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Total Synthesis of (+)-Asteltoxin

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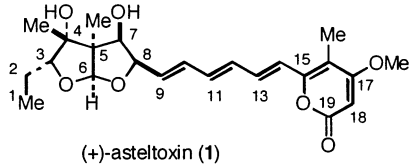
Abstract: A convergent synthesis of (+)-asteltoxin (**1**) has been achieved by the Horner−Emmons olefination of bis(tetrahydrofuran) aldehyde **53** and α-pyrone phosphonate **5**. A key step features the stereoselective construction of a sterically congested quaternary center embedded in the densely functionalized bis(tetrahydrofuran) subunit by a Lewis acid-catalyzed, pinacol-type rearrangement of an epoxy silyl ether. This pivotal rearrangement methodology parallels the proposed biosynthetic pathway of **1** and is ripe for applications to the stereocontrolled synthesis of structurally complex natural products.

Introduction

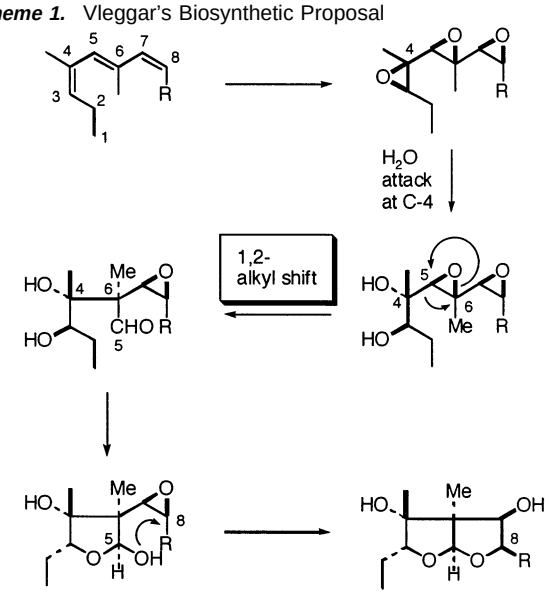
Asteltoxin (**1**) was isolated by Steyn, Vleggaar, and coworkers from toxic maize cultures of *Aspergillus stellatus* Curzi.[1a] Its structure, including relative stereochemistry, was



(+)-asteltoxin (**1**)

determined by spectroscopic methods and single-crystal X-ray analysis,[1] and the absolute configuration was subsequently established by a partial synthesis starting with (*R*)-isopropylidene glyceraldehyde.[2c] This mycotoxin belongs to a group of structurally related trienic α-pyrones, such as citreoviridin, verrucosidin, and the aurovertins, which are known to function as inhibitors of oxidative phosphorylation.[3,4] Asteltoxin was later shown to possess similar inhibitory activity of *E. coli* BF_1-ATPase and to provide a fluorescent probe of mitochondrial F_1- and bacterial BF_1-ATPase.[4b] Unlike other α-pyrone mycotoxins of the same family, **1** is characterized by the presence of a unique, highly functionalized 2,8-dioxabicyclo[3.3.0]octane containing a quaternary carbon embedded in an array of six stereogenic centers. On the basis of extensive ^{13}C and ^{18}O labeling experiments, Vleggaar advanced the biosynthesis of **1** involving polyepoxidation of a linear polyene precursor; his intriguing postulate for formation of the bis(tetrahydrofuran) moiety featured an epoxide-mediated 1,2-alkyl shift of a polyketide chain to generate a branched aldehyde (Scheme 1).[1b−d] A related pinacol-like rearrangement was also implicated in the oxidative rearrangement of (+)-averufin to versiconal acetate in the biosynthetic pathway of aflatoxins B_1 and B_2, in which the branched aldehyde of versiconal acetate was derived from the straight side chain of (+)-averufin.[5,6] The amalgamation of the fascinating architecture, unusual biogenesis, and interesting biological activity of **1** has attracted considerable

Scheme 1. Vleggar's Biosynthetic Proposal



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(1) (a) Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441. (b) Steyn, P. S.; Vleggarr, R. *J. Chem. Soc., Chem. Commun.* **1984**, 977. (c) de Jesus, A. E.; Steyn, P. S.; Vleggarr, R. *J. Chem. Soc., Chem. Commun.* **1985**, 1633. (d) Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239.

