Tetrahedron Letters,Vol.28,No.32,pp 3659-3662,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF (+)-MIKROLIN

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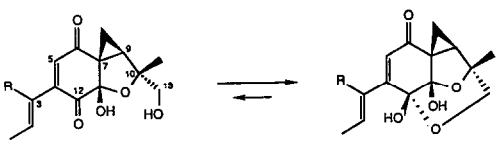
Abstract: The total synthesis of (+)-mikrolin (1a), a novel fungal metabolite derived from Gilmaniella humicola Barron, has been achieved. The key step entailed a stereoselective hydroxyl-directed cis-hydrogenation to set the requisite stereogenic center at C(9).

Culture filtrates of the fungus Gilmaniella humicola Barron have yielded a small family of architecturally novel compounds. Mikrolin (1a) and dechloromikrolin (1b) were the first to be isolated. Their structures including absolute configurations were assigned by Bollinger and Zardin-Tartaglia.[2] Both were identified as having the tetracyclic skeleton ii via single crystal X-ray analysis of 1a. However, during the course of biosynthetic studies, Tamm and Chexal[3] demonstrated that these compounds actually exist in solution as a mixture of tautomers, with the tetracyclic form ii predominating.



i ii

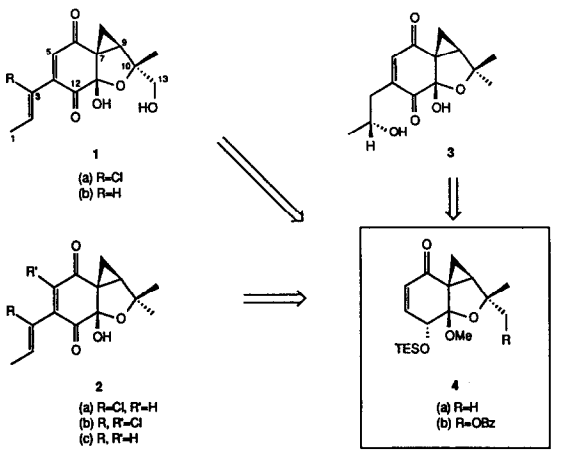
1
(a) R=Cl
(b) R=H

Other members of the family include the mycorrhizins (2a-b) and gilmicolin (3).[4] Collectively, these compounds possess varying degrees of antifungal and antibiotic activity.[3,4] In addition, they exhibit a number of interesting architectural features. Particularly attractive to us were the spirocyclopropane, the chlorinated diene-dione, and in the case of the mikrolins and gilmicolin, the bis-hemiketal unit.

In 1982 and 1984 respectively, we recorded the first total synthesis of the mycorrhizins (2a and 2c) and gilmicolin (3);[5] we now wish to disclose the culmination of the first synthesis of the most highly functionalized member, mikrolin (1a). The synthesis was achieved by exploiting our unified strategy for this class, wherein an enone of type 4 serves as the advanced intermediate.[6]

From the synthetic perspective, the mycorrhizins (2a and 2b) and gilmicolin (3) are non-stereogenic at C(10), and therefore could be prepared from enone 4a (R=H, Scheme 1). In the case of mikrolin (1a) however, the C(13)-hydroxyl introduces an additional stereogenic center. This structural feature requires the establishment of a cis relationship between the C(10)-hydroxymethyl and the C(9)-methine hydrogen. From a tactical viewpoint, we also recognized that a free hydroxymethyl

