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A General Diastereoselective Strategy for Both *cis*- and *trans*-2,6-Disubstituted Tetrahydropyrans: Formal Total Synthesis of (+)-Muconin

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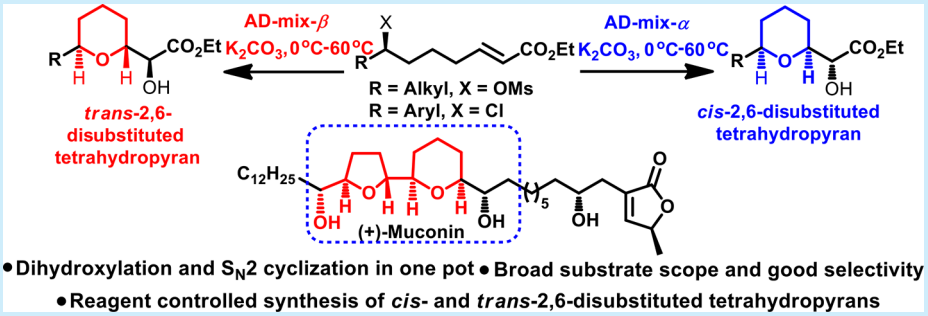
Supporting Information



ABSTRACT: A protocol for general diastereoselective tandem dihydroxylation followed by S_N2 cyclization was developed for the convenient and efficient synthesis of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans from ζ-mesyloxy α,β-unsaturated esters. The application of this novel method was demonstrated through the concise formal synthesis of (+)-muconin, a nonclassical acetogenin, with sequential THP−THF ring formation.

Tetrahydropyran (THP) rings are an important structural motif present in an array of natural products such as marine toxins, polyether antibiotics, and pheromones (Figure 1). THP-ring-containing natural products have diverse and potent biological activities and have attracted significant attention in recent years.[1] Over the past few decades, increasing numbers of natural products with THP backbones have been isolated from different sources.[1] The importance of their biological activities and structural architecture has led to a significant development in synthetic strategies for the preparation of both *cis*- and *trans*-2,6-disubstituted pyrans.[2a−d] To our knowledge, very few reports are available on the synthesis of both *cis*- and *trans*-2,6-disubstituted pyrans from a common substrate.[2e−j] Very recently, Nicolaou et al.[2e] reported a stereoselective and practical method for constructing both *cis*- and *trans*-2,6-disubstituted dihydro- and tetrahydropyran ring systems following a Heck/Saegusa−Ito/oxa-Michael cyclization sequence. As very few methods are currently available, the development of an efficient and highly stereocontrolled protocol for the preparation of substituted tetrahydropyrans is highly desirable.

Our group has also developed several new synthetic strategies for the synthesis of *cis*- and *trans*-2,6-disubstituted pyrans and applied these to the synthesis of many natural products.[3] Continuing our research on developing methodologies for the synthesis of either *cis*- or *trans*-tetrahydropyran rings, we were interested in developing a protocol that could be used to synthesize both *cis*- and *trans*-tetrahydropyran rings starting from a common precursor. In 2005, Marshall's group reported the synthesis of *cis*- and *trans*-2,5-disubstituted tetrahydrofurans by tandem dihydroxylation followed by S_N2 cyclization (Scheme 1a).[4] From these results, we envisioned that it could be possible to synthesize both *cis*- and *trans*-2,6-disubstituted pyrans following the above conditions. Herein we describe the development of the reagent-controlled synthesis of both *cis*- and *trans*-2,6-disubstituted tetrahydropyrans starting from common substrates (Scheme 1b) and the application of the developed synthetic method to the formal synthesis of (+)-muconin.

We initiated our study with the synthesis of cyclization precursor **16** as a model substrate. For this, commercially available aldehyde **12** was converted to chiral epoxide **13** under Corey−Chaykovsky conditions[5] followed by hydrolytic kinetic resolution using Jacobsen's catalyst,[6] [(*R*,*R*)-Co^{III}(salen)(OAc)], for 24 h at room temperature in 48% yield with 96% *ee*. Chiral epoxide **13** was treated with 4-bromo-1-butene in the presence of Mg and CuI at −40 °C to produce olefin **14** in 92% yield[7] (Scheme 2). The cross-metathesis reaction of olefin **14** with ethyl acrylate using Grubbs' second-generation catalyst afforded hydroxy ester **15** in 79% yield.[8] Finally, the mesylation of secondary alcohol in **15** was carried out with mesyl chloride and Et_3N in CH_2Cl_2 to obtain ζ-mesyloxy-α,β-unsaturated ester **16** in 93% yield (Scheme 2).[4] After the development of a general synthetic route for the preparation of

