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Stereocontrolled Synthesis of (−)-Macrolactin A

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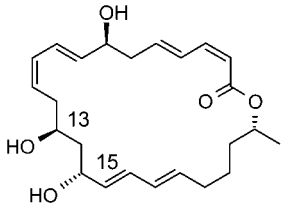
Abstract: The total synthesis of (−)-macrolactin A, a 24-membered macrolide, has been achieved using a newly developed 1,3-diol synthon for the introduction of two key stereogenic centers. The synthon was derived from sequential use of the Noyori asymmetric reduction followed by chiral sulfoxide methodology. Tellurium-derived cuprate organometallics offered an efficient and highly stereoselective means for installation of the C8 *Z/E*-diene, while the C15 *E/E*-segment was derived from a Julia−Lythgoe olefination. Yamaguchi lactonization was used to secure the macrocycle in a convergent approach with the longest linear sequence of 19 steps from Noyori alcohol **6**.

Introduction

The macrolactins are a structurally diverse class of secondary metabolites isolated from a deep-sea bacterium.[1] The parent aglycone, macrolactin A (Figure 1), is representative. Some members of this class possess pendant glucose-β-pyrannosides, while others differ in the oxidation state and degree of unsaturation. Macrolactin A exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties including inhibition of B16-F10 murine melanoma cell replication with in vitro IC_{50} values of 3.5 μg/mL. Macrolactin A also has implications for controlling human HIV replication and is a potent inhibitor of *Herpes simplex* types I and II. Because of its unique structural architecture and the potential for broad therapeutic applications, macrolactin A has been an attractive target for synthesis and has further led to the development of novel synthetic methodology.[2] Fenical and co-workers discovered the macrolactins[1] and reported with their initial findings general structural assignments for macrolactins A−F. The absolute stereochemistry was later established for macrolactins B and F through degradation, chemical correlation, and ^{13}C-acetonide analysis.[3] The stereochemical assignments for macrolactin A were made initially through comparative spectral data, but later were confirmed by Smith and Ott in the first total synthesis[4] and later by Carreira and co-workers.[5] Synthetic efforts are essential for additional pharmacological investigations and understanding the mode of action of these molecules. Typical recoveries from 16 L of cell culture give 6−9 mg of macrolactin A and less of the other macrolactins. Notably, the bacterial source of the macrolactins apparently no longer produces macrolactins A−E, only F.[2a]



(-)-**1**

Figure 1. (−)-Macrolactin A.

Results and Discussion

We report herein the stereocontrolled synthesis of (−)-macrolactin A based upon four principal components **2**−**5** (Scheme 1). This synthesis features the transmetalation of a stereodefined *Z*-vinylic telluride, the novel application of chiral sulfoxides, and the critical use of a recently developed, versatile 1,3-diol synthon. Our key disconnection involved assembly of advanced intermediates **2** and **3** via a Julia−Lythgoe[6] coupling. The northern portion of the molecule containing the C7 stereocenter we envisioned would involve the asymmetric addition of an organometallic, formally represented as subunit **5**. Macrocyclic ring closure would consummate the synthesis

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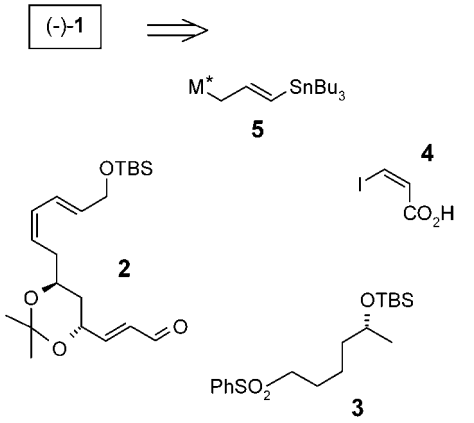
Scheme 1



through intramolecular Pd-catalyzed Stille cross-coupling[7] or by traditional macrolactonization.[8]

