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A novel ring expansion of the pleuromutilin skeleton†

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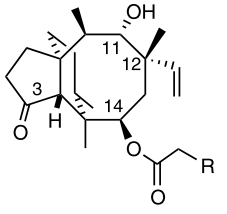
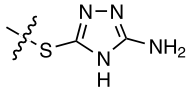
Abstract—An unprecedented cyclooctane to cyclononene ring expansion in the pleuromutilin skeleton, affording two main products, has been discovered. The process entails an intramolecular cyclization of an olefin onto an oxonium ion, followed by 1,2 migration of a carbon of the cyclooctane ring.

1. Introduction



1 Pleuromutilin R = OH

2 Azamulin R = 

The diterpene antibiotic pleuromutilin (**1**) was first isolated by Kavanagh in 1951.[1] The compound is active against a variety of drug-resistant Gram-positive bacteria and mycoplasmas, and is an inhibitor of bacterial protein synthesis.[1,2] Anchel[3] initiated the chemical and structural studies of pleuromutilin, an area of investigation more fully developed in the work of Arigoni and Birch.[4,5] Arigoni was the first to determine the complete structure of pleuromutilin,[4] a unique fused 5-6-8 tricyclic skeleton with eight asymmetric centers, three of which are quaternary.

Although pleuromutilin has succumbed to total synthesis efforts,[6,7] the major method for analog discovery has been semi-synthesis from the readily available and inexpensive natural product itself. A group at Sandoz has published extensively on further chemical modifications of the natural product produced in efforts to develop an agent for human use that has sufficient efficacy and is less prone to metabolic degradation than pleuromutilin.[8] Their efforts resulted in the development of azamulin,[9] a C-14 derivative that was found to be quite safe in healthy volunteers during Phase I trials.[10] Unfortunately, azamulin was rapidly inactivated by extensive cytochrome p450 mediated metabolism,[11] and the program at Sandoz for human therapy was subsequently abandoned. Recently, a group at GlaxoSmithKline has begun to describe their efforts on the development of a pleuromutilin derivative for human use.[12]

The chemistry of the pleuromutilin ring system, as described by Arigoni, Birch and the Sandoz group, is replete with transannular chemistry of the medium ring, intramolecular reactivity, fragmentations, and unexpected rearrangements. As part of a group at Bristol-Myers Squibb exploring potential therapeutic opportunities in the pleuromutilin class, we encountered an unprecedented rearrangement of the cyclooctane ring of a pleuromutilin intermediate. Here we report this interesting ring expansion, and propose a mechanistic rationale for the process.

2. Chemistry

For some of our efforts, we required large quantities of the C-11 methoxymethyl, C-14 *tert*-butyl diphenylsilyl,

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† This paper is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

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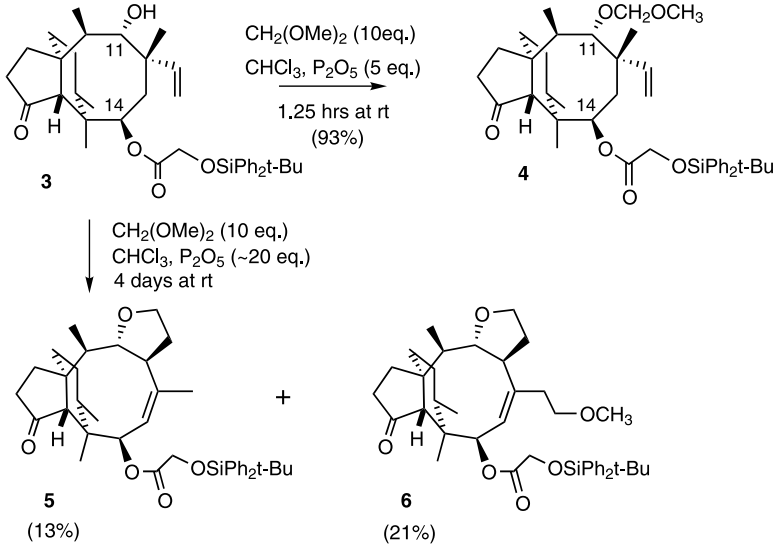
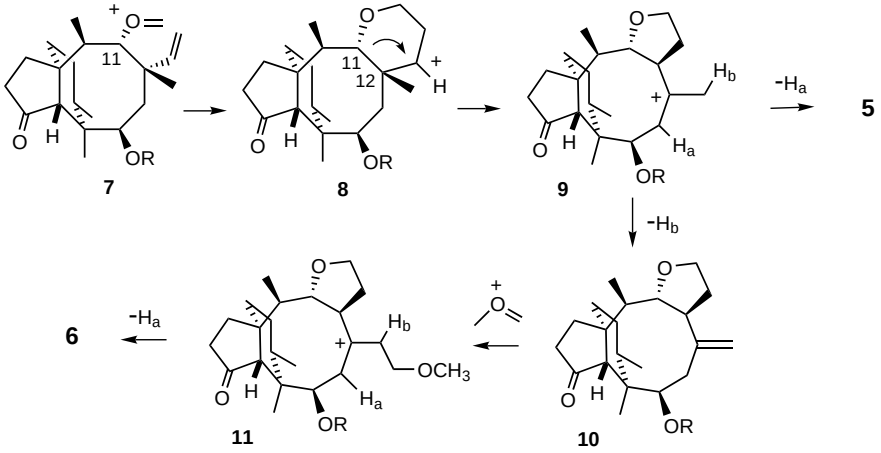
orthogonally protected intermediate **4** (Scheme 1). We produced C-14 silyloxy protected derivative **3** by treating pleuromutilin with *t*-butyl diphenylchlorosilane and imidazole in DMF using standard conditions (97% yield). Conversion of **3** to C-11 methoxymethyl protected **4** was readily achieved (~93% yield) on large scale batches (~65 g) using dimethoxymethane and P_4O_{10} in chloroform for short periods of time at room temperature.[13]

