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CESIUM FLUORIDE MEDIATED INTRAMOLECULAR CONJUGATE-ADDITION REACTIONS OF ALPHA SULFONYL ESTER TO ENONES AND ALPHA-CHLOROENONES[1]

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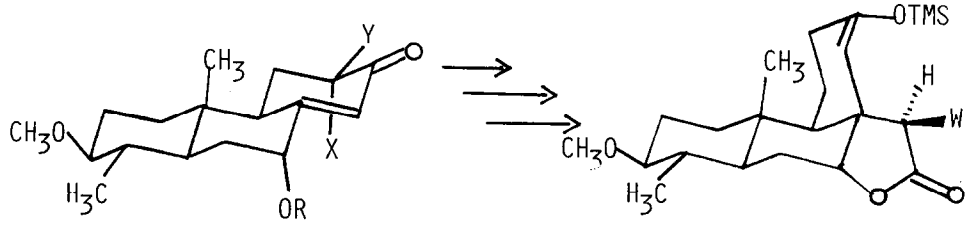
Abstract - Cesium fluoride is a useful catalyst to effect the intramolecular conjugate-addition of alpha-sulfonyl esters to enones; similar reaction with alpha-chloroenones provides fused cyclopropane adducts.

In the course of our studies directed toward the total synthesis of the quassinoidal antileukemia agent bruceantin we required a regiospecific method for conversion of the readily available gamma-hydroxy enone 1[2] to trimethylsilyl enol ether 5.



5

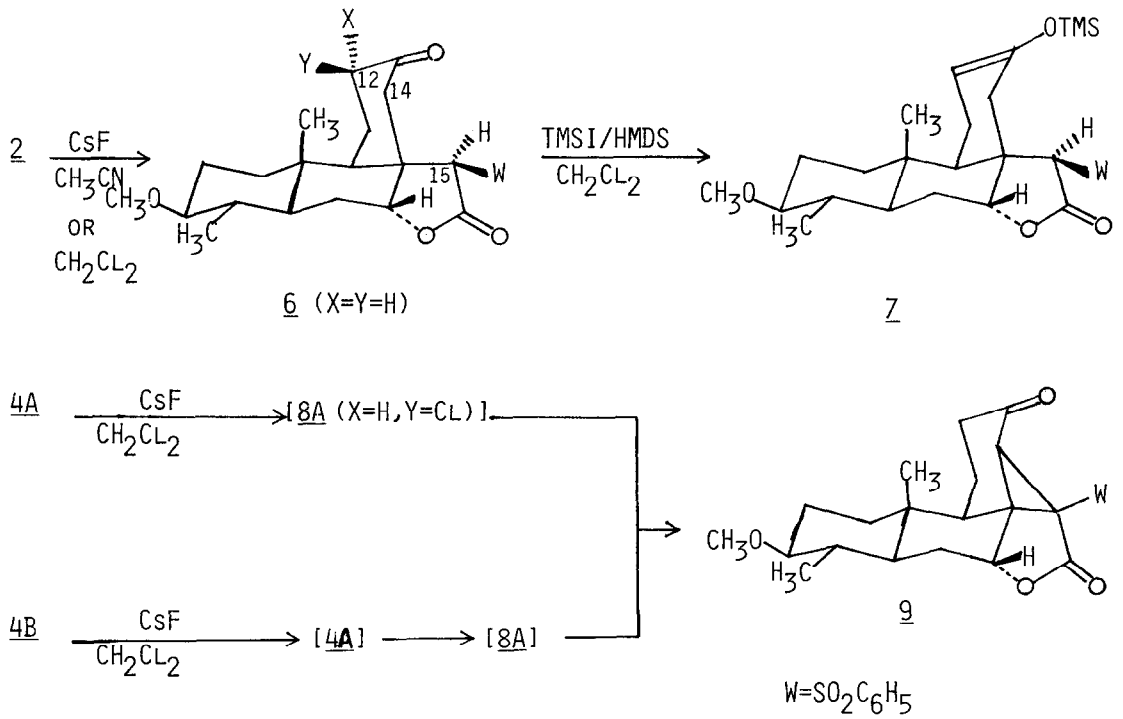
W = $SO_2C_6H_5$

1 (X=Y=H, R=H)
2 (X=Y=H, R=$COCH_2W$)
3A (X=Cl, Y=H, R=H)
3B (X=H, Y=Cl, R=H)
4A (X=Cl, Y=H, R=$COCH_2W$)
4B (X=H, Y=Cl, R=$COCH_2W$)

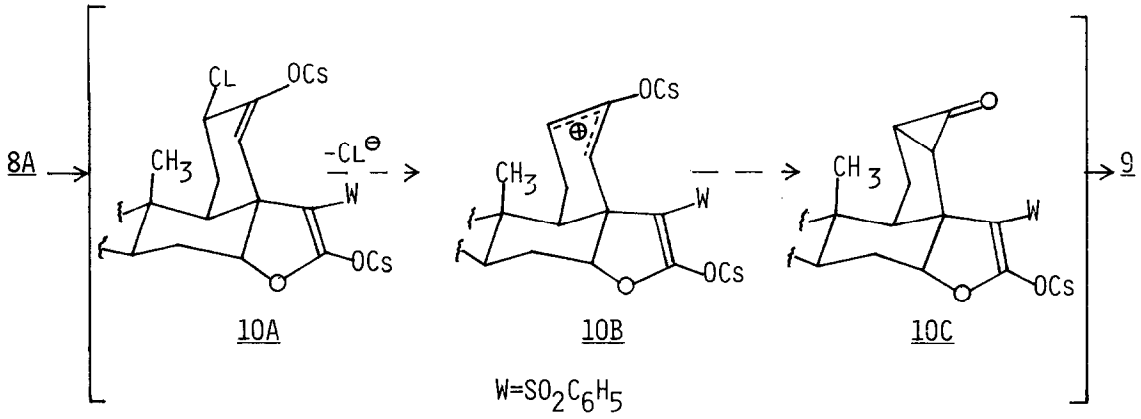
Treatment of 1 with benzenesulfonylacetic acid and DCC in methylene chloride from 0° C to 25° C over two hours affords the activated ester 2 (mp 143-45° C) in 90% isolated yield.[3] Cyclization of 2 to the tetracyclic lactone 6 (mp 214-15° C) is most effectively accomplished by treatment with anhydrous cesium fluoride[4] in either acetonitrile or methylene chloride (84% yield). Silylation of 6 under the conditions of

