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TOTAL SYNTHESIS OF DECHLOROMIKROLIN: A STRUCTURAL REASSIGNMENT WITH BIOSYNTHETIC IMPLICATIONS

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Abstract: The total synthesis of dechloromikrolin (2Z), a minor fungal metabolite derived from Gilmaniella humicola Barron, has been achieved. The synthesis resulted in a reassignment of the stereochemistry of the C(2,3)-disubstituted olefinic bond from E to Z. The biosynthetic implications of this reassignment are discussed.

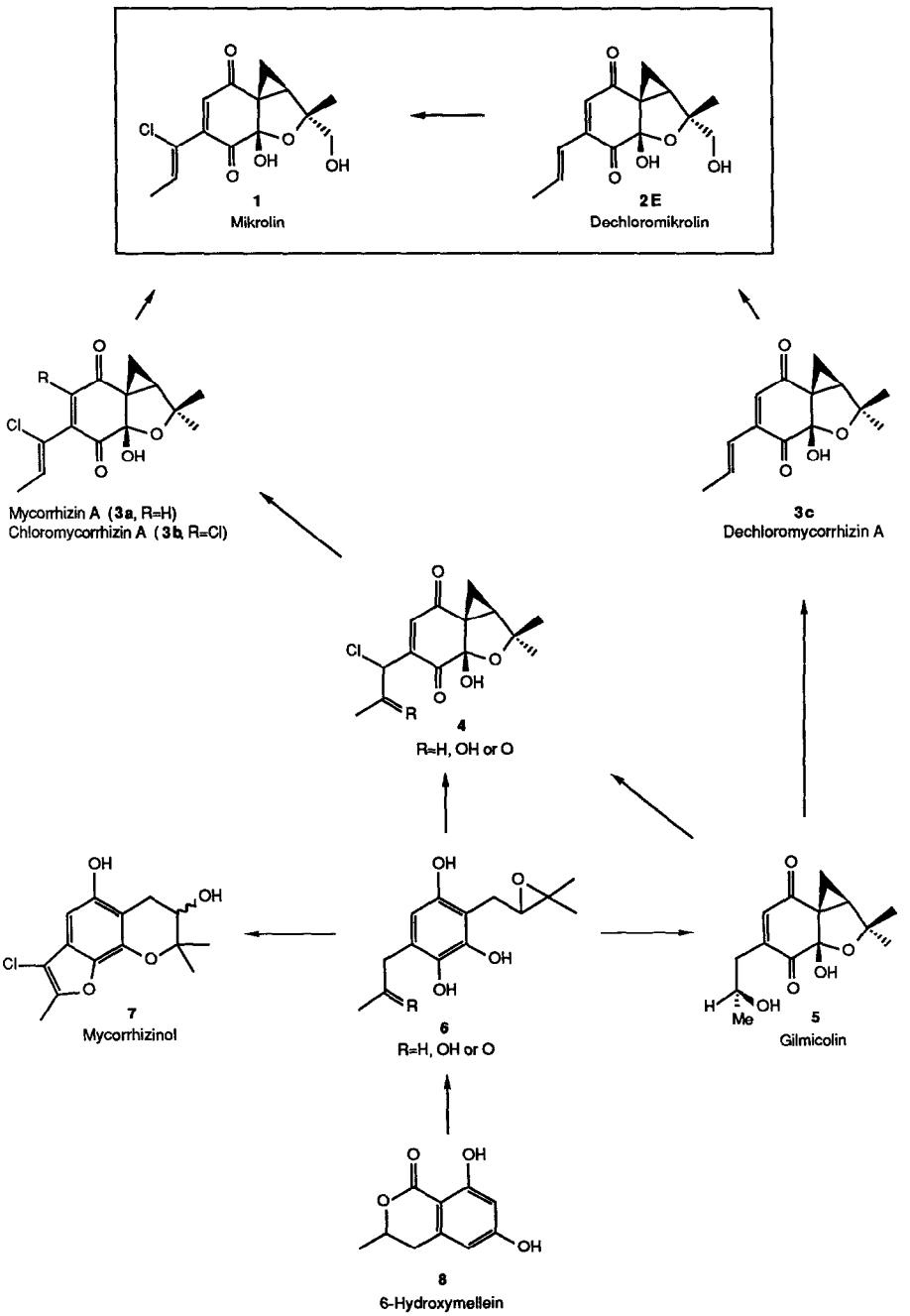
In 1976 Bollinger and Zardin-Tartaglia[2] reported the isolation and structural elucidation of mikrolin (1) and dechloromikrolin (2E), two members of an architecturally novel class of fungal metabolites, which now includes the mycorrhizins (3a-b)[3] and gilmicolin (5).[4] The structure of mikrolin (1), initially assigned on the basis of extensive NMR studies, was confirmed by X-ray analysis; the latter also provided the absolute stereochemistry.[5] The structure of dechloromikrolin (2E) however rested solely on the basis of spectral data and chemical correlation with mikrolin (1).[2]

