

Total Synthesis of (–)-Ratjadone

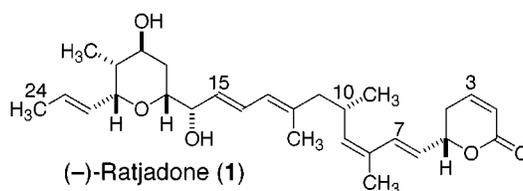
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ABSTRACT



A convergent asymmetric synthesis of (–)-ratjadone (**1**) has been achieved, confirming the assignments of stereochemistry for the naturally occurring antifungal metabolite.

Myxobacteria have proven to be a rich resource for biologically active secondary metabolites exhibiting novel molecular architecture.^{1,2} In 1994, the polyketide ratjadone (**1**) was isolated from cultures of *Sorangium cellulosum* strain So ce360.³ Höfle and co-workers described the structural connectivity of **1** and determined the relative stereochemistry for substituents of the tetrahydropyran ring. However, the stereochemical features of **1** at C₅, C₁₀, and C₁₆, as well as the absolute configuration, were not elucidated. Ratjadone displays potent in vitro antifungal activity with MIC values in the range from 0.04 to 0.6 µg/mL for *Mucor hiemalis*, *Phytophthora drechsleri*, *Ceratocystis ulmi*, and *Monilia brunnea*.⁴ Additionally, significant cytotoxicity in mammalian L929 cell lines (IC₅₀ = 0.05 ng/mL) and HeLa cell line KB3.1 (IC₅₀ = 0.04 ng/mL) has been demonstrated.⁴

Structural features of **1**, including the 5,6-dihydropyran-2-one and the arrangement of the C₅–C₁₅ bisdiene segment, suggest similarities with natural products such as callistatin

A,⁵ leptomycin B,⁶ anguinomycins,⁷ and leptofuranins.⁸ Biological studies of these natural products have indicated antitumor properties and imply important roles in chemical transduction of cell morphology and cellular transport phenomena.

Total syntheses of leptomycin B⁹ and callistatin A¹⁰ have been reported. Studies directed toward **1** were described in the course of our investigations,¹¹ and these efforts have recently culminated in the first total synthesis of (+)-ratjadone.¹² Since the objective of our efforts was also to address the issues of relative and absolute asymmetry in **1**,

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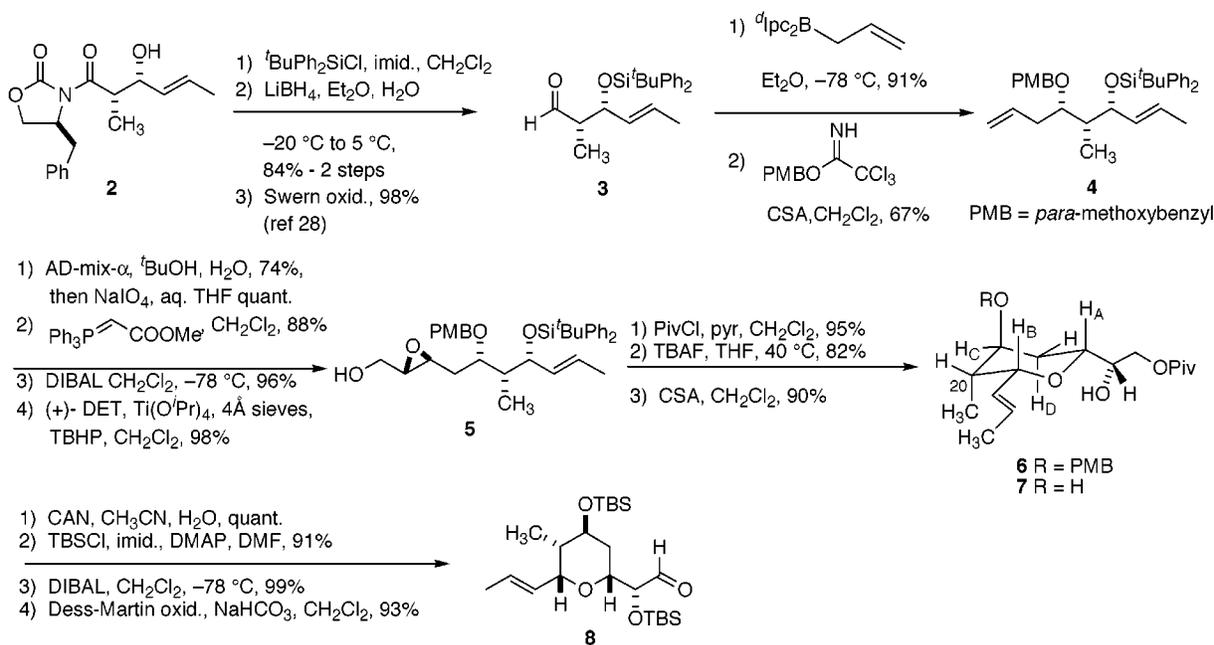
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Scheme 1