During one of our runs, we observed that new products began to form if the reaction leading to **4** was allowed to proceed for longer periods of time. In an effort to produce more of these by-products for analytical characterization and structural determination, we allowed the reaction to stir for 4 days at room temperature. We also added additional equivalents of P_4O_{10} to try and drive the reaction to completion. After 4 days, TLC analysis indicated the presence of two new main components along with minor amounts of other impurities. Two chromatographic resolutions (taking center cuts) were required to isolate the major new products in pure form. Careful inspection of ^1H–^1H COSY, HMBC, HMQC and nOe NMR spectra has allowed us to assign to these two new components the structures **5** and **6**.[14] The isolated yields of **5** and **6** were 13% and 21%, respectively. More of each component is present in mixed chromatographic fractions, thus the actual yields of **5** and **6** are much higher. Cyclononene **5** is part of a high R_f pair (~0.75 in 35% EtOAc/hexane) with what appears to be a trace amount of remaining **4**. A low R_f pair forms later (~0.25 in 35% EtOAc/hexane) and is constituted of cyclononene **6**, and an uncharacterized minor product.

A possible mechanism for the production of **5** and **6** from **4** is illustrated in Scheme 2. The C-11 methoxymethyl protecting group of **4** fragments under acid catalysis to afford the oxonium ion **7**. This oxonium ion is then intercepted by the vinyl group at C-12,



Scheme 1.



Scheme 2.

in an intramolecular cyclization process.[15] Formation of the cationic intermediate **8** is followed by the 1,2 migration of C-11 from C-12 to the carbonium ion, generating the more stable tertiary cation **9**. The cyclization occurs through a transition state where the nascent pyran ring has a chair-like structure, yielding stereoselectively the *trans*-fused 9-5 ring system. In the alternative possibility where **8** is not a discrete intermediate, migration of C-11 to the proximal carbon atom of the olefin at C-12 might occur in concert with trapping of the oxonium ion. In this concerted scenario, the face selectivity of the migration step is dictated by the chair-like structure of the transition state for the cyclization.

The thermodynamic impetus for the migration is certainly the formation of the more stable tertiary cation **9**. Once formed, **9** can suffer alternate fates. The first is the loss of the proton designated H_a to produce cyclononene **5**. Another is the loss of the proton designated H_b to generate the *exo*-methylene intermediate **10**. Attack of a methoxymethylene oxonium electrophile (formed by acid-catalyzed cleavage of dimethoxymethane) on the olefin of **10** regenerates a tertiary cation in the form of **11**, that can lose proton H_a to yield cyclononene **6**.[16]

We decided to explore a few Lewis acidic conditions to attempt to improve upon the yield of **5** and/or **6** from the C-11 methoxymethyl derivative **4**. Five equivalents of $ZnBr_2$ in methylene chloride at room temperature for 3 hours completely removed the MOM group of **4** to yield alcohol **3**; no rearranged products were detected. Similar results were obtained using 5 equiv. of $ZnCl_2$ (0°C to rt, 3 h) or 8 equiv. of $SnCl_4$ (−20°C, 45 min). No reaction occurred with titanium(IV) isopropoxide in methylene chloride (2 equiv., rt, 45 min). It should be noted that these reactions were conducted in the absence of dimethoxymethane. It is possible that the presence of extra dimethoxymethane with the P_4O_{10} in the reaction mixture is crucial to the rearrangement process. When **4** is exposed to 10 equiv. P_4O_{10} in $CHCl_3$ for a period of days, very little reaction is observed. A trace amount of alcohol **3** is formed, along with a small amount of other components. When **4** is exposed to 10 equiv. P_4O_{10} and 10 equiv. dimethoxymethane in $CHCl_3$, the rearrangement proceeds normally. Thus, it appears that conditions that favor *repeated* acquisition of an intermediate such as **7** are necessary to drive the reaction to completion.

