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SYNTHETIC STUDIES OF 1,7-DIOXASPIRO[5.5]UNDECAN-4-ONES

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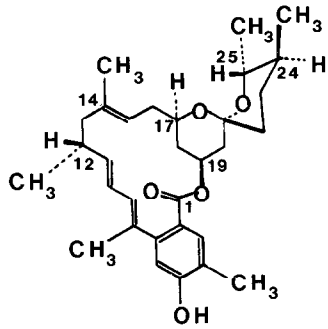
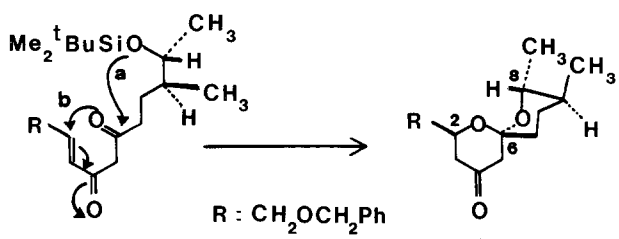
Summary: A strategy for preparation of functionalized 1,7-dioxaspiro[5.5]undecanes has been explored using β-diketone precursors.

Discovery of the milbemycin-avermectin family of antibiotics has stimulated widespread interest in the chemistry of these agents owing to their potent and specific pesticidal activity.[1] In connection with our efforts[2] toward the total synthesis of milbemycin β_3 1, we have sought an effective strategy for formation of the 1,7-dioxaspiro[5.5]undecane 2. Herein we describe the utility of 1,3-diketone intermediates as precursors to this spiroketal moiety.



Milbemycin β_3 **1**

Our plan recognized a cascading cyclization to be initiated by deprotection of the secondary alcohol at C-8 of the β-diketone as shown below.[3] The resulting stereochemistry of the spirocenter (C-6) was anticipated by thermodynamic control with each of the oxygens in pseudoaxial dispositions in accord with the anomeric effect.[4] Likewise the requisite side chain (R) would occupy a pseudo-equatorial position establishing the stereochemistry at C-2.