From the biosynthetic prespective, Tamm et al. proposed that mikrolin (1) and dechloromikrolin (2E) are the ultimate products of a metabolic cascade, beginning with 6-hydroxymellein (8), which also produces the mycorrhizins (3a-b), gilmicolin (5) and mycorrhizinol (7) as intermediates (Scheme I).[4,6] Support for this hypothesis stems from feeding experiments and the co-occurence of these metabolites in culture filtrates of Gilmaniella humicola Barron that also produce the mikrolins.[6] While the exact timing of the chlorination event(s) is unknown, Tamm et al. suggested that dechloromikrolin (2E) and/or the hypothetical intermediate 6 may serve as the chlorination substrate(s).[4] Alternatively, chlorination may take place at the polyketide stage.[4]

In connection with our program to develop a unified synthetic strategy to this class of fungal metabolites, we disclosed in the preceding Letter the first total synthesis of (+)-mikrolin (1);[7,8] here we wish to record the synthesis of dechloromikrolin. We note in advance that this synthetic venture conclusively demonstrates that the structure of dechloromikrolin actually possesses the Z-disubstituted olefinic configuration, and not E as orginally assigned by Bollinger and Zardin-Tartaglia.[2,9]

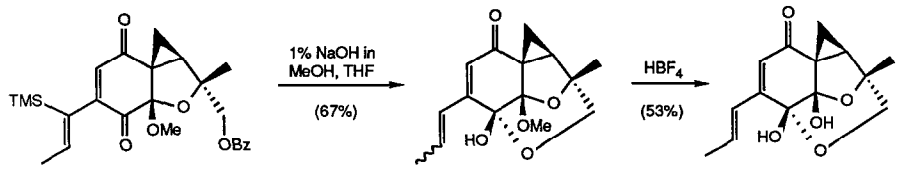
We began this effort with a synthesis of trans-dechloromikrolin (2E). The synthetic sequence is outlined in Scheme II. Treatment of 9, readily available from our mikrolin synthesis,[8] with 1% NaOH in methanol and THF (1:10) resulted not only in the anticipated removal of the benzoyl group but

SCHEME I: BIOSYNTHESIS OF THE MYCORRHIZIN FUNGAL METABOLITES[4]



also in removal of the TMS group to afford 10[10a] in 67% yield.[10b] Presumably the latter transformation proceeds via initial vinylogous Michael addition of hydroxyl ion, followed by a Peterson olefination "like" elimination of trimethylsilanol.[11] The resultant product, a mixture of olefinic configurational isomers as well as tautomeric forms,[12] was next subjected to HBF_4 [60% aq HBF_4-dioxane (1:1), 75°, 15 min] to hydrolyze the methyl acetal. In the event, isomerization of the Z-isomer also took place to afford only trans-dechloromikrolin (2E);[10] the yield was 53%.

