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Atom Transfer Reactions of TMM Diyls Directed toward the Synthesis of Rudmollin

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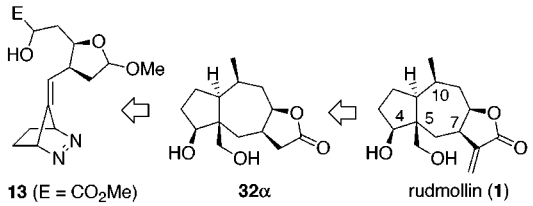
ABSTRACT



13 (E = CO_2Me) **32α** rudmollin (**1**)

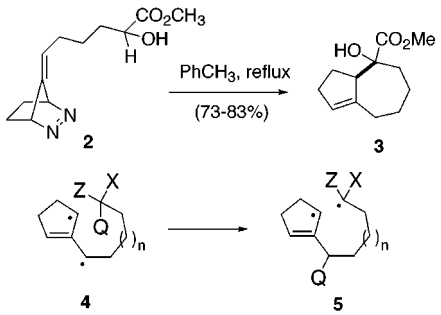
Intramolecular hydrogen atom transfer to a trimethylenemethane (TMM) diradical has been explored as a route to the antileukemial agent, rudmollin (1).

The pseudoguaianolide rudmollin (**1**) displays in vivo activity against P-388 lymphoid leukemia. Isolated from a coneflower, its structure was elucidated by Herz, Kumar, and Blount[1] and it was first synthesized by Wender and Fisher.[2] Their route used the arene olefin meta-photocycloaddition reaction to properly establish three of the six stereogenic centers, C_1, C_5, and C_{10}.

Our approach utilizes a comparatively new reaction of trimethylenemethane diradicals, that of atom transfer−cyclization. This process, illustrated by the conversion of diazene **2** to the [5.3.0] adduct **3** in 73−83% yield, features the transfer of an atom Q from a remote site on the tether to the radical positioned exocyclic to the five-membered ring (e.g., **4** to **5**).[3] This leads to a new radical, **5** (Scheme 1), stabilized by substituents X and Z, that subsequently engages in σ bond formation. The present research features three important stages: (a) construction of diazene **13**, (b) the atom transfer−diyl recombination reaction (**13** to **15**), and (c) introduction of the angular hydroxymethylene unit cis to the hydroxyl group found at C_4 (**26** to **29**).

Endo peroxide **6**, readily constructed from 1,3-cyclohexadiene and singlet oxygen, efficiently (94%) undergoes ring opening to afford **7** when treated with vinyllithium. This interesting peroxide cleavage provides a simple and general means of assembling unsymmetrically substituted cyclohexene-1,4-diols from endoperoxides; Grignard and organolithium reagents have proven to be the most effective nucleophiles examined thus far.[4] When heated in refluxing xylenes, vinyl ether **7** smoothly undergoes a Claisen rearrangement; treatment of the resulting lactol with methanol

Scheme 1



(1) Herz, W.; Kumar, N. Blount, J. F. *J. Org. Chem.* **1981**, *46*, 1356−1361.
(2) Wender, P. A.; Fisher, K. *Tetrahedron* **1986**, *27*, 1857−1860.
(3) Billera, C. F.; Little, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 5487−5488.

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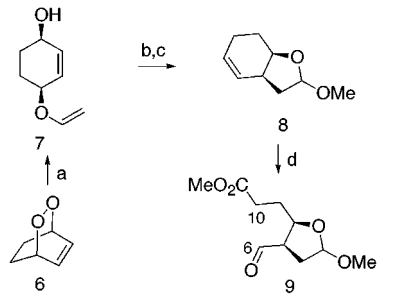
and CSA at room temperature afforded ether **8** in greater than 80% yield over the latter two steps (Scheme 2).

Scheme 2

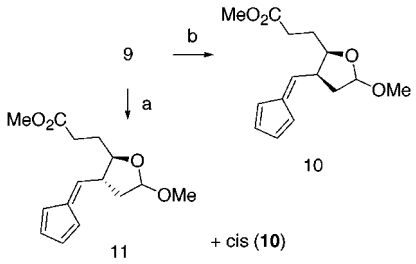


a, CH_2=CHLi, THF (94%); b, refluxing xylenes; c, CSA, MeOH (>80%, b+c); d, O_3, CH_2Cl_2, -78 °C; Ac_2O, Et_3N, 0 °C (96%)

Ozonolytic cleavage of the alkene provided aldehyde **9** regioselectively; **9** is an important building block, incorporating within it C_6 through C_{10} as well as most of the C-ring of the target structure.