Enal **2** contains a 1,3-diol motif which is common to four of the macrolactins. We have designed a bifunctional 1,3-diol synthon (Figure 2)[9] with this subunit in mind. Because this motif is ubiquitous among polyol and polyfunctional natural products,[10] this synthon could enjoy general use in natural product synthesis. Nucleophilic ring opening of the epoxy terminus allows extension in one direction, while manipulation of the α-carbon occurs through use of Pummerer-type[11] conditions. The requisite diastereomer for macrolactin A was prepared according to Scheme 2. Noyori reduction[12] of ethyl 4-chloroacetoacetate furnished *β*-hydroxy ester **6** which was subsequently protected as its *tert*-butyldimethylsilyl (TBS) ether. Addition of the anion of (R_S)-(+)-methyl *p*-tolyl sulfoxide[13] to the ester terminus afforded *β*-ketosulfoxide **8**. Stereoselective reduction[14] with DIBAL (d.s. ≥ 97:3) gave hydroxy sulfoxide **9** as a single diastereomer after crystallization. Epoxide **10** formed smoothly upon treatment with cesium(I) fluoride in THF/CH_3CN. All four diastereomers of the diol motif have been prepared using this methodology.[9] Naturally the enantiomer of the Noyori catalyst can be used to produce the diastereomer at the *δ* position. Additionally, chelation-controlled reduction of the *β*-ketosulfoxide **8** can be used to generate diastereomers at the *β* position. The requirement for CsF in the epoxide formation step is also worth noting. While CsF did cleanly deliver the epoxide, we also explored other reagents such as NaOH. Interestingly, almost exclusive furan formation resulted from 5-endo cyclization of the hydroxy *β* to the sulfoxide. The cesium ion arguably plays a role in coordination to the adjacent chlorine, allowing for facile epoxide formation.[9]

Completion of subunit **2** was achieved by opening the epoxy terminus of **10** with a tellurium-derived cuprate (Scheme 3). (*E*)-Pent-2-ene-4-yne-1-ol was protected as its TBS ether **11** and stereoselectively hydrometalated to give vinylic telluride

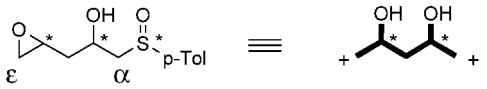
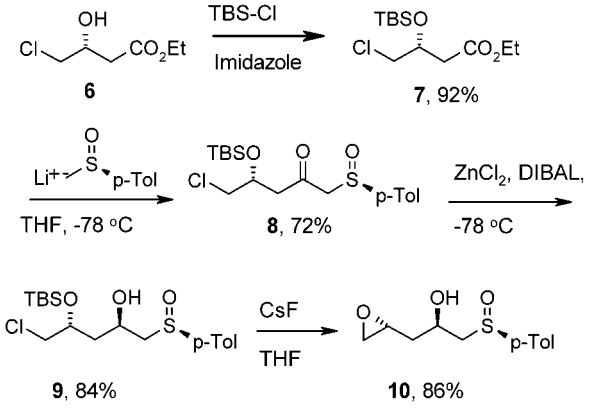
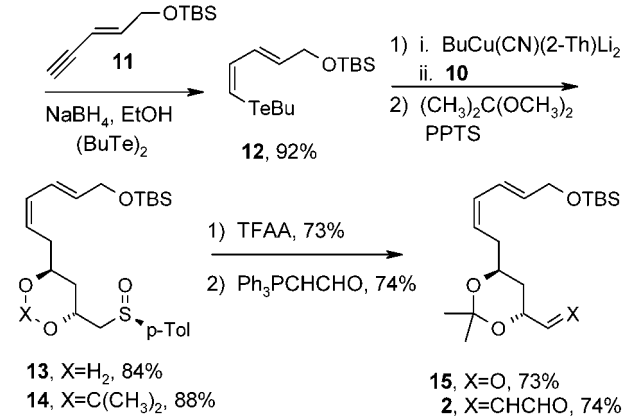


Figure 2. 1,3-Diol synthon.

