Tetrahedron Letters,Vol.30,No.19,pp 2465-2468 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF (-)-REISWIGIN A. ASSIGNMENT OF ABSOLUTE AND RELATIVE CONFIGURATION

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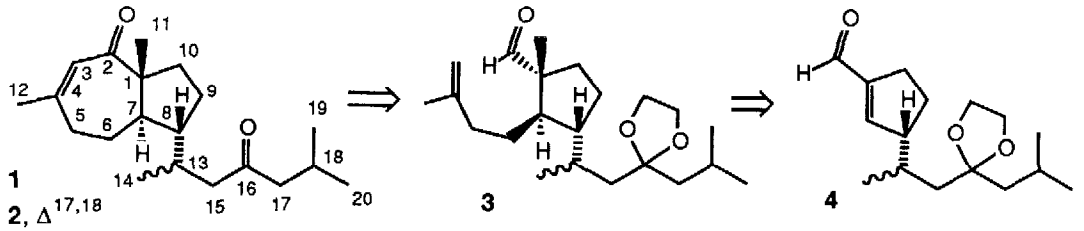
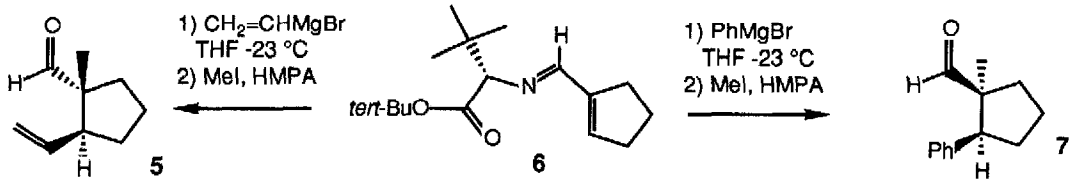
Summary: The synthesis of the anti-viral agent (-)-reiswigin A (**1**) was accomplished in 8 steps in 7% overall yield. The absolute stereochemistry and configuration of the side chain methyl group of the natural product were assigned as shown in **17**.

Diterpenes reiswigins A (**1**) and B (**2**),[1] recently isolated from a deepwater marine organism Epipolasis reiswigi, show potent in-vitro activity against Herpes simplex type I virus and murine A59 hepatitis virus. The gross structure and relative stereochemistry at three of the four chiral centers (carbons 1, 7 and 8) were determined by 2D NMR spectroscopy.[1] The configuration at carbon 13 and the absolute stereochemistry were not assigned. The structural novelty and potentially useful biological activity of these compounds prompted us to develop an efficient and practical total synthesis of **1** that would permit the facile preparation of analogues.

We chose to develop a synthesis of **1** which would control the relative and absolute stereochemistry at carbons 1, 7 and 8, but would lead to a mixture of isomers at carbon 13 so that we would be assured of producing both reiswigin A and its epimer at carbon 13. Retrosynthetic analysis suggested that the cycloheptenone moiety of **1** could be easily made by an intramolecular ene reaction of unsaturated aldehyde **3** followed by oxidation and conjugation. Aldehyde **3** could be prepared by conjugate addition to enal **4** followed by methylation of the enolate. Conjugate addition to **4** should occur selectively from the β-face. Methylation of the enolate, however, would be expected to occur predominantly from the less hindered α-face rather than the desired β-face.

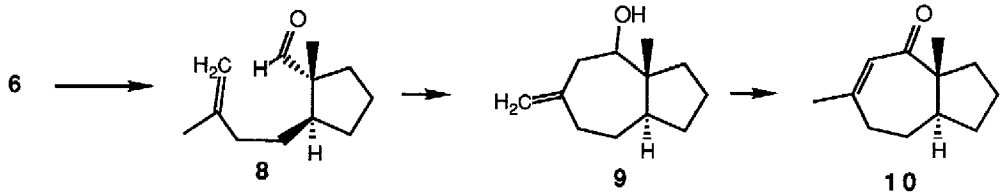


The elegant studies of Koga and co-workers provided an efficient solution to this problem.[2] They found that addition of vinylmagnesium bromide to the *tert*-leucine *tert*-butyl ester imine of 1-cyclopentenecarboxaldehyde (**6**) followed by quenching of the anion with methyl iodide and hydrolysis gives **5** in 62% yield and 92% enantiomeric excess. The chiral auxiliary directs both the addition of the Grignard reagent from the β-face, and the addition of the methyl group from the "more-hindered" β-face. This result suggested that the conversion of **4** to **3** proposed above could be accomplished by Koga's method. However, addition of phenylmagnesium bromide and methyl iodide to **6** gave **7** and aliphatic Grignard reagents were not investigated.[2]

