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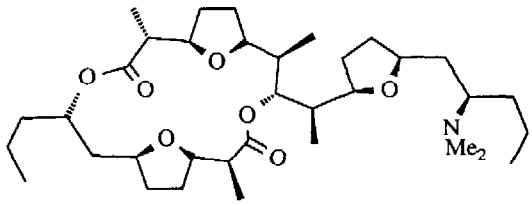
A NEW APPROACH TO THE PREPARATION OF 2-SUBSTITUTED TETRAHYDROFURANS WITH ALPHA-SYN SELECTIVITY

Keith T. Mead* and Hui-Li Yang
Department of Chemistry, Mississippi State University, Mississippi State, MS 39762

Abstract: A strategy for selectively preparing 2-substituted tetrahydrofurans bearing α-syn side chain stereochemistry, based on intramolecular 2-oxetanone ring opening, has been demonstrated. A new approach to the preparation of 3,4-disubstituted 2-oxetanones is also presented.

A substituted oxygen heterocycle possessing side chain chirality is a characteristic feature of a multitude of biologically-active natural products, and an array of methodologies directed at assembling these structural fragments in stereocontrolled fashion has been reported in recent years.[1]

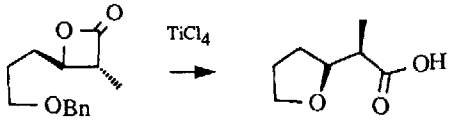
We are currently interested in the polyether antibiotic pamamycin-607 (Figure 1), a molecule that has recently been shown to consist of a series of cis 2,5-disubstituted tetrahydrofuran units bearing both syn and anti stereocenters alpha to a ring.[2] It is our observation that while adequate methodology exists for the selective generation of furanoid systems with α-anti side chain stereochemistry,[3] few routes specific to the syn arrangement have been reported.[4]



Pamamycin-607

Figure 1

Addressing this problem, we set out to see if intramolecular ring opening of a trans disubstituted 2-oxetanone derivative by an internal oxygen atom would provide a viable solution (see Figure 2). Model studies using 4-(3-benzyloxypropyl) analogs have already shown that this mode of ring formation can be initiated by a wide range of Lewis acids.[5] Our next goal was to prepare the 3-methyl derivative (1) stereoselectively to see if the reaction proceeds in a stereospecific manner with inversion of stereochemistry at the point of ring cleavage.



(1)

Figure 2

In our approach to lactone (1), our first initiative was to try to use face selectivity to secure the desired stereocontrol (see Figure 3). Mulzer has shown that enolates of 3,4-disubstituted 2-oxetanones can be generated and alkylated at low temperatures with high diastereofacial selectivity.[6] However, he also found that lactones unsubstituted at C-3 could not be intercepted, owing to problems of self-condensation. This, indeed, was our own observation.

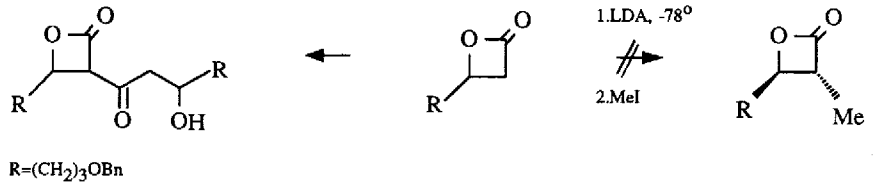


Figure 3

3-Trimethylsilyl-substituted 2-oxetanones, readily available by 2+2 cycloaddition reaction,[7] appeared to offer a solution to this dilemma. We reasoned that if fluoride-mediated enolate formation from these intermediates were possible, the problems previously encountered would be circumvented. After numerous attempts using a variety of fluoride reagents (e.g. Bu_4NF, CsF) we were pleased to find some success with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF).[8] Thus, desilylative alkylation of lactone (2) was eventually acheived, albeit in moderate and variable yield, by the slow addition of this 2+2 adduct to a rapidly-stirred suspension of TASF and methyl iodide (5 molar equivalents) in tetrahydrofuran at 0°C (Figure 4).