Scheme 2



Scheme 3



12. While the stereoselectivity of this reaction has been well established,[15] to our knowledge this is the first reported use of vinyl tellurides in the synthesis of a natural product. Transmetalation[15] with a mixed higher-order cyanocuprate occurs at room temperature. Subsequent addition of epoxide **10** gave the anti 1,3-diol **13**. Two equivalents of the curprate and use of unprotected alcohol **10** were required. When the alcohol is protected as its methyl or silyl ether, *β*-elimination results, thus lowering significantly the yield of the desired adduct. Ring opening of the epoxy terminus occurs readily at room temperature under very mild conditions. After protection of diol **13** as its acetonide derivative, the aldehyde was unveiled through a Pummerer reaction on the sulfoxide terminus of **14**. This aldehyde was surprisingly stable when buffered mercury(II) chloride (pH 6.7) was employed in the hydrolysis of the Pummerer intermediate. Epimerization of the α stereocenter was not observed. Wittig homologation of aldehyde **15** gave subunit **2** as a single stereoisomer which set the stage for coupling to **3**.

Installation of the C23 stereocenter in subunit **3** occurred through diastereoselective reduction of *β*-ketosulfoxide **16** (Scheme 4).[14] The anion of (R_S)-(+)-methyl *p*-tolyl sulfoxide was added to methyl 5-benzyloxypentanoate[16] to give *β*-keto-

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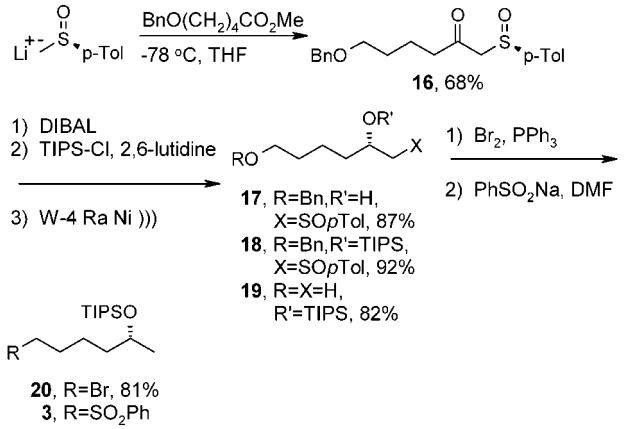
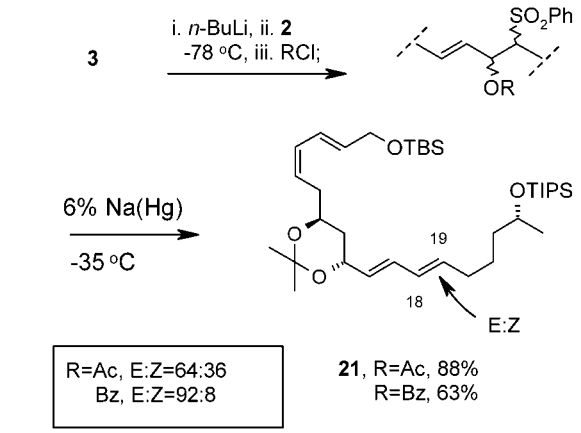
Scheme 4