we developed a flexible but stereochemically reliable synthesis pathway. Herein we communicate our labors, which have provided four individual diastereomers of **1** for detailed spectral comparisons leading to a synthesis of (–)-ratjadone, the antipode of the natural metabolite.

Utilizing a strategy of acyclic stereocontrol, an unambiguous pathway for construction of the C_{15} – C_{24} tetrahydropyran component was deployed (Scheme 1). Aldehyde **3** was prepared via standard conversions from the known Evans aldol product **2**.¹³ A crucial element of stereochemistry at C_{19} was introduced using the Brown asymmetric allylation methodology¹⁴ via *B*-allyldiisocampheylborane derived from (+)- α -pinene affording a *syn*-homoallylic alcohol (91% yield, 94% de). Purification and protection¹⁵ led to **4**, which was subjected to a chemoselective Sharpless dihydroxylation¹⁶ of the terminal alkene. Oxidative cleavage of the mixture of diastereomeric diols (60:40 ratio) with sodium *m*-periodate was followed by Wittig olefination with methyl (triphenylphosphoranylidene)acetate producing the expected (*E*)- α,β -unsaturated ester in 88% yield. No evidence was observed for elimination of the PMB ether from the intermediate β -alkoxy aldehyde.¹⁷ Reduction of the ester with diisobutylaluminum hydride and subsequent Sharpless asym-

metric epoxidation¹⁸ resulted in pure epoxide **5** (98% yield, 95% de) after flash chromatography.

Synthesis of the tetrahydropyran component was anticipated via C–O bond formation from **5** with stereochemical inversion. Our earlier studies for the stereocontrolled preparation of 2,3,4-trisubstituted tetrahydrofurans had documented the stereochemical integrity in similar cases of internal backside displacements under acidic conditions.¹⁹ Hence, we were gratified to observe the exclusive formation of **6** following protection of **5** as the pivaloate, removal of the silyl ether, and acid-catalyzed oxirane opening in a 6-*exo-tet* fashion.²⁰

Stereochemical assignments were supported by data obtained from ^1H NMR studies of diol **7** following quantitative deprotection of **6** with ceric ammonium nitrate.²¹ For example, the irradiation of the signal for H_B (δ 4.41) led to NOE enhancement of H_A (δ 3.86), and irradiation of the C_{20} methyl group (δ 0.88) provided NOE enhancement of H_D (δ 1.83). A series of decoupling experiments indicated an axial relationship ($J = 11.6$ Hz) for H_A/H_D , and the apparent quartet for H_C (δ 4.00) was attributable to three coupled hydrogens of similar J values (~ 2.7 Hz each) following D_2O exchange.