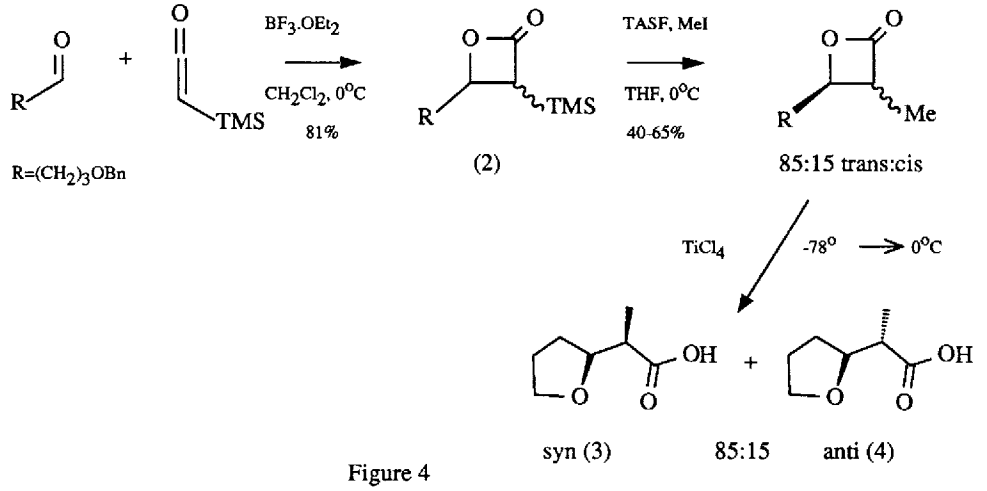


Figure 4

300 MHz Proton NMR identified the major product as the trans isomer,[9] and HPLC analysis (hexane-THF 15:1) was used to establish 85:15 as the trans-cis ratio. More important, treatment of this mixture with titanium tetrachloride (1 molar solution in CH_2Cl_2) gave the same ratio of α-methylated tetrahydrofuran stereoisomers.[10] Following chromatographic separation of the isomers, spectral analysis identified the syn

stereoisomer (3) as the major component.[11] It appears, then, that intramolecular lactone ring opening proceeds, as expected, with complete inversion of stereochemistry.

Other features of the alkylation step are worthy of mention. Rapid addition of lactone (2) to TASF resulted in the formation of significant amounts of dimethylated product along with unmethylated material, presumably a result of rapid proton exchange between the initially-formed enolate and unenolized lactone (Figure 5). The use of lower temperatures also led to increased dimethylation with, surprisingly, no increased trans selectivity observed in the monomethylated product. Using the conditions described, however, the ratio of monomethylated to dimethylated product was increased to 11:1.

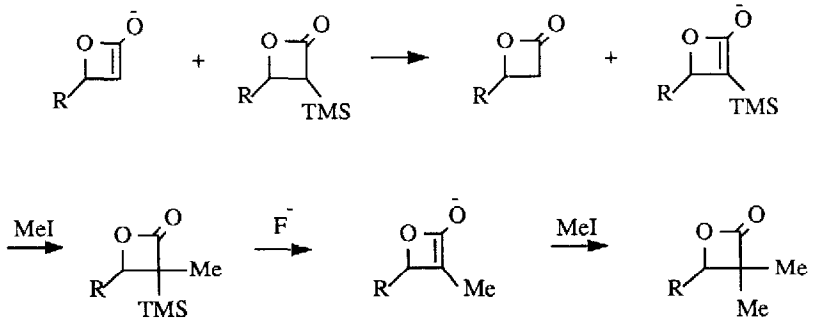


Figure 5

It should be stated that the alkylation of lactone (2) as described (see Figure 4) was often accompanied by significant amounts of unalkylated (desilylated) material, the reasons for which are unclear at this stage. Attempted high vacuum distillation of lactone (2) prior to alkylation unfortunately resulted in substrate decarboxylation, forcing us to rely on chromatographic separation (silica gel, pentane-ether) for purification purposes. Inadequate purification of (2) not being ruled out as a potential source of our problem, an extensive alkylation study involving distillable relatives of this lactone[7] is currently underway in our laboratory, the results of which we hope to report in due course. Whatever the outcome, we believe the use of methyl trimethylsilyl ketene in the 2+2 cycloaddition reaction will provide for us a useful alternative route to lactones such as (1).[12]