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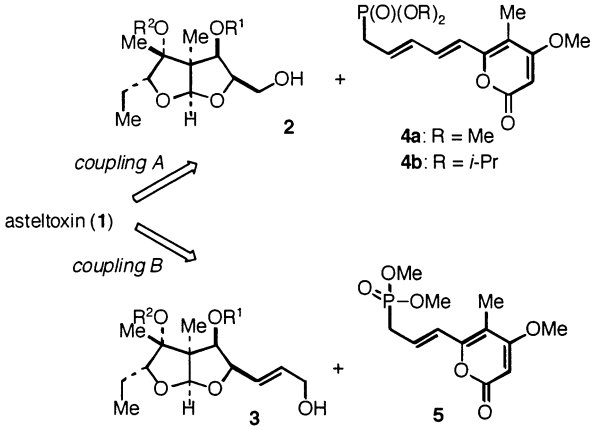
synthetic interest that has culminated in two total syntheses: Schreiber's first synthesis utilized an innovative application of the [2 + 2] furan−carbonyl photocycloaddition.[2] Takano and co-workers employed a D-glucose-based chiron approach in the second synthesis.[7] Stereoselective syntheses of the bis(tetrahydrofuran) centerpiece have been achieved by two other groups[8,9] and also in our laboratory.[10a,b] We herein report the details of our synthetic studies leading to an enantioselective synthesis of (+)-**1**.[10c]

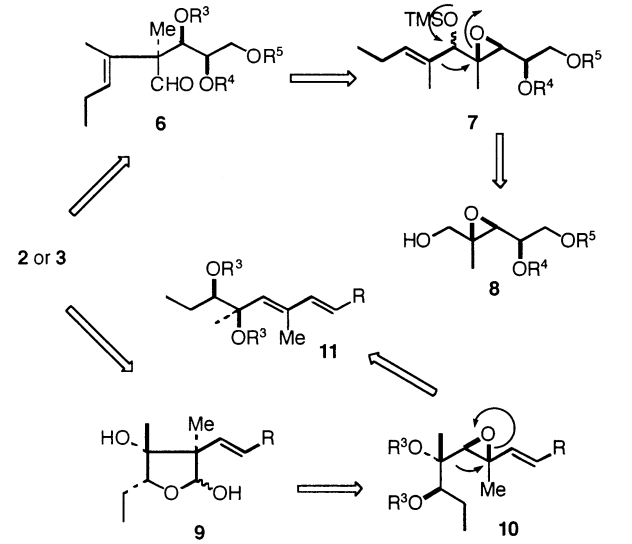
Results and Discussion

Retrosynthetic Analysis. Our initial task focused on the enantio- and diastereoselective preparation of the unusual bis(tetrahydrofuran) core **2** or **3** for eventual coupling with phosphonate **4** or **5** for a convergent synthesis of (+)-**1**. Inspired



by Vleggaar's biosynthetic postulate, we were attracted to an epoxide-mediated pinacol-type rearrangement approach. Particularly alluring was the preparative power of the underlying methodology for the convenient, enantioselective construction of quaternary carbons starting with readily available, enantiomerically pure epoxides.[11] Among the known repertoire of stereoselective 1,2-rearrangement reactions of epoxides and their derivatives, the Tsuchihashi−Suzuki[12] and Yamamoto[13] procedures seemed particularly well suited for an enantioselective synthesis of **2** or **3** in close parallel with the proposed biogenesis (Scheme 2). At the inception of our synthetic studies, the Sharpless asymmetric epoxidation of allylic alcohols was demonstrated to be one of the most general and reliable methods

Scheme 2. Retrosynthetic Analysis



for preparing enantiomerically pure or enriched 2,3-epoxy alcohols.[14] The requisite substrate **7** for the Tsuchihashi−Suzuki rearrangement (**7** → **6**) was expected to be readily available by employing a straightforward sequence of well-precedented transformations involving **8**. In comparison, the Yamamoto rearrangement (**10** → **9**) required the preparation of *threo*-epoxide **10**, which was deemed to be more challenging and could possibly entail a mismatched case of the Sharpless asymmetric epoxidation, depending on the choice of a side chain. These considerations thus prompted us to investigate the epoxy silyl rearrangement by the method of Tsuchihashi and Suzuki. During the course of our synthetic investigations, this rearrangement has received renewed attention by other laboratories, and further progress in the methodology development for preparing various β-hydroxy carbonyls and 1,3-diols was reported in the literature.[15−17] In passing, we also note that Jung