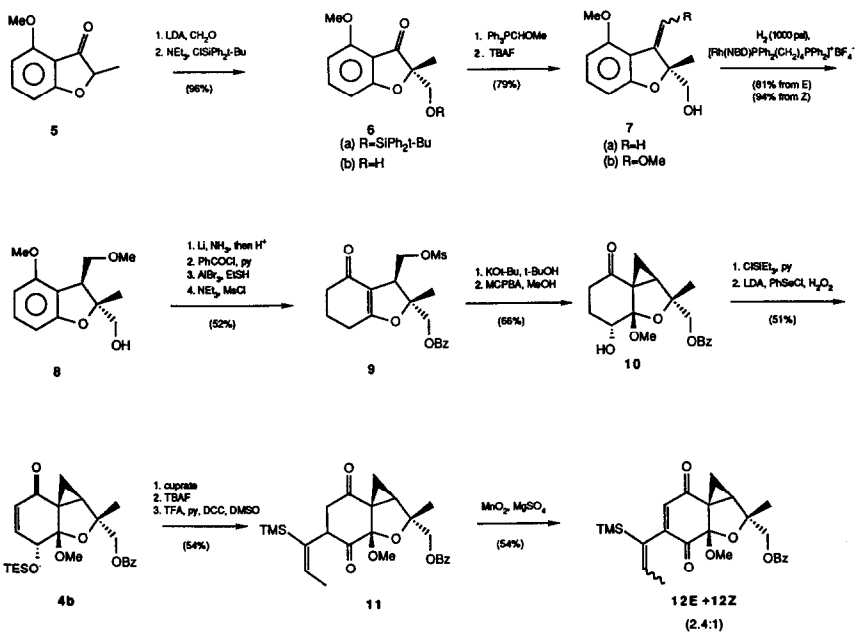
Scheme 1



at C(10) in advanced intermediates possessing the C(12)-carbonyl would lead to tautomeric mixtures (open and hemiketal forms), and thereby greatly increase the difficulty of spectral analysis as the synthesis advanced.

With this as background, the synthesis of 4b (R=OBz) began in analogy to that of 4a[5a] (Scheme 2), employing 2,6-dimethoxypropiophenone as the starting material to obtain 5.[7,8] Condensation with formaldehyde followed by protection (TBDPSCl, Et_3N) of the derived hydroxymethyl then afforded 6a. To prepare mikrolin (1a) in homochiral form, ketone 6a was resolved using Johnson's sulfoximine protocol.[9-11]

Scheme 2

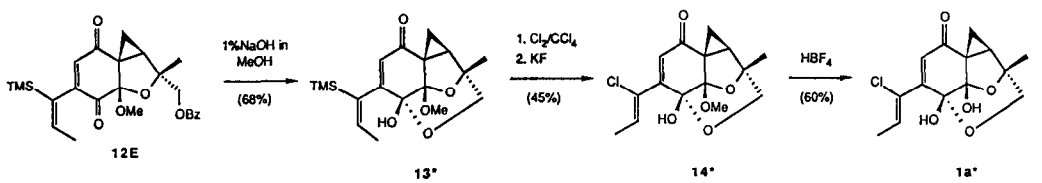


In the synthesis of the mycorrhizins and gilmicolin, we introduced the cyclopropyl unit via methylenation of the C(9)-carbonyl, followed by a hydroboration-oxidation, Birch reduction, and an extended enolate-trapping reaction sequence.[5] For mikrolin (1a), we envisioned that a hydroxyl-directed hydroboration of 7a would establish the stereochemistry at C(9) relative to C(10), as well as introduce appropriate functionality to elaborate the cyclopropyl ring. Unfortunately, all attempts to effect the requisite hydroxyl-directed hydroboration failed.

Undaunted, we conjectured that a hydroxyl-directed hydrogenation of enol ether 7b would accomplish the same overall goal. Towards this end, reaction of 6b with (methoxymethylene)triphenylphosphorane, followed by removal of the TBDPS group provided 7b in 79% overall yield. Subsequent hydrogenation at 1000 psi, employing Brown's rhodium catalyst[12] (i.e., $[Rh(NBD)PPh_2(CH_2)_4PPh_2]^+ BF_4^-$) afforded 8 as a single stereoisomer. Birch reduction, followed by protection of the C(13)-hydroxyl as its benzoate, demethylation ($AlBr_3$, EtSH)[13] and mesylation then led to 9, which in turn was converted to 10 via a similar extended enolate trapping and m-CPBA oxidation reaction sequence as exploited for 4a.[5] To complete the synthesis of 4b, the requisite C(5,6)-unsaturation was introduced, after hydroxyl protection (TESCl, pyr) via a Sharpless-Reich[14] selenenylation oxidative-elimination sequence.

With a viable route to 4b secure, addition of the side chain was achieved by reaction with the cuprate derived from (E)-(1-lithio-1-propenyl)trimethylsilane.[15] Selective O-desilylation and Moffatt oxidation[16] led to diketone 11, which was then oxidized with MnO_2.[17] The result was a 2.4:1 mixture of isomers (12E and 12Z, respectively). While at first we were somewhat disappointed by the partial loss of configurational control, we quickly recognized that this event would permit access to dechloromikrolin (1b).[6]

At this point there remained only chlorination, desilylchlorination and removal of the hydroxyl protecting groups in 12E to complete the synthesis. While seemingly straightforward, the propensity for elimination of HCl from the side chain demanded a very specific sequence of reactions. The first was deprotection of the C(13)-hydroxyl, exploiting 1% NaOH in methanol (0°, 15 min.) to afford 13 which, like the natural product, exists as a mixture of tautomers.[18] Chlorination, followed by desilylchlorination, then proceeded smoothly to yield O-methylmikrolin 14, again a tautomeric mixture. Finally, hydrolysis of the mixed-methyl ketal afforded (+)-mikrolin (1a), identical in all respects, including optical rotation, to that of an authentic sample of (+)-mikrolin kindly provided by Professor Christoph Tamm (University of Basel).[19]



12E 13* 14* 1a*

* indicates that the compound exists as a mixture of tautomers.