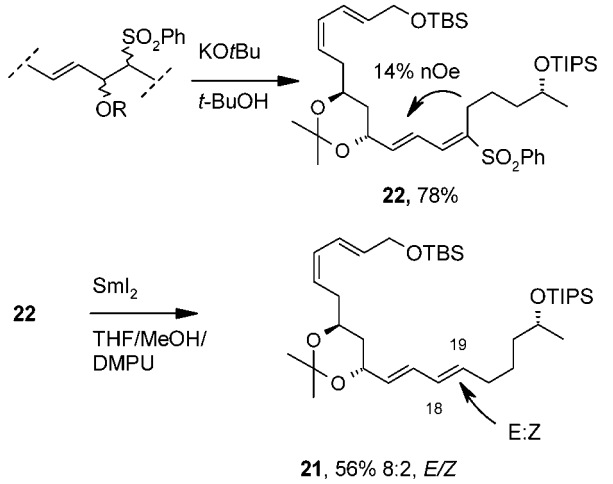
Scheme 5



sulfoxide **16**. Reduction with DIBAL (d.s. ≥ 97:3) and protection of the alcohol as its triisopropylsilyl ether gave sulfoxide **17**. Concomitant removal of the benzyl protecting group and the sulfoxide terminus was accomplished with freshly prepared W-4 Raney nickel[17] and sonication.[9] Treatment of alcohol **19** with bromine and triphenylphosphine[18] gave bromide **20** which was substituted with sodium benzene sulfinate[19] to afford the desired sulfone **3**.

Convergent coupling of subunits **2** and **3** was accomplished using a Julia−Lythgoe protocol. Sulfone **3** was treated with *n*-butyllithium and coupled to enal **2** (Scheme 5). The alkoxy anion was trapped in situ with acetyl chloride prior to treatment with 6% sodium amalgam. Unfortunately, the stereoselectivity of the elimination in this case was only 2:1, *E/Z*. We subsequently evaluated the Keck variant[20] of the Julia reaction which involves the isolation of dienyl sulfone **22** (Scheme 6). A mixture of acetoxy sulfones was initially treated with diazobicyclo[5.4.0]undec-7-ene (DBU) at room temperature. Unfortunately, this led to a mixture of alkenyl sulfone and isomerized allyl sulfone.[21] However, potassium *tert*-butoxide in *tert*-butyl alcohol[22] at room temperature afforded dienyl sufone **22** as a single diastereomer. The stereochemistry[23] was

Scheme 6



confirmed by ^{1}H NMR using nOe enhancements. The most telling effect was observed upon irradiation of the allylic methylene. Treatment of sulfone **22** with samarium diiodide[20] delivered diene **21** as a mixture of diastereomers (8:2, *E/Z*). The intermediacy of a vinyl radical in this process has been proposed,[20] and thus the formation of *E/E* isomers depends on a facile equilibration of the vinyl radical prior to H-abstraction. While this approach afforded a modest improvement over the standard Julia approach, we felt that further exploration was warranted. Interestingly, the olefinic selectivity problem was resolved by returning to the original Julia method. Use of benzoate rather than acetate (Scheme 5) resulted in a diastereomeric ratio of 92:8 (*E/Z*). The undesired isomer could be easily removed by chromatography. This result was indeed fortuitous. We postulated that the improvement in stereoselectivity may be attributed to the greater propensity of the benzoyloxy group toward elimination ($K_a = 6.46 \times 10^{-5}$ vs acetic acid $K_a = 1.76 \times 10^{-5}$). Keck and co-workers have nicely demonstrated using deuterium labeling studies that two mechanisms are likely to be operative in the Julia−Lythgoe reaction and that the pathway depends heavily on the reducing agent.[20] Interestingly, they suggest that elimination to the vinyl sulfone is the first step when Na(Hg) is employed. Subsequent reduction steps then lead to the olefin.

With **21** in hand, the stage was set for installation of the final stereogenic center. Selective deprotection of the TBS group was desirable; however, when TBAF was employed at room temperature, competitive cleavage of the triisopropylsilyl group occurred and thus necessitated the use of lower temperature. The use of TBAF in THF at −5 °C led cleanly to alcohol **23** (Scheme 7). Initial attempts to oxidize the alcohol to aldehyde **24** using Dess−Martin conditions[24] resulted in stereoscrambling of the conjugated dienal, giving an inseparable mixture of *E/E*,*Z/E*-aldehyde and *E/E*,*E/E*-aldehyde in a 4:1 ratio. A control experiment with isolated aldehyde suggested that the isomerization was not caused by the Dess−Martin reagent itself, but may be promoted by acetic acid. Oxidation with tetrapropylammonium peruthenate (TPAP)[25] with 4-methylmorpholine *N*-oxide was found be be superior in this case, providing the desired aldehyde **24** in 77% yield free of contamination from the undesired diastereomer.