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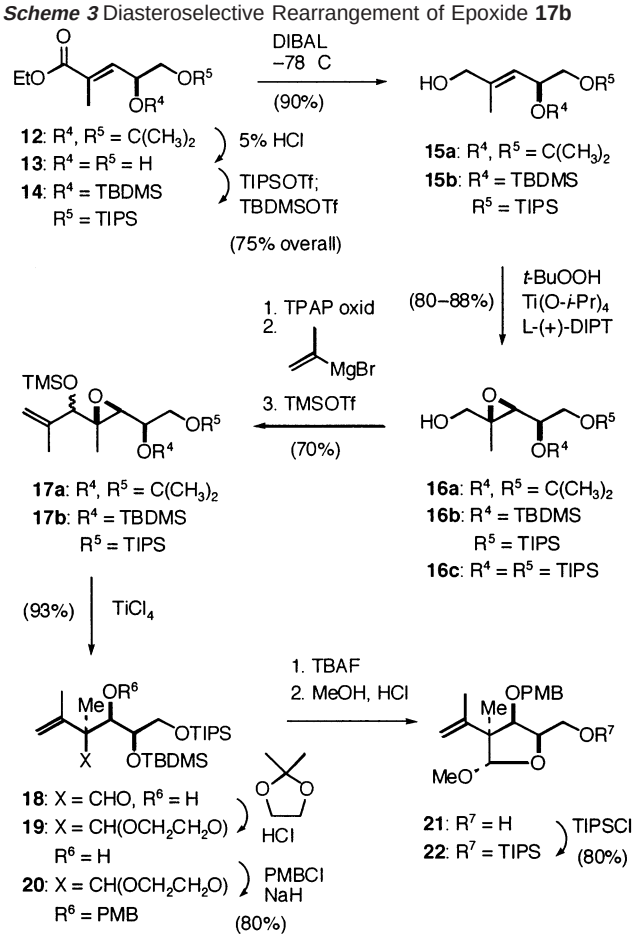
Scheme 3 Diasteroselective Rearrangement of Epoxide **17b**



subsequently developed a useful variant of the Yamamoto rearrangement involving vinyl epoxides and that **10** → **9** could be considered an example of the Jung rearrangement.[18] Recent impressive advances in enantioselective epoxidation reactions of (*Z*)- and (*E*)-olefins, namely, the Jacobsen and Shi epoxidations,[19,20] would certainly allow several variants of these stereoselective 1,2-epoxide rearrangements to be synthetically viable.[21]

First-Generation Synthesis of 2. Our synthesis commenced with the known and readily available allylic alcohol **15a** (Scheme 3). However, acetonide **15a** had previously been shown to be one of the very rare *E*-allylic alcohols among poor substrates for the Sharpless asymmetric epoxidation: use of (+)-DET had been reported to give the desired diastereomer **16a** in 4:1 diastereoselectivity (75% yield),[14] and only a modest increase (~5:1; 70% yield) was observed by employing L-(+)-diisopropyl tartrate. More significantly, it became apparent that the acetonide group [e.g., **17a**] was incompatible with a Lewis acid required to induce the key Tsuchihashi–Suzuki rearrangement (vide infra). Thus, silyl protecting groups were chosen because of their anticipated robustness toward Lewis acids. Removal of the acetonide protecting group of **12** with HCl/THF afforded diol **13** (85%), which was sequentially protected by standard methods to give **14** (88%). Subsequent DIBAL reduction provided alcohol **15b** in 90% yield. The Sharpless asymmetric epoxidation of **15b** furnished epoxy alcohol **16b** in 80–88% yield and 94% diastereoselectivity. PCC or TPAP oxidation of **16b**, followed by addition of 2-propenylmagnesium bromide and silylation with TMSCl, provided the rearrangement substrate **17b** in 70% overall yield. For convenience, commercially available 2-propenylmagnesium bromide was employed instead of 2(*E*)-pentenylmagnesium bromide in the first-generation synthesis. The pivotal rearrangement of the epoxy silyl ether **17b** was accomplished by the action of $TiCl_4$ to provide aldehyde **18** in 90% yield, which was found to be surprisingly robust and well behaved. Since both epimers smoothly underwent the acid-catalyzed pinacol-type rearrangement, no attempt was made to enhance the diastereoselectivity of addition of the Grignard reagent to the aldehyde. As noted above, the cognate rearrangement of **17a** in the presence of $TiCl_4$ or $SnCl_4$ gave only poor (40–45%) yields of the desired product.

Conversion of the aldehyde **18** to the corresponding acetal **19** was achieved by transacetalization with 2,2-dimethyl-1,3-dioxolane or conventional acetalization with ethylene glycol, and subsequent protection of **19** with *p*-methoxybenzyl chloride gave **20** in 80% overall yield. No conditions were found for selective removal of the TBDMS group from **20**. Both silyl protecting groups were thus removed by using *n*-Bu_4NF, and subsequent treatment with methanolic hydrogen chloride cleanly gave **21** as a single diastereomer. A fully protected acetal, **22**, was then obtained in 80% overall yield by treatment of **21** with TIPSCl and imidazole.

