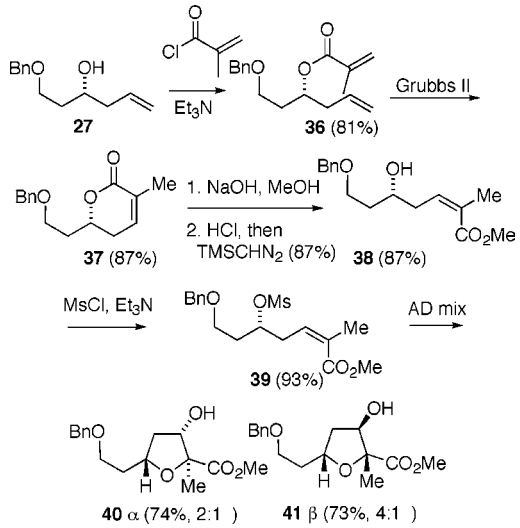
Dihydroxylation of the conjugated ester mesylate **31** with AD-mix α afforded the *cis*,*trans* adduct **32** as a 5:1 mixture of diastereomers whereas the *trans*,*trans* adduct **34** was favored by 20:1 in the reaction of ester **31** with AD-mix *β* (Scheme 7). Reactions of the methylated homologue **30** with AD-mix α and *β* proceeded analogously to afford the *cis*,*trans* and *trans*,*trans* adducts **33** and **35**, but with diminished selectivity reflecting the lower diastereoselectivity of the dihydroxylation reaction.

The (*Z*)-isomer **39** of ester **30** was prepared by a sequence involving ring-closing metathesis[11] of the methacrylate **36** followed by methanolysis of the derived lactone **37** and mesylation (Scheme 8). Exposure of mesylate **39** to AD-mix α converted this ester to the *trans*,*cis* adduct **40**, whereas the *cis*,*cis* adduct **41** was obtained from the reaction with AD-mix *β*. Once again the decreased selectivity of the AD-mix reactions on the (*Z*)-esters resulted in poor diastereoselectivity

A second line of investigation was briefly explored in which two fused or attached tetrahydrofuran rings were generated in the dihydroxylation reaction. For the first case, the mesylate derivative **28** of alcohol **7** was subjected to the

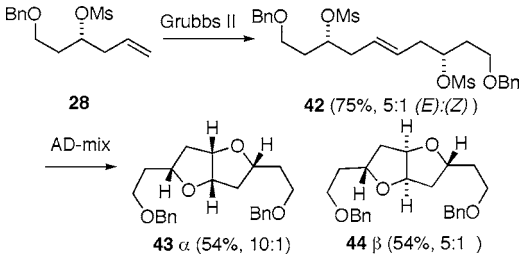
(11) Furstner, A.; Thiel, O. R.; Ackermann, L.; Nolan, S. P.; Schanz, H. J. *J. Org. Chem.* **2000**, *65*, 2204.

Scheme 8



Grubbs II catalyst to afford the dimer **42**, a 5:1 mixture of (*E*)- and (*Z*)-isomers (Scheme 9). Treatment with the

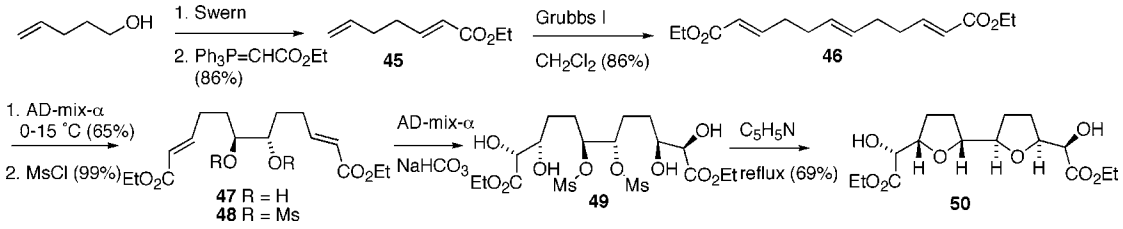
Scheme 9



Sharpless AD-mix α reagent gave the all-*cis* fused bis-furan **43** in 54% yield (67% based on the available (*E*)-isomer). The (*Z*)-isomer of olefin **42** would not be expected to yield a fused bis-furan owing to the strain present in two *trans* fused five-membered rings. The isomeric bis-furan **44** was obtained similarly by treatment of the unsaturated dimesylate **42** with AD-mix *β*.

The sequence leading to attached bis-tetrahydrofurans is summarized in Scheme 10. Unsaturated ester **45** was prepared from 4-penten-1-ol by a Swern−Wittig sequence. Dimerization of **45** was effected with the Grubbs I olefin metathesis catalyst ($Ru{=}CHPh(PCy_3)_2Cl_2$ affording triene **46** in 86% yield. Selective dihydroxylation of the central nonconjugated double bond was effectively achieved by exposure to AD-mix α $NaHCO_3$ at 0 °C. A byproduct resulting from internal 1,4-addition of the hydroxyl substituents to the conjugated ester groups was also formed in varying amounts. By using $NaHCO_3$ to buffer the dihydroxylation, we were able to suppress but not eliminate its formation. The diol **47** was converted to the mesylate **48**, which was subjected to a second exposure to AD-mix α to effect dihydroxylation of the two conjugated double bonds.

Scheme 10



Unlike the previous examples, the dihydroxylation product did not cyclize in situ and the tetrol **49** was isolated in moderate yield. Upon exposure to refluxing pyridine, the tetrol **49** cyclized to afford the bis-tetrahydrofuran **50**.[12] Surprisingly, attempts to effect cyclization with NaH in THF, 2,6-lutidine, or DBU at room temperature or above led to lower yields of less pure tetrahydrofuran product.

In summary, the in situ Sharpless asymmetric dihydroxylation-internal S_N2 cyclization cascade of δ- and ϵ-mesyloxy α,β-unsaturated esters provides an efficient and convenient route to 2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofurans of interest as possible segments of certain bioactive natural products. The reactions proceed efficiently and with moderate to high levels of enantioselectivity. Extensions to fused and attached bis-tetrahydrofurans have also proved effective. These latter ring systems constitute a key structural element of Annonaceous acetogenin natural products.[3,13]

The low diastereoselectivity observed with certain (Z)-esters somewhat limits the generality of the methodology. However, use of alternative dihydroxylation ligands[7] could provide a remedy for this limitation.

Acknowledgment. Support for this work was provided by research grant R01 CA090383 from the National Cancer Institute.

Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) These conditions were employed for construction of one of the tetrahydrofuran rings of the acetogenins asimicin and bullatacin by a "naked carbon skeleton" approach. Avedission, H.; Sinha, S. C.; Yazbek, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.

(13) The vast majority of the syntheses reported for Annonaceous acetogenins have employed various forms of acid-catalyzed alcohol-epoxide cyclizations or catalyzed Re(VII) oxidative cyclizations[3] to construct the bis-tetrahydrofuran core unit. A recent exception is the allylsilane [3 + 2] annulation approach. Tisley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818.