Initial efforts to transform **9** to fulvene **10** using CpH and pyrrolidine in methanol led to the production of the desired cis and unwanted trans-isomeric fulvenes **10** and **11** in a 2:1 ratio (Scheme 3). Control experiments revealed that aldehyde

Scheme 3



a, pyrrolidine, MeOH, CpH, room temp (70%); b, CpLi, THF, -78 °C to rt; AcOH (51%)

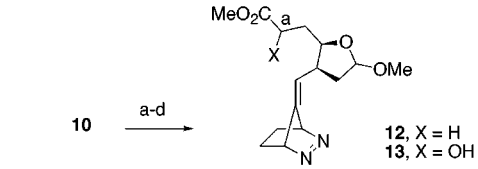
9 undergoes complete epimerization when treated with pyrrolidine in methanol at room temperature. These problems were circumvented by using lithium cyclopentadienide at low temperature. For best results, it proved necessary to slowly warm the reaction mixture to room temperature prior to recooling to 0 °C and quenching with acetic acid.

Diazene **12** was obtained from **10** using our standard protocol of Diels−Alder cycloaddition, diimide reduction of the Δ-5,6 π-bond of the cycloadduct, and conversion of the biscarbamate unit to the diazene functionality.[5] As illustrated in Scheme 4, each of these processes was efficient. We have previously found that atom transfer to a trimethylenemethane diyl occurs most efficiently when the radical formed at the

(4) Schwaebe, M. K.; Little, R. D. *Tetrahedron Lett.* **1996**, *37*, 6635−6638.

(5) Little, R. D. *Chem. Rev.* **1996**, *96*, 93−114.

Scheme 4

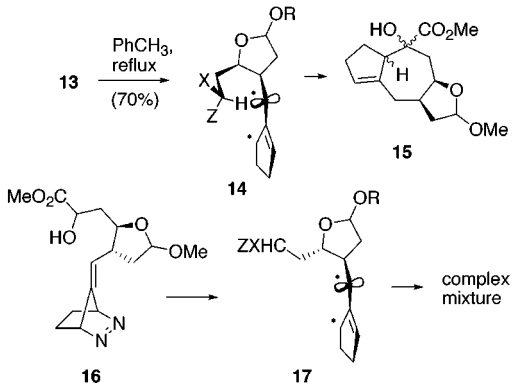


a, $Cl_3CCH_2O_2CN$=$NCO_2CH_2CCl_3$, CH_2Cl_2, 0 °C; b, AcOH, KO_2CN=NCO_2K, AcOH, 0 °C (85-95%, a + b); c, -1.7V (*vs* AgAgCl), $LiClO_4$, DMF; aq $CuCl_2$ (78%) or Zn/Cu, MeOH, 0 °C
to rt; $K_3Fe(CN)_6$ (75-85%); d, camphorsulfonyl oxaziridine, NaHMDS, DMPU, THF, T < -85 °C (58%; 78% based upon recovered starting material)

site from which transfer occurs is captodatively stabilized. For this reason, we elected to insert an hydroxyl group α to the ester in **12** to afford **13**. This was best accomplished using sodium hexamethyldisilazide as the base and camphor sulfonyl-oxaziridene as the hydroxylating agent.

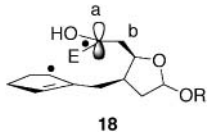
Like the intramolecular TMM diyl trapping reactions (cycloadditions), the atom transfer−recombination reaction is exceptionally easy to conduct. In the present instance, a dilute solution of diazene **13** dissolved in toluene was added dropwise to refluxing toluene via an addition funnel to give a final diazene concentration of 3 mM. Following the consumption of starting material, workup consists simply of solvent removal followed by chromatographic isolation of the products. When heated to reflux in toluene, diazene **13** was efficiently (70%) converted to the desired tricyclic hydroazulene **15**. It was at this stage that the importance of avoiding epimerization in the fulvene-forming step became apparent. In particular, diazene **16** did *not* undergo atom transfer. This result is a direct consequence of the trans relationship between the vicinal substituents that was created during the fulvene-forming step. In contrast to diyl **14**, the radical and hydrogen to be transferred in **17** simply cannot reach and transfer does not occur (Scheme 5).