SCHEME II



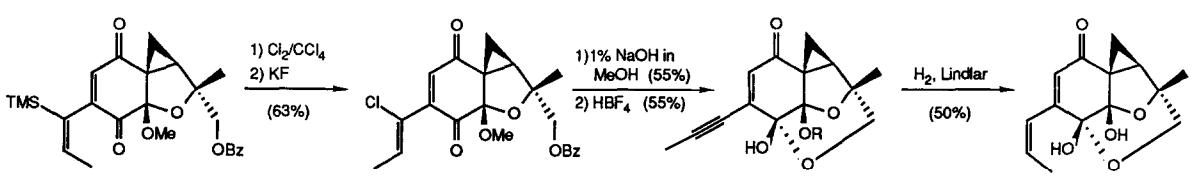
9 10* 2E*

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

Careful NMR (250 and 500 MHz) comparison quickly revealed that 2E, while quite similar, was not identical to authentic dechloromikrolin.[13] Significant differences occurred in the olefinic region. For example, the coupling constant for the C(2,3)-vinyl hydrogens of synthetic 2E was 15.8 Hz, while that of natural dechloromikrolin was 11.8 Hz.[14a] Furthermore, we observed a marked steric compression effect (shielding) in the ^{13}C-NMR chemical shift of the C(1)-allylic methyl carbons for authentic dechloromikrolin versus synthetic 2E (15.4 vs 19.4 ppm, respectively).[14b]

Given the strong suggestion provided by the above NMR data that dechloromikrolin actually possesses the cis-configuration at C(2,3), we turned our efforts toward the synthesis of the cis-isomer (2Z). The synthetic sequence, depicted in Scheme III, began with 11, also an intermediate in our mikrolin work.[8] Given the propensity with which the Z-C(2,3)-olefinic bond was known to undergo isomerization (vide supra), we anticipated that it would be prudent to introduce the cis geometry late in the synthetic sequence. This could best be accomplished with high configurational control by semi-hydrogenation of the corresponding alkyne. Towards this end, chlorination-desilylchlorination of 11, as used to advantage previously in our mycorrhizin A and mikrolin syntheses, led to vinyl chloride 12.[10] Removal of the benzoate group [1% aq. NaOH in MeOH (1:7), 0°, 5 min] proceeded with concomitant loss of HCl to provide hemiacetal 13.[10] The mixed-methyl ketal unit of 13 was then hydrolyzed [aq. HBF_4, dioxane (1:1), 75°, 15 min] to afford 14, previously prepared in connection with the chemical correlation of mikrolin with dechloromikrolin.[2] Finally, hydrogenation [Lindlar catalyst (0.3 mg/ 0.05 mmol substrate), 1 atm H_2, 10 min] provided isomerically pure cis-dechloromikrolin, which was identical in all respects [250 and 500 MHz NMR, MS and TLC behavior (2 solvent systems)] with natural dechloromikrolin.

SCHEME III



11 12 13* R = Me 14* R = H 2Z*

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

In summary, the first total synthesis of dechloromikrolin (2Z) has been achieved. The synthesis served not only to permit reassignment of the C(2,3)-olefinic configuration, but importantly provides circumstantial evidence concerning the point of chlorination in the biosynthetic sequence. In particular, isolation of dechloromikrolin, now known to possess the cis configuration at C(2,3), suggests that chlorination takes place at this point and not through the intermediacy of 6. Mechanistically, this would appear quite reasonable in that addition of the elements of XCl across the Z-olefin, followed by elimination of the elements of HX via the usual antiperiplanar rotamer would lead directly to the C(3)-chloro derivative. It would also seem reasonable to suggest that dechloromycorrhizin,[4,7] which has not as yet been isolated, will possess the Z-configuration in analogy with dechloromikrolin. and may well prove to be a pivitol intermediate in the biosynthetic cascade. Studies directed at confirming the intermediacy of dechloromycorrhizin A as well as determination of the point of chlorination will be reported in due course.

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9. The coupling constant, 14 Hz, reported by Bollinger and Zaardin-Tartaglia,[2] is consistent with the assigned trans configuration; see for example: Jackman, L. M.; Sternhell, S. "Nuclear Magnetic Resonance Spectrometry in Organic Chemistry," Pergamon, N.Y., N.Y., 1969, p. 301. However, given the complexity of the olefinic region at 90 MHz, the splitting pattern must have been misinterperted.

10. (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%)]. All yields recorded here are based upon isolated material that was >97% pure.

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12. The mikrolins, gilmikolin and related systems exist in solution as equilibrating tautomers, with the tetracyclic forms predominating.

13. Authentic samples of dechloromikrolin were available from the Tamm laboratory.

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