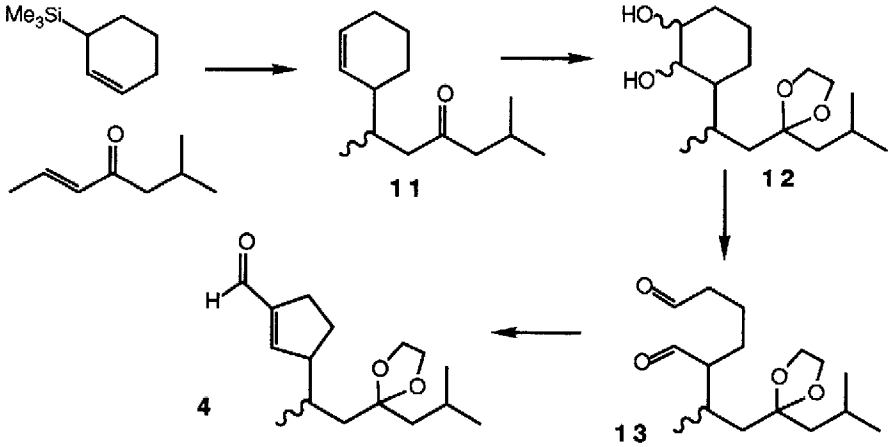


Model studies were carried out with racemic **6**, prepared from 1-cyclopentenecarboxaldehyde[3] and racemic *tert*-leucine *tert*-butyl ester.[4] Addition of 4 equiv of 3-methyl-3-butenylmagnesium bromide to **6** in THF at -25 °C

(7 h) followed by addition of 6 equiv of methyl iodide and 7 equiv of HMPA (0.5 h, -25 °C; 15 h, 25 °C) and hydrolysis provides **8** in 66% yield. The stereochemistry of **8** was assigned based on its ^{13}C NMR spectrum in which the ring methyl group absorbed at δ 13.9 as expected for a methyl group cis to an adjacent substituent.[2] The intramolecular ene reaction is most easily accomplished by treatment of **8** with 1.1 equiv of Me_2AlCl[5,6] in CH_2Cl_2 at 0 °C for 30 min to give a 91% yield of **9** as predominantly a single diastereomer of unassigned stereochemistry. Oxidation of **9** with PCC in CH_2Cl_2 followed by conjugation of the double bond (benzene, catalytic TsOH and H_2O, reflux, 12 h) gives the desired enone **10** in 82% yield. The ^1H and ^{13}C NMR, IR and UV spectra of **10** are similar to those of reiswigin A.[7]

