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Seven-Membered Ring Synthesis Based On Arene Olefin Cycloadditions: The Total Synthesis of (±)-Rudmollin[1,2]

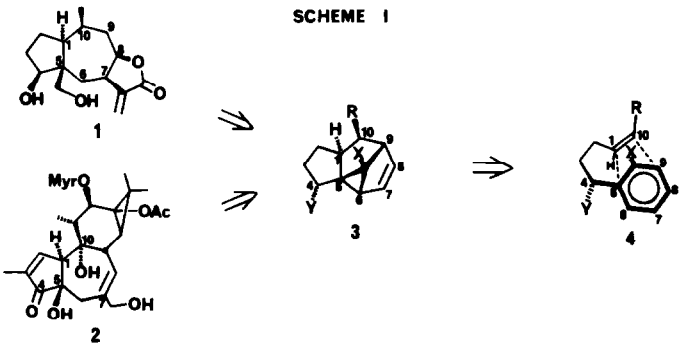
Paul A. Wender* and Karl Fisher
Department of Chemistry, Stanford University, Stanford, CA 94305 USA

Abstract: *The total synthesis of the antileukemic agent rudmollin* (1) *is described, based on a new approach to complex seven-membered ring synthesis involving the arene olefin meta photocycloaddition.*

Since its first application to natural product synthesis,[1a,3] the arene olefin meta-cycloaddition has become a general and efficient strategy level reaction for the synthesis of complex polycyclopentanoids. As documented, thus far, in syntheses of cedrene,[1a] pipitizol,[1b] isocomene,[1c] hirsutene,[1d] coriolin,[1e] modhephene,[1f] isoiridomyrmecin,[1g] silphinene,[1h] and the three silphiperfolenes,[1i] this versatile reaction can be used for the preparation of stereochemically complex spiro, bridged and fused ring systems. As a continuation of our studies on this process, we report herein its extension to seven-membered ring synthesis in the first total synthesis of (±)-rudmollin (1), an antileukemic pseudoguaianolide reported by Herz and coworkers in 1981.[4] This study establishes a new strategy for pseudoguaianolide synthesis[5] and the basis for an approach to the tumor promoting diterpenes represented by phorbol myristate acetate (2).[6]

The pseudoguaianolides represent a large class of sesquiterpenes which for synthesis design considerations can be divided into two major sub-groups, the ambrosanolides represented by rudmollin (1) and the helenanolides. Both classes have in common a trans-fused perhydroazulene nucleus but differ due to their C10 stereochemistry. It was recognized at the outset of our studies that a general approach to these perhydroazulenes as well as to more complex targets incorporating this ring system (e.g., 2) could, in principle, be realized through the use of an arene olefin cycloaddition strategy. As depicted in Scheme I, the meta

SCHEME I



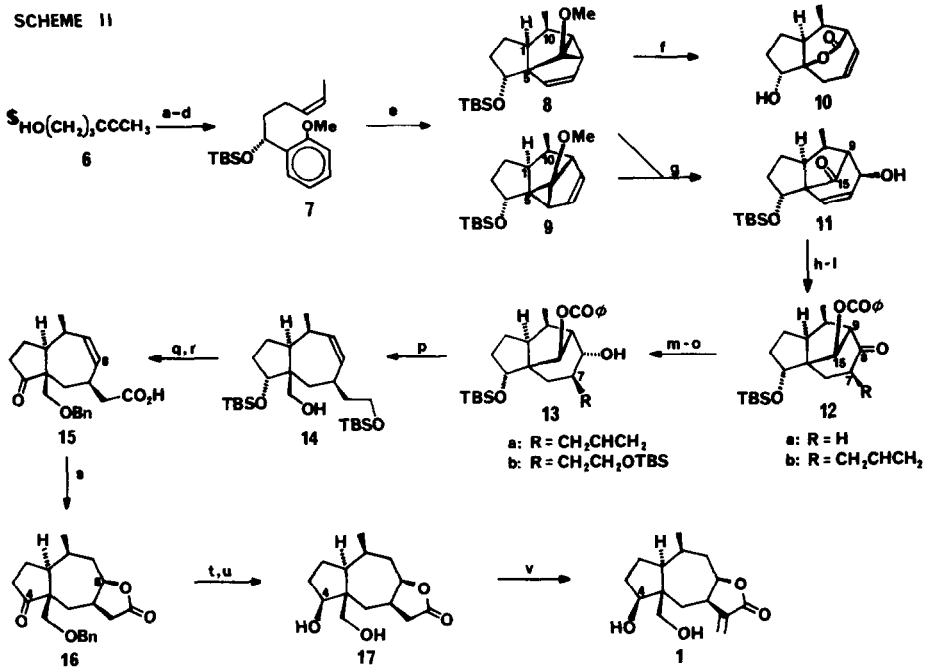
cycloaddition was expected to provide the desired seven-membered ring through the addition of a 5 carbon fragment (C5-C9) across a 2 carbon unit, the C1, C10 double bond.[7] The intramolecular nature of this process would allow for the simultaneous formation of the A ring and would serve to restrict addition to occur through exo exciplex 4,[8] thereby establishing the trans relationship between the angular substituents at C5 and C1. Moreover, since these additions generally proceed with retention of olefin stereochemistry,[1c,1e,3] the relative stereochemistry between C1 and C10 in the cycloadduct would be determined by the geometry of the C1, C10 double bond in the cycloaddition precursor. Accordingly, for a Z olefin, the ambrosanolide or rudmollin stereochemistry would be expected.