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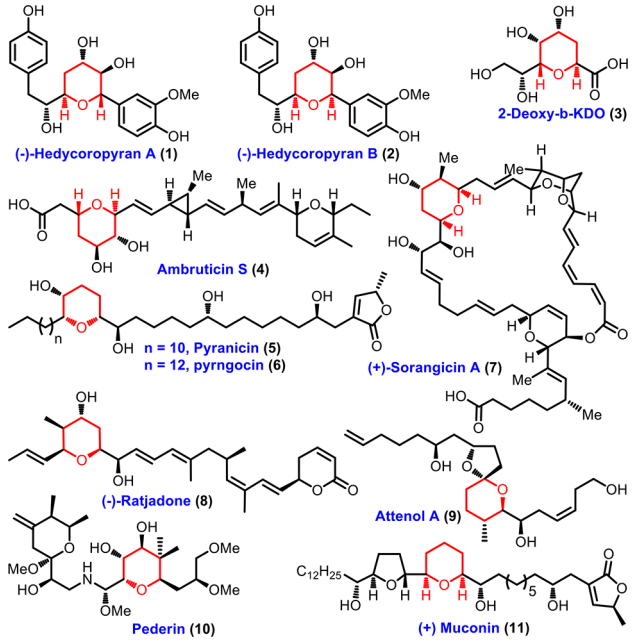
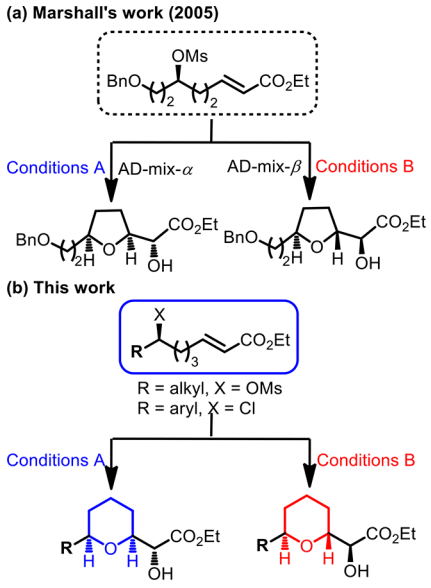
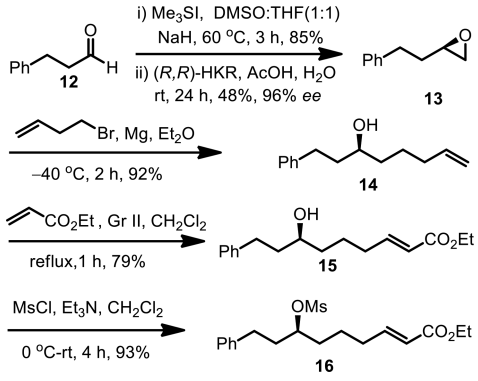


Figure 1. Representatives structures of natural products containing 2,6-disubstituted pyrans.

Scheme 1. Background and Present Work



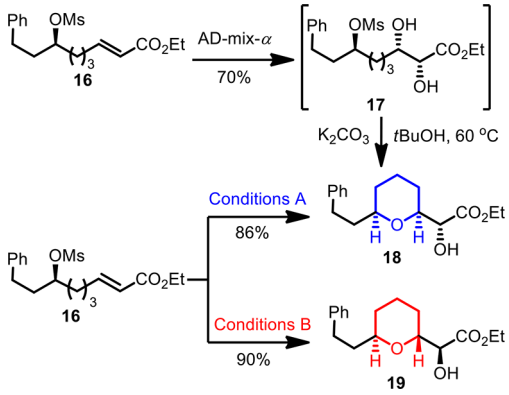
Scheme 2. Synthesis of ζ-Mesyloxy α,β-Unsaturated Esters



common mesylate precursors, the synthesis of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans was initiated.

