Tetrahedron Letters,Vol.26,No.13,pp 1607-1610,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

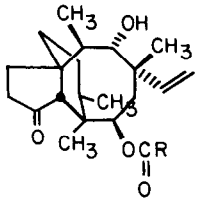
A RELAY APPROACH TO (+)-PLEUROMUTILIN. II. PREPARATION OF AN ADVANCED OPTICALLY PURE INTERMEDIATE[1]

Leo A. Paquette* and Philip C. Bulman-Page[2]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Summary: A four-step degradation of (+)-pleuromutilin (**1a**) to levorotatory lactone **5** is detailed. The conversion of **5** into (-)-bicyclic diketone **9**, an intermediate containing all 20 carbon atoms of the target molecule, is also described.

The efficacy of pleuromutilin (**1a**) against the growth of mycoplasms has held considerable interest over the years because mycoplasms have, at an increasing rate, been diagnosed as causative agents of several infectious diseases found in both man and animals. With the aim of improving upon the potency of **1a**, a large number of semisynthetic pleuromutilin derivatives have been prepared.[3] One of these, known as tiamulin (**1b**),[4] possesses activity significantly in excess of the parent compound[5] and is currently being marketed



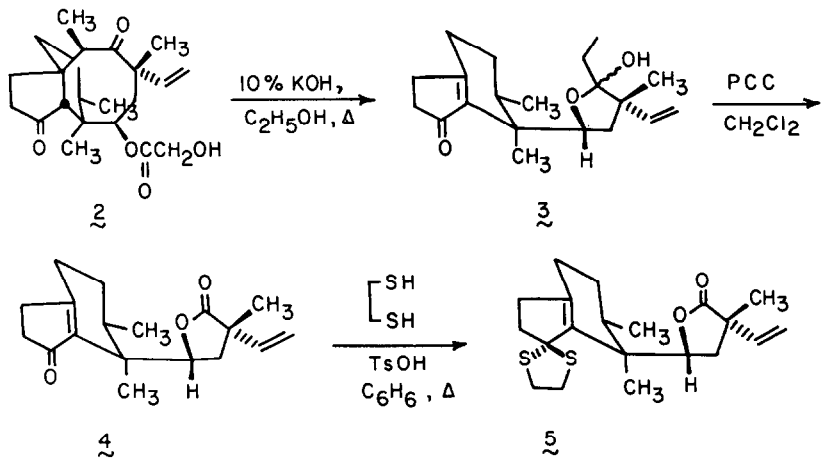
1a , R = CH_2OH
b , R = $CH_2SCH_2CH_2N(C_2H_5)_2$

for the treatment of infections in animals. As a result, these substances are available in quantity[6] and offer an attractive supply source for development of a relay synthesis.

A de novo preparation of the levorotatory tricyclic lactone **5** was previously described.[1] The linkup strategy was to involve rupture of the cyclooctane ring within **1** in a way suitable for expedient arrival at this relay intermediate. In actuality, only four laboratory manipulations are required to achieve this end result (Scheme I).

Thus, oxidation of **1a** with pyridinium chlorochromate (PCC) leads efficiently (94%) to

SCHEME I

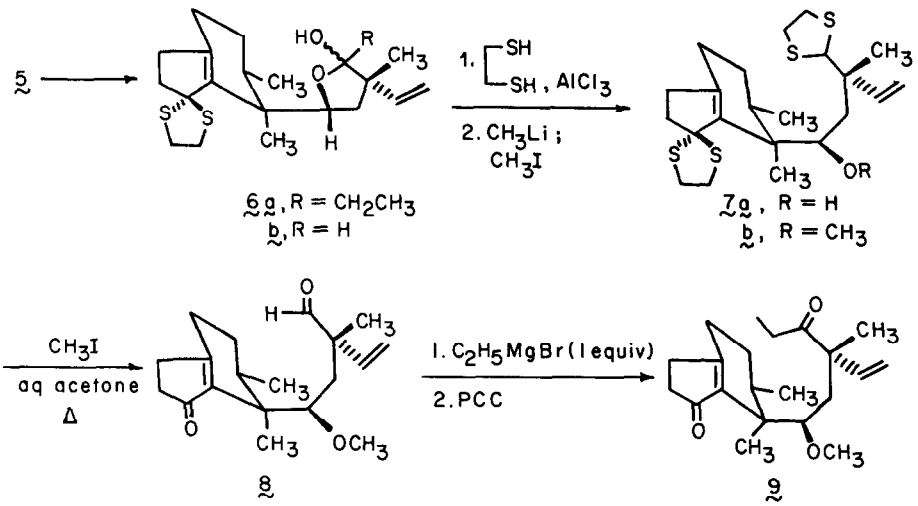


pleuromutilone (2).[7] When **2** is heated at the reflux temperature with 10% KOH in ethanol, concurrent saponification and retrograde Michael addition occur. Intramolecular cyclization of the hydroxy diketone so generated delivers **3**.[8,9] On subsequent PCC oxidation, smooth cleavage of the ethyl group occurs. This process, which has been encountered with other tertiary lactols,[8] probably proceeds by C → O migration of the alkyl group in the chromate ester (with ejection of $HCrO_3^-$) followed by covalent capture of water (or the equivalent) at the rearranged carbocation center. Whatever the actual mechanistic situation, the end result is formation of keto lactone **4** (56% from **2**, $[\alpha]_D^{24}$ -16.9° ($CHCl_3$)). Since dithioketalization of **4** delivers **5**, $[\alpha]_D^{20}$ -6.86° ($CHCl_3$), in 78% yield, it becomes feasible to prepare appreciable amounts of this tricyclic lactone in a short period of time.

