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Furans in Synthesis. The Preparation of (±)-Lactaral

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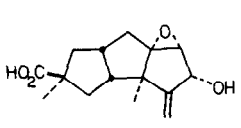
Summary: The Functionalized Grignard reagent 13 reacts with allylic chloride 14, in the presence of Li_2CuCl_4, to provide lactarol-THP ether 15a which is subsequently converted to (±)-lactaral 5 in 72% overall yield from 13.

The Basidomycotina subdivision of fungi have provided a myriad of terpenoid metabolites.[2] Notable among these structurally diverse natural products are the hirsutane sesquiterpenoids such as hirsutic acid 1,[3] the marasmanes illustrated by marasmic acid 2,[4] the fomannosanes such as fomannosin 3,[5] the lactaranes represented by lactarorufin A 4,[6] and the secolactarane lactaral 5[7]. As a result of the unique structures and the promising antibacterial and antitumor activities exhibited by several compounds of these types there has been considerable effort directed toward their total synthesis. These efforts have culminated in elegant syntheses of 1[3],2[4],3[5] and related compounds. However the lactaranes and seco-lactaranes have not been as thoroughly studied.[6b-d,7c]



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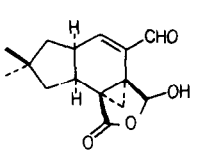

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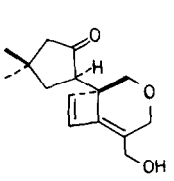

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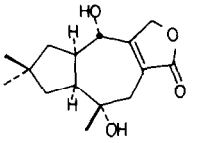

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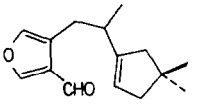

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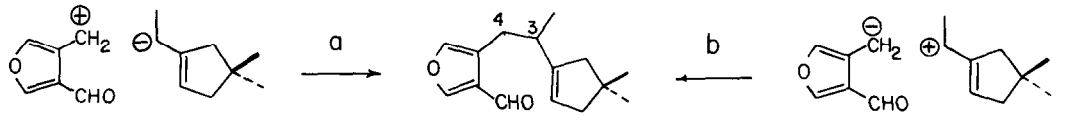
As part of a program directed toward the total synthesis of furan containing natural products we have undertaken a synthesis of (±)-lactaral 5. Central to the preparation of 5 and related compounds is the development of highly functionalized furans as viable synthons. In this letter we wish to report an efficient and convergent synthesis of (±)-5.

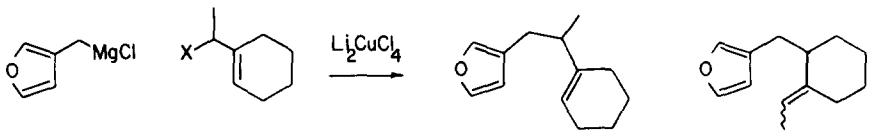


(1)

5

Intially we focused our attention upon the formation of the C-3 - C-4 bond (lactarane numbering) as the crucial step in the synthesis of (±)-5 (eq.1). This bond can be constructed in either of two polar senses. Path a utilizes an allylic nucleophile while path b employs a benzylic type nucleophile in the bond forming process. Based upon our earlier work[8] we have chosen the reverse polarity, relative to the normal use of substituted furyl methyl derivatives, path b route as the method of choice. This approach has a distinct regiochemical advantage over the path a construction in which an allylic carbanion is added to an electrophilic furyl methyl residue. Whereas an allyl organometallic may undergo rearrangement, the carbanion approach described in equation 1 allows the regiochemical integrity of the trisubstituted double bond to be retained.

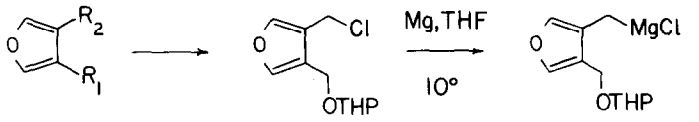
The synthesis of (±)-lactaral 5 via a path b approach requires a displacement by the furyl methyl carbanion upon the requisite allylic halide which proceeds in an SN_2 fashion and not SN_2'. Previously[8] we have noted the tendency of related furyl organometallics to yield mixtures of products resulting from SN_2 and SN_2' displacement when the halogen bearing carbon and the terminal olefinic carbon are sterically similar. To determine if mixtures of products might be obtained in the preparation of 5, we examined the model system illustrated in equation 2.



