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Alkoxy Radicals in Organic Synthesis. A Novel Approach to a Key Intermediate in Milbemycin Chemistry.

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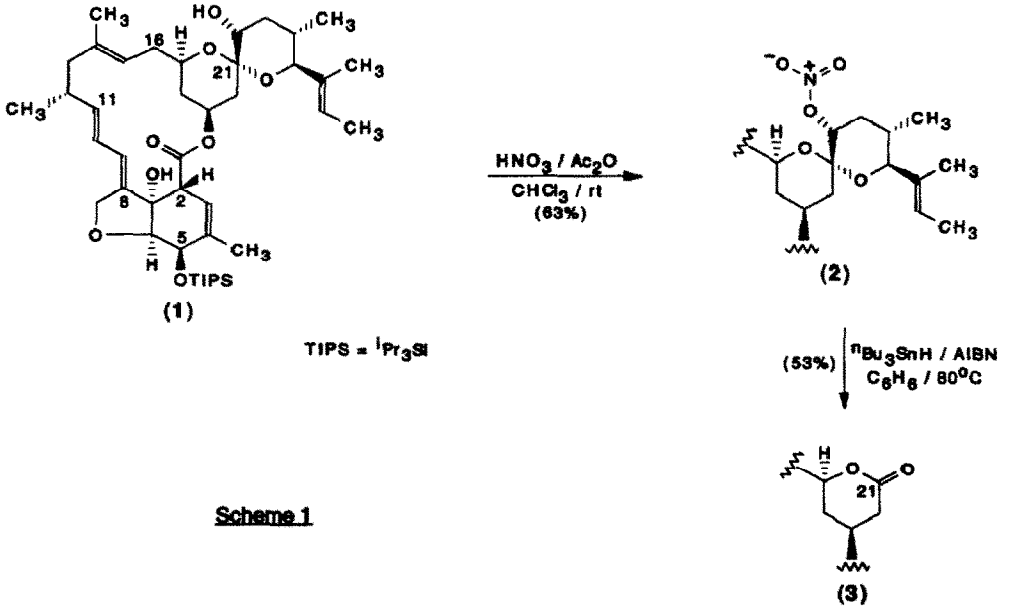
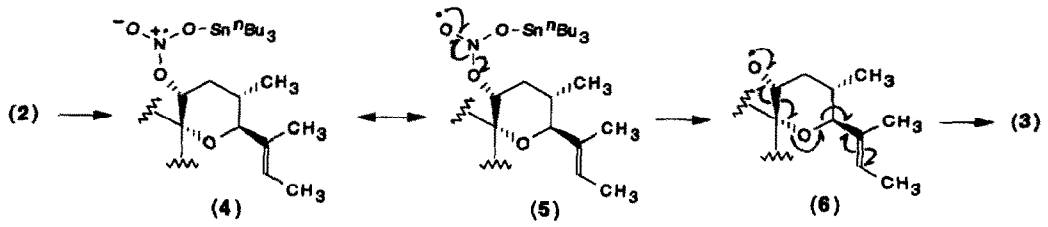
Abstract: The fragmentation of nitrate ester (2) via an alkoxy radical to lactone (3) is described. This lactone is a key intermediate in the synthesis of semisynthetic milbemycins.

In recent years the use of radical chemistry has seen immense growth. In particular carbon radicals have been extensively used in synthesis.[1] By contrast the formation and uses of alkoxy radicals have been less well documented.[2a-c] We now wish to report the use of nitrate esters as alkoxy radical precursors.[3]

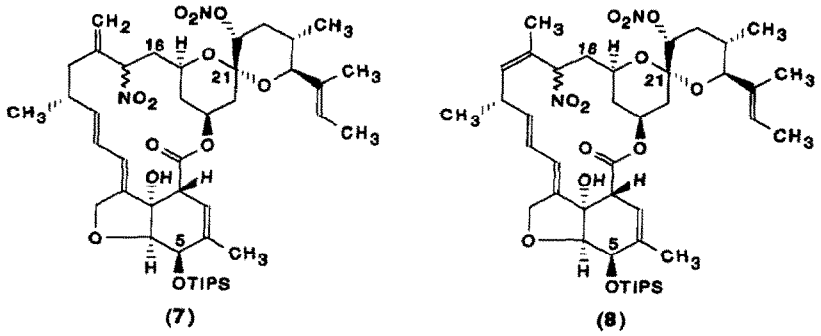
From these laboratories we have previously reported the synthesis of lactones such as (3) and have shown these to be highly versatile intermediates for the preparation of semi-synthetic milbemycins.[4a-c] We have actively been looking for alternative ways to make lactone (3) and postulated that an alkoxy radical such as (6) might fragment to give the desired lactone (Scheme 1). The nitrate ester (2),[5,6] formed from (1) using fuming nitric acid (2 equivalents) and acetic anhydride, was smoothly converted to the radical (6) using tributyltin hydride (1.5 equivalents), which underwent rapid fragmentation to provide lactone (3). The yields in Scheme 1 are of isolated products and are unoptimized.