The oxidation of **3** is seen to excise two carbon atoms whose reinsertion must be accomplished on the return pathway to **1a**. Although **5** can be transformed into **6a** by reaction with ethyllithium at -20°C, we have been singularly unsuccessful in our attempts to capture the hydroxy ketone tautomer of this hemiketal. Conditions recognized to be eminently suitable for the functionalization of secondary γ-lactols[10] proved completely ineffective in this instance. This may be a reflection of the heightened steric congestion in the oxygenated region of the molecule. For this reason, the necessary homologation was displaced to a later stage of the synthetic construction.

Of the various alternative approaches that were considered, one seemed uniquely

SCHEME II



qualified. In fact, diisobutylaluminum hydride reduction of **5** smoothly gave **6b**. Quite unlike the inertness of **6a**, **6b** could readily be trapped in its carbonyl tautomeric form (58% for the two steps, Scheme II). With arrival at **7a**, it becomes possible to exploit the free nature of the hydroxyl group and to achieve its selective methylation in good yield (90%). The unmasking of both carbonyl groups was subsequently realized by heating **7b** with excess methyl iodide in aqueous acetone.[11] All attempted hydrolyses with heavy metal thiophiles[12] resulted in destruction of the starting material.

Despite the neopentyl nature of the aldehyde carbonyl group in **8**, it remains possible to achieve chemoselective addition to this center because of the almost equally congested topography in the region surrounding the cyclopentenone moiety. The reactivity difference was revealed upon addition of 1 equiv of ethylmagnesium bromide to **8** in ether solution at -100°C. These conditions served to give largely the desired secondary alcohol (47% after chromatography), whose PCC oxidation provided **9** $[\alpha]_D^{23}$ -65.5° ($CHCl_3$), in quantitative yield.

Since none of the stereocenters in **9** has been disturbed during the 10-step transit from **1a**, its level of optical purity and that of its precursors should be very high. This conclusion has been independently verified.[13] Completion of the synthesis of (+)-pleuromutilin now requires installation of the final cyclooctane C-C bond, adjustment of the oxidation of one carbonyl group, and deblocking of the methyl ether. The latent stereochemistry

in **9** is expected to guide enantiospecific installation of the last four chiral centers.

Acknowledgements: This research was supported by grants from the National Institutes of Health (GM 30827) and the Eli Lilly Company. The degree of cooperation of the three persons named in footnote 6 is particularly appreciated.

References and Notes

1. Part I: Paquette, L. A.; Wiedeman, P. E. preceding paper.

2. NATO Postdoctoral Fellow of the Science and Engineering Research Council, 1981-1983.

3. (a) Brandl, E.; Knauseder, F.; Schmid, E.; Thym, H. Austrian Patent 261,804 (May 10, 1968); Chem. Abstr. **1968**, 69, 76054r. (b) Riedl, K. J. Antibiot. **1976**, 29, 132.

4. Hogenauer, G. in "Mechanism of Action of Antibacterial Agents," Hahn, R. E., Ed. Springer-Verlag, New York, 1979, pp 344-360.

5. (a) Egger, H.; Reinshagen, H. J. Antibiot. **1976**, 29, 915, 923. (b) Drews, J.; Georgopoulos, A.; Laber, G.; Schultze, E.; Unger, J. Antimicrob. Agents Chemother. **1975**, 7, 507. (c) Laber, G.; Schultze, E. Ibid. **1975**, 7, 517.

6. Our efforts in this area have been made possible by the generosity of the following individuals in supplying us with quantities of **1a** and/or **1b**: Dr. Russ Buchman (SDS Biotech), Dr. R. Nagarajan (Eli Lilly Company), and Dr. Heinz Berner (Sandoz Forschungsinstitut).

7. Naegeli, P. Ph.D. Thesis, ETH, Zurich, 1961.

8. Dihydropleuromutilin has previously been subjected to comparable reaction conditions: Buzzolini, M. Ph.D. Thesis, ETH, Zurich, 1966.

9. All new compounds described herein gave correct elemental analysis and/or accurate mass spectral data. All ^{1}H NMR, ^{13}C NMR, and IR spectra are also in accord with the assigned structures.

10. Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. Tetrahedron Lett. **1983**, 3555.

11. (a) Takano, S.; Hatakeyama, S.; Ogasawara, K. J. Am. Chem. Soc. **1976**, 98, 3022. (b) Fetizon, M.; Jurion, M. J. Chem. Soc., Chem. Commun. **1972**, 382. (c) Takano, S.; Hatakeyama, S.; Ogasawara, K. Ibid. **1977**, 68.

12. For example: (a) Ho, T.-L.; Wong, C. M. Can. J. Chem. **1972**, 50, 3740. (b) Reece, C. A.; Rodin, J. O.; Brownlee, L. G.; Duncan, W. G.; Silverstein, R. M. Tetrahedron **1968**, 24, 4249. (c) Ho, T.-L.; Ho, H. C.; Wong, C. M. J. Chem. Soc., Chem. Commun. **1972**, 791. (d) Smith, R. A. J.; Hannah, D. J. Tetrahedron Lett. **1979**, 301. (e) Fujita, E.; Nagao, Y.; Kaneko, K. Chem. Pharm. Bull. Japan **1978**, 26, 3743.

13. Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. ensuing paper.

(Received in USA 19 November 1984)