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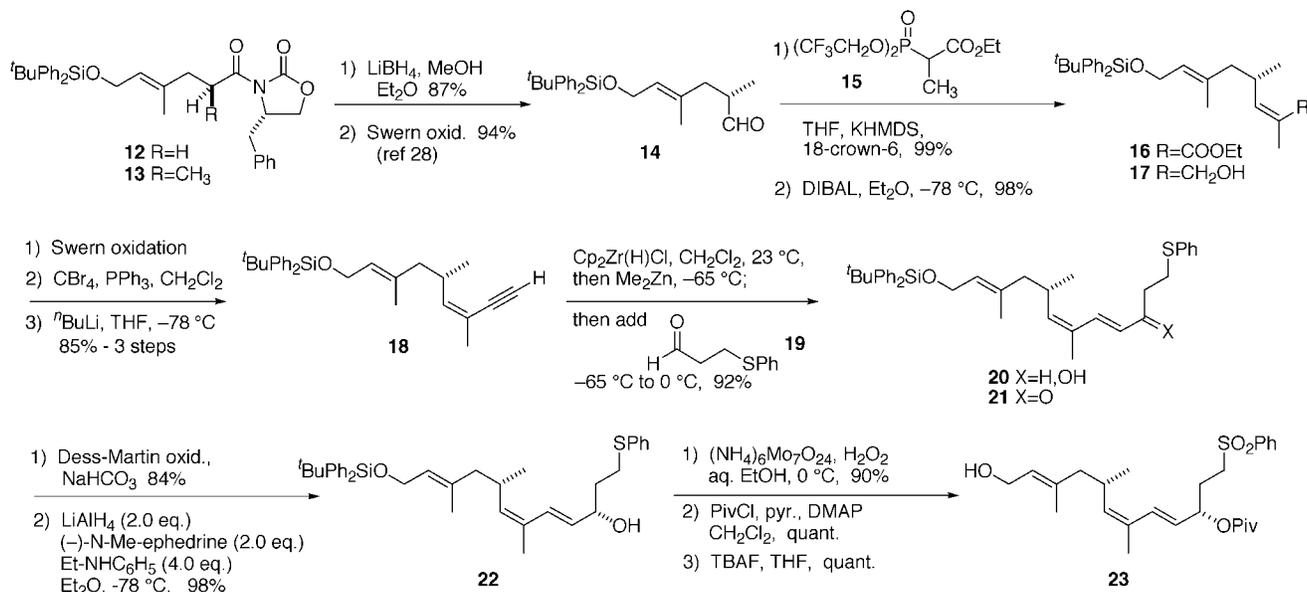
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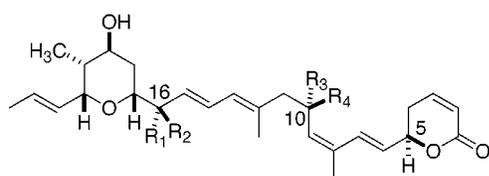
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Scheme 2



Protection of **7** as the corresponding bis-*tert*-butyldimethylsilyl (TBS) ether, removal of the pivalate, and buffered oxidation with Dess–Martin periodinane²² gave the desired tetrahydropyran aldehyde **8** in high overall yield without migration of the silyl ether to the less hindered primary position. During the course of our work, Kalesse et al. independently illustrated formation of tetrahydropyran system **6** via a similar strategy.^{11b}

The pathway for production of the C_1 – C_{14} segment required careful attention for the incorporation of stereochemical features at C_5 and C_{10} . Justifications for these concerns were amply proven upon syntheses of the three diastereomers **9**, **10**, and **11** as well as **1**. In fact, the NMR



- 9** $\text{R}_1=\text{OH}$; $\text{R}_2=\text{H}$; $\text{R}_3=\text{CH}_3$; $\text{R}_4=\text{H}$
10 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{H}$; $\text{R}_3=\text{H}$; $\text{R}_4=\text{CH}_3$
11 $\text{R}_1=\text{H}$; $\text{R}_2=\text{OH}$; $\text{R}_3=\text{H}$; $\text{R}_4=\text{CH}_3$

spectra of isomers **9** and **10** showed only slight line variations, absolutely requiring direct comparison with authentic natural product, whereas isomer **11** was clearly unique.²³ The preparation of this series of ratjadone isomers utilized a common route as summarized for synthesis of **1**.

As shown in Scheme 2, alkylation of the readily available imide **12**²⁴ via the Evans protocol (NaHMDS , THF at -78

$^\circ\text{C}$; then MeI (81%)) provided a mixture (11:1 ratio) of separable diastereomers favoring the desired **13** (*S*-configuration at C_{10}).²⁵ Standard transformations permitted conversion of **13** to the homochiral aldehyde **14** for chain extension via the Still modification of the Horner–Emmons reaction.²⁶ Under the usual conditions, reaction of **14** with the bis(trifluoroethyl) phosphonate **15** yielded exclusive formation of (*Z*)- α,β -unsaturated ester **16**, as confirmed by proton and carbon NMR data. Hydride reduction to **17** led to Mosher ester formation^{27a,b} and a direct comparison with the corresponding Mosher ester prepared from the C_{10} enantiomer of **17**.²⁷ These results verified the absence of C_{10} epimerization in the preceding Swern oxidation²⁸ or Horner–Emmons reaction.