Our attention was next directed to the stereocontrolled attachment of the left-hand tetrahydrofuran moiety. Osmylation of **22** took place with complete stereoselectivity to give diol **23** as an anomeric mixture in 85% yield (Scheme 4). Extensive scrambling at the anomeric center was observed under the dihydroxylation conditions, but the other possible stereoisomers were not found in the crude reaction mixture. The stereochemical assignment of the dihydroxylation products was initially made on the basis of difference NOE measurements of the cyclization product **25** (and also **26**, vide infra) and was unequivocally confirmed by its ultimate conversion to **2**. The origin of the observed diastereoselectivity in osmylation is discussed in detail later. Swern oxidation of **23** and subsequent chelation-controlled addition of EtMgBr to the resulting aldehyde allowed an efficient, stereoselective introduction of the ethyl side chain to provide **24** as a single epimer at the newly generated stereocenter, but as a 1.3:1 anomeric mixture. Acid-catalyzed cyclization of **24** with *p*-TsOH or CSA in CH_2Cl_2 then afforded bis(tetrahydrofuran) **25** in 70% overall yield (from **23**). As noted by Mulzer,[9] a large difference in the rate of cyclization was found between these anomers when a small (10 mol %) amount of an acid catalyst was employed. This difference in rate could

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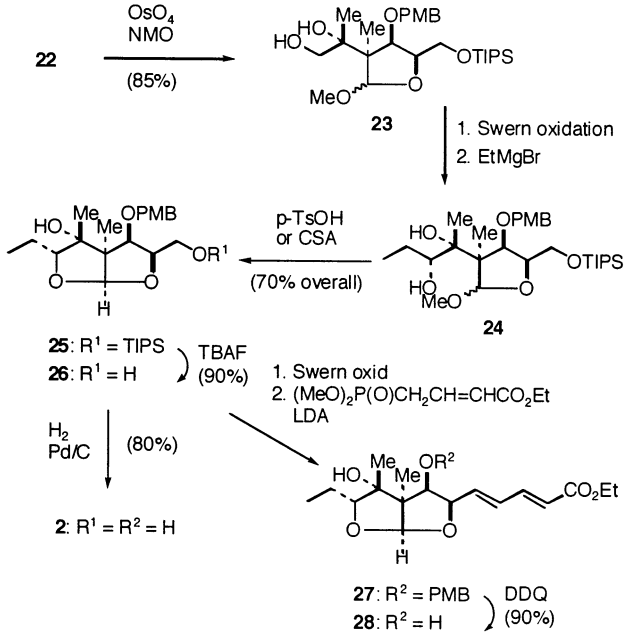
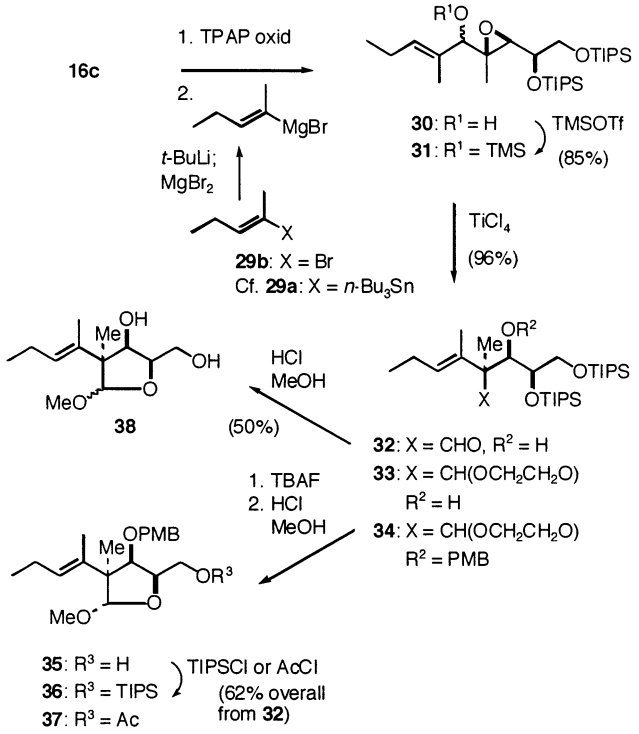
Scheme 4. Stereoselective Synthesis of Bis(tetrahydrofuran) **2**



