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MACROLIDE CLOSURE *VIA* FLUORODESILYLATION. A TOTAL SYNTHESIS OF d,l-17-O-METHYLLYTHRIDINE

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Abstract. A synthesis of the macrolide 17-O-methyllythridine is reported in which cyclization is initiated by fluorodesilylation of a trimethylsilylacetate.

The broad range of biological activity associated with macrocyclic lactones has occasioned extensive development of methodologies for the elaboration of this structural unit. Among these, lactonization of the derived seco acid, or an appropriately activated derivative, has emerged as the standard protocol.[2] The cyclic β-hydroxy ester lythridine (1a), isolated from *Heimia salicyfolia* (family *Lythraceae*),[3] exemplifies a compound whose stereoselective assembly precludes application of this technique; efficient synthesis of 1 *via* seco acid 2 would require the inclusion, with proper relative chirality, of a protected alcohol or suitable equivalent, Y, prior to cyclization. Indeed, synthetic efforts in the area of lactonic *Lythraceae* alkaloids have concentrated on the cyclization of β-norhydroxy carboxylic acids (*i.e.* 2, Y=H)[4] and thus have not addressed this issue. It must also be noted that 1 is not accessible by hydration of the α,β-unsaturated lactone lythrine (4) since attempts to effect such a conversion result in the exclusive formation of 13-*epi*-lythridine derivatives.[5]

In this communication, we report a synthesis of 17-O-methyllythridine (1b) in which ring closure, initiated by fluorodesilylation of trimethylsilylacetate 3a, fashions the requisite β-hydroxy ester in a highly stereoselective manner. The fluoride-catalyzed intermolecular addition of trimethylsilyl esters to aldehydes and ketones has been amply documented by Kuwajima.[6]

Ullman reaction[7] of 2-iodo-4-cyanoanisole (6), prepared by iodination (I_2, aq. $NaHCO_3$) and methylation (CH_3I, K_2CO_3, acetone) of 4-cyanophenol, and 6-bromoveratraldehyde (5)[8] gave biphenyl aldehyde 7 in 30% yield after purification by silica gel chromatography.[9,10] The condensation of pelletierine[11] with 7, followed by equilibration of the resulting isomeric quinolizidinones in refluxing

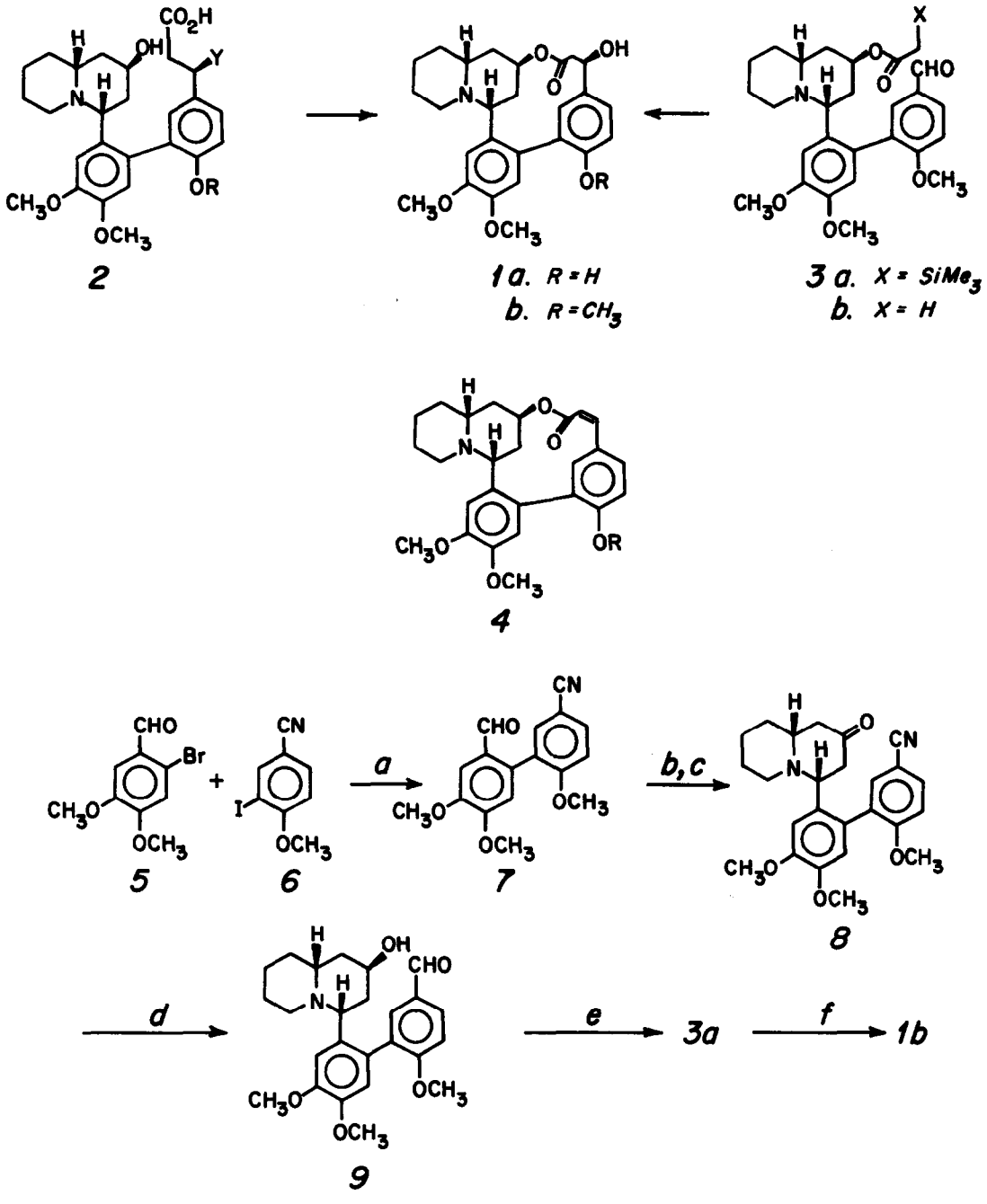
methanol, gave *trans*-quinolizidinone 8[9,10] (IR, film: 2850, 2801, 2762 cm^{-1}, Bohlman bands[12]) in 70% overall yield from 7.

