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AN APPROACH TO ERIOLANIN. SYNTHESIS OF α-METHYLENE LACTONES OF TRANS-1,3-DIHYDROXYCYCLOHEXANES

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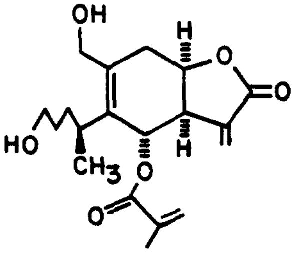
Abstract: A new synthesis of α-methylene lactones is discussed which incorporates an intramolecular epoxide opening with a vinyl anion.

As part of our proposed synthesis of eriolanin (1),[1] we required methodology for the synthesis of the lactone portion of 1 which incorporated stable, latent functionality that could be easily transformed into the α-methylene lactone moiety. Although numerous methods exist for the synthesis of α-methylene-γ-butyrolactones fused to cyclohexanes,[2a] few direct methods are available for the preparation of α-methylene-γ-butyrolactones of trans-1,3-dihydroxycyclohexanes.[2b] We wish to report the successful synthesis of 2, a model for the lactone portion of 1. The α-methylene lactone of a trans-1,3-diol is a structural unit also found in the pseudoguaianolide helenalin (3).[3]



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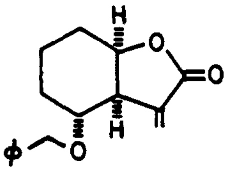

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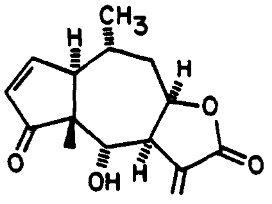

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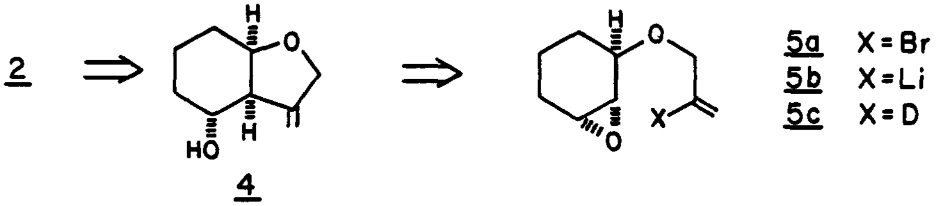
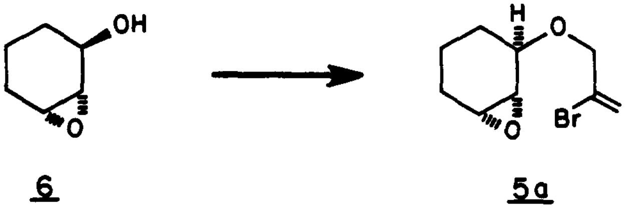
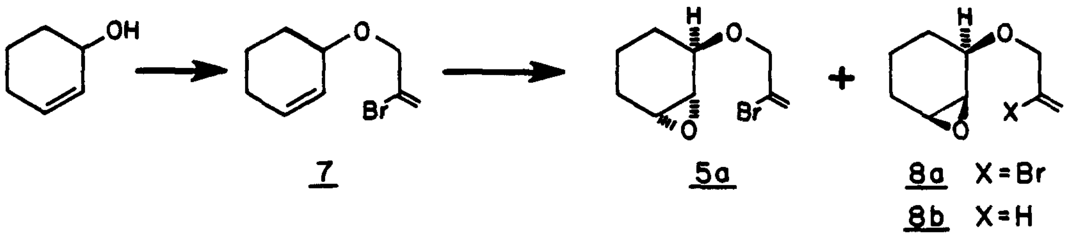
Our plan was to use an intramolecular epoxide opening of vinyl anion 5b to give 4. We felt that allylic ether 4 would serve as stable latent functionality which could be easily converted to the α-methylene lactone 2 by selective allylic oxidation.



The initial attempts to synthesize 5a were not promising. Alkylation of epoxy alcohol 6[4] using 2,3-dibromopropene under a variety of different conditions[5] gave only low yields (5-10%) of vinyl bromide 5a. However, using



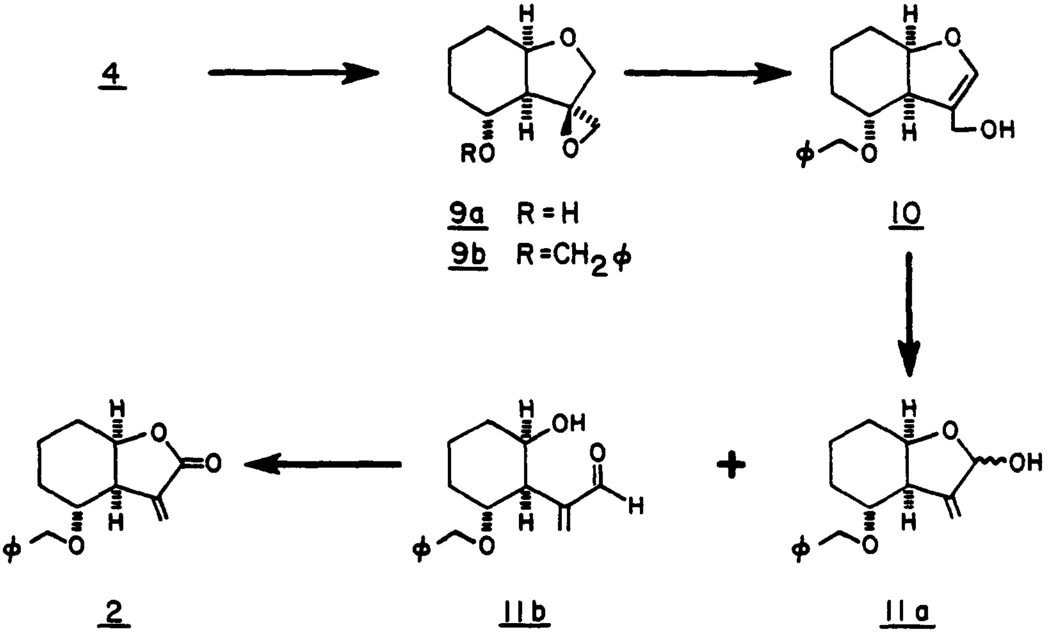
solvolytic conditions, epoxy bromide 5a could be prepared in good yield. Treatment of 2-bromo-2-propenol[6] with cyclohexenol (2.0 equiv. in 3 portions) and a catalytic amount of p-toluenesulfonic acid in benzene at 65°C for 18 h gave an 81% yield of ether 7. Epoxidation (mCPBA, 25°C, CCl_4, 12 h)