In practice, photolysis of arene olefin 7[9] in cyclohexane (ca. 0.04 molar) with Vycor-filtered light from a Hanovia 450W medium pressure lamp did indeed provide the cycloadducts 8 and 9 (2.3:1, respectively) in 63% yield. The yield for this cycloaddition was relatively unaffected by the scale of the reaction although the irradiation time varied from 3 hours for a 0.2 gram run to 8 hours for a 30 gram run. In accord with the above analysis and the intermediacy of exciplex 4, the cycloadducts possess the relative stereochemistry at C5, C1 and C10 found in rudmollin (1) and phorbol myristate acetate (2).[8]

While the above reaction produces two cycloadducts, it was shown previously[1a] that such cyclopropane isomers could be transformed into a common product by bromine-induced cleavage of the internal cyclopropane bond. We have now found that mercuric acetate will effect this same type of cleavage, producing in the present case alcohol 11 from either cycloadduct 9 (71% yield) or cycloadduct 8 (58% yield). 7% or less of the isomeric C-6 allylic alcohol is obtained in these reactions. Thus, in two steps, a general precursor for pseudoguaianolide synthesis is obtained from the readily available arene 7. Moreover, as an indication of the potential of this method for tigliane synthesis, cycloadduct 8 can be readily converted in a three step sequence to lactone 10 possessing the AB ring system and functionality required for the synthesis of the most active tumor promoter of this class, phorbol myristate acetate (2).

For the synthesis of rudmollin from 11, introduction of an appendage at C7 and cleavage of the C9, C15 bond were required. For the former task, alcohol 11 was converted in 83% overall yield to ketone **12a** which through the reaction of its boron enolate with allyl iodide gave allylated ketone **12b** in 75% yield at 75% conversion.[11] The virtually complete stereoselectivity of this alkylation is an expected consequence of addition to the sterically less-encumbered exo (convex) face of the boron enolate intermediate. The use of other alkylation procedures resulted in low yields of 12b and in the formation of diallylated product. C9, C15 bond cleavage was investigated next but when our initial plan based on a retro-aldol reaction proved problematic, a somewhat longer sequence involving a fragmentation step was employed. Accordingly, the C8 ketone of 12b was reduced to give alpha alcohol **13a** in 72% yield along with the corresponding beta hydroxy isomer (27% yield).[12] In anticipation of the chemoselectivity problems that would arise after formation of a C8, C9 double bond, we converted the olefin in the C7 appendage of 13a through ozonolysis and reduction to the alcohol which was then selectively protected as a tert-butyldimethylsilyl ether **13b**. Mesylation of the C8 alcohol followed by lithium aluminum hydride-induced fragmentation gave olefin **14** in 84% yield from which keto acid **15** was prepared by a three step sequence.

SCHEME II



a) H_2, 10-40 psig, $Pd/CaCO_3$ (Lindlar), quinoline, pentane, 25°; 94%; Z:E = 40:1; b) PCC, CH_2Cl_2, 0-25°, 2 h; 54%; c) o-methoxyphenyl magnesium bromide (5: from o-bromoanisole and Mg), THF, 0°, 1.5 h; 98%; d) t-butyldimethylsilyl chloride, DMAP, Et_3N, DMF, 25°, 10 h; 97%; e) hν, Vycor filter, pentane, 25°; 63%; 8:9 = 1:2; f) H_2SO_4, H_2O, CH_3COCH_3, reflux, 15 min; TBSCl, Et_3N, DMAP, DMF, 25°; TMSTf, $(TMSO)_2$, CH_2Cl_2, -30°, 40 h (reference 10); g) $Hg(OAc)_2$, THF, H_2O, 25°, 15 min; 71% (11) + 6% allylic isomer; h) $NaBH_4$, MeOH, 25°; 15 min; 94%; i) MnO_2, CH_2Cl_2, 25°, 24 h; 93%; j) H_2 (1 atm), 5% Pd/C, Et_2O, 25°, 11 h; 99%; k) $(PhCO)_2O$, DMAP, Et_3N, DMF, 46-50°, 36 h; 12a (95%, mp 89.5-90.0°); l) $KN(TMS)_2$, DME, 0°, 15 min; then Et_3B, THF, 5 min; ICH_2CHCH_2, 25°, 13 h; m) $NaBH_4$, $CeCl_3$, MeOH, -78°, 3 h; n) O_3, MeOH, CH_2Cl_2, -78°; $NaBH_4$, -78° to 25°; 98%; o) TBSCl, imidazole, DMF, 25°, 5 h; 97%; p) MsCl, pyr, 25°, 17 h; remove solvent then LAH, DME, 0° to 25°, 17 h; 84%; q) KH, THF, $PhCH_2Br$, 25°, 1.5 h; 96%; r) HF/H_2O, CH_3CN, THF, 25°, 3 h; remove solvent then Jones reagent, CH_3COCH_3, 0° to 25°, 15 min; 15 (82%, mp 135-136°); s) I_2, 2,4,6-collidine, CH_3CN, 25°, 35 min; crude product treated with Bu_3SnH, AIBN, PhH, 80°, 6 h; 53%; t) $NaBH_4$, MeOH, -78° to 25°; 92%; u) H_2 (40 psig), 10% Pd/C, 70% $HClO_4$ cat., MeOH, 25°; 82%; (v) $((CH_3)_2N)_3CH$, 90°, 50 h; remove solvent then DIBAL, THF, 0°, 1 h; (±)-1 (54%, mp 167-168°).