A variety of reducing conditions were examined for the conversion of 8 to 9. Diisobutylaluminum hydride (DIBAL) gave a mixture of epimeric hydroxy aldehydes. An axial hydroxy nitrile was secured with lithium tri-*sec*-butylborohydride (L-Selectride), however, further treatment with DIBAL was thwarted by the limited solubility of this derivative in hydrocarbon media while reduction with Raney alloy in aqueous formic acid[13] was accompanied by epimerization of the alcohol. The desired transformation was ultimately achieved in one step by reaction of 8 with a seven-fold excess of L-Selectride to afford axial quinolizidinol 9 in 93% yield after purification by silica gel chromatography.[9,10] This previously unreported reduction of nitrile to aldehyde by a trialkylborohydride is not general and appears to be limited to benzonitriles substituted with electron-donating groups. Exposure of *p*-methoxybenzonitrile with excess L-Selectride in tetrahydrofuran afforded *p*-anisaldehyde in 75% yield, while benzonitrile gave only traces of benzaldehyde and octanonitrile was recovered unchanged.

Acylation of 9 with trimethylsilyl ketene[14] yielded TMS-acetate 3a in 60% yield.[9,10] The 60 MHz proton NMR spectrum of 3a exhibited multiplicity of the acetate, aldehyde, aromatic and trimethylsilyl signals. This phenomenon was also observed for acetate 3b. The absence, or great diminution, of this effect in the spectra of 8, 9 and the equatorial acetate corresponding to 3b suggests that torsional interaction between the axially-oriented ester and substituents on the aromatic ring results in restricted biphenyl rotation.

Addition of 3a to a stirred suspension of tetra-*n*-butylammonium fluoride[15] in tetrahydrofuran at -78°C gave d,l-17-O-methyllythridine (1b) in 35% yield, mp 143-144°C (M^+, calculated: 467.2286, found: 467.2264). For comparison purposes, authentic lythridine was methylated (Me_2SO_4, dioxane, aq. Na_2CO_3) to provide naturally-derived 1b, mp 143.5-145°C (M^+, calculated: 467.2286, found: 467.2316). The IR (KBr) and 360 MHz NMR ($CDCl_3$) of the two samples of 1b were identical in all respects. The sole significant by-product of the cyclization was desilylated acetate 3b. The high stereoselectivity of enolate addition to the aryl aldehyde was demonstrated by the absence of detectable amounts of 13-*epi*-methyllythridine. The isomeric alkaloid was prepared by hydroxymercuration/reduction of methyllythrine according to the procedure of Lantos, *et al.*[5] (*vide supra*) and could be readily distinguished from 1b by thin layer- or high performance liquid chromatography.

The synthesis of 17-O-methyllythridine demonstrates the utility of fluorodesilylation as a method for triggering intramolecular enolate anion additions. This cyclization method, which avoids extreme temperatures and highly reactive reagents, should find application in the synthesis of other β-hydroxy macrolides.



a) naphthalene, Cu bronze, 220°C, 2 hr. b) pelletierine, aq. NaOH, THF, MeOH, room temp., 48 hr. c) MeOH, reflux, 4 hr. d) 7 eq. L-Selectride, THF, −78°C to −20°C, 12 hr. e) trimethylsilyl ketene, THF, −20°C, 40 hr. f) tetra-n-butylammonium fluoride, THF, −78°C, 3 min., then H_2O, −78°C to room temperature.

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9. All new compounds gave correct elemental analyses (C,H) or high resolution mass spectra.
10. NMR data were recorded with a Varian T-60 spectrometer in $CDCl_3$ solution. Chemical shifts are reported in parts per million downfield from tetramethylsilane or internal trimethylsilyl. Coupling constants are reported in hertz (Hz). 7: 9.58 (s, 1H); 7.63 (dd, 1H, J=8,2 Hz); 7.48 (s, 1H); 7.03 (d, 1H, J=8 Hz); 6.72 (s, 1H); 3.97 (s, 6H); 3.82 (s, 3H). 8: 7.68 (dd, 1H, J=8,2 Hz); 7.35 (d, 1H, J=2 Hz); 7.17 (s, 1H); 6.98 (d, 1H, J=8 Hz); 6.50 (s, 1H); 3.93 (s, 6H); 3.83 (s, 3H). 9: 9.90 (s, 1H); 7.87 (dd, 1H, J=8,2 Hz); 7.58 (d, 1H, J=2 Hz); 7.20 (s, 1H); 7.02 (d, 1H, J=8 Hz); 6.55 (s, 1H); 4.78 (br. m, 1H); 3.92 (s, 3H); 3.82 (s, 6H). 3a: 9.97, 9.93 (s, 1H); 7.90 (br. d, 1H, J=8 Hz); 7.60 (d, 1H, J=2 Hz); 7.17 (s, 1H); 7.15 (d, 1H, J=8 Hz); 6.57 (s, 1H); 4.93 (br. m, 1H); 3.93 (s, 3H); 3.83 (s, 3H); 3.78 (s, 3H); 1.68, 1.55 (s, 2H); 0.03, 0.00 (s, 9H).
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