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SILICON IN SYNTHESIS: USE OF THE HIGHLY NUCLEOPHILIC TRIMETHYLSILYLALLYL ANION FOR THE SYNTHESIS OF STEROIDAL 17-SPIRO-γ-LACTONES

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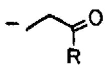
Summary. Trimethylsilylallylzinc chloride 2 (M = ZnCl) reacts with 17-ketosteroids to give adducts 4 that can be converted into 17-spirolactones.

Despite the impressive amount of research devoted to β-acylanion equivalents 1 based upon the ambident reactivity of allylanions,[1] this effort has not culminated in any single reagent that exhibits the required nucleophilicity to add to a 17-ketosteroid.[2] Here we report that the allyltrimethylsilyl anion 2, under properly defined conditions, functions as a β-acylanion (homoenolate) equivalent with both excellent regioselectivity (γ-attack) and high nucleophilicity towards 17-ketosteroids.[3]

Treatment of allyltrimethylsilane[4] with s-butyllithium (1M in cyclohexane)



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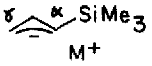

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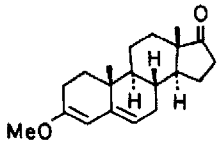
in tetrahydrofuran containing tetramethylethylenediamine (1.0 equiv.) at -70°, then warming to -40° gave solutions of 2 (M = Li). Treatment of this solution with 3-methoxyandrost-3,5-dien-17-one 3, gave 4, (65%) along with starting material 3, and a small amount of diene 5 (*ca*. 5%) resulting from *α*-attack and elimination of Me_3SiO^-.[5] This unsatisfactory state of affairs was resolved by treating the solution of 2 (M = Li) with freshly dried zinc chloride at -40° to give 2 (M = ZnCl).[5] This solution, when treated with 3 gave the adduct 4 , which on acid hydrolysis of the dienolether 4 gave 6, in 82% overall yield, and *ca*. 1% testosterone. No trace of diene 5 could be detected when the trimethylsilylallylzinc chloride 2 (M = ZnCl) was used. Attempts to epoxidize the vinylsilane double bond in 6 using various peracids under a number of conditions gave complex mixtures that had the A-ring enone destroyed. The Sharpless procedure



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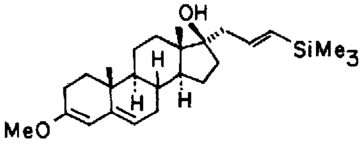

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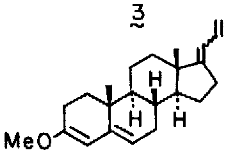

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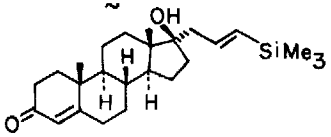

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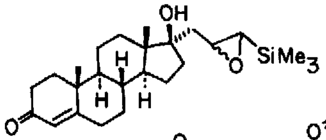
[VO acac$)_2$/t-BuOOH in benzene][6] solved this problem and gave selective oxidation of the vinylsilane double bond in 6 without any destruction of the ring-A-enone, yielding 7 (90%), as a mixture of diastereomers. Exposure of the *α,β*-epoxysilane 7 to methanol containing a catalytic amount of borontrifluoride etherate gave the O-methyllactol 8, as a mixture of epimers at the acetal (C-22) carbon in 90% yield. The spirocyclic *O*-methyl lactol 8, is a precursor to the spirolactone 9, a useful aldosterone antagonist.[7]

Oxidation of 8 with Jones reagent gave the spirolactone 10, ν_{max} 1765, 1665 ($CHCl_3$) cm^{-1}. m.p. 145-148° in 80% yield.

An entirely analogous sequence of reactions starting with estrone-methylether 11 gave the estrogen-17-spiro-γ-lactone 12.