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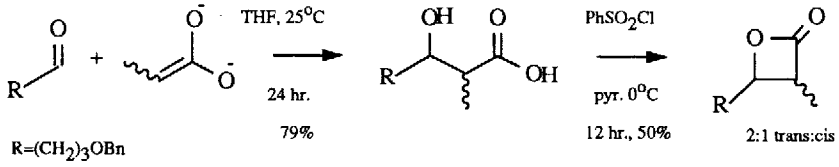
References and Notes

1. For leading references on this topic, see: M. F. Semmelhack and N. Zhang, *J. Org. Chem.* 1989, 54, 4483; M. McCormick, R. Monahan III, J. Soria, D. Goldsmith, and D. Liotta, *J. Org. Chem.* 1989, 54, 4485, and

references cited therein.

2. S. Kondo, K. Yasui, M. Katayama, S. Marumo, T. Kondo, and H. Hattori, *Tetrahedron Lett.* 1987, 28, 5861.
3. For recent examples, see: M. J. Taschner and D. J. Black, *J. Am. Chem. Soc.* 1988, 110, 6892; A. Warm and P. Vogel, *Tetrahedron Lett.* 1986, 27, 5615.
4. For a recently reported approach to these systems, and its application to the synthesis of the southern portion of pamamycin-607, see: R. D. Walkup and G. Park, *Tetrahedron Lett.* 1988, 29, 5505. For other α-syn selective routes to 2-substituted tetrahydrofurans, see: S. Batmangherlich, A. H. Davidson, and G. Procter, *Tetrahedron Lett.* 1983, 24, 2889; R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, *J. Org. Chem.* 1980, 45, 48
5. (a) K. T. Mead and B. Samuel, *Tetrahedron Lett.* 1988, 29, 6573; (b) K. T. Mead and H.-L. Yang, paper submitted to the *Journal of Organic Chemistry*.
6. J. Mulzer and T. Kerkmann, *J. Am. Chem. Soc.* 1980, 102, 3620.
7. W. T. Brady and K. Saidi, *J. Org. Chem.* 1979, 44, 733.
8. Purchased from Aldrich Chemical Company.
9. Spectral data for the lactone mixture: IR (soln. CCl_4) 1840cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.3-7.4 (5H,m), 4.5 (2H,s), 4.22 (1H,dt, J=3.75Hz, 6.6Hz), 3.49-3.60 (2H,m), 3.23 (1H,dq, J=6Hz, 3Hz), 1.67-1.96 (4H,m), 1.36 (3H,d, J=6Hz *trans*), 1.27 (3H,d, J=6Hz *cis*). These spectral data matched those of the same lactone mixture prepared (see below) using standard methods.[13]



The trans stereoisomer was identified by the coupling constant between the C-3 and C-4 protons (3Hz). See: W. T. Brady and L. Smith, *Tetrahedron Lett.* 1970, 2963.

10. The ratio of isomeric products (3) and (4) was determined by 300 MHz proton NMR spectroscopy and confirmed by HPLC analysis of their benzyl esters.
11. Syn acid (3): IR (soln. CCl_4) 1725cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 4.13 (1H,m), 3.92-3.77 (2H,m), 2.62 (1H,dq, J=7Hz, 7Hz), 2.08-1.87 (3H,m), 1.70-1.63 (1H,m), 1.25 (3H,d, J=7Hz); ^{13}C NMR (75.6 MHz, $CDCl_3$): 179.42, 79.99, 68.26, 44.14, 29.22, 25.71, 13.35; methyl ester:^{1}H NMR 1.23 (3H,d, J=7Hz), lit.[14]: 1.25; anti acid (4):^{1}H NMR 1.18 (3H,d, J=7Hz).
12. While this work was in progress, Kocieński and Pons reported the preparation and 2+2 cycloaddition of hexyl trimethylsilyl ketene as an efficient route to the trans 3,4-disubstituted 2-oxetanone moiety of (-)-tetrahydrolipstatin: J.-M.Pons and P. Kocienski, *Tetrahedron Lett.* 1989, 30, 1833.
13. W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.* 1972, 94, 2000.
14. F. H. Gouzoules and R. A. Whitney, *Tetrahedron Lett.* 1985, 26, 3441.

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