Scheme 5. Stereoselective Synthesis of **36** and **37**



be attributed to the stereoelectronic control, where the α-anomer could more readily adopt the requisite conformation with an electron pair of the ring oxygen antiperiplanar to the leaving group.[22] By utilizing 1 equiv of *p*-TsOH, both anomers could be cyclized to **25** conveniently within 2 h, but the reaction had to be carefully monitored to avoid the unwanted cleavage of the PMB group. Finally, deprotection [(1) TBAF; (2) H_2, Pd/C)] gave bis(tetrahydrofuran) **2** ($R^1 = R^2 = H$), the spectral data of which were in excellent agreement with literature values.[2a,8,9] For additional characterization, **26** was also converted into diene ester **28**.[2a,7] Thus, Swern oxidation of **26** and subsequent olefination with trimethyl 4-phosphonocrotonate or the corresponding ethyl ester[23] furnished diene ester **27**, along with a small amount of its C-8 (asteltoxin numbering) epimer. Deprotection of the PMB group with DDQ then furnished ester **28**, which exhibited spectral characteristics identical to literature values.[2a,7b,9]

Second-Generation Synthesis of 2. Use of 2(*E*)-pentenylmagnesium bromide in place of 2-propenylmagnesium bromide in the preparation of the requisite rearrangement substrate (i.e., **16b** → **17b**) should streamline the above-mentioned synthesis of **2** by eliminating several transformations which were necessary to introduce the ethyl side chain. Additionally, the diastereoselectivity of osmylation of the resulting *E*-trisubstituted olefin was anticipated to be comparable to that of the corresponding isopropenyl moiety (e.g., **22**). Toward this end, we undertook the second-generation synthesis of **2** and planned to further reduce attendant protection/deprotection steps as well. 2(*E*)-Pentenyllithium is known to be readily available from transmetalation of 2(*E*)-pentenyl(tributyl)stannane (**29a**), which was in turn prepared starting with the trisylhydrazone of acetone;[24] in our hands, the reported sequence of transformations was capricious, and more importantly, it proved to be very difficult to obtain pure **29a** free from impurities. We thus developed a convenient, preparative-scale route to (*E*)-2-bromo-2-pentene (**29b**) by relying on reiteration of the bromination−decarboxylative elimination sequence on (*E*)-2-methyl-2-pentenoic acid.[25] Since it was unnecessary to differentiate two silyl protecting groups (R^4 and R^5), our second-generation synthesis began with bis(TIPS) ether **16c** (Scheme 5). Sequential treatment of **29b** with 2.0 equiv of *tert*-BuLi and 1.0 equiv of $MgBr_2$, followed by addition of the aldehyde derived from **16c**, cleanly afforded **30**, silylation (with TMSCl) of which provided the rearrangement substrate **31** in 85% overall yield. In parallel with **16b** → **17b**, treatment of the epoxy silyl ether **31** with $TiCl_4$ gave aldehyde **32** in 96% yield. By adaptation of the previously developed procedure for **17b**, the aldehyde **32** was then converted to the fully protected tetrahydrofurans **36** and **37** in good overall yield; surprisingly, protection of **32** by means of transacetalization with 2,2-dimethyl-1,3-dioxolane was considerably slower than that of **18** at room temperature. Direct acetal formation with ethylene glycol was instead achieved under standard conditions (a catalytic amount of *p*-TsOH, benzene, reflux) without competing desilylation in excellent (95%) yield. Upon exposure to methanolic HCl, **32** gave the unprotected tetrahydrofuran **38** as a 2:1 mixture of the two anomers in 50% (unoptimized) yield.

Osmylation of the trisubstituted olefin **36** was drastically slower than that of the respective disubstituted olefin **22** (Scheme 6). For example, in marked contrast to facile dihydroxylation (4 h, room temperature; 85% yield) of **22**, osmylation of **36** took 2 weeks at room temperature (0.15 equiv of OsO_4 and 2−3 equiv of NMO in 2:1 acetone−water) or 2 days at 50 °C (in 2:1 acetonitrile−water). Osmylation of the free alcohol **35** proceeded more slowly than that of **36** or **37**. More surprisingly, diastereoselectivity of these osmylation reactions was found to