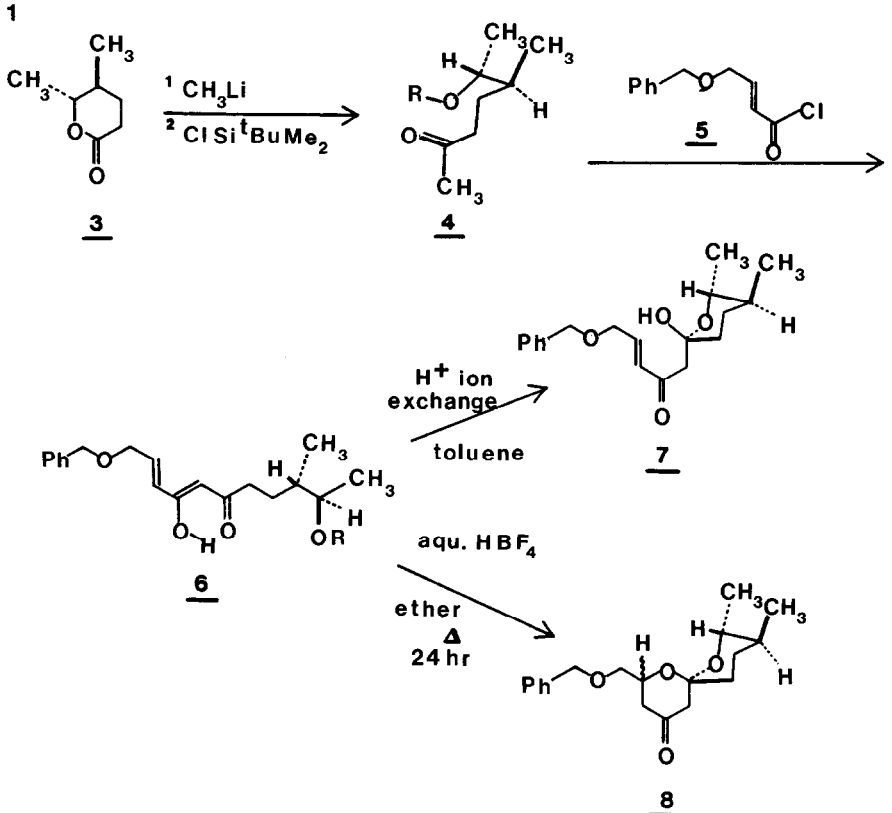


2

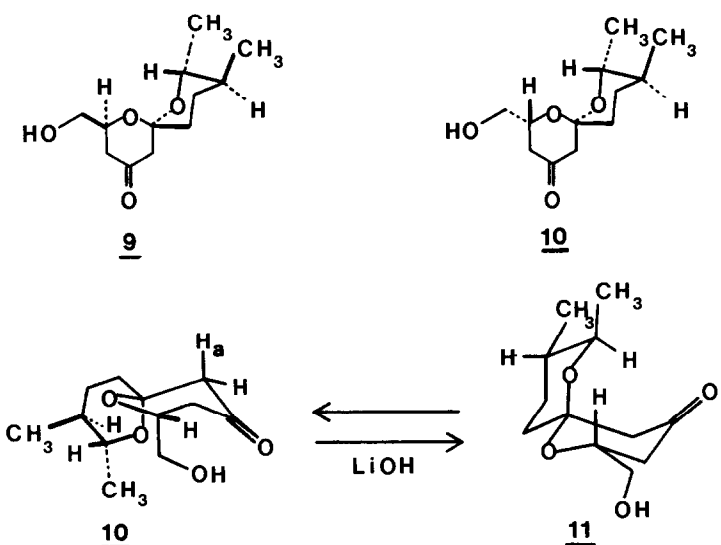
Results are illustrated in Scheme 1.[5] Addition of methyllithium (1 equiv, THF, -78 °C) to *trans*-4,5-dimethylvalerolactone 3, and subsequent silyl ether protection (Cl-Si^{t}BuMe$_2$, CH_2Cl_2, DMAP) gave methyl ketone 4 in 65% yield for the two steps.[6] Kinetic deprotonation (LDA, 2 equivs, THF, HMPA, -78 °C) and reaction with *trans*-4-benzyloxycrotonyl chloride 5 afforded the β-diketone adduct which was shown to exist primarily in the enolized form 6 (>90% by NMR and IR). Unfortunately yields of 30 to 35% are generally obtained with 60 to 70% recovered methyl ketone 4. None of the usual techniques, such as lower reaction temperatures, additional quantities of bases, or inverse addition, gave improved yields of 6 and no other isolable products were formed.[7] Attempts for direct acylation, promoted by Lewis acids, utilizing the corresponding trimethylsilyl enol ether of 4 and acid chloride 5 also failed in this case.[8]

The desired cyclization was attempted by basic fluoride initiation (n-$Bu_4N^+F^-$, THF); however, the higher temperatures required for deprotection also caused complete decomposition. Under acid conditions (H^+ Bio-Rad AG50W-X4 exchange resin, toluene at 100 °C) partial cyclization of 6 afforded 7 which proved stable to silica gel chromatography. However, a two-phase reaction of 6 with aqueous 20% fluoroboric acid in ether (2 ml acid with 5 ml Et_2O) at reflux with vigorous stirring for 24 hr gave the desired spiroketal 8 in 40% yield as a mixture of isomers at C-2 (ratio 60:40). All starting diketone was consumed with some decomposition to polar materials.

Scheme 1



Stereochemical assignments at C-2 and C-6 followed from separation of the corresponding alcohols 9 and 10 (silica gel chromatography).[9] Epimer 10, bearing an axial hydroxymethyl substituent, was easily isomerized with lithium hydroxide (THF, H_2O, MeOH, 22°C, 15 min) affording a thermodynamic equilibrium of spiroketals 10 and 11 (ratio 2:1), each of which were fully characterized following chromatography (silica gel). The equilibration is complicated by recognition of a second conformer 10a which is available by inversion of the tetrahydropyranone (ring A) of epimer 10. Thus, conformer 10a, while relieving the 1,3-diaxial interaction of the hydroxymethyl substituent, can maintain only a single anomeric stabilization. Note the tetrahydropyran moiety (ring B) is highly biased in a single conformation by preference of the vicinal methyl groups. Likewise, diastereomer 11 has similar conformational considerations, and it is not surprising that epimers 10 (and 10a) and 11 (and 11a) offer similar thermodynamic stabilities. However, 11 is not observed in the acid-catalyzed cyclization of 6, and spiroketal 9 is unchanged under these basic conditions. Moreover, neither 10 nor 11 undergoes isomerization to 9 which is obviously the most thermodynamically favorable situation. Observations suggest a stereoelectronic requirement for an *anti*-alignment with selective removal of H_a in 10, allowing for elimination to an intermediate dihydropyranone with conjugate addition of hydroxyl reoccurring from the opposite face of the unsaturated system providing 11. The corresponding elimination to an intermediate analogous to ketone 7 does not take place.[5]



Further investigations of these strategies for natural product synthesis are underway.

