The Total Synthesis of (±)-Rishirilide B

John G. Allen[1] and Samuel J. Danishefsky[1,2]

Sloan-Kettering Institute
New York, New York 10021
Department of Chemistry
Columbia University
New York, New York 10028

Received September 5, 2000

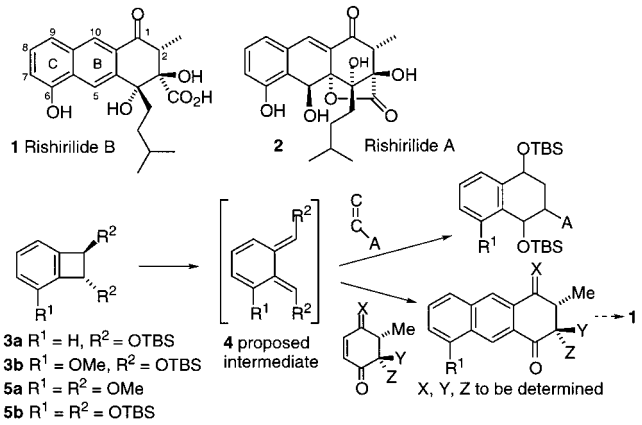
Rishirilides B and A were isolated from *Streptomyces rishiriensis* OFR-1056 in 1984 by Naki and co-workers.[3] They exhibit antithrombotic activity[4] through selective α_2-macroglobulin inhibition, thereby leading to the activation of plasmin. Rishirilide B is substantially more potent than A in this assay. The structure of rishirilide A (although not its absolute configuration) was established, by crystallographic means, to be **2**. The assignment of structure **1** to rishirilide B was not supported by crystallographic data, but was rendered under the assumption of its biogenetic connectivity to **2**. In addition to their novel mechanism of action, impinging on a crucial biological cascade, the structures of the rishirilides interested us as focusing targets for total synthesis.

Recently, we have described the use of systems **3** as viable equivalents of quinodimethides (**4**) for intermolecular cycloaddition reactions with a range of dienophiles (Scheme 1).[5] With peri-substituents ($R_1 \neq H$), as in **3b**, **5a**, or **5b**, the rate of cycloaddition is significantly reduced. Although substituted cyclohexenones failed to react usefully with **5**, we nonetheless proposed the synthetic route to rishirilide B shown in Scheme 1 (vide infra).[6]

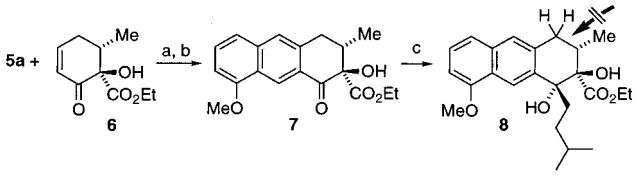
Central to the success of the proposal was the need to deal with the serious retardation effect of peri-substituents required to reach the C6 phenolic hydroxyl of **1**. In particular, we sought to exploit a discovery of Masamune,[7] wherein a strategically placed hydroxyl group could enhance the dienophilicity of an acyclic α,β-unsaturated ketone, presumably by internal hydrogen bonding. We wondered whether the Masamune effect could be realized with an α'-hydroxylated cyclohexenone, to the extent that it would react with quinodimethide precursors such as **5**. This line of conjecture led to the selection of **6**[6] to serve as a putative dienophile. In this modeling phase, we used the readily prepared[8] **5a** as the presumptive quinodimethide precursor.

In the event, reaction of **5a** and **6** did occur at 160 °C over 15 h (Scheme 2). The crude cycloadduct was treated with camphorsulfonic acid in methanol under reflux, providing a 65% yield of **7**. In the next step, the β-disposed hydroxyl group of **7** cleanly directed the reaction of isoamylmagnesium bromide to the β face of the ketone to afford **8** (mp 128−129 °C) in 70% yield. The structure of this compound was verified by X-ray crystallography.