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(24) Cooke, M. P. Jr. *J. Org. Chem.* **1982**, *47*, 4963.
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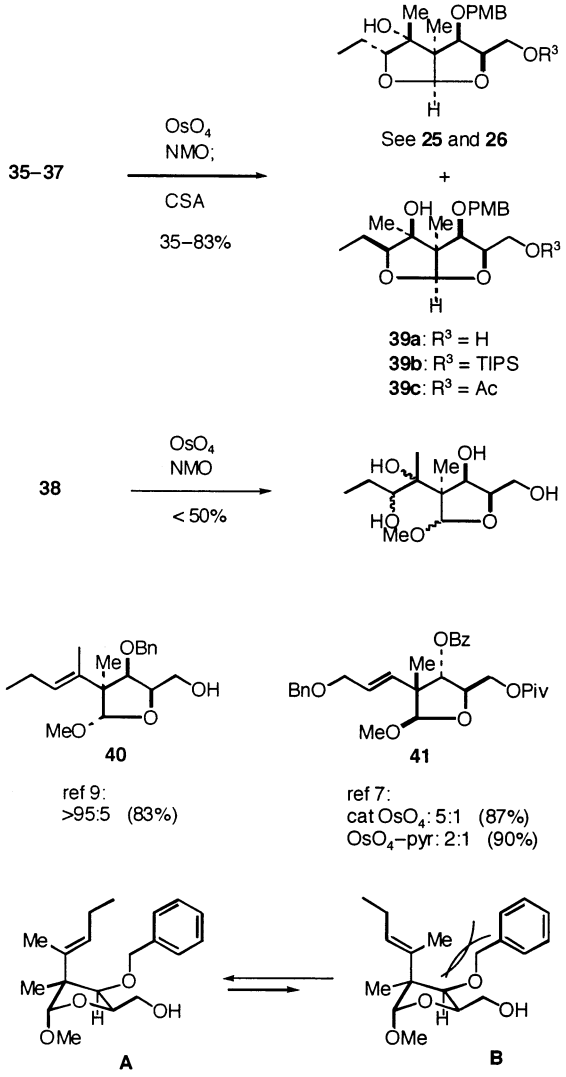
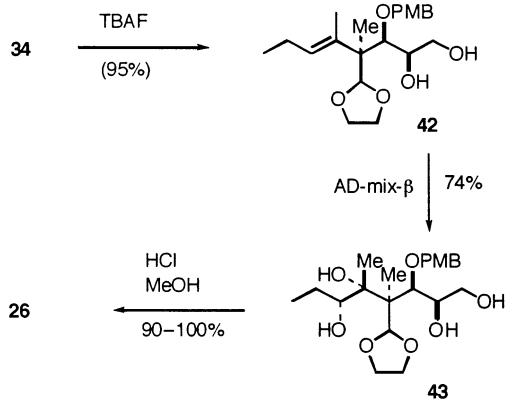
Scheme 6. Osmylation Reactions of Tetrahydrofurans **35**−**37**



Scheme 7. Second-Generation Synthesis of **26**



be not only modest, but also dependent on R_3 (e.g., **35**−**37**) and reaction temperature; since all four possible diastereomers were produced in each case, the crude reaction mixtures were subjected, after partial purification (instead of separation and individual characterization of each isomer), to acid-mediated cyclization with CSA in CH_2Cl_2, to afford two diastereomeric products (i.e., **25**/**26** and **39a**−**c**) in low diastereoselectivity, thus negating any potential advantage of directly introducing the 2(*E*)-pentenyl group. Osmylation of diol **38** proved to be nonstereoselective and also suffered from poor yields.

This stereorandom dihydroxylation of **38** might be suggestive of the stereodirecting effect of the alkoxy substituent at C-7 (asteltoxin numbering), presumably as a consequence of allylic strain.[26] Other laboratories reported osmylation of the related compounds **40** and **41**, as summarized in Scheme 6. The Mulzer group put forward an attractive rationalization on the basis of difference NOE measurements: the reactive conformer was believed to be **A**, where osmium tetroxide was expected to approach the double bond away from the aryloxy group. The minor conformer **B** would suffer from nonbonding interactions between the aryloxy group and the methyl substituent on the double bond. Lack of diastereocontrol in the osmylation reactions of **38** and Takano's example **41** is consistent with the allylic strain-based rationalization. These results suggested that the presence of both groups was essential for high diastereoselectivitity in osmylation. On the other hand, the unusually sluggish dihydroxylation of the trisubstituted olefins **35**−**37** and the observed low diastereoselectivities were incongruent with the Mulzer model; they were unexpected and perplexing, especially because these olefins are tantalizingly similar to Mulzer's substrate **40**; the origin for the striking divergence between disubstituted olefin **22** and related trisubstituted olefins **35**−**37** in osmylation is unclear at present, whereas difference NOE measurements of **22** and **36** indicated their similar conformational preference. Subtle, yet unidentified, factors seem to play an important role in determining the stereochemical outcome of these dihydroxylation reactions. However, these factors were not thoroughly examined because of the successful outcome of an alternate approach.