Accordingly, unsaturated mesylate **16** was treated under Sharpless reaction conditions[4] using AD-mix-α to furnish the desired product **18** in only 10% yield, and the intermediate diol **17** was formed in 70% yield. However, treatment of diol **17** with excess K_2CO_3 (3 equiv) in *t*BuOH did not improve the conversion of **17** to the desired product, even after 24 h. Interestingly, when the same reaction mixture was heated to 60 °C for another 12 h, the yield of the desired pyran product was increased to 74% (Scheme 3). Then the same reaction was

Scheme 3. Optimization of the Synthesis of *cis*- and *trans*-2,6-Disubstituted Tetrahydropyrans from a Common Substrate[a]



[a]Reaction conditions A: **16** (1 mmol), $K_3[Fe(CN)_6]$ (3 mmol), $K_2OsO_2(OH)_4$ (0.005 mmol), $(DHQ)_2PHAL$ (0.01 mmol), K_2CO_3 (6 mmol), and $CH_3SO_2NH_2$ (1 mmol) in *t*BuOH/H_2O (1:1) at 0 °C for 12 h and then at 60 °C for 12 h, unless otherwise mentioned. Conditions B: **16** (1 mmol), $K_3[Fe(CN)_6]$ (3 mmol), $K_2OsO_2(OH)_4$ (0.005 mmol), $(DHQD)_2PHAL$ (0.01 mmol), K_2CO_3 (6 mmol), $CH_3SO_2NH_2$ (1 mmol) in *t*BuOH/H_2O (1:1) at 0 °C for 12 h and then at 60 °C for 12 h, unless otherwise mentioned.

repeated under the AD-mix-α conditions with excess K_2CO_3 (6 equiv) for 12 h at 0 °C and then heated to 60 °C to obtain *cis*-tetrahydropyran derivative **18** in 86% yield with a 99:1 diastereomeric ratio (as analyzed by HPLC). Similarly, when mesylate **16** was treated with AD-mix-β under the optimized conditions, the corresponding *trans* product **19** was obtained in 90% yield (Scheme 3). Both products were characterized by spectral (^{1}H and ^{13}C NMR) and analytical data, and the *cis* and *trans* orientations at the pyran rings of compounds **18** and **19** were confirmed through 2D NOE experiments. These results confirm that the cyclization reaction took place in an S_N2 manner.

With the optimized conditions, further studies were designed to investigate the scope and stereochemical outcomes of cyclization (Table 1). ζ-Mesyloxy α,β-unsaturated esters **16a–i** were well-designed and prepared to have a variable carbon side chain containing OBn (entry 2), OPMB (entries 3 and 5), long chain (entries 4 and 5), methyl (entry 6), OMOM (entry 7), and substituted aryl (entries 8–10) groups in the corresponding cyclic products.

One-pot cyclization was carried out on these substrates under standard conditions A or B to furnish the corresponding *cis*- or *trans*-2,6-disubstituted pyrans in moderate to good yields (Table 1). Unfortunately, substrate **16f** did not give the cyclic product under conditions B (entry 7). This might have

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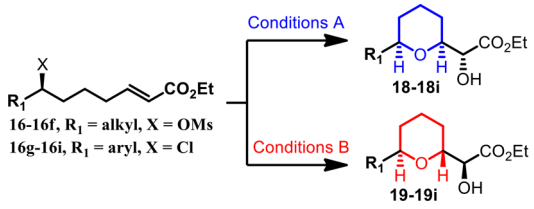
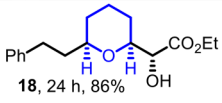
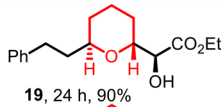
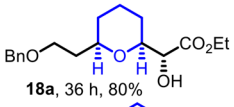
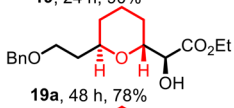
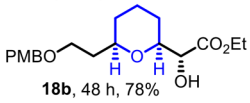
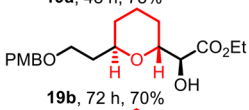
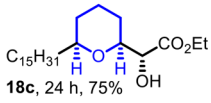
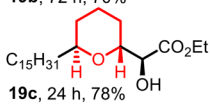
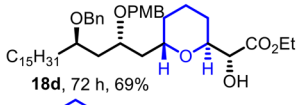
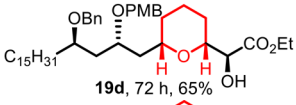
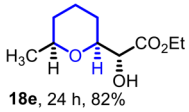
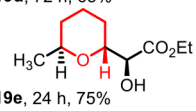
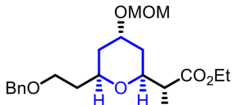
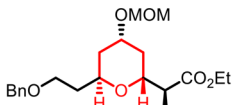
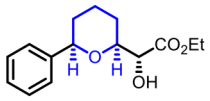
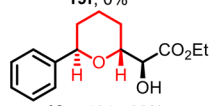
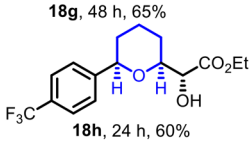
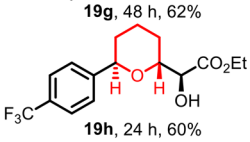
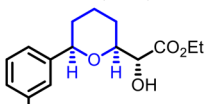
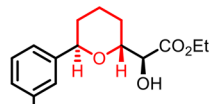
Table 1. Substrate Scope for the Synthesis of *cis*- and *trans*-2,6-Disubstituted Tetrahydropyrans[a]