Scheme 1



Scheme 2[a]



[a] (a) 160 °C, toluene-d_8 15 h; (b) CSA, MeOH, 65%, 2 steps; (c) isoamylmagnesium bromide (1.08 M), THF, 70%.

Thus, the tertiary alcohols of **6** and **7** exerted two critical directivity functions. Reaching **1** from **8** required oxidation at C1 (see arrow). However, various attempts to accomplish this transformation failed, thereby prompting us to a rather more interesting solution.

Toward this end, we synthesized the enedione **12**.[6] Condensation of 2-(trimethylsilyl)ethyl acetoacetate **9**[9] with crotonaldehyde gave **10**.[10] Formation of the silyl dienol ether, followed by selective Rubottom-type oxidation using dimethyl dioxirane,[11] presumably under guidance of the proximal secondary methyl function, provided **11**. Allylic bromination was found to be the only effective method for functionalizing the γ-position. The resulting bromide was smoothly converted to enedione **12** (Scheme 3).

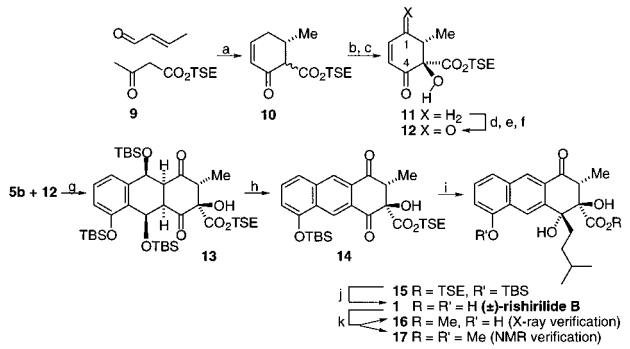
It was expected that enedione **12** would be a much more reactive dienophile than was **6**.[12] Furthermore, it was envisioned that through hydrogen bonding, the C4 ketone would be differentially activated relative to that at C1.[7c,d] If this bias were complementary to the bias introduced by the silyloxy peri-substituent in **5b**, there seemed to be a chance of gaining control over the regiochemistry issue.

All expectations were realized in the Diels−Alder-like cycloaddition of **12** and **5b**. The predominant product (**13**, 90% yield) was shown by extensive NMR measurements to be the result of endo addition, anti to the Me and CO_2TSE functions with the desired regiochemistry, as shown. At this stage, however, the stereochemistry at C3, relative to that at carbons 2 and 4a, in the proposed **13** could not be rigorously established. Dehydration and aromatization were accomplished through the action of CSA to give **14**. Reaction of **14** with excess isoamylmagnesium

(1) Bioorganic Chemistry Laboratory, Sloan-Kettering Institute.
(2) Department of Chemistry, Columbia University.
(3) Iwaki, H.; Nakayama, Y.; Takahashi, M.; Uetsuki, S.; Kido, M.; Fukuyama, Y. *J. Antibiot.* **1984**, *37*, 1091.
(4) Plasmin, an enzyme important in fibrin degradation, is inhibited by α_2-macroglobulin. Agents such as the rishirilides that inhibit α_2-macroglobulin may be useful in the treatment and prevention of thrombosis by fibrinolytic accentuation.
(5) (a) Allen, J. G.; Hentemann, M. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 571. (b) Hentemann, M. F.; Allen, J. G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1937.
(6) See Supporting Information.
(7) (a) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (b) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137. Other examples include (c) Kelly, T. R.; Fu, Y.; Sieglen, J. T., Jr.; De Silva, H. *Org. Lett.* **2000**, *2*, 2351, and (d) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743.
(8) (a) Bill, J. C.; Tarbell, D. S. *Org. Synth.* **1954**, *34*, 82. (b) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 415. (c) Nozaki, H.; Noyori, R.; Kozaki, N. *Tetrahedron* **1964**, *20*, 641.
(9) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936.
(10) (a) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 815. (b) Bohlmann, F.; Prezewowsky, K. *Chem. Ber.* **1964**, *97*, 1176.
(11) Use of wet DMDO avoided silyl transfer, cf. (a) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249. (b) Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783.
(12) Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183.