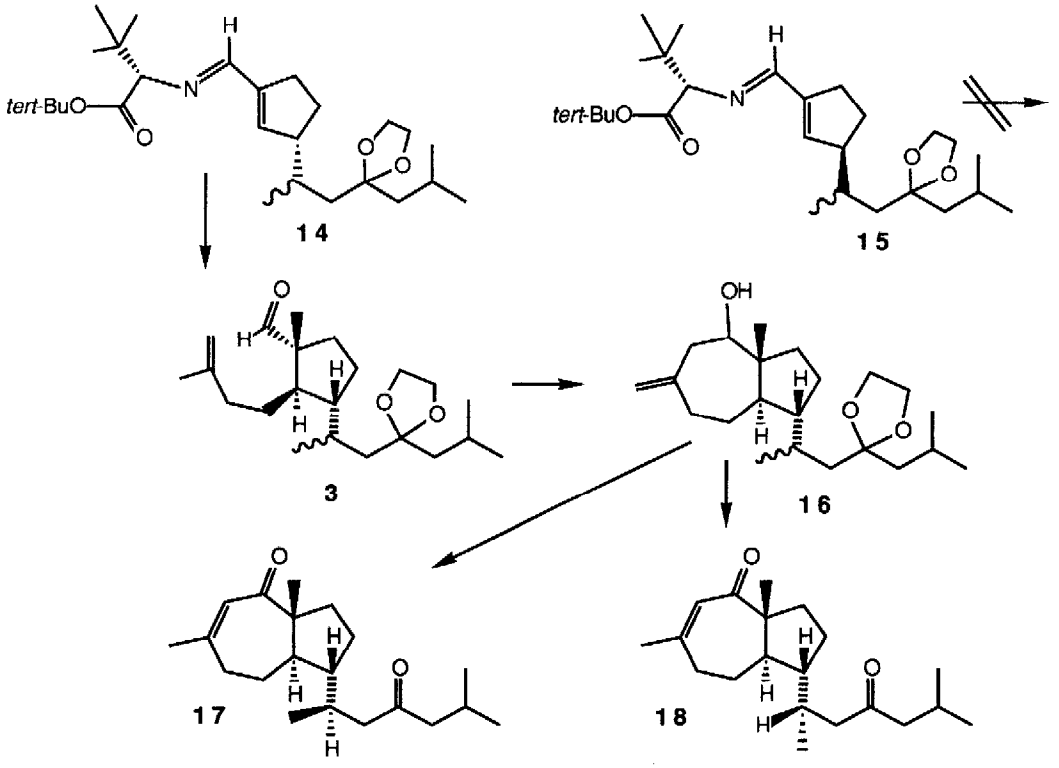


Having established that Koga's procedure could be used to convert **4** to **3**, we developed a four step route to enal **4**. Sakurai reaction[8] of 2-cyclohexenyltrimethylsilane[9] with 6-methyl-2-hepten-4-one[10] (1 equiv $TiCl_4$, CH_2Cl_2, -40 °C, 1 h) gives **11** in 88% yield. Protection of the ketone as the ketal with ethylene glycol (TsOH, benzene, reflux, 12 h, azeotropic removal of H_2O), followed by oxidation with osmium tetroxide (1 mol %) and N-methymorpholine N-oxide[11] in aqueous acetone affords diol **12** in 78% yield. Cleavage of the diol with sodium periodate in aqueous acetone gives **13** which undergoes an aldol condensation catalyzed by piperidine and acetic acid in toluene (0 °C, 12 h)[12] to give **4** in 69% yield from **12** as a racemic mixture of diastereomers.



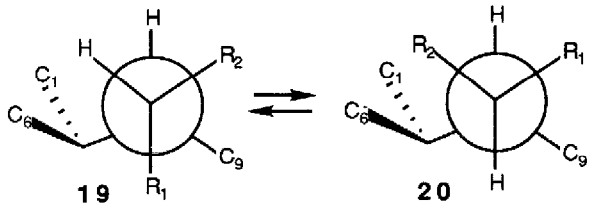
Reaction of (L)-*tert*-leucine *tert*-butyl ester[13] and **4** in hexane for 12 h at 25 °C in the presence of 4A molecular sieves[2] gives a mixture of diastereomeric imines **14** and **15** in 94% yield. Reaction of this mixture with 3-methyl-3-butenylmagnesium bromide in THF at -20 °C followed by alkylation of the enamide with methyl iodide and hydrolysis as described above gives **3** and minor amounts of other diastereomers in 32% yield along with 50% recovered optically active **4**. This key step in the synthesis not only controls the relative stereochemistry at carbons 1,7 and 8 but also results in a kinetic resolution, converting **14** selectively to reiswigin precursor **3** and leaving **15** largely unreacted. The *tert*-butyl group of the imine and the side chain on the cyclopentane in **14** both direct the delivery of the 3-methyl-3-butenyl and methyl groups from the less hindered β-face. In **15** the *tert*-butyl group of the imine directs delivery from the β-face while the side chain directs delivery from the α-face. Imine **15** therefore reacts much more slowly than **14** and gives rise largely to recovered **4** and small amounts of diastereomers, rather than enantiomers, of **3**.

The synthesis is completed by treatment of **3** with Me_2AlCl in CH_2Cl_2 at 0 °C for 30 min to give a mixture of **16** and the corresponding keto alcohol resulting from hydrolysis of the ketal. Oxidation of this mixture with PCC in CH_2Cl_2 followed by treatment with TsOH in wet benzene at reflux for 12 h to complete hydrolysis of the ketal and bring the double bond into conjugation gives a 3:2 mixture of reiswigin A (**17**) and **18** in 84% yield from **3**. Separation by preparative HPLC[14] gives pure samples of reiswigin A (**17**) and its carbon 13 epimer **18**.[15] The ^1H and ^{13}C NMR and IR spectral data and the HPLC retention time of synthetic reiswigin A are identical to those of the natural product.[16,17]