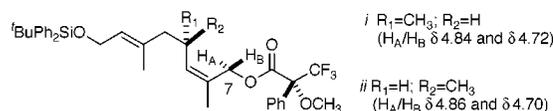
The Corey–Fuchs procedure²⁹ led to the isolation of the conjugated enyne **18** (85% overall), and the adaptation of a hydrozirconation process, described by Wipf and co-workers,³⁰ facilitated a reductive alkylation of the terminal alkyne via initial transmetalation with dimethylzinc. The resultant

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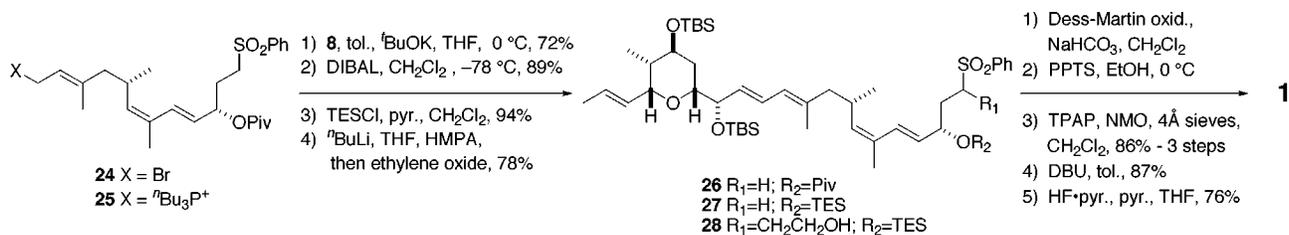
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(23) Isomer **11** was formed in small quantities from **10** via oxidation of the allylic alcohol (MnO_2) and hydride reduction (NaBH_4), providing a separable mixture of C_{16} isomers favoring the Cram chelation product **10**.

Scheme 3



vinylzinc species underwent smooth addition to aldehyde **19**,³¹ providing a separable mixture of alcohols **20** (92% yield).

We sought the precedence of an established methodology for introduction of the (*S*)- C_5 stereochemistry. After a survey of several reactions, the Terashima reduction³² of the unstable enone **21**, using (–)-*N*-methylephedrine as a chiral modifier, resulted in a 5:1 mixture of alcohol diastereomers. The major allylic alcohol **22** was converted to sulfone **23** by careful oxidation with ammonium molybdate to avoid olefin oxidations, and subsequent protection gave the corresponding pivaloate.

As shown in Scheme 3, the convergent coupling of aldehyde **8** and the $\text{C}_3\text{--C}_{14}$ segment **23** was accomplished via Wittig olefination. To this end, treatment of **23** with methanesulfonyl chloride (CH_2Cl_2 ; collidine at 0 °C) was followed by lithium bromide in THF, yielding allylic bromide **24**, contaminated with substantial amounts of the analogous chloride (82% overall from **23**). This mixture was efficiently utilized for nucleophilic displacement to produce the tri-*n*-butylphosphonium salt **25** (Scheme 3). Addition of potassium *tert*-butoxide in THF into a solution of salt **25** and aldehyde **8** in toluene resulted in a 16:1 *E/Z* mixture leading to the purification of *E,E*-diene **26** in 72% yield.

Finally the construction of the sensitive 5,6-dihydropyran-2-one was undertaken by low-temperature alkylation of the α -sulfonyl carbanion of **27** with ethylene oxide to yield primary alcohol **28** (78%).³³ Unfortunately attempts to utilize **26** led to internal acyl transfer of the pivaloyl unit upon deprotonation. However, the triethylsilyl (TES) ether **27** proved to be an ideal choice. Thus, the TES unit did not undergo $\text{O} \rightarrow \text{C}$ migration or nucleophilic cleavage under

the basic conditions of the alkylation, but it provided for facile deprotection in the presence of mild acid during subsequent oxidations without effecting the premature elimination of the sulfonyl group.³⁴ In the event, treatment of **28** with buffered Dess–Martin periodinane gave a crude β -phenylsulfonylaldehyde. Removal of the TES ether and oxidation of the resulting lactol with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO)³⁵ produced a saturated lactone. Exposure of this species to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in spontaneous elimination. Removal of the silyl ethers using buffered HF·pyridine in tetrahydrofuran provided (–)-ratjadone (**1**). Our material was identical in all respects except rotation ($[\alpha]_{\text{D}}^{25}$ –48 (*c* 0.12, CHCl_3)) with data obtained from a sample of the natural product.³⁶

In summary, our synthesis efforts have provided a flexible and convergent scheme for the preparation of ratjadone and various derivatives. These efforts have unambiguously incorporated key features of relative and absolute stereochemistry, demonstrating **1** as the antipode of (+)-ratjadone.

Acknowledgment. The authors gratefully acknowledge the National Institute of Health (GM-42897) for the generous support of our work.

Supporting Information Available: Experimental procedures and spectral data for all compounds on the synthesis pathway and a proton NMR spectra for **1**, **9**, **10**, and authentic (+)-ratjadone. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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