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A novel method for the 1,2-carbonyl transposition of pleuromutilins

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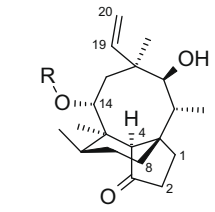
ABSTRACT

A new and efficient 1,2-carbonyl transposition procedure for the formation of 2-keto pleuromutilin compounds is described. The synthetic sequence is performed in four steps and 26% overall yield.

Pleuromutilin is a naturally occurring, structurally complex tricyclic diterpene antibiotic first isolated in 1951 from basidiomycetes microorganisms.[1] Optimization of the antibacterial activity, concentrating predominantly on modifying the ester side-chain at C-14, led to the approval of the veterinary drug tiamulin (Fig. 1).[2] There are no pleuromutilin compounds approved for oral human use[3] in part because of their rapid first-pass metabolism to a pool of hydroxylated metabolites (predominantly C-2 and C-8 hydroxylation) which are mostly devoid of antibacterial activity.[4] Throughout the 1970s and 1980s, chemists at Sandoz disclosed numerous accounts rich in pleuromutilin chemistry documenting their effort to improve the metabolic stability of the mutilin tricyclic core.[5] More recent reports have emerged revealing similar strategies.[6,7]

Similar to previous approaches to minimize or block metabolic oxidation at the 2-position, we aimed to prepare an isomeric mutilin with the ketone at C-2 of the tricyclic core as a valuable intermediate for further manipulation. It was reported by Berner that 2-keto-19,20-dihydromutilin **3** can be synthesized from **1** via isomerization of the α-hydroxy ketone **2** followed by reduction of the corresponding acetate with lithium metal (Scheme 1).[8] We obtained low yields of **3** after isolation from a complex mixture of products, which included α-hydroxyketone isomers and mixtures of acetylated products derived from **1**, **2**, and **3**.

We began to investigate alternative routes to prepare 2-keto mutilin compounds, and quickly realized that the many 1,2-carbonyl transpositions methods reported failed when attempted on the tricyclic core of mutilin.[9] Ultimately, we discovered a straightforward and practical method for the 1,2-carbonyl transposition of 10,14-diacetyl-19,20-dihydromutilin **4** (Scheme 2). Following reduction of **4**, we chose to prepare the mesylate of **5** as a suitable precursor of a delta $\Delta^{2,3}$-olefin. However, treatment of **5** with



Pleuromutilin R = $HOCH_2C(O)$-
Mutilin R = H
Tiamulin R = $Et_2NCH_2CH_2SCH_2C(O)$-

Figure 1. Structures of pleuromutilin, mutilin, and tiamulin.

methanesulfonyl chloride led directly and regiospecifically to $\Delta^{3,4}$-unsaturated **6**. The absence of the mesylate product in the reaction mixture suggests that the elimination proceeds smoothly and is highly favored for the $\Delta^{3,4}$-isomer. The precise mechanism for product formation is not clear but can be rationalized as either (1) direct elimination or (2) isomerization of the $\Delta^{2,3}$-isomer.[10]

Application of a dirhodium(II) caprolactamate catalytic allylic oxidation[11] to **6** afforded the enone **8** in 40% yield without overoxidation,[12] along with the allylic alcohol **7** as a single diastereomer.[13] Use of a dissolving metal reduction[14] allowed for the regeneration of the natural mutilin stereochemistry at C-4 to give **9** in 20% yield. The side products were isolated individually in a combined 44% yield and identified as the monoacetylated products.

In summary, we have developed a new approach for the 1,2-carbonyl transposition of pleuromutilin derivatives which requires only four practical steps.[15] Facile and regiospecific formation of a $\Delta^{3,4}$-mutilin set the stage for a dirhodium catalyzed allylic oxidation followed by a selective enone reduction to selectively regenerate the C-4 stereochemistry. This new, short, and convenient method provides access to novel pleuromutilin analogs.

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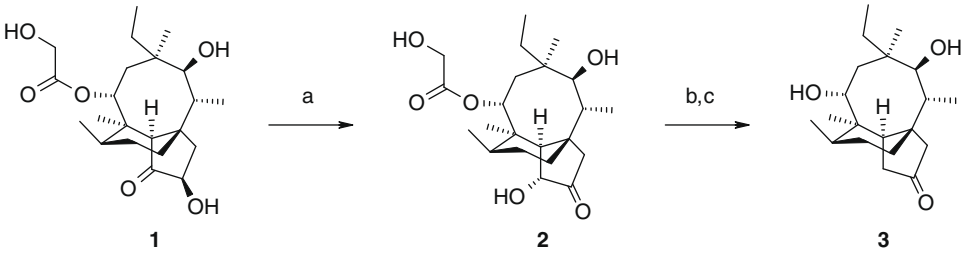
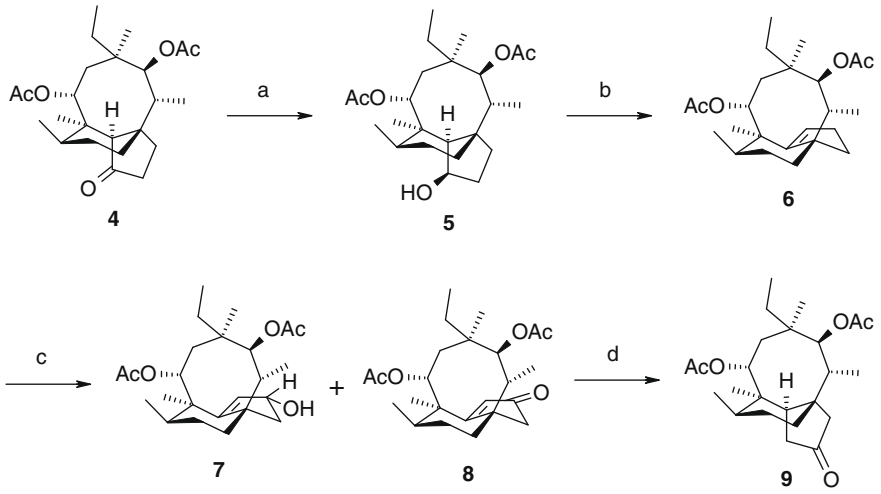


Scheme 1. Berner synthesis of 2-ketomutilin **3**. Reagents and conditions: (a) KOH, $(Bu)_4NHSO_4$, CH_2Cl_2, H_2O (76%); (b) acetic anhydride, pyridine (74%); and (c) Li (s), NH_3 (liq), Et_2O.



Scheme 2. Synthesis of 2-ketomutilin **9**. Reagent and conditions: (a) $NaBH_4$, EtOH/THF (98%); (b) CH_3SO_2Cl, triethylamine, CH_2Cl_2 (87%); (c) $Rh_2(cap)_4$, K_2CO_3, CH_2Cl_2 (40% **7**/47% **8**); and (d) Li, NH_3, Et_2O/THF (20% + 44% monoacetylated products).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.014.

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