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3. Studies have indicated that while these ring closure processes are allowed under basic conditions, they should be even more facile with acid catalysis. J.E. Baldwin, R.C. Thomas, L.I. Kruse, L. Silberman, *J. Organic Chem.*, *42*, 3846 (1977).
4. For recent examples of thermodynamic control in the formation of 6,6-spiroketals see; R. Baker, R.H. Herbert, A.H. Parton, *Chem. Commun.*, 601 (1982). P. Deslongchamps, D.D. Rowan, N. Pothier, T. Sauve, J.K. Saunders, *Can. J. Chem.*, *59*, 1105 (1981). D.A. Evans, C.E. Sacks, W.A. Kleschick, T.R. Taber, *J. Am. Chem. Soc.*, *101*, 6798 (1979). G.R. Martinez, P.A. Grieco, E. Williams, K. Kanai, C.V. Srinivasan, *J. Am. Chem. Soc.*, *104*, 1436 (1982).
5. All yields are reported for purified samples, characterized by infrared, nuclear magnetic resonance and mass spectral data. The ^{1}H-NMR and ^{13}C-spectra were recorded on a 360 MHz instrument in $CDCl_3$ (0.1% Me_4Si) solutions. ^{1}H-NMR characterization is as follows: **6**: δ 15.23 (s,1), 7.36 (m,5), 6.85 (dt,1,J=15.6 Hz,J=4.4 Hz), 6.15 (dt,1,J=15.6 Hz,J=1.8 Hz), 5.54 (s,1), 4.58 (s,2), 4.20 (m,2), 3.65 (m,1), 2.45 (m,1), 2.30 (m,1), 1.77 (m,1), 1.40 (m,2), 1.06 (d,3, J=6.5 Hz), 0.85 (s,12), 0.04 (s,3), 0.03 (s,3); **9**: δ 3.98 (m,1), 3.80 (dd,1,J=11.7 Hz,J=2.3 Hz), 3.62 (dd,1,J=11.6 Hz,J=5.4 Hz), 3.26 (dq,1,J=9.8 Hz, J=6.1 Hz), 2.50-2.25 (m,4), 2.0 (br s,1), 1,87 (m,1), 1.57 (m,3), 1.27 (m,1),1.09 (d,3,J=6.3 Hz), 0.84 (d,3,J=6.6 Hz); **10**: δ 4.10 (m,1), 3.79 (m,1), 3.69 (dq,1,J=9.8 Hz,J=6.2 Hz), 3.62 (m,1), 2.62 (dd,1,J=15.5 Hz,J=9.6 Hz), 2.55 (s,1), 2.54 (s,1), 2.44 (br s,1), 2.36 (dd,1,J=15.6 Hz,J=4.1 Hz), 1.88 (m,1), 1.60-1.42 (m,3), 1.27 (m,1), 1.14 (d,3,J=6.2 Hz), 0.87 (d,3,J=6.6 Hz); **11**: δ 4.48 (m,1), 3.88 (m,1), 3.60 (m,1), 3.29 (dq,1,J=9.1 Hz,J=6.1 Hz), 3.04 (dd,1,J=13.9 Hz,J=1.1 Hz), 2.60 (dd,1,J=14.2 Hz,J=11.5 Hz), 2.32 (s,1), 2.28 (s,1), 1.95 (br s,1), 1.84 (m,1), 1.75 (m,2), 1.30 (m,2), 1.14 (d,3,J=6.1 Hz), 0.86 (d,3,J=6.1 Hz).
6. For preparation of lactone **3** see ref. 2.
7. Standard acylation attempts from the thio ester, and imidazolide corresponding to acyl chloride **5** offered no improvement.
8. T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, *16*, 817 (1977); and P.A. Bartlett, K.K. Jernstedt, *Tetrahedron Lett.*, *21*, 1607 (1980) have demonstrated formation of aldol products without elimination. Subsequent oxidations provide the desired β-dicarbonyl compounds.
9. Alcohol **9** has been unambiguously prepared by an independent route (see ref. 2). The benzoate of **10** was reduced ($NaBH_4$, DME) and protected (Cl-Si^{t}BuPh$_2$). Saponification of the benzoate and Swern oxidation gave an aldehyde which readily gave epimerization (DBU, THF) to an identical aldehyde obtained in similar fashion from **9**.

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