Introduction of the C8 oxygen was stereospecifically achieved by iodolactonization[13] and dehalogenation which furnished lactone 16 in 53% overall yield. The correct stereochemistry at C4 was then specifically set by treatment of this lactone with sodium borohydride. Hydrogenolysis of the resultant benzyl ether (16) afforded desmethylene rudmollin 17 in 84% yield for the two reduction steps. The final task of methylenation was accomplished[14] in 54% yield by heating 17 with tris(dimethylamino)methane followed by DIBAL reduction and aqueous workup. Racemic rudmollin obtained in this fashion was identical (300 MHz NMR, ^{13}C NMR, TLC) with an authentic sample of natural 1 kindly provided by Professor Herz.[15]

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References and Notes

1. Part IX in this series. This work was presented at the 20th Western Regional ACS meeting, October, 1984 (Paper IX: Total Synthesis of (+)-Rudmollin). For previous work in this series, see: a) Wender, P. A. and Howbert, J. J. J. Am. Chem. Soc. 1981, 103, 688; b) Ph.D. dissertation of J. J. Howbert, Harvard University, 1983; c) Wender, P. A. and Dreyer, G. B. Tetrahedron 1981, 37, 4445; d) Wender, P. A. and Howbert, J. J. Tetrahedron Lett. 1982, 3983; e) Wender, P. A. and Howbert, J. J. Tetrahedron Lett. 1983, 5325; f) Wender, P. A. and Dreyer, G. B. J. Am. Chem. Soc. 1982, 104, 5805; g) Wender, P. A. and Dreyer, G. B. Tetrahedron Lett. 1983, 4543; h) Wender, P. A. and Ternansky, R. J. Tetrahedron Lett. 1985, 2625; i) Wender, P. A. and Singh, S. K. Tetrahedron Lett. 1985, 5987.
2. Taken in part from the Ph.D. dissertation of K. Fisher, Harvard University, 1985.
3. For recent reviews and lead references pertinent to the mechanistic and synthetic applications of this reaction, see: a) Welzel, P. Nachr. Chem. Tech. Lab. 1983, 31, 262; b) Wender, P. A. in "Selectivity--A Goal for Synthetic Efficiency," Bartmann, W. and Trost, B., eds. Verlag Chemie 1984; c) Houk, K. N. Pure Appl. Chem. 1982, 54, 1633; d) Reedich, D. E. and Sheridan, R. S. J. Am. Chem. Soc. 1985, 107, 3360; e) Morrison, H. Accts. Chem. Res. 1973, 12, 383; f) Gilbert, A. Photochemistry 1984, 15, 291; g) Osselton, E. M. and Cornelisse, J. Tetrahedron Lett. 1985, 527.
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6. For a recent review, see: Evans, F. J. and Taylor, S. E. Progress in the Chemistry of Organic Natural Products 1983, 1.
7. The pseudoguaiane numbering has been substituted for the tigliane numbering in 2 for the purpose of correlating structural features and for economy of discussion.
8. While the intermolecular meta cycloadditions proceed with endo selectivity, this orientation in the intramolecular reaction is disfavored by a poor orbital alignment resulting from the geometrical restrictions introduced by the 3 atom tether between the arene and olefin units. For a discussion bearing on this point, see references 1 and 3.
9. Although a single enantiomer is depicted for convenience, racemic material was used throughout this work. All new compounds gave satisfactory ^{1}H NMR, IR, low resolution mass spectra and combustion or exact mass analysis.
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13. Hauser, F. M. and Mal, D. J. Am. Chem. Soc. 1984, 106, 1098; Bartlett, P. A. and Myerson, J. ibid., 1978, 100, 3950.
14. The procedure used was a modification of methods reported by Wasserman, H. H. and Ives, J. L. J. Org. Chem. 1978, 43, 3238 and by Ziegler, F. E. and Fang, J. M. ibid. 1981, 46, 827.

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