(2)

6 7 X = Br 8 X = Cl 9 (60%, 7:3) (47%, 100:0) 10

The reaction of Grignard reagent 6[8] with allylic bromide 7,[9b] in the presence of Li_2CuCl_4[10], afforded a 60% yield of a mixture 9[11] and 10[11] in the ratio of 7:3 as determined by 250MHz ^{1}H-NMR. However the coupling of 6 with the corresponding chloride 8[9c] provides only the desired 9 in 47% yield. It was gratifying to observe only the desired SN_2 substitution product from the reaction of 6 and 8, although the reasons for the observed selectivity are not immediately obvious.[12]



(3)

11a $R_1 = R_2 = CO_2Et$

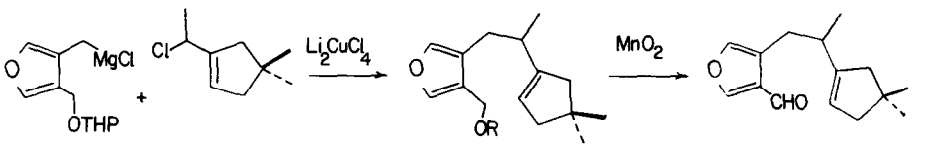
11b $R_1 = R_2 = CH_2OH$ (77%)

11c $R_1 = CH_2OTHP$, $R_2 = CH_2OH$ (50%)

12 (77%) 13

With this information in hand we prepared a precursor to the nucleophilic furyl residue outlined in equation 1, path b (eq.3). The commercially available diethyl furan-3,4-dicarboxylate 11a was reduced ($LiAlH_4$) providing alcohol 11b (77%). Protection as a mono-THP ether was accomplished by the procedure of Grieco[13] affording 11c[7c] in 50% yield after chromatography. Numerous

attempts to perform the chlorination of 11c in the usual way[14] afforded only trace quantities of 12. When the procedure of Meyers[8,15] was employed (MsCl,LiCl,DMF) chloride 12[15] was obtained as a viscous water-white liquid in 77% yield. Initial attempts to convert 12 to Grignard reagent 13, at room temperature, provided low yields of 13 as determined by titration.[16] Earlier work investigating the formation of Grignard reagents in the presence of acetalic functions suggested attempting the conversion at a lower temperature.[17] At 10° (internal), 13 was formed rapidly, and quantitatively.



(4)

13 14 15a R = THP(75%) 5(96%)
15b R = H(100%)

The reaction of 13 with chloride 14[18] afforded lactarol-THP ether 15a[6b] (75%) as the sole product. Deprotection[13] (MeOH PPTS, 100%) and oxidation of 15b[6c] with activated manganese dioxide[19] provided (±)-lactaral 5[6c] in 96% yield. Synthetic 5 was identical in all respects when compared with spectral data and a sample of authentic lactaral 5 kindly provided by Professor G. Magnusson.

Further studies of the utility of functionalized furans in natural products synthesis, and the conversion of (±)-5 to the lactaranes are currently under way. These results will be reported in due course.

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9) Prepared from acetyl cyclohexene by the following sequence a) $NaBH_4$,Ce^{III} according to Gemal, A.L.; Luche, J.L. J. Am. Chem. Soc. 1981, 103, 5454; BP 84-86°(9mm), 89% yield; b) ϕ_3P, CBr_4, Et_2O, Hooz, J.; Giliani, S. Can. J. Chem. 1968, 46, 86; 98%, BP 67-70°(2mm); c) $(Bu_3)P$, CCl_4; 47%, BP 58-62°(5mm).

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11) The ratio of 9:10 was determined by a comparison of the integrated areas of the β-furyl protons of 9 [δ=6.22(brd,J=1.95Hz)0.6H] and 10 [6.27(brd,J=1.96Hz)0.4H)], the olefinic resonances of 9 [5.39(m,0.6H)] and 10 [5.16(dq,J=2,6.78Hz)0.4H)] as well as the methyl signals attributed to 9 [0.97(d,J=6.7Hz)1.8H] and 10 [1.42(dd,J=2,6.95Hz)0.2H)]. An examination of the 250MHz ^{1}H-NMR spectrum of pure 9, prepared from choride 8 corroborated this assignment.

12) For other examples of the reaction of organometallic compounds with allylic electrophiles see Stork, G.; Grieco, P.A.; Gregson, M. Tetrahedron Lett. 1969, 1393; Anderson, R.J.; Henrick, C.A.; Siddall, J.B. J. Am. Chem. Soc. 1970, 93, 735; Anderson, R.J.; Henrick, C.A.; Siddall, J.B.; Zurfluh, R. J. Am. Chem. Soc. 1972, 96, 5379; Fouquet, G.; Schlosser, M. Angew. Chem. Int. Ed. 1974, 13, 82; Goering, H.L.; Singleton, V.D. Jr. J. Am. Chem. Soc., 1976, 98, 7854; Rossi, R; Giorgi, R. Gazz. Chim. Ital. 1976, 106, 215; Ziegler, F.E.; Tam, C.C. J. Org. Chem. 1979, 44, 3428; Yamamoto, Y; Yamamoto, S.; Yatagai, H.; Maruyama, K. J. Am. Chem. Soc. 1980, 102, 2318; and references cited therein.

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