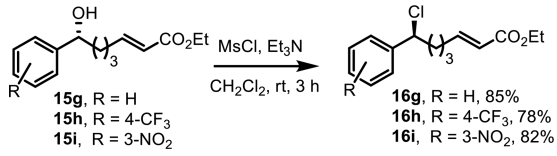
entry	conditions A	conditions B
1	 **18**, 24 h, 86%	 **19**, 24 h, 90%
2	 **18a**, 36 h, 80%	 **19a**, 48 h, 78%
3	 **18b**, 48 h, 78%	 **19b**, 72 h, 70%
4	 **18c**, 24 h, 75%	 **19c**, 24 h, 78%
5	 **18d**, 72 h, 69%	 **19d**, 72 h, 65%
6	 **18e**, 24 h, 82%	 **19e**, 24 h, 75%
7	 **18f**, 72 h, 30%	 **19f**, 0%
8	 **18g**, 48 h, 65%	 **19g**, 48 h, 62%
9	 **18h**, 24 h, 60%	 **19h**, 24 h, 60%
10	 **18i**, 48 h, 62%	 **19i**, 48 h, 65%

[a]Reaction conditions A and B are the same as reported in Scheme 3, unless otherwise mentioned.

been due to the steric strain of the MOM group on the transition state, which could have prevented cyclization from happening. It is noteworthy that mesylation of substrates **15g–i** gave only chloro-substituted products **16g–i** in yields of 78–85%, rather than the mesylated products with the inverted orientation (Scheme 4).[9] Interestingly, these substrates also gave the cyclic products **18g–i** and **19g–i** (entries 8–10) smoothly under same reaction conditions in good yields.

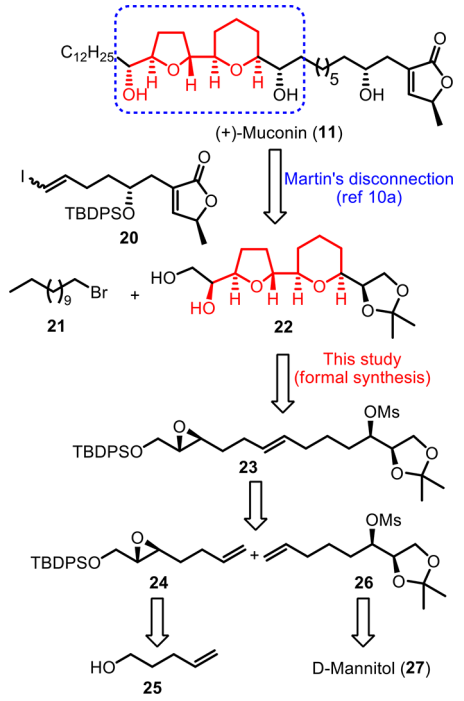
Empowered by our newly developed synthetic strategy and successful study of the scope of cyclization, we were able to

Scheme 4. Synthesis of Chloro Compounds 16g–i



demonstrate the synthetic utility and generality of this novel methodology using the readily available required building blocks for the synthesis of the complex biologically active natural product (+)-muconin (**11**), a nonclassical acetogenin with sequential THP–THF ring systems. In 1996, McLaughlin et al.[10f] isolated **11** from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae) and showed it to have potent in vitro cytotoxicity against human pancreatic and breast tumor cells. The key structural features of muconin contain sequential THF and THP rings attached between a long carbon chain and a 2,4-disubstituted α,β-unsaturated-γ-lactone of which six out of eight stereogenic centers are found in the middle part (THF/THP rings).[10] Scheme 5 outlines our retrosynthetic approach