gave rise to an 85% yield of a 7:1 mixture of desired epoxide 5a and the corresponding cis isomer 8a.

The cyclization/epoxide opening proved troublesome.[7] The conversion of 5a to 4 was first attempted through the intermediacy of lithium reagent 5b. Initial experiments led only to the formation of allyl ether 5c after quenching the anion (tBuLi, Et_2O, -78°C) with a solution of D_2O in THF. None of the desired bicyclic alcohol was obtained even after 8 h at -78°C. Epoxy alcohol 6 was the only product formed at higher temperatures (-40°C, -20°C). However, we found that the cuprate formed from vinyl bromide 5a produced the desired result.[8] Treatment of vinyl bromide 5a with 4 equiv of nBu_2CuLi (2 h, Et_2O) at -78°C provided alcohol 4 in 89% yield. (Under the same conditions, cis epoxy bromide 8a gave rise to ether 8b.) ^1H NMR (270 MHz) and ^1H NOE difference experiments confirmed the stereochemistry of 4.[9] The successful cyclization/epoxide opening of 5a to give alcohol 4 establishes the cis ring fusion and the trans-1,3-diol functionality necessary for the synthesis of 1.

Conversion of 4 to α-methylene lactone 2 was carried out in the following way. Directed epoxidation ($VO(acac)_2$, tBuOOH, 25°C, 3 h)[10] in chloroform gave epoxide 9a (80% yield) as a single isomer, which was subsequently converted to benzyl ether 9b (THF, NaH, HMPA (4x), ϕCH_2Br, 16 h, 25°C, 91%). Base catalyzed rearrangement of the epoxide[11] using lithium diethylamide (3 equiv, Et_2O, 0°C, 4 h) yielded allylic alcohol 10 (61% yield).[12,13] Acid catalyzed rearrangement (5% H_2SO_4, THF, 30 min, 25°C) of 10 gave a mixture of 11a and 11b (90% yield) which was oxidized (MnO_2, CH_2Cl_2, 15h, 25°C)[14] to provide α-methylene lactone 2 (74% overall yield from 10).[15]



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2. a) Grieco, P.A. Syntheses 1975, 67. Hoffman, H.M.R.; Rabe, J. Angew. Chem. Int. Ed. Engl. 1985, 24, 94. b) For a related example, see: Marino, J.P.; Farina, J.S. J. Org. Chem. 1976, 41, 3213.

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5. Similar problems have been observed for the alkylation of alkoxides with 2,3-dibromopropene. Shi, L.; Narula C.; Mak, K.; Xu, Y.; Heck, R.F. J. Org. Chem. 1983, 48, 3894.

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9. ^{1}H NMR data 4 (CDCl$_3$): δ5.12 (bs, 1H); 4.94 (bs, 1H); 4.5 (d, J = 14 Hz, 1H), 4.31 (dt, J = 14, 2.5, 1H), 4.05 (dd, J = 3.5, 7.0, 1H) 3.46 (ddd, J = 10, 10, 4.5, 1H), 2.27 (dd, J = 10, 4.5, 1H), 1.9 (m, 2H), 1.6 (m, 3H), 1.35 (m, 1H).

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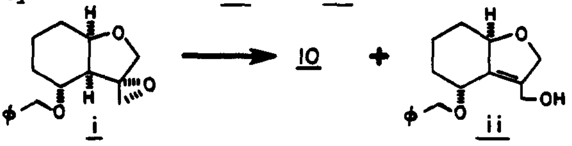
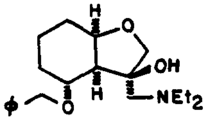
11. Crandall, J.K.; Apparu, M. Organic Reactions 1983, 29, 345.

12. Base catalyzed rearrangement of epoxide i [Prepared in 91% overall yield (5:1 mixture of i:9b) by the alkylation of 4 (NaH, THF, ϕCH$_2$Br, HMPA, 25°C, 8 h) followed by epoxidation (mCPBA, CCl$_4$, 25°C, 6 h)] gave a 2:1 mixture of allylic alcohols 10 and ii.



13. Ca. 10% of amine iii was observed in the ^{1}H NMR of the crude reaction mixture.



iii

14. Marshall, J.A.; Cohen, N. J. Amer. Chem. Soc. 1965, 87, 2773.

15. Major compounds have been characterized by ^{1}H NMR (270 MHz), IR, ^{13}C NMR, MS and combustion analysis or high resolution mass spectroscopy; all other compounds gave satisfactory spectral data.

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