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(23) While it is not immediately obvious why a single diastereomer is produced, this result is consistent with previous examples, see ref 20. An $E1_{cb}$ mechanism may be operative.
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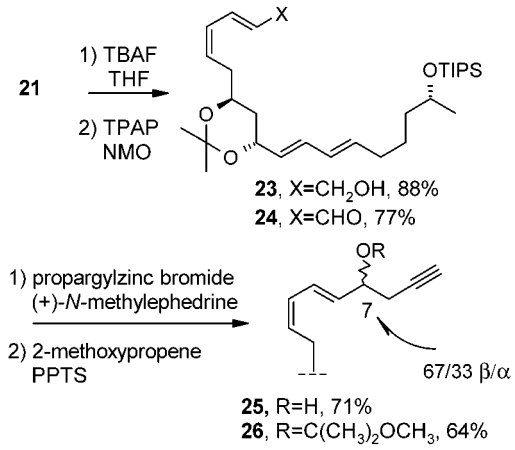
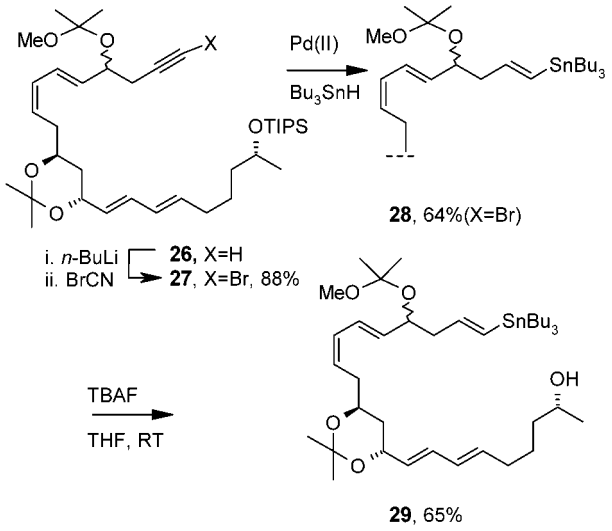
Scheme 7



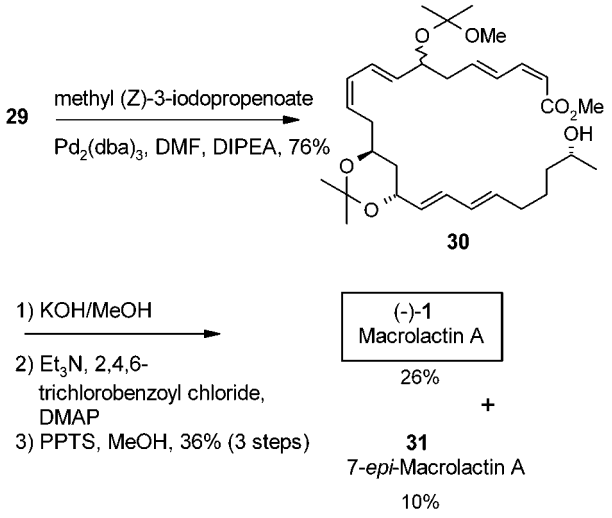
Our initial strategy for installing the C7 stereocenter relied upon successful addition of a chiral allenyl borane[26] or, alternatively, the use of an achiral allenyl stannane[27] in the presence of a chiral Lewis acid. Unfortunately, these methods resulted in low conversion rates and scrambling of dienal **24**. Consequently, addition products possessing olefinic scrambling were also observed. We turned then to more nucleophilic achiral organometallics such as propargylmagnesium bromide or propargylzinc bromide. These reagents could be added cleanly to the aldehyde and thus led naturally to the consideration of an asymmetric modification. To our knowledge, there are no documented cases for enantioselective additions of propargylmagnesium or propargylzinc species to aldehydes. In sharp contrast, very high selectivities have been reported with the use of divinyl or dialkyl organozinc reagents containing chiral ligands.[28] Specifically, Oppolzer[28a] reported the use of vinyl organozinc reagents complexed with (+)-*N*-methylephedrine. As an extension of Oppolzer's methodology, the lithium salt of (+)-*N*-methylephedrine was added to propargylzinc bromide prior to addition of dienal **24**. Modest asymmetric induction (67:33, β/α) resulted in an inseparable mixture of alcohols **25**. The ratio and absolute sense of asymmetric induction were determined by ^{1}H NMR methods previously described by Mosher et al.[29] We were also able to verify that the stereoselectivity could be reversed by using the (−)-enantiomer of *N*-methylephedrine. The ratio of diastereomers was within experimental error, identical to (+)-*N*-methylephedrine, but with the opposite sense of asymmetric induction. The alcohols were protected as the methoxyisopropylidene acetal **26**. The facility with which this group could be removed was attractive not only because it offered an opportunity to remove the acetonide in the same operation, but because of the known sensitivities of the *Z/E*-dienes. Final stage deprotection would require removal in the presence of two *Z/E* dienes, one of which is in conjugation with the lactone carbonyl. The MOM ether was also prepared, but cleavage conditions presented difficulty in maintaining stereochemical integrity of the *Z/E*-diene(s).