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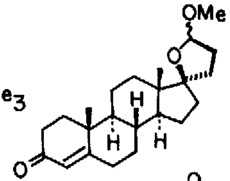

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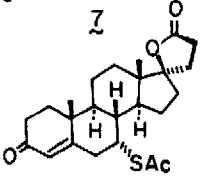

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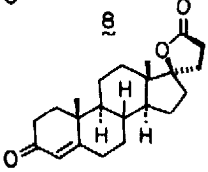

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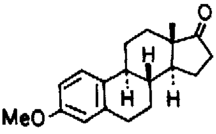

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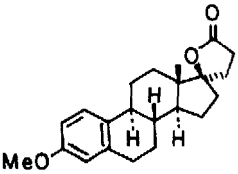

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In conclusion the allyltrimethylsilylanion 2, as described here, provides a highly nucleophilic species that adds to 17-ketosteroids in excellent yields. The mild and selective oxidation of the 4-hydroxyvinylsilane 6 to the α,β-epoxyvilane 7 illustrates that this functional array may be manipulated in the presence of other oxidizable groups to provide important steroidal γ-lactones.

Acknowledgment. The authors gratefully thank the UpJohn Company for their support of this research.

References and Notes

1. For a recent comprehensive study of phosphonamide stabilized allylanions and extensive references to allylanions see - Evans, D.A.; Takacs, J.M.; Hurst, K.M., J. Am. Chem. Soc., 1979, 101, 371.

2. For another solution that avoids the ambident reactivity of allyl anions, the diphenylsulfonium cyclopropylide → oxaspiropentane → cyclobutanone → γ-lactone sequence developed by Trost offers a versatile solution - Trost, B.M.; Bogdanowicz, M.J., J. Am. Chem. Soc., 1973, 95, 5321. Lithium β-lithiopropionate adds 17-ketosteroids albeit in rather low yield (28%) to give a γ-lactone. Caine, D.; Frobese, A.S.; Tetrahedron Letters, 1978, 883.

3. For references to Allyltrimethylsilylanion see - Chass, A.C.; Ehlinger, E.; Magnus, P.; *J.C.S. Chem. Comm.*, 1977, 772; Corriu, R.J.P.; Masse, J; *J. Organometallic Chem.*, 1973, **57**, C5; Corriu, R.J.P.; Masse, J.; Samate, D. *Ibid.*, 1975, **93**, 71; Corriu, R.J.P.; Lanneau, G.F.; Masse, J.P.; Samate, D., *Ibid.*, 1977, **127**, 281; Lau, P.W.K.: Chan, T.H., *Tetrahedron Letters*, 1978, 2383. Chan reports that **2** (M = MgBr) reacts with ketones to give mixtures of *α* and *γ* products. Recently *gem*-chloro(trimethylsilyl)allyllithium has been reported Seyferth, D.; Mammarella, R.E.; *J. Organometallic Chem.*, 1978, **156**, 279; Ehlinger, E.; Magnus, P.; *J.C.S. Chem. Comm.*, 1979, 548.
4. Allyltrimethylsilane is commercially available from Petrarch Systems, Inc.,
5. Dr. J. R. Parikh (UpJohn) is thanked for this initial observation. For examples of zinc allyl species where *α*-attack is promoted see - Evans, D. A.; Andrews, G. C.; Buckwalter, A. B.; *J. Am. Chem. Soc.*, 1974, **96**, 5560; and Martin, S. F.; DuPriest, M. T.; *Tetrahedron Lett.*, 1977, 3925.
6. Sharpless, K.B.; Michaelson, R.C.; *J. Am. Chem. Soc.*, 1973, **95**, 6136; Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K.B.; Michaelson, R.C.; Cutting, J.D.; *J. Am. Chem. Soc.*, 1974, **96**, 5254.
7. Cella, J.A.; Kagawa, C.M.; *J. Am. Chem. Soc.*, 1957, **79**, 4808; Cella, J.A.; Brown, E.A.; Burtner, R.R.; *J. Org. Chem.*, 1959, **24**, 743; Heusler, K.; *Helv. Chim. Acta.*, 1962, 1939, Atwater, N.W.; Bible, R.H., Jr.; Brown, E.A.; B. Burtner, R.R.; Mihina, J.S.; Nysted, L.N.; Sollman, P.B.; *J. Org. Chem.*, 1961, **26**, 3077. For recent extensions of this area of steroid research see - Lenz, G.R.; Schulz, J.A.; *Ibid.*, 1978, **43**, 2334; Neef, G.; Eder, U.; Wiechert, R.; *Ibid.*, 1978, **43**, 4679. Bormann, D., *Chem. Brit.*, 1979, 72.
8. J. Timko (UpJohn) is thanked for an authentic sample of **10**.

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