ORGANIC LETTERS

2001
Vol. 3, No. 9
1383−1386

Total Synthesis of (−)-Ratjadone

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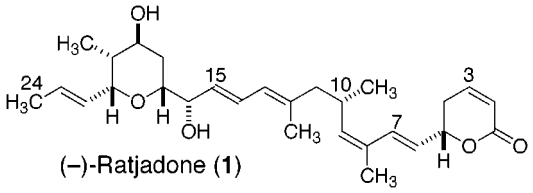
Received February 22, 2001

ABSTRACT



(−)-Ratjadone (**1**)

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 tetrahydropyranyl ring. However, the stereochemical features of **1** at C_5, C_{10}, and C_{16}, 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*, *Phythophthora drechsleri*, *Ceratocystis ulmi*, and *Monilia brunnea*.[4] Additionally, significant cytotoxicity in mammalian L929 cell lines (IC_{50} = 0.05 ng/mL) and HeLa cell line KB3.1 (IC_{50} = 0.04 ng/mL) has been demonstrated.[4]

Structural features of **1**, including the 5,6-dihydropyran-2-one and the arrangement of the C_5-C_{15} bisdiene segment, suggest similarities with natural products such as callystatin 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 B[9] and callystatin A[10] 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**,

(1) For a review and some recent reports: (a) Reichenbach, H.; Höfle, G. *Drug Discovery from Nature*; Grabley, S., Thericke, R., Eds.; Springer: Berlin, 1999; pp 149−179. (b) Sasse, F.; Steinmetz, H.; Heil, J.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **2000**, *53*, 879. (c) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *J. Org. Chem.* **2000**, *6*, 913.

(2) For a recent review of synthesis studies, see: Williams, D. R.; Li, J. J.; Hutchings, R. H. *Org. Prep. Proced. Int.* **2000**, *32*, 409.

(3) Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1995**, 685.

(4) Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 973.

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(9) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291.

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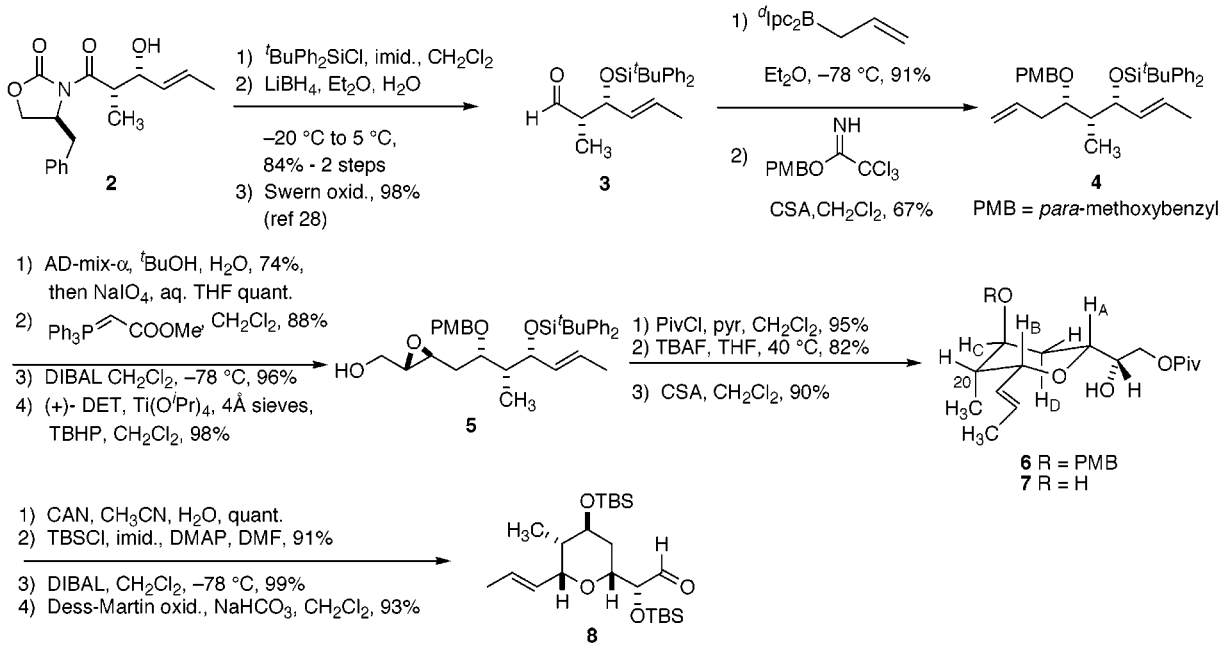
(11) (a) Claus, E.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 4157. (b) Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7201. (c) Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263. (d) Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1269.