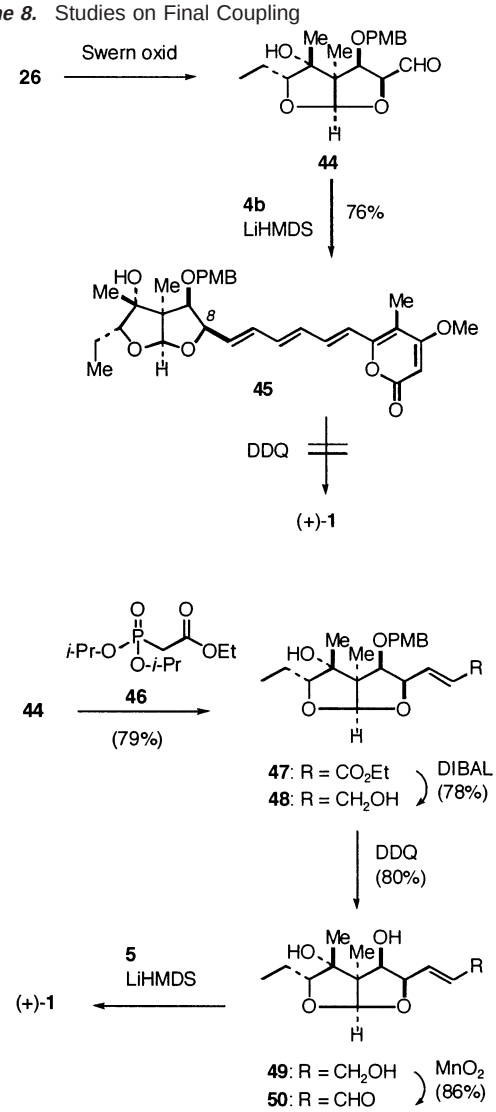
This disappointing result of the key osmylation reaction prompted us to perform the Sharpless asymmetric dihydroxylation (AD)[27] prior to formation of the tetrahydrofuran ring (Scheme 7). The Sharpless AD reaction of **34** with AD-mix-β was not encouraging, and the desired diol was isolated in only poor yield from a complex reaction mixture. However, when both silyl protecting groups were first removed, the resulting diol **42** was found to be an excellent substrate for the Sharpless AD reaction, which proceeded with a 10:1 diastereoselectivity. The tetrol **43** was isolated in 74% yield after purification by column chromatography. Interestingly, the Sharpless AD reaction of **42** with AD-mix-α was less stereoselective (a 1:6 diastereoselectivity to give **26** and **39a**, respectively, after cyclization) and less clean (43%). Subsequent treatment of **43** with methanolic HCl gave the desired bis(tetrahydrofuran) **26** in nearly quantitative yield. The Sharpless AD reactions of **35** and **36** were not diastereoselective and offered no particular advantage over the above-mentioned catalytic osmylation reactions. Overall, the second generation of **26** was thus achieved efficiently by utilizing the Sharpless AD reaction in nine steps from **16c** (in 45% overall yield).

Total Synthesis of (+)-1. Primarily because of the ready availability of phosphonates **4a** and **4b**, which had been prepared in our laboratory during our total synthesis of (−)-citreoviridin,[3e] we first examined the final coupling of **4b** and the aldehyde

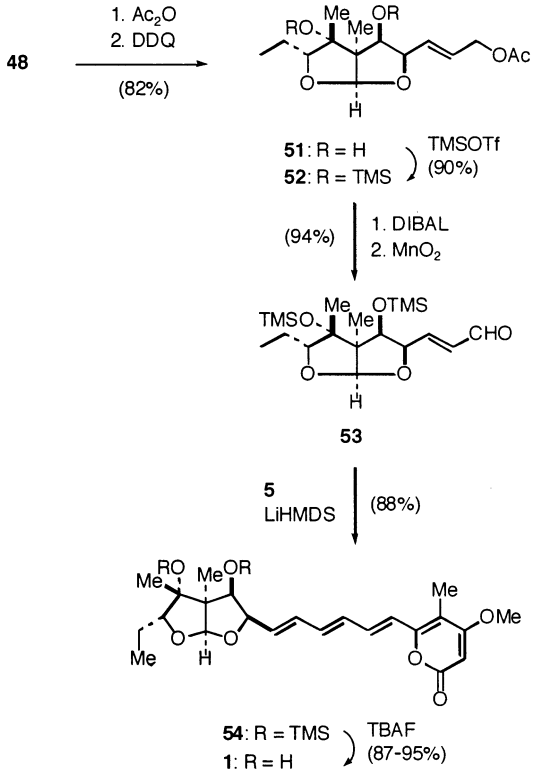
(26) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