Scheme 5. Retrosynthetic Analysis



for the formal synthesis of (+)-muconin.[10a] We planned that the sequential THP–THF rings could be achieved using tandem dihydroxylation, S_N2 cyclization, and intramolecular nucleophilic ring opening of the epoxide in compound **23**, which in turn could be synthesized by cross-metathesis of epoxide **24** and mesylate **26**. Epoxide intermediate **24** was prepared from commercially available pent-4-en-1-ol (**25**), and mesylate intermediate **26** was obtained from D-mannitol.

The formal synthesis of (+)-muconin was initiated with the stereoselective synthesis of epoxide fragment **24** from **25** (Scheme 6). Unsaturated ester **28** was synthesized from **25** by sequential Swern oxidation and Wittig olefination in one pot in 75% yield.[4] Next, α,β-unsaturated ester **28** was reduced with DIBAL-H at −78 °C to furnish allyl alcohol **29** in 85% yield. Asymmetric Sharpless epoxidation of alcohol **29** using

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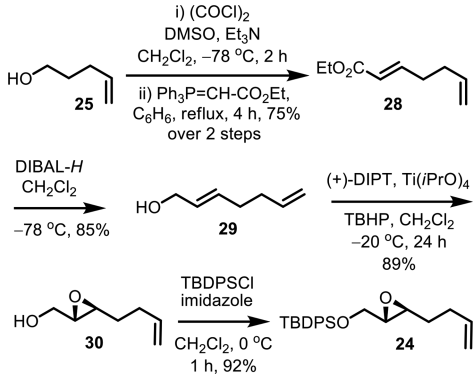
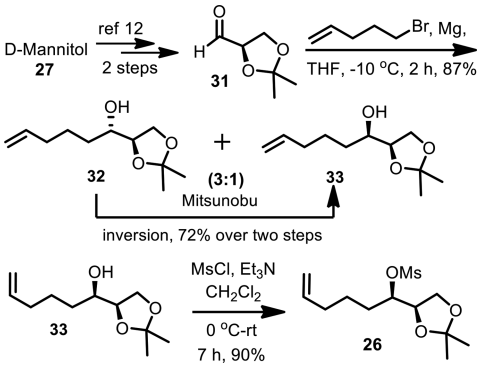
Scheme 6. Synthesis of Epoxide Fragment 24



(+)-DIPT, $Ti(O^iPr)_4$, and TBHP in CH_2Cl_2 at −20 °C furnished epoxy alcohol **30** in 89% yield,[11] which was protected as its TBDPS ether with TBDPSCl and imidazole in CH_2Cl_2 to get compound **24** in 92% yield with 92% *ee* (as analyzed by HPLC) (Scheme 6).

After obtaining a good quantity of epoxy olefin **24**, we synthesized the other olefin partner **26** required for the Grubbs' cross-metathesis reaction (Scheme 7). Commercially

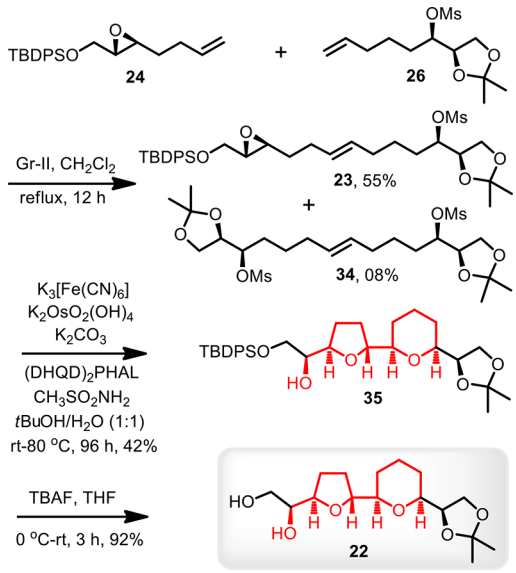
Scheme 7. Synthesis of Mesylate Fragment 26