Scheme 5



We wondered whether the atom transfer−cyclization reaction could occur with retention of configuration at the site of transfer, *viz.*, at C_a of structure **13** (Scheme 4). While

radicals are known to very rapidly loose configuration,[6] we suspected that complete or partial retention might occur since the radical−radical coupling reaction of the 1,7-diyl **18** is expected to occur rapidly due to the presumed proximity of the two radical centers (Figure 1). Retention could occur if



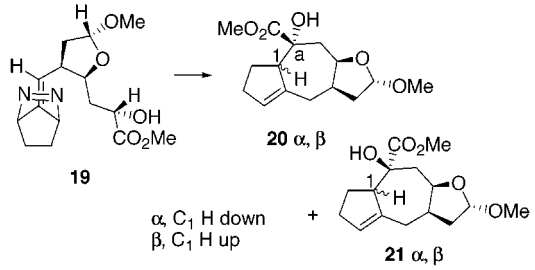
18

Figure 1. Planar captodative radical.

σ bond formation (cyclization) is fast relative to pyramidal inversion of the initially formed radical. A net retention could also occur if the radical assumed a planar geometry, as portrayed by **18**. In that case, cyclization must occur at a rate exceeding that of rotation about the C_a-C_b bond. If rotation occurs more rapidly, then cyclization following rotation would be the experimental equivalent of inversion.

To address these issues we synthesized and isolated the enantiomerically pure diazene **19** and subjected it to the atom transfer cyclization reaction conditions. Characterization of the four isomeric products, **20**α,β and **21**α,β, allowed them to be grouped into two pairs depending upon the configuration at C_a and revealed that they were formed with a 70:30 preference for **20**α,β, the products of *net* retention (Scheme 6).

Scheme 6

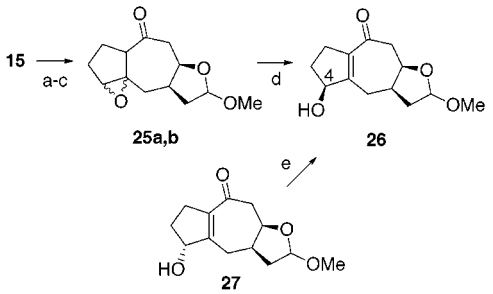


At this point, the synthesis of rudmollin (**1**) was resumed; the ester and hydroxyl groups were removed by treating **15** with LAH followed by sodium periodate. The resulting ketone was epoxidized using dimethyldioxirane to afford epoxides **25a**,**b** (Scheme 7). When exposed to sodium methoxide in methanol, the epoxides underwent β-elimination to afford a mixture of α- and β-oriented allylic alcohols **26** and **27**. Fortunately, it proved to be a simple matter to convert **27** to **26** using a Mitsunobu inversion.

We were now in a position to use the β-oriented C_4-hydroxyl group to direct the introduction of the angular

(6) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

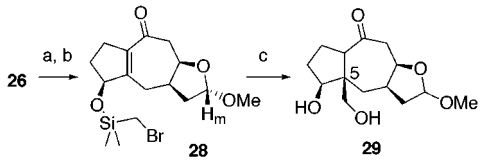
Scheme 7



a, LAH, THF, -78 to rt (94%); b, $NaIO_4$, MeOH/H_2O, 0 °C (79%, 2 steps); c, dimethyldioxirane, acetone, rt, 1h (95%); d, NaOMe, MeOH, 0 °C, 1h (90-95%); e, Ph_3P, DEAD, 3,5-$(NO_2)_2C_6H_3CO_2H$; NaOMe, MeOH (80%)

hydroxymethylene unit. In preparation for this event, **26** was converted to the bromomethyldimethylsilyl ether **28** by exposing **26** to $ClSiMe_2CH_2Br$ and triethylamine in methylene chloride (Scheme 8). AIBN-promoted radical cyclization followed by Tamao−Fleming oxidation did provide a useful means of introducing the angular substituent.[7] The need to form a cis-fused silacycle prior to oxidation assurred the desired stereochemical outcome at C_5.