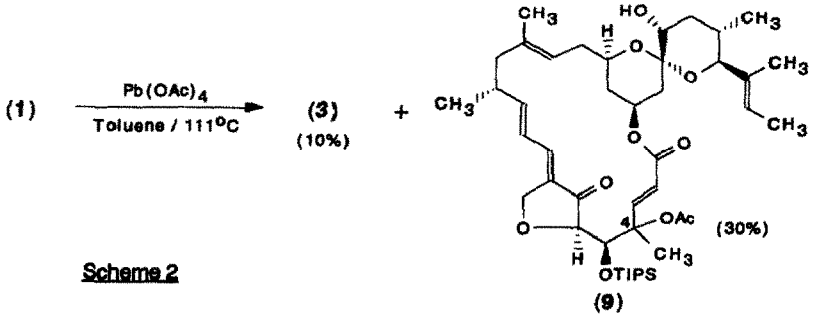
Scheme 1



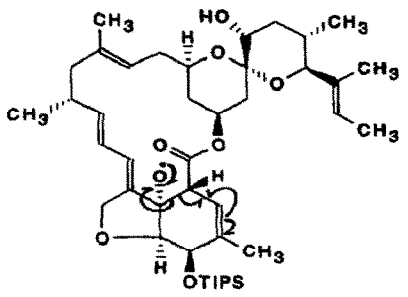
A probable mechanism involves (4) - (6) and is shown above. It is interesting that no alcohol (1) was formed from the radical (6), implying that the fragmentation is preferred to H-abstraction. During the nitration step two by-products are formed (combined yield of 6%) and found to be over-nitrated products (7) and (8). To overcome this and the potential explosive hazard of fuming nitric acid and acetic anhydride, alternative methods for generation of (2) were briefly investigated. Treatment of alcohol (1) with nitronium tetrafluoroborate gave no nitrate ester (2) but deprotection at C5 occurred. The addition of collidine (2,4,6-trimethyl pyridine) to nitronium tetrafluoroborate has been reported to produce a milder nitrating agent[7] and indeed with our substrate did provide the nitrate ester (2). The reaction gave no by-products (7) or (8) but the yields of (2) were low (41%) mainly due to decomposition.



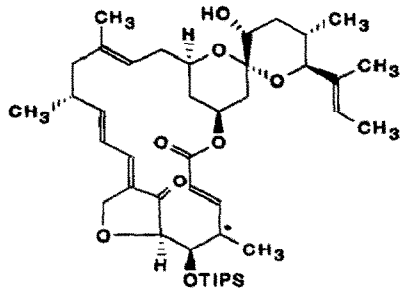
Lead tetraacetate has been used previously to form cyclic ethers from alcohols[8] and is presumed to involve an alkoxy radical. Thus, the alcohol (1) was heated at reflux in toluene with lead tetraacetate (3 equivalents) and resulted in the formation of lactone (3) in very low yield (10%) but gave, in far greater quantities, the enone (9)[9] (Scheme 2). This material presumably arises from radical (10) which is converted to radical (11) before conversion to (9). The stereochemistry at C4 in (9) was not determined, although it was found to be a single isomer.



Scheme 2

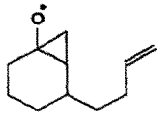


(10)

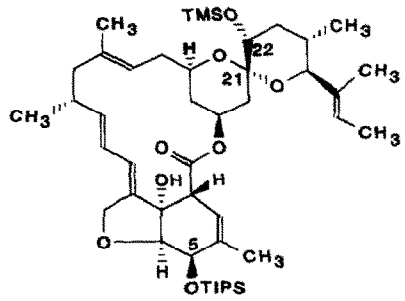


(11)

Recently Booker-Milburn[10] has reported the ring expansion and tandem cyclization of cyclopropyl silyl ethers when treated with ferric chloride. The process is implied to involve an alkoxy radical (12). This chemistry was repeated on the silyl ether (13) [formed in good yield from (1) using trimethylsilyl chloride and imidazole in DMF] with a view to generating radical (6) but only removal of the C22 - trimethylsilyl group occurred.[11] Many other methods to generate radical (6) have been investigated but with little success to date.



(12)



(13)

In conclusion it has been demonstrated that nitrate esters are good precursors for alkoxy radicals and in our case an elegant synthesis of lactone (3) is achieved.

ACKNOWLEDGEMENTS:

We thank the Analytical Services Unit at Great Burgh for the spectral data. We are indebted to Dr. David C. Lathbury (SmithKline Beecham Pharmaceuticals, Tonbridge, Kent.) and Dr. Roderick J. J. Dorgan (SmithKline Beecham Animal Health, Tadworth, Surrey.) for helpful advice and suggestions.