(12) (a) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4364. (b) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885.

10.1021/ol015753k CCC: $20.00
Published on Web 04/03/2001

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 methodology[14] via *B*-allyldiisocampheylborane derived from (+)-α-pinene affording a *syn*-homoallylic alcohol (91% yield, 94% de). Purification and protection[15] led to **4**, which was subjected to a chemoselective Sharpless dihydroxylation[16] 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 asymmetric epoxidation[18] 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 ^{1}H 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.

(13) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260.

(14) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(15) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

(16) (a) Andrus, M. B.; Lepore, S. D.; Sclafani, J. A. *Tetrahedron Lett.* **1997**, *38*, 4043. (b) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.

(17) Related experiences in our rhizoxin total synthesis had forced us to adapt a plan for use of a sterically demanding *tert*-butyldimethylsilyl ether to avoid α-hydrogen abstraction. See: Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett.* **1997**, *38*, 6825.

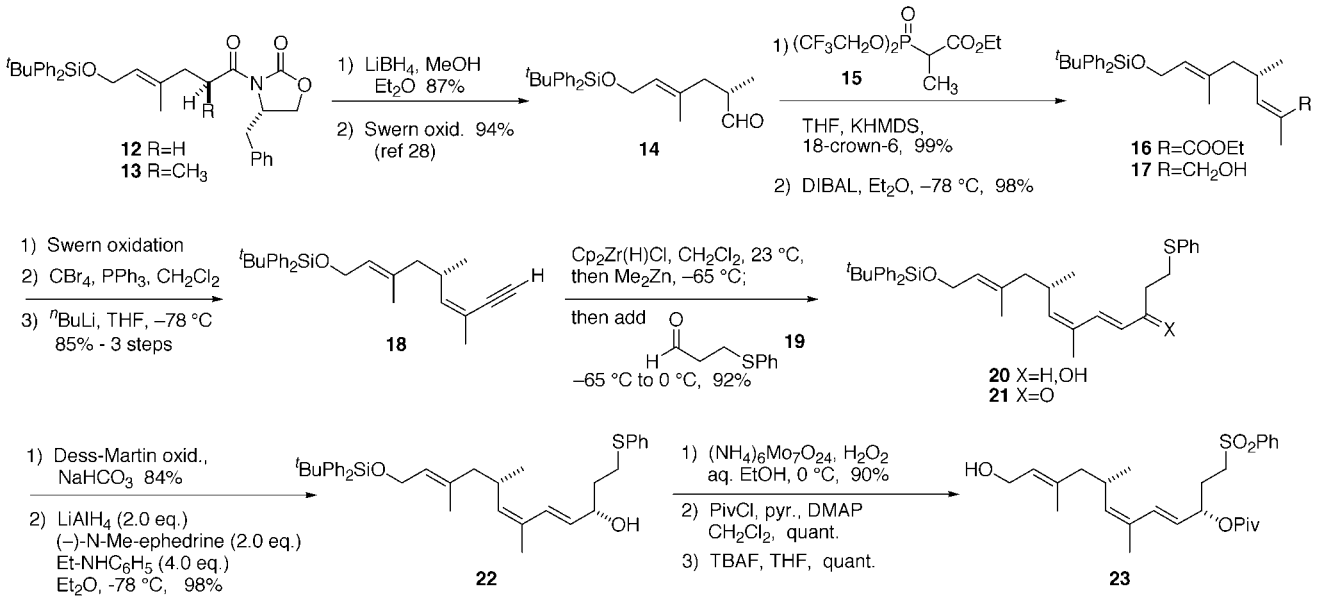
(18) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(19) Williams, D. R.; Grote, J.; Harigaya, Y. *Tetrahedron Lett.* **1984**, *25*, 5231.