Initial palladium-catalyzed hydrostannation of terminal alkyne **26** resulted in modest regiocontrol (7:3 β/α). Guibé and co-workers have shown that heteroatoms can lead to deleterious regioselectivity in the hydrostannation of alkynes, presumably due to coordinative effects with palladium. They also showed that significant improvements in regiocontrol could be achieved by hydrostannation of the 1-bromoalkyne derivative under palladium catalysis using 2 molar equiv of tri-*n*-butyltin hydride.[30] Indeed, this was the case with **27** (9:1, β/α). Desilylation with TBAF at room temperature gave stannyl alcohol **29** (Scheme 8). A Stille cross-coupling with methyl (*Z*)-3-iodopropenoate[31] further extended the linear chain to give the macrocyclization precursor **30** (Scheme 9).

Scheme 8



Scheme 9



Saponification with methanolic KOH followed by esterification using the Yonemitsu modification of the Yamaguchi protocol[32] for macrolactonization gave the protected macrocycle. Deprotection with PPTS in wet methanol gave, after separation with HPLC, (−)-**1** and 7-epi-macrolactin A **30** (36% over four steps). The structure of (−)-**1** was confirmed by 2-D ^{1}H NMR and by comparison with authentic spectra.

In summary, our synthesis of macrolactin A is highly convergent and efficient, allowing for the preparation of

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analogues with ease. The synthesis features a newly developed 1,3-diol synthon and the novel use of chiral sulfoxides. While modest selectivity was obtained with the use of an asymmetric propargylic zinc reagent, further study of this reaction could lead to practical selectivities for formation of homopropargylic alcohols.[33] Finally, the first use of vinly tellurides in total synthesis offers future possibilities in the development of new organometallic approaches to *Z/E*-dienes.

Acknowledgment. This work is dedicated to the memory of Professor José Tércio Barbosa Ferreira of the Universidade Federal de São Carlos, Brazil. We thank Professors Amos B. Smith, III of the University of Pennsylvania and William Fenical of the Scripps Institute of Oceanography for sending copies of (−)-**1** for comparison. We gratefully acknowledge CNPq/FAPESP (Brazil) for financial support (fellowship to F.C.T.). We appreciate assistance provided by Don Johnson of Pfizer in the hydrogenation of ethyl 4-chloroacetoacetate for compound **6**.

Supporting Information Available: Full experimental details and spectral analyses for **1**−**3**, **6**−**31** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA017177T

(33) For recent and related examples, see also: (a) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199. (b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017.