available D-mannitol was converted to aldehyde **31** in quantitative yield by following a known protocol in two steps.[12] **31** was then subjected to the Grignard reagent generated from 5-bromopent-1-ene and magnesium in THF to afford a diastereomeric mixture of alcohols **32** and **33** in a 3:1 ratio (Scheme 7) in 87% yield.[13] The two alcohols were easily separated through silica gel column chromatography, and the absolute stereochemistry of the newly generated hydroxyl group in both compounds was assigned by modified Mosher's ester analysis.[14] Esterification of minor alcohol **33** with both (*S*)- and (*R*)-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) showed positive chemical shift differences [$\Delta\delta = (\delta_S - \delta_R) \times 10^3$] for protons on C5 through C2, while protons on C7 through C10 showed negative chemical shift differences, which confirmed that C6 bears an *R* configuration (see the Supporting Information). After the absolute configuration was confirmed, the undesired major alcohol **32** was inverted to the required alcohol **33** by Mitsunobu inversion[15] using TPP, DIAD, and 4-nitrobenzoic acid followed by ester hydrolysis with K_2CO_3 in MeOH in 72% yield over the two steps. Alcohol **33** was then treated with methanesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 to obtain mesylate **26** in 90% yield.[4]

With the two required olefin partners in hand, we next focused on the key cross-metathesis reaction. Subjecting epoxy olefin **24** and mesylate **26** to cross-metathesis using Grubbs' second-generation catalyst[8] in CH_2Cl_2 under reflux conditions furnished the desired fragment **23** in 55% yield along with the homocoupled product **34** in 8% yield (Scheme 8). The

Scheme 8. Formal Synthesis of (+)-Muconin



intermediate compound **23** having the reactive epoxide, olefin, and mesyl functionalities was then ready for the crucial one-pot dihydroxylation followed by S_N2 cyclization and intramolecular nucleophilic ring opening of the epoxide. Accordingly, intermediate **23** was treated with AD-mix-β under the standard optimized conditions (conditions B) to obtain the required THF−THP compound **35** in 42% yield. The structure of compound **35** was confirmed by 2D NOE studies, and the key NOE correlations are shown in Figure 2.

Finally, deprotection of the TBDPS ether was achieved with TBAF in THF to afford known (+)-muconin fragment **22** in 92% yield (Scheme 8).[10a] The spectral (^1H and ^{13}C NMR) and

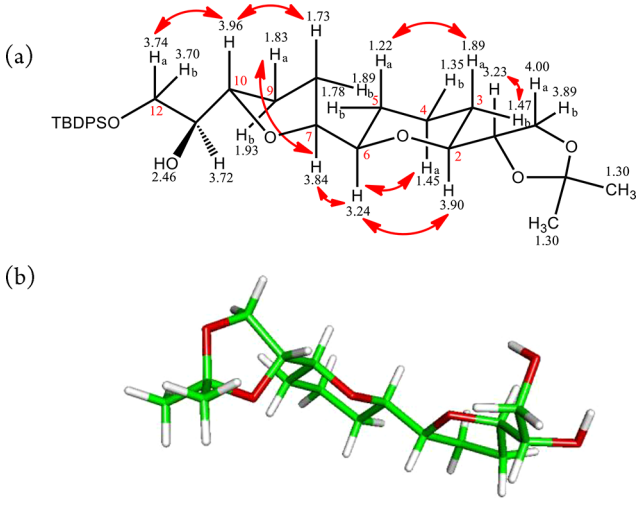


Figure 2. (a) Key NOE correlations in **35**. (b) Energy-minimized structure of **35**.

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analytical data for compound **22** were in good agreement with those reported previously in the literature.[10a]

In conclusion, we have developed a practical and stereoselective synthesis of both *cis*- and *trans*-2,6-disubstituted tetrahydropyrans utilizing in situ Sharpless asymmetric dihydroxylation followed by intramolecular S_N2 cyclization of substituted ζ-mesyloxy α,β-unsaturated esters. The reaction featured good substrate scope and proceeded efficiently in moderate to good yields. This synthetic method was also demonstrated for the formal synthesis of (+)-muconin in a concise and highly stereoselective manner. The key reactions involved in this formal synthesis were Sharpless asymmetric epoxidation, Mitsunobu inversion, Grubbs' cross-metathesis, and one-pot Sharpless asymmetric dihydroxylation/S_N2 cyclization/intramolecular nucleophilic epoxide ring opening. The strategy opens up new avenues for the preparation of novel bioactive natural products with a similar structure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03053.

Detailed experimental procedures and spectral data (^{1}H, ^{13}C and 2D-NMR) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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