ORGANIC LETTERS

1999
Vol. 1, No. 2
335−336

Total Synthesis of (±)-Methyl Rishirilide B

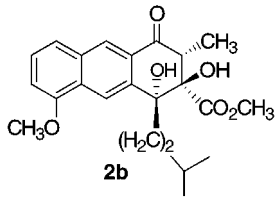
Frank M. Hauser* and Yong-jin Xu

Department of Chemistry, State University of New York at Albany, Albany, New York 12222

fh473@sarah.albany.edu

Received May 11, 1999

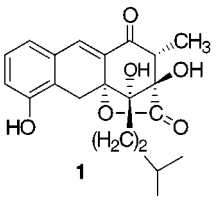
ABSTRACT



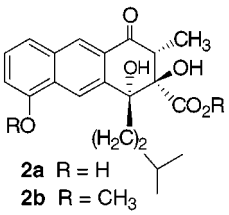
2b

A regio- and stereospecific total synthesis of (±)-methyl rishirilide B (2b), an $(\alpha)_2$-macroglobulin inhibitor, is described. A key feature of the synthetic plan was regiospecific construction of a hydroanthracenone intermediate through condensation of a phenylsulfonyl isobenzofuranone with a functionalized 2-cyclohexen-1-one. Introduction of the vicinal *trans*-hydroxyl groups in the densely functionalized A-ring was accomplished via a novel one-pot procedure that involved oxidation of enolate anions with the Davis reagent.

The rishirilides A (**1**) and B (**2a**), isolated from *Streptomyces rishirinsis* by Iwaki and co-workers,[1] are $(\alpha)_2$-macroglobulin inhibitors that are potentially useful for the treatment and/or prevention of thrombosis.[2] We report herein the first total



1



2a R = H
2b R = CH_3

synthesis of **2b**, the methylated derivative of rishirilide B (**2a**), which is the more biologically active substance. Novel aspects of the preparation are regiospecific construction of the hydroanthracenone intermediate **11a**[3] and discovery of a one-pot procedure for introduction of the vicinal *trans*-dihydroxy functionality in the densely fuctionalized A-ring of **2b** through oxidation of enolate anions with the Davis reagent, 2-phenylsulfonyloxaziridine.[4]

As shown in Scheme 1, Diels−Alder reaction of piperylene (**3**) with (*E*)-6-methyl-2-heptenoic acid (**4**) in benzene in a sealed tube at 180 °C gave the expected unsaturated carboxylic acid **5** in 45% yield as a 2:1 mixture of diastereoisomers, with **5a** predominating. A novel separation of the isomers was achieved. Upon iodo-lactonization (I_2, collidine, CH_3CN) of the mixture, only **5a** underwent reaction.[5] The resultant iodolactone **6** was dehydrohalogenated to the bicyclic lactone **7** and then subjected to methanolysis (K_2CO_3, CH_3OH, 87%) to give **8**. Oxidation of **8** with MnO_2 furnished the cyclohexenone **9**[6] as the sole olefinic isomer.

The anion of the phenylsulfonyl isobenzofuranone[3] **10** was

(1) Iwaki, H.; Nakayama, Y.; Takaheshi. M.; Uetsuki, S.; Kido, M.; Fukuyama, Y. *J. Antibiot.* **1984**, *37*, 1091−93.

(2) Aoki, N. *Prog. Cariovasc. Dis.* **1979**, *21*, 267−86.

(3) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. For use of this reaction in natural products syntheses, see: Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. Hauser, F. M.; Tomassi, R. A. *J. Org. Chem.* **1991**, *56*, 5758. Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.

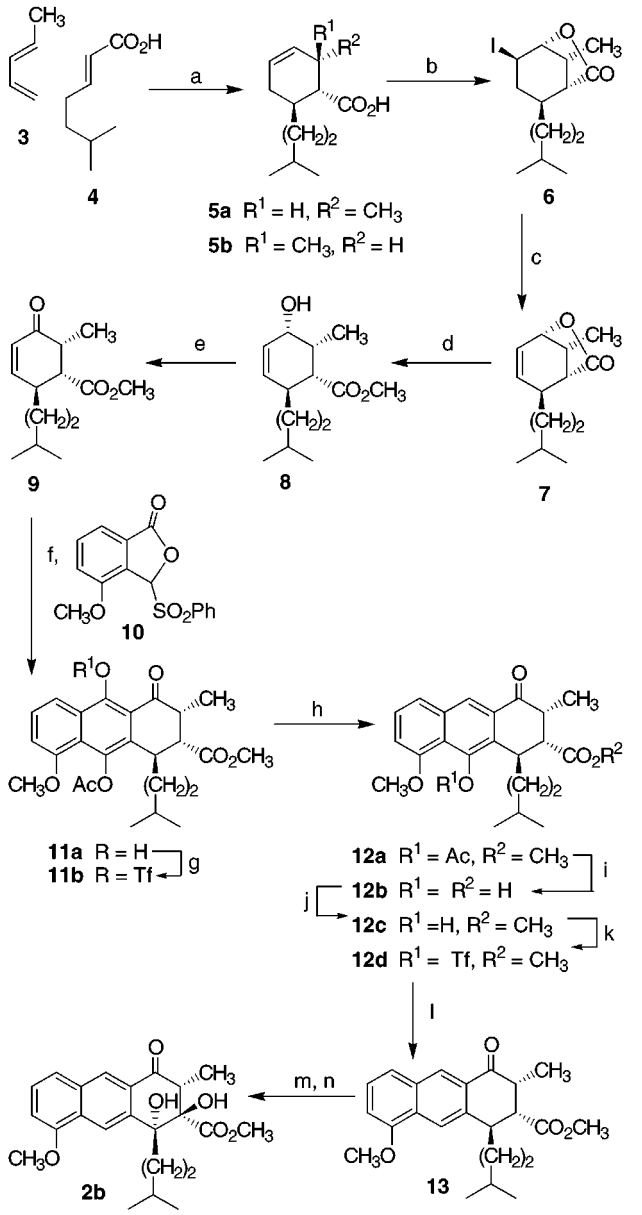
(4) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