The availability of both **17** and **18** permits the assignment of structure **17** to natural reiswigin A. The ^1H and ^{13}C NMR spectra of **17** and **18** are quite similar except for the chemical shift of the 14-methyl group which absorbs at δ 0.90 and δ 20.1 in reiswigin A (**17**) and δ 0.80 and δ 13.6 in **18** and the chemical shift of carbon 15 which occurs at δ 45.4 in **17** and δ 49.9 in **18**. Although the use of chemical shift data to assign configuration to conformationally mobile molecules is fraught with danger, the differences in this case are sufficient to permit tentative assignment as shown. In a variety of related molecules, the methyl group in the stereoisomer corresponding to **17** absorbs downfield by 0.1 to 0.2 ppm in the ^1H NMR spectrum, and downfield by 4-7 ppm in the ^{13}C NMR spectrum.[18,19] The origins of these shift differences can be seen in the Newman projections **19** and **20** of the two low energy conformations of **17** and **18**. Conformation **20** has only 2 gauche butane interactions, but has a high energy syn-axial interaction between R_2 and carbon 6. Conformation **19** has 3 gauche butane interactions, but no high energy interactions with carbon 6. In conformation **19**, the 14 methyl group of **18** is in a gauche relationship with carbons 7 and 9 and should be shifted upfield from the 14 methyl group of **17** which is in a gauche relationship only with carbon 9. In conformation **20**, the methyl groups of both **17** and **18** are in a gauche relationship with one carbon. However, the 14 methyl group of **17** is in a deshielding syn-axial relationship with carbon 6.[19] Therefore, in each conformation the methyl carbon 14 of **17** should absorb downfield from the

methyl carbon of **18** permitting a tentative structural assignment to be made. Similar analysis predicts that the methylene carbon 15 of **17** should absorb upfield from the methylene carbon of **18** as is observed.



17, R_1 = side chain, R_2 = CH_3
18, R_1 = CH_3, R_2 = side chain

The absolute configuration of reiswigin A (**1**) can be assigned as shown in **17** by comparison of the CD spectrum with that of the synthetic material. Natural reiswigin A has a CD maximum of [θ] = -4400 ° at 300 nm. The synthetic material has an identical CD maximum. The absolute stereochemistry of synthetic **17** and **18** is known since Koga determined the direction of addition to (L)-*tert*-leucine *tert*-butyl ester imines; natural (-)-reiswigin A therefore has the absolute configuration shown. Furthermore, kinetic resolution in the Grignard addition to **14** and **15** must be very efficient since [θ] for synthetic **17** is comparable to that of natural reiswigin A.

A practical synthesis of reiswigin A has been accomplished in 8 steps in 7% overall yield. The absolute stereochemistry and configuration at carbon 13 of the natural product have been determined.

References and Notes

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7. **10**: ^{1}H NMR ($CDCl_3$) δ 5.83 (br s, 1), 2.2-2.4 (m, 2), 1.4-2.1 (m, 9), 1.90 (br s, 3), 1.08 (s, 3); ^{13}C NMR ($CDCl_3$) δ 207.5, 152.2, 127.4, 55.7, 43.1, 36.3, 34.9, 30.9, 28.6, 25.6, 19.4, 19.0.
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13. We thank Dr. Karl Heinz Drauz of Degussa AG for a generous gift of (L)-*tert*-leucine.
14. HPLC separation was accomplished on a 10 mm x 25 cm ODS column with 70:30 methanol-H_2O as eluent at a flow rate of 2 ml/min. The retention times are 128 min (**18**) and 137 min (**17**).
15. **18**: ^{1}H NMR ($CDCl_3$) δ 5.80 (br s, 1), 1.90 (br s, 3), 1.10 (s, 3), 0.93 (d, 6, J = 6.6), 0.80 (d, 3, J = 6.5); ^{13}C NMR ($CDCl_3$) δ 210.3 (C_2), 152.5 (C_4), 127.4 (C_3), 56.4 (C_1), 52.6 (C_{17}), 49.9 (C_{15}), 46.4 and 44.8 (C_7 and C_8), 35.2 and 34.9 (C_5 and C_{10}), 28.6 (C_{12}), 28.6 (C_{13}), 24.5 (C_{18}), 24.2 (C_6), 22.6 and 22.6 (C_{19} and C_{20}), 20.5 (C_9), 19.8 (C_{11}), 13.6 (C_{14}); Carbon 16 was not observed.
16. We thank Dr. Frank Koehn for spectral data and a sample of natural reiswigin A.
17. The ^{1}H NMR data reported for **1** in reference 1 are not referenced correctly. 0.08 ppm should be subtracted from the reported δ values.
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(Received in USA 28 February 1989)