In summary, the first total synthesis of mikrolin (1a) has been achieved. This success further demonstrates the adaptability of our unified synthetic strategy for this class of fungal metabolites.

Acknowledgements: Support for this investigation was provided by the National Institutes of Health through grants GM-24680 and CA-22807.

REFERENCES

1. (a) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983, NIH Career Development Awardee, 1980-1985, and J. S. Guggenheim Fellow, 1985-1986. (b) NIH NRSA Postdoctoral Fellow, 1985-1986.

2. (a) Bollinger, P.; Zardin-Tartaglia, T. Helv. Chim. Acta 1976, 59, 1809; (b) Weber, H. P.; Petcher, T. J. ibid. 1976, 59, 1821.

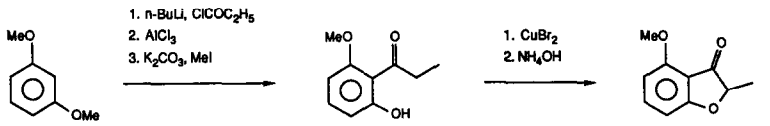
3. Chexal, K. K.; Tamm, C. Helv. Chim. Acta 1978, 61, 2002.

4. Chexal, K. K.; Tamm, C.; Clardy, J.; Kirotsu, K. Helv. Chim. Acta 1979, 62, 1129.

5. (a) Koft, E. R.; Smith, A. B., III. J. Am. Chem. Soc. 1982, 104, 2659. (b) Smith, A. B., III, Huryn, D. M. J. Org. Chem. 1985, 50, 1342.

6. In the accompaning Letter, we present synthetic studies which culminate in the re-assignment of the structure of dechloromikrolin; see: Smith, A. B. III; Dunlap, N. K.; Yokoyama, Y.; Tamm, C. Tetrahedron Letters (accompaning communication).

7. For benzofuranone 5 see: Levine, R.; Sommers, J. R. J. Org. Chem. 1974, 39, 3559.



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(42% for 5 steps)

8. (a) The structure assigned to each compound was in accord with its infrared and NMR (250 and 500 MHz) spectra, as well as elemental composition data [HRMS (parent ion identification) and/or combustion analysis (± 0.4%)]. (b) All yields recorded here are based upon isolated material that was > 97% pure.

9. Johnson, C. R.; Zeller, J. R. J. Am. Chem. Soc. 1982, 104, 4021.

10. Addition of (R)-N-methyl-S-phenylsulfoximine to ketone 6a afforded three adducts (34:50:10, 94% yield), which could be readily separated by flash chromatography. Thermolysis of the adducts eluting first and third afforded homochiral 6a in 42% overall yield. In the preliminary experiment using (S)-sulfoximine, we found that the desilylation of the adduct eluting second afforded material which crystallized nicely from acetone (mp 127-129 °C, decomp). On X-ray analysis, this proved to be a 1:1 complex of the deprotected sulfoximine adduct and the retro-addition product (i.e. 6b). Assignment of absolute configuration followed directly from the S configuration of the sulfoximine.

11. The enantiomeric excess was determined to be 97% by analysis of the (+)-MTPA ester of 8.

12. Brown, J. M.; Naik, R. G. J. Chem. Soc., Chem. Commun. 1982, 348.

13. Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. J. Org. Chem. 1980, 45, 4275.

14. a) Reich, H. J.; Reich, I. C.; Renga, J. M. J. Am. Chem. Soc. 1973, 95, 5813; b) Sharpless, B. K.; Lauer, R. F. J. Am. Chem. Soc. 1973, 95, 2697.

15. (a) Prepared from (Z)-(1-bromo-1-propenyl)trimethylsilane[14b] by halogen-metal exchange with tert-butyllithium. (b) Zweifel, G.; Lewis, W. J. Org. Chem. 1978, 43, 2739.

16. Pfitzner, K. E.; Moffatt, J. G. J. Am. Chem. Soc. 1965, 87, 5661.

17. Hyatt, J. A.; Krutak, J. J. J. Org. Chem. 1977, 42, 169.

18. Although deprotection at this stage necessitated carrying forward a mixture of tautomers, it was required due to the observed extreme base-lability of the chlorinated diene-dione system.

19. We thank Professor Christoph Tamm (University of Basel) for the generous samples of (+)-mikrolin.

(Received in USA 26 December 1986)