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SYNTHESIS OF A PODOPHYLLOTOXIN ANALOG USING A NOVEL IODOTRIMETHYLSILANE MEDIATED FRAGMENTATION[1]

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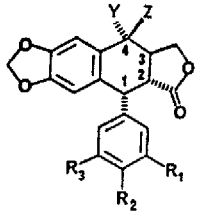
Summary: The bromoisoxazoline functionality of podophyllotoxin analog intermediate 3 was fragmented by iodotrimethylsilane (TMSI) to a β-oxynitrile which subsequently formed γ-lactone 4 by interaction with the neighboring benzhydryl ester.

Etoposide (VP-16-213), 1, a semisynthetic cytotoxic agent, has been shown to be an effective clinical agent with cis-platin in treating testicular cancer and appears to be effective against small cell lung carcinoma.[3] Previous work in these laboratories has resulted in a novel route to (±)-4-epi-podophyllotoxin (2), the aglycone, by utilizing a [3+2] dipolar cycloaddition strategy for the regio- and stereoselective introduction of the four contiguous stereocenters.[4] During the course of a program utilizing this methodology for the preparation of etoposide analogs, a novel fragmentation of bromoisoxazoline intermediate 3 using TMSI was observed. The resulting nitrile-lactone 4 was converted to (±)-3',4',5'-tridesmethoxy-4'-phenylmethyloxypodophyllotoxin (5), a protected form of an aglycone analog.

Bromoisoxazoline 3,[5] mp 167.5-169.5°,[6] was prepared by previously reported methods[4] from 4-phenylmethyloxybenzaldehyde in 15% (nine steps) overall yield. Modification of bromoisoxazoline 3 with Ra-Ni/H_2 and LAH,[4] hydrogen at moderate to high pressures over platinum, palladium, or rhodium catalysts, or hydrogen chloride or trifluoroacetic acid in protic and aprotic solvents failed to effect a useful transformation. When bromoisoxazoline 3 was treated with TMSI as described below an easily isolable product formed.

Under nitrogen a dry flask was charged with 15 mL of anhydrous chloroform and 546.6 mg (0.794 mmol) of 3. The stirred partial solution was cooled in an ice-water bath and treated dropwise over 30 sec with 210 μL (295 mg, 1.48 mmol) of TMSI. The intense orange-red solution was allowed to warm slowly to room temperature and stirred for a total of 22.5 h. Addition of methanol to quench the reaction was followed by decolorization with aqueous sodium bisulfite. The pale yellow organic phase was washed once with saturated brine, dried over anhydrous magnesium sulfate, concentrated, and purified by preparative tlc (silica gel developed in dichloromethane) affording 211.1 mg (0.496 mmol, 62%) of 4,[5] mp 227-228°.[6]

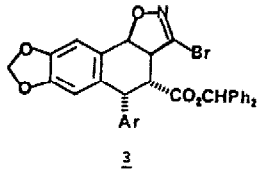
We speculate the initial step in this conversion to be nitrogen-oxygen bond cleavage



1: Y=H, Z=4,6-O-Ethylidene-β-D-glucose, $R_1=R_3=OCH_3$, $R_2=OH$

2: Y=H, Z=OH, $R_1=R_2=R_3=OCH_3$

5: Y=OH, $Z=R_1=R_3=H$, $R_2=OCH_2Ph$



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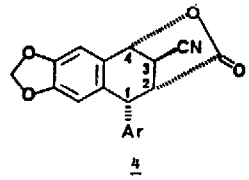

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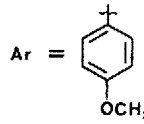

mediated by nucleophilic attack of iodide on bromine or oxygen, forming the cyano functionality, followed by backside displacement of the oxygen functionality of C4 by an oxygen of the ester. Loss of the benzhydryl group is probably mediated by TMSI as well. The large change in coupling constants (3: J_{12}=4.8; J_{23}=10.6; J_{34}=10.2 Hz. 4: J_{12}=4.8; J_{23}=4.5; J_{24}=0.6; J_{34}=5.0 Hz.) observed for the reaction support the relative stereochemistry shown for 4. In addition, a coupling of 0.6 Hz observed in the signal for H2 is interpreted as long-range coupling to H4; a model shows that in the bicyclic system of 4 H2 and H4 are locked in a W-configuration. Preliminary x-ray crystallographic analysis confirms the structure as shown for 4.[7] To our knowledge, this elaboration of the isoxazoline functionality mediated by TMSI represents a new application of this versatile reagent.

Treatment of nitrile-lactone 4 with 3N sodium hydroxide in THF formed the carboxylate salt which was converted to the α-amino acid by cobalt (II) chloride mediated sodium borohydride reduction.[8] This amino acid was treated as previously reported[4] with 50% aqueous acetic acid and sodium nitrite at 0°, and the podophyllotoxin analog 5[9] was isolated in 26% yield (not optimized) from 4. The comparable characteristics in the pmr of 5 were analogous to those previously reported for podophyllotoxin and different from those reported for epi-podophyllotoxin (which is the C4 epimer) and picro-podophyllotoxin.[10]

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References

1. Dedicated to Professor Kenneth L. Rinehart, Jr., in honor of his 60th birthday.
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9. HRMS: Theory, 430.1416; Measured, 430.1408. Ir(KBr): 3640-3130, 1770, 1610, 1510, 1480, 1460, 1240, 1180, 1040, 990 cm^{-1}. MS(EI): 430(M^+), 412, 340, 321, 293, 277, 247, 91 (base peak). PMR (360 MHz, $CDCl_3$, δ rel to TMS): 7.41-7.31 ppm, m, 5H; 7.11, s, 1H; 7.03, 6.82, approximated as AB quartet, 4H, 8.7 Hz; 6.43, s, 1H; 5.93, s, 2H; 4.98, s, 2H; 4.73, d, 1H, 9.0; 4.56, m, 2H; 4.06, t, 1H, 9.3; 2.81, dd, 1H, 14.2, 4.8; 2.75, m, 1H.
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