(20) Reports of stereo- and regiocontrolled intramolecular openings of allylic oxiranes have provided an important advance in the synthesis of cyclic ethers. See: (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Huang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Huang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. For Baldwin's rules: Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

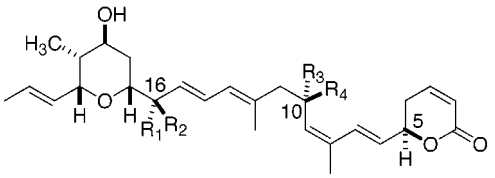
(21) (a) These NOE studies were unsuccessful in the presence of the PMB ether. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

Scheme 2



Protection of **7** as the corresponding bis-*tert*-butyldimethylsilyl (TBS) ether, removal of the pivaloate, and buffered oxidation with Dess−Martin periodinane[22] gave the desired tetrahydropyranyl 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 R_1=OH; R_2=H; R_3=CH_3; R_4=H
10 R_1=OH; R_2=H; R_3=H; R_4=CH_3
11 R_1=H; R_2=OH; R_3=H; R_4=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 °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 bistrifluoroethyl 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 oxidation[28] or Horner−Emmons reaction.

The Corey−Fuchs procedure[29] 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

(22) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

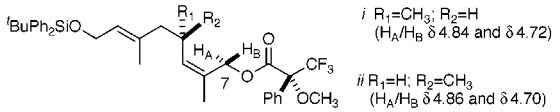
(23) Isomer **11** was formed in small quantities from **10** via oxidation of the allylic alcohol (MnO_2) and hydride reduction ($NaBH_4$), providing a separable mixture of C16 isomers favoring the Cram chelation product **10**.

(24) (a) Plé, P. A.; Hamon, A.; Jones, G. *Tetrahedron* **1997**, *53*, 3395. (b) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, M. *Tetrahedron Lett.* **1998**, *39*, 8291.

(25) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(26) Still, C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(27) (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (b) Ohtani, I.; Kusumi, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) Although proton NMR spectra were very similar, diastereomeric (*R*)-esters *i* and *ii* were distinguished by different chemical shifts observed for the diastereotopic C_7 methylene hydrogens as indicated below.



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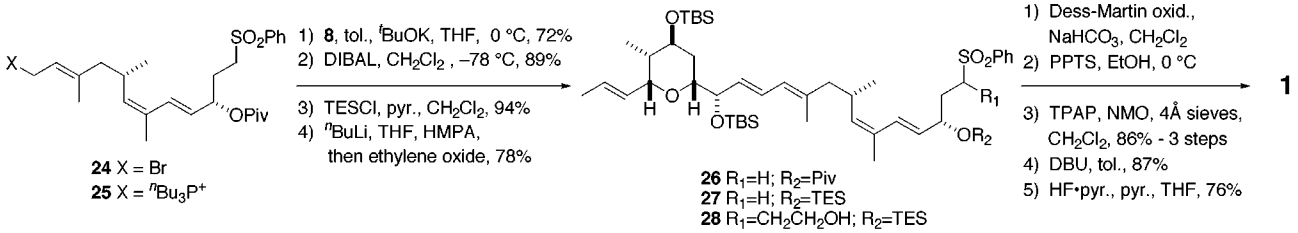
(29) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

(30) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

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 reduction[32] 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 C_3-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 O → 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 ($[\alpha]^{25}_D$ −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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(32) (a) Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1026. (b) Terashima, S.; Tanno, N.; Koga, K. *Chem. Lett.* **1980**, 981.

(33) (a) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, *16*, 1007. (b) Carretero, J. C.; Ghosen, L. *Tetrahedron Lett.* **1988**, *29*, 2059.

(34) Alternative protection schemes led to sulfone elimination yielding the (*E*)-unsaturated aldehyde, thus thwarting lactol formation. Unfortunately the TES ether did not withstand conditions leading to **25**.

(35) Griffith, W. P.; Ley, S. V.; Whitecombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(36) Since our studies had previously led to isomers **9** and **10**, which were not readily distinguished from reported data for the natural product, we are particularly grateful to Professor Gerhard Höfle (GBF, Braunschweig, Germany) for generously assisting these efforts by providing a pure sample of (+)-ratjadone for our direct comparisons.