(5) Had **5b** undergone iodo-lactonization, the product would have had three substituents with 1,3-diaxial relationships, which would be highly unfavorable. Furthermore, calcuations (Cache) indicate that there is a substantial difference (6.39 kcal/mol) in relative energy between **5a** and the iodolactone that would have been formed from **5b**.

(6) The use of other oxidizing agents invariably produced regioisomeric mixtures of olefinic products.

10.1021/ol9906561 CCC: $18.00
Published on Web 06/04/1999

Scheme 1[a]



[a] Key: (a) *tert*-butylcatachol (5 mol %), PhH, sealed tube, 180 °C (45%); (b) I_2, collidine, CH_3CN (60%); (c) DBU, PhH, (70%); (d) K_2CO_3, CH_3OH (87%); (e) MnO_2, CH_2Cl_2 (80%); (f) Li*O*t*Bu*, THF, 10, then Ac_2O (81%); (g) NaH, Tf_2O, 0 °C (51%); (h) Pd/C/H_2 (75%); (i) Claisen's alkali; (j) K_2CO_3, CH_3I (73%); (k) Li*O*t*Bu*, Tf_2O, 0 °C (77%); (l) Pd/C/H_2 (84%); (m) TMSOTf, Et_3N, PhH; (n) KHMDS, THF, 2-phenylsulfonyloxaziridine.

condensed with the cyclohexenone **9**, initially at −78 °C, followed by warming to 0 °C, cooling to −78 °C, and quenching of the dilithium phenolate with acetic anhydride. The regiospecifically constructed, chemospecifically acetylated, hydroanthracene carboxylate **11a** was obtained in 81% yield. Triflation of **11a** to **11b** proved to be challenging due to competitive formation of the enol triflate of the ketone. Ultimately, it was found that conversion of **11a** to the sodium phenolate (NaH, 1 equiv) followed by reaction with Tf_2O at 0 °C for 1 min and then quenching gave optimum results: a 4:1 mixture of **11a** and triflate **11b**. Seven repetitions of the sequence on reisolated **11a** gave a 51% overall yield of **11b**. Reductive replacement of the triflate in **11b** through catalytic hydrogenation gave **12a** in 75% yield.

The acetate group in **12a** proved to be extraordinarily resistant to hydrolysis under standard acidic or basic conditions; undoubtedly, this is due to steric hindrance caused by the peri substituents. Under more forcing conditions (Claisen's alkali,[7] 80 °C, 24 h) concomitant hydrolysis of the methyl ester and the acetate was accomplished. To facilitate purification, the acid **12b** was methylated (K_2CO_3, $DMSO_4$, acetone) to the ester **12c**. Triflation of the phenol in **12c** (Li*O*t*Bu*, Tf_2O, 0 °C; 77%) gave **12d**, which on reduction (Pd/C, H_2) produced **13** in 84% yield.

Attempted conversion of **13** to **2b** through initial aromatization of the terminal ring and then oxidation of the resultant phenol with introduction of a 4-hydroxyl group was unsuccessful. In an effort to minimally introduce the hydroxyl group α to the carboxyl, we decided to explore oxidation of the enolate anion of the ester.[4] It was recognized that this approach might also introduce the remaining benzylic hydroxyl, but this was less certain[8] since the benzylic position was only modestly activated. This plan required prior protection of the ketone, and the propensity of this carbonyl group to form enol derivatives, which was initially an aggravation, was now exploited. Treatment of **13** with TMSOTf in the presence of Et_3N cleanly gave the TMS enol ether which was not purified but treated directly with an excess of KHMDS and then the Davis reagent, 2-phenylsulfonyloxaziridine. We were surprised to discover that both of the required hydroxyl groups in **2b** had been successfully introduced (66%) in one step. Strikingly, the stereochemistry of the introduced vicinal hydroxyls was cleanly *trans*. The ^1H and ^{13}C NMR spectra were identical with those reported by Iwaki and co-workers[1] for the methyl derivative of **2b**. Although the exact order in which the hydroxyl groups in **2b** are introduced is uncertain, we would expect that the enolate anion of the ester is formed first and then oxidized by oxaziridine, leading to an α alkoxide product. The benzylic carbanion is then formed and likewise oxidized by the oxaziridine. The stereochemical outcome is likely a consequence of steric approach control of the oxidant by the initially formed alkoxide.

In future work we will explore single enantiomer preparation of **2b** and a route to rishirilide A (**1**) from one or more of the intermediates that have been prepared.

Acknowledgment. This work was generously supported by the National Cancer Institute and the National Institute of General Medical Sciences of the National Institutes of Health (CA 18141).

OL9906561

(7) Claisen, L. *Ann.* **1919**, *418*, 96.
(8) Coburn, C. E.; Anderson, D. K., Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1982**, 987.