The scale-up of this reaction has afforded gram quantities of **5** and **6** for use as intermediates in the production of novel pleuromutilin derivatives.[17] We believe that the process described here will be of interest to those engaged in the synthesis of pleuromutilins, and others interested in medium ring syntheses.

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14. Unoptimized procedure: Alcohol **3** (1.56 g) is dissolved in 12 mL $CHCl_3$. Dimethoxymethane (2.25 mL) is added, followed by 1.8 g P_4O_{10}, and the mix is stirred 20 h at room temperature. Another 1.8 g P_4O_{10} is added, and stirring continued another 20 h. More P_4O_{10} (1 g) is added, and after 48 h the mix is partitioned (carefully) with ether and sat. $NaHCO_3$. The aqueous is extracted with ether, and the combined organic phase is washed with water, then brine. The ether layer is dried ($MgSO_4$) and evaporated to afford an oil that is chromatographed on silica (2×) using EtOAc/hexanes to afford **5** (0.206 g) and **6** (0.359 g) as clear oils. Data for **5**: (300 MHz, $CDCl_3$, partial) δ 7.73–7.68 (m, 4H), 7.46–7.37 (m, 6H), 5.99 (d, 1H, $J=6$ Hz), 5.24 (d, 1H, $J=6$ Hz), 4.23 (d, 1H, $J=10$ Hz), 4.13 (d, 1H, $J=10$ Hz), 3.82 (dd, 2H, $J_1=J_2=4$ Hz), 3.39 (dd, 1H, $J_1=J_2=4$ Hz), 3.36–3.29 (m, 1H), 2.77 (dq (quintet), 1H, $J_1=J_2=4$ Hz), 2.24–2.15 (m, 2H), 2.10–2.00 (m, 2H), 1.99 (br s, 1H), 1.95–1.87 (m, 1H), 1.81 (s, 3H), 1.65–1.50 (m, 3H), 1.47 (s, 3H), 1.34–1.27 (m, 1H), 1.24–1.15 (m, 1H), 1.11 (s, 9H), 1.04 (d, 3H, $J=4$ Hz), 0.70 (d, 3H, $J=4$ Hz). Data for **6**: (300 MHz, $CDCl_3$) δ 7.60 (d, 4H, $J=4$ Hz), 7.37–7.27 (m, 6H), 5.90 (d, 1H, $J=6$ Hz), 5.16 (d, 1H, $J=6$ Hz), 4.14 (d, 1H, $J=10$ Hz), 4.03 (d, 1H, $J=10$ Hz), 3.86–3.78 (m, 1H), 3.70–3.63 (m, 1H), 3.40–3.32 (m, 3H), 3.30–3.21 (m, 1H), 3.20 (s, 3H), 2.62 (dq (quintet), 1H, $J_1=J_2=4$ Hz), 2.35–2.25 (m, 2H), 2.14–2.06 (m, 2H), 2.00 (br s, 1H), 1.98–1.89 (m, 2H), 1.86–1.80 (m, 2H), 1.61–1.33 (m, 3H), 1.38 (s, 3H), 1.27–1.18 (m, 1H), 1.14–1.05 (m, 1H), 1.02 (s, 9H), 0.93 (d, 3H, $J=4$ Hz), 0.62 (d, 3H, $J=4$ Hz).
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16. While other mechanisms may possibly explain the formation of **5** and **6** from **4**, to us the events of Scheme 2 appear to be the most likely explanation. It is possible that continued reaction may eventually lead to more of **6** at the expense of **5**; however, we did not further expose **5** to the reaction conditions to test this surmise.
17. We synthesized a number of C-14 derivatives in this cyclononene class of compounds; however, almost all of these compounds were devoid of anti-bacterial activity. This is not too surprising since pleuromutilin structure–activity relationships indicate a free hydroxyl at C-11 is critical for antibacterial potency. We attempted to cleave the tetrahydrofuran ether ring to form a hydroxyl substituted nonene, but were not successful after application of a few reaction conditions.