Scheme 8



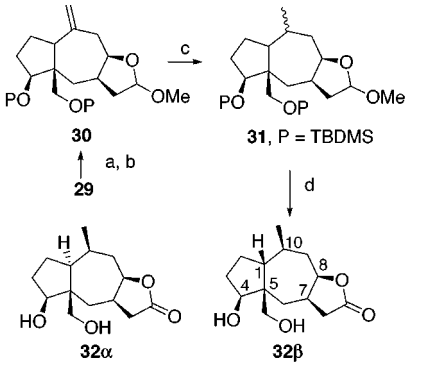
a, $ClSi(CH_3)_2CH_2Br$, TEA, 0 °C, CH_2Cl_2 (87%); b, *n*-Bu_3SnH, AIBN, PhH, reflux 10 h; c, KF, $KHCO_3$, H_2O_2 (50% overall, *i.e.* a+b+c)

From **29** our goal was to converge with the Wender−Fisher total synthesis of rudmollin (**1**) at structure **32**α.[2] This required introduction of the C_{10} methyl group and conversion of the lactol methyl ether to a lactone (Scheme 9). The former was achieved by protecting the diol as the corresponding bis-silyl ether, followed by Wittig olefination to afford **30** as a single isomer of uncertain stereochemistry at C_1. Hydrogenation provided a 1.7:1 mixture of diastereomers **31** that were epimeric at C_{10}. Treatment of **31** with MCPBA and boron trifluoride etherate in methylene chloride served both to generate the lactone *and* deprotect the silyl ethers.[8] Neither of the resulting C_{10}-isomeric lactones corresponded to the Wender−Fisher intermediate **32**α. X-ray analysis of the major product, **32**β, revealed a most perplexing result.

(7) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826−6828. (d) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854. (e) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. In *Organic Syntheses*; Paquette, L. A., Ed.; Wiley: New York, 1990; Vol. 69, pp 96−105.

(8) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419−420.

Scheme 9



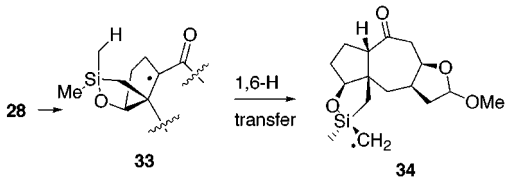
a, TBDMSCl, imidazole, DMF (92%); b, Ph_3PCH_3Br, n-BuLi, THF, 0 °C (80%); c, H_2, Pd/C (>90%); d, $BF_3.OEt_2$, MCPBA, CH_2Cl_2, 0 °C (85%)

Thus, while each of the stereocenters located at C_4, C_5, C_7, C_8, and C_{10} had been properly established, C_1 proved epimeric. Remarkably, this requires pickup of "H" from the more hindered concave face, thereby leading to the cis—rather than the requisite trans-fused—AB-ring junction.

We believe that the incorrect stereochemistry was established in the radical quenching portion of the 5-exo, trig cyclization step, **28** to **29** (Scheme 8), via an *intra*molecular hydrogen atom transfer from the proximal silylmethyl group of silacycle **33** to the radical center located alpha to the carbonyl, *viz.*, **33** to **34** (Scheme 10).[9] Models show the centers to be close enough to render such a process feasible.

(9) (a) Control experiments established that epimerization at C_1 of **29** did not occur during exposure to basic conditions. (b) Malacria and coworkers have demonstrated that intramolecular hydrogen atom transfer from a silylmethyl group does occur in systems where the radical and atom to be transferred are near one another. Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764−6765.

Scheme 10



They also show that the acetal methine hydrogen of **28**, H_m, cannot reach the radical site without setting up a severe steric interaction between the methylene protons of the silylacycle and the lactol. Once transferred, the silylmethyl radical **34** is presumably quenched *inter*molecularly by tributyltin hydride to afford a silylacycle that is subsequently oxidized to afford diol **29**.

While the chemistry described herein did not culminate in the total synthesis of rudmollin (**1**), it did provide a useful and interesting forum for the exploration of new chemistry. The work clearly establishes the utility of both the endo peroxide desymmetrization sequence for the construction of useful building blocks and the diyl atom transfer−recombination process for the rapid assembly of relatively complex materials.

Acknowledgment. The authors thank the National Science Foundation for their support of our research and Dr. X. Bu for X-ray structural determinations of the mandelate derivative of diazene **13**, atom transfer products **20**α,*β*, and lactone **32**.

Supporting Information Available: Spectral data for **19**, **20**α, **20***β*, **30**, and **32***β*. This material is available free of charge via the Internet at http://pubs.acs.org.

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