10.1021/ja003272a CCC: $20.00
Published on Web 12/21/2000

Scheme 3[a]

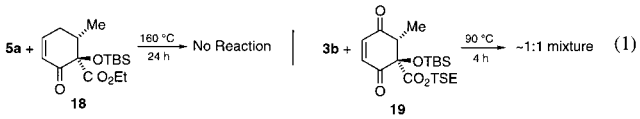


[a] TSE = 2-(trimethylsilyl)ethyl; (a) 1. TSEOH, ether, Na; 2. $HCl_{(g)}$, 34%; (b) NaH, DMF, TBSOTf; (c) DMDO (0.061 M), 76%, 2 steps; (d) NBS, AIBN, CCl_4, 91%; (e) Ag_2CO_3, acetone:H_2O (8:1), 63%; (f) Dess−Martin, CH_2Cl_2, 92%; (g) toluene-d_8, 90 °C 12 h; (h) CSA, pyridine, MeOH; 72% 2 steps; (i) isoamylmagnesium bromide (0.73 M), THF; (j) TAS-F, THF, 65%, 2 steps; (k) CH_2N_2, Et_2O, MeOH, 15% **16**, 43% **17**, 31% **1**.

bromide resulted in monoalkylation[13] cis to the neighboring hydroxyl group (see compound **15**). Desilylation via TAS-F reagent[14] afforded (±)-rishirilide B (**1**) in 47% overall yield from dienophile **12**.

At this point we still could not rigorously assert the stereochemisty at C3. There was indeed some concern, since the ^{13}C NMR data obtained from our synthetic material, presumed to be **1**, did not match those tabulated for the natural product in the original publication.[3,15] Furthermore, no specimen samples of **1** or any derivative thereof were available to us for direct comparison. Fortunately, we were able to obtain crystallographic verification of the structure of **16** (mp 94−96 °C) obtained from partial methylation of our synthetic **1** with diazomethane. We were also able to obtain[3,16] a copy of the high-field ^1H NMR spectrum of **17** derived from naturally occurring **1**. This spectrum was superimposable with that of **17** derived by bis-methylation of our synthetic **1**. Accordingly, the structure of rishirilide B is now rigorously established to be **1**.[17,18]

Two further experiments serve to support the key role of the hydroxyl group in directing these Diels−Alder-like reactions. Benzocyclobutene **5a** failed to react with the TBS derivative **18**. Moreover, in reaction with **3b, 19** provided a highly activated dienophile, but with the C3 alcohol protected, a total loss of regiocontrol resulted.[6]



It seems likely that the chemistry and insights developed for this total synthesis will find wider application.

Acknowledgment. This paper is dedicated to Professor Satoru Masamune of the Massachusetts Institute for his discovery of the hydrogen bonding effect in Diels−Alder reactions. This work was supported by the National Institutes of Health: AI 16943/CA 28824 (S.J.D.) and CA-80356 (J.G.A.). We thank Brian M. Bridgewater and David G. Churchill for providing X-ray data. We thank Dr. George Sukenick for mass spectral analyses.

Supporting Information Available: Experimental, spectral and crystallographic information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003272A

(13) No dialkylation was observed, even with excess Grignard reagent, possibly due to intramolecular lactol or lactolate formation.

(14) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 1215.

(15) ^1H NMR data for **1** was in excellent agreement with those previously published. IR data was not available for the natural product.

(16) Personal communication from Professor Yoshiyasu Fukuyama, Faculty of Pharmaceutical Sciences, Tokushima Bunri University.

(17) Presumably the discrepancy in the ^{13}C NMR of synthetic **1** with the tabulated data reported for the natural product reflects the concentration, pH, or other experimental inconsistencies in the measurements.

(18) Since the ^1H NMR spectra of **17** obtained from both synthetic and natural sources differ markedly from that of the same terminal product of a previously claimed synthesis by Hauser (Hauser, F. M.; Xu, Y. *Org. Lett.* **1999**, *2*, 335), reformulation of that work will be necessary.