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2. For examples see: a) Akhtar M., *Adv. in Photochemistry*, **1964**, *2*, 263. b) Kraus G. A. and Thurston J., *Tetrahedron Lett.*, **1987**, *28*, 4011. c) Senkoku H., Suginome H. and Tsunetoshi A., *J. Chem. Soc. Perkin Trans. I*, **1992**, 2917.
3. For previous examples of the generation of alkoxy radicals by $^{n}Bu_3SnH$ treatment of nitrate esters see: 1. Vite G. D. and Fraser-Reid B., *Synth. Commun.*, **1988**, *18*, 1339. 2. Begley M. J., Fletcher R. J., Murphy J. A. and Sherburn M. S., *J. Chem. Soc., Chem. Commun.*, **1993**, 1723 and references cited therein.
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5. All new compounds were characterized by Mass-spec., ^{1}H nmr and ^{13}C nmr.
6. Partial ^{1}H nmr (270MHz, $CDCl_3$): δ 5.72(2H, m), 5.44(1H, m), 5.30(3H, m), 4.95(1H, m), 4.72(1H, m), 4.55(3H, m), 3.81(1H, d(J=5.2Hz)), 3.78(1H, bs), 3.55(1H, m), 3.50(1H, d(J=9.3Hz)), 3.36(1H, m), 1.86(3H, s), 1.66(3H, d(J=6.3Hz)), 1.60(3H, s), 1.55(3H, s), 1.11(18H, bs), 0.99(3H, d(J=6.6Hz)) and 0.76(3H, d(J=5.8Hz)). ^{13}C nmr (67.8MHz, $CDCl_3$): 173.66ppm, 142.34, 139.91, 137.74, 137.52, 133.28, 124.52, 123.41, 120.33, 119.16, 117.17, 97.05, 81.80(2 carbons), 80.58, 80.00, 69.39, 68.29, 68.02, 67.71, 48.47, 45.86, 36.72, 35.79(2 carbons), 34.38, 32.37, 31.30, 22.33, 20.19, 18.17(3 carbons), 18.02(3 carbons), 17.24, 15.58, 13.15, 12.70(3 carbons) and 10.90. MS (FAB, NOBA/Na): m/z 808(MNa^+) and 785(M^+).
7. Cupas C. A., Narang S. C., Olah G. A., and Pearson R. L., *Synthesis*, **1978**, 452.
8. March J., *Advanced Organic Chemistry*; John Wiley and Sons,Inc.:New York, 1985; pp. 631-632.
9. Partial ^{1}H nmr (400MHz, $CDCl_3$): δ 6.79(1H, m), 6.64(1H, d(J=16.0Hz)), 5.85(2H, m), 5.77(1H, d(J=16.0Hz)), 5.32(2H, m), 5.00(1H, m), 4.77(1H, dd(J=14.3 and 2.2Hz)), 4.62(1H, dd(J=14.3 and 2.5Hz)), 4.58(1H, d(J=1.1Hz)), 4.06(1H, s), 3.61(1H, m), 3.36(1H, d(J=10.2Hz)), 3.32(1H, m), 2.55(1H,m), 1.95(3H,s), 1.84(3H, s), 1.63(3H, d(J=6.7Hz)), 1.60(3H, s), 1.53(3H, s), 1.12(18H, bs), 1.01(3H, d(J=6.7Hz)) and 0.68(3H, d(J=6.6Hz)). ^{13}C nmr (100MHz, $CDCl_3$): 199.02ppm, 169.10, 164.51, 154.25, 148.41, 136.26, 134.23, 132.64, 129.24, 124.97, 123.45, 122.05, 120.70, 98.77, 86.48, 85.17, 81.88, 77.16, 71.44, 68.02, 67.20, 67.10, 47.67, 37.11, 36.97, 36.66, 35.79, 34.45, 32.04, 22.40, 21.82, 18.12(6 carbons), 17.56(2 carbons), 16.15, 13.07, 12.93(3 carbons) and 10.85. MS (FAB, NOBA/Na): m/z 821(MNa^+).
10. Booker-Milburn K. I., *Synlett.*, **1992**, 809.
11. During the preparation of this manuscript another paper by Booker-Milburn K. I. and Thompson D. F. (*Synlett.*, **1993**, 592) was published and implied that the radical (**12**) in fact originates from an iron (III) homoenolate and not from direct fragmentation of the parent cyclopropylsilyl ether. This was further substantiated by treatment of cyclohexanol trimethylsilyl ether under the same conditions resulting in hydrolysis to cyclohexanol and not to the generation of the alkoxy radical. Thus, our result is consistent with these recent findings.

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