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

Scheme 8. Studies on Final Coupling



Scheme 9. Total Synthesis of (+)-**1**



44, obtained by Swern oxidation of **26**, to provide the PMB-protected asteltoxin derivative **45** admixed with a small amount of its epimer (structure not shown) at C-8 (Scheme 8). Unfortunately, the PMB protecting group could not be removed from **45**, but instead extensive decomposition took place on exposure to DDQ. This result was not surprising in view of the presumably facile oxidation of the trienic α-pyrone moiety, coupled with the location of the PMB group in the hindered, concave face of the bis(tetrahydrofuran) subunit. Of some concern was the observation that the aldehyde **44** was somewhat prone to epimerization, especially under basic conditions (see also **27** in Scheme 4). In view of the lability of **44**, it seemed prudent to eschew the *coupling A* approach (i.e., **2** + **4**), but to adopt *coupling B* (i.e., **3** + **5**). It is noteworthy that both of the previous two syntheses of **1** relied on a third tactic of utilizing the bis(tetrahydrofuran) subunit containing a diene unit.[2b,7b] In both syntheses, moreover, the introduction of the diene functionality was carried out prior to the construction of the bis(tetrahydrofuran) moiety, thus bypassing potential complication due to epimerization.

Toward this end, **3** (e.g., **47**−**49**) was next prepared virtually free from epimerization under carefully controlled conditions: Swern oxidation of **26** and subsequent Horner−Emmons olefination of **44** with phosphonate **46** provided the desired ester **47** in 79% yield, along with less than 5% of its easily separable epimer. On the other hand, use of carbethoxy(triphenyl)-phosphorane gave a 1:1 mixture of **47** and its C-8 epimer. Aldehyde **50** was then prepared by standard methods in three straightforward steps and was found to be configurationally stable. The final union of the two segments was achieved by treatment of phosphonate **5**[3e] with LiHMDS, followed by addition of aldehyde **50** at −78 °C; the product yield was estimated to be 80% on the basis of ^{1}H NMR analysis of the crude reaction mixture, but we were disappointed that removal of an excess amount of the α-pyrone partner **5** by chromatography was an acutely onerous task and that pure (+)-**1** was isolated in only 35% yield.

To preclude laborious chromatographic purification, the use of only a stoichiometric amount of **5** was necessary, which in turn prompted us to prepare a fully protected derivative of **50**. The presence of a free alcohol had previously been found to be detrimental to a similar coupling reaction in the synthesis of citreoviridin.[3b,c,e] A straightforward sequence of functional group manipulation gave aldehyde **53** in good overall yield starting with **48** (Scheme 9). The final union of **53** and **5** in the presence of LiHMDS furnished a bis(trimethylsilyl)-protected asteltoxin derivative, **54**, free from the epimerization product, in 88% yield. Finally, both alcohols were unmasked by TBAF to afford, in 87−95% yield, (+)-asteltoxin (**1**), the spectral data and chromatographic properties of which were identical to the literature values.[28]

Future Studies

This work illustrates the synthetic utility of the stereoselective 1,2-rearrangement of readily available 2,3-epoxy alcohols or

(28) The ^{1}H NMR spectrum of natural (+)-asteltoxin was kindly provided by Professor Vleggaar, but unfortunately an authentic sample is no longer available due to extensive decomposition during storage.

silyl ethers in an efficient construction of a new quaternary center embedded in a challenging array of multiple stereocenters in an easily predictable and well-defined configuration. The mechanistic details of the underlying pinacol rearrangement and its several variants have been investigated through extensive and imaginative studies in the laboratories of Tsuchihashi−Suzuki, Yamamoto, Jung, Fukumoto−Nemoto, and others.[12−18] Compared to innovation in the methodology development, applications of these powerful rearrangement reactions of epoxides in natural product synthesis lag behind. A few spectacular examples notwithstanding,[29] a paucity of these synthetic applications is surprising, especially in view of recent dazzling advances in enantioselective epoxidation reactions.

Conclusion

In summary, we have achieved a convergent synthesis of (+)-asteltoxin (**1**) by the Horner−Emmons olefination of bis(tetrahydrofuran) aldehyde **53** and α-pyrone phosphonate **5**. A sterically congested quaternary center embedded in the densely functionalized bis(tetrahydrofuran) subunit was stereoselectively assembled by a Lewis acid-catalyzed, pinacol-type rearrangement of epoxy silyl ethers. This pivotal rearrangement strategy is analogous to the proposed biosynthetic pathway of **1**. Further applications of the reliable 1,2-rearrangement reactions of enantiomerically pure epoxides to the total synthesis of structurally complex natural products are currently in progress.

Acknowledgment. This work is dedicated to Professor Drury S. Caine. We thank the National Institutes of Health (Grant GM35956) for generous financial support.

Supporting Information Available: Experimental procedures and spectral data for new intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA034332Q

(29) Two recent notable examples are Suzuki's synthesis of furaquinocins and Harran's synthesis of nominal diazonamide A featuring an epoxy alcohol rearrangement and a pinacol rearrangement, respectively: (a) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc*. **1998**, *120*, 11633. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed*. **2001**, *40*, 4765.