Miller and McKean[5] provides a single silyl enol ether 7 (95%)[3] which is regioisomeric with the desired silyl enol ether 5.

An efficacious solution to this problem was provided in the following manner: Reaction of 1 with LDA (2.2 eq) at -78° C for 1 hr followed by addition of N-chlorosuccinimide (2.2 eq) and allowing the reaction mixture to warm to 25° C affords a mixture of alpha-chloroenones 3A (44%, mp 106-10° C {d})[3] and 3B (33%, mp 150-55° C {d})[3] after chromatography on silica. Individual treatment of each of these enones with DCC and benzenesulfonylacetic acid provides 4A (94%, mp 169-70° C)[3] and 4B (95%, mp 179-80° C)[3] respectively. Cyclization of either 4A (12hr, 25° C) or 4B (24 hr, 25° C) under the cesium fluoride-mediated conditions affords the same pentacyclic cyclopropane 9 (91% and 83% respectively, mp 220-21° C).[3,6] Careful HPLC analysis of the course of this reaction reveals that 4A produces a mixture of intermediates (presumably 8A as well as its C-12 and C-15 epimers) along with minor amounts of isomer 4B.[7] Similar examination of the cyclization of 4B reveals isomerization to 4A along with production of the same group of intermediates prior to conversion to pentacyclic cyclopropane 9.



While it seems highly likely that both isomers 4A and 4B cyclize to 9 through the intermediacy of chloride 8A, the further mechanistic details of this transformation are less obvious. The manifold of potential intermediates would seem to include enolate 10A, oxallyl cation 10B, and/or cyclopropanone 10C.[8] Cyclopropanone 10C would seem to be a less likely candidate than 10A and/or 10B since it requires front-side attack by the lactone enolate; a choice between 10A and 10B cannot be made with the current information in hand.[9]



Mechanistic details notwithstanding, tricyclic 9 is an excellent progenitor for the requisite silyl enol ether 5. Simple treatment of 9 in the presence of trimethyl chlorosilane under reductive conditions ($(CH_3)_2CuLi$) produces 5 as a single regioisomer (94%).

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1. Bruceantin Support Studies 6. For Paper 5 see R. J. Pariza, P. L. Fuchs, J. Org. Chem., 48, 2306 (1983).
2. S. N. Suryawanshi, P. L. Fuchs, Tetrahedron Lett., 4201 (1981).
3. All new compounds have satisfactory 470 MHz ^{1}H NMR, ^{13}C NMR, exact mass and/or combustion analysis. Experimental details for this transformation will be published in a full paper in due course.
4. For use of fluoride ion as a base in organic synthesis see (a) J. H. Clark, Chem. Rev., 80, 429 (1980); (b) G. G. Yakobson, N. E. Akhmetova, Synthesis, 169 (1983); (c) E. Vedejs, G. R. Martinez, J. Am. Chem. Soc., 101, 6452 (1979).
5. R. D. Miller, D. R. McKean, Synthesis, 730 (1979).
6. For preparative purposes the 3A/3B mixture is not separated but directly converted to 4A/4B and cyclized to 9 in 60% yield on a 40 mmol scale.
7. Supportive evidence for the presence of monocyclized adduct 8A was obtained in a related cyclization of the C-3 ketal-protected analog of 4A. This substrate, when cyclized with cesium fluoride in acetonitrile afforded a highly insoluble monocyclized adduct which proved to be the C-3 ketal of 8A. Further subjection of this material to cesium fluoride in methylene chloride provided the C-3 ketal of 9 in near-quantitative yield.
8. These intermediates are all written as their C-15 enolates, although it seems apparent that reversible deprotonation is also occurring at C-12, C-14, and C-15.
9. Examples of the S_N2' reaction of an alpha-sulfonyl ester with beta'-enol ether derivatives (palladium [0]-pi allyl intermediate) have been recorded by Trost and Gowland: [J. Org. Chem., 44, 3448 (1979)]; A failure of the intramolecular variant of this strategy which would have lead to a cis-fused bicyclo[4.3.0] system has also been recorded by Trost, Bernstein, and Funfschilling [See reference 13 in J. Am. Chem. Soc., 101, 4378 (1979)]; "Harder" nucleophiles such as organometallic reagents are also known to undergo S_N2' addition to the enolates (and enol ether derivatives) of alpha-substituted ketones: [See J. P. Marino, J. C. Jaen, J. Am. Chem. Soc., 104, 3165 (1982) and P. A. Wender, J. M. Erhardt, L. J. Letendre, J. Am. Chem. Soc., 103, 2114 (1981) and references therein].

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