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EFFICIENT SYNTHETIC ENTRY TO OXYGEN-BRIDGED LACTARANES USING ORGANOMETALLIC METHODOLOGY: A SHORT SYNTHESIS OF FURANETHER B

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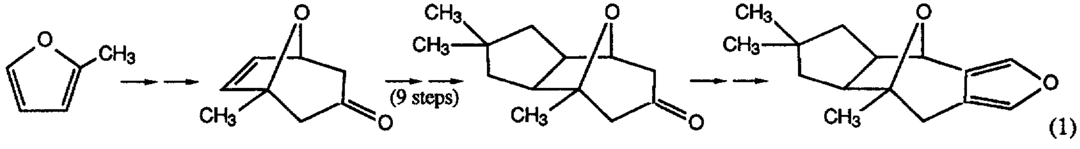
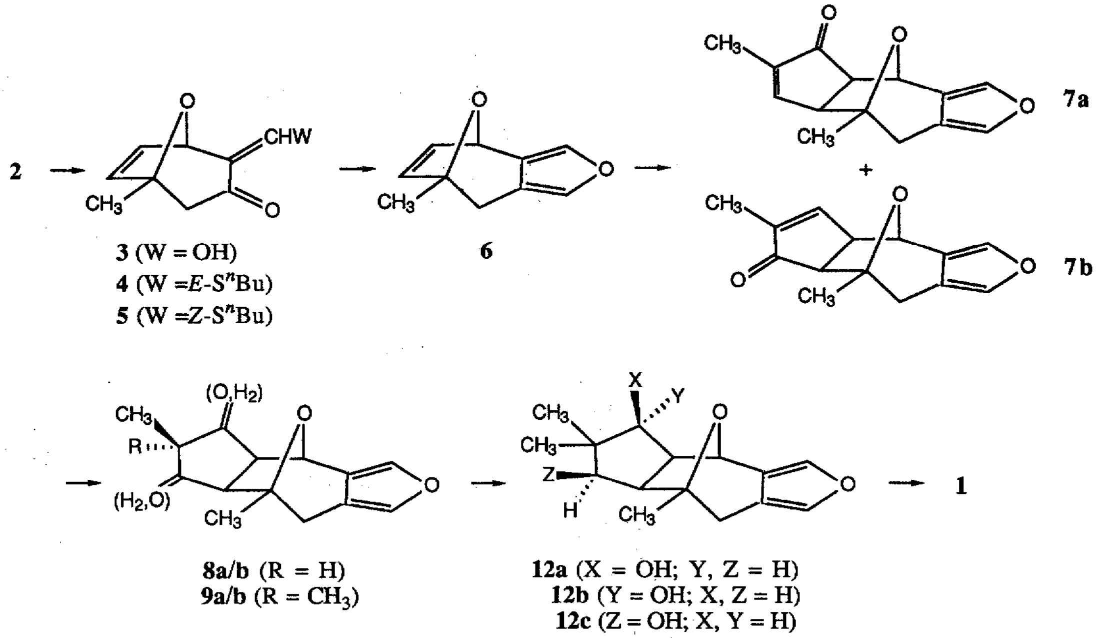
SUMMARY: A 9-step synthesis of the sesquiterpene furanether B from 2-methylfuran is described; the furan moiety is carried through the last 5 steps, which include Pauson-Khand cycloaddition, the key to the synthesis.

Natural products in the lactarane family are frequently encountered as fungal metabolites in several varieties of mushrooms. These compounds possess a hydrazulene framework, and two in particular, the stereoisomeric sesquiterpenes furanether A and B, isolated by Vita-Finzi in 1980, contain the oxygen-bridged 11-oxatricyclo[5.3.1.0^{2,6}]undecane ring system.[1] Synthetic work in this area has to date been very limited.[2,3,4] Building on earlier methodology, we recently completed a rather lengthy sequence to furanether B which is outlined in much abbreviated form, below (eq 1).[5,6] Use of Pauson-Khand cycloaddition permitted convenient annulation of the five-membered ring onto **2**, but necessitated considerable additional manipulation to suitably differentiate the ketone in **2** from that introduced in the cycloaddition. We report herein that the simple expedient of early construction of the furan moiety eliminates this problem, and makes possible a much shorter synthetic entry which completely avoids the use of protecting groups or other excessive functional group manipulation. Several new methodological questions are addressed as well, including tolerance of the furan ring to organometallic cycloaddition conditions and selective enone reduction in a five-membered ring.



2 furanether B (**1**)

Scheme



3 (W = OH)
4 (W =*E*-S^{n}Bu)
5 (W =*Z*-S^{n}Bu)

6

7a

7b

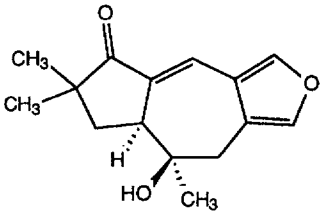
8a/b (R = H)
9a/b (R = CH_3)

12a (X = OH; Y, Z = H)
12b (Y = OH; X, Z = H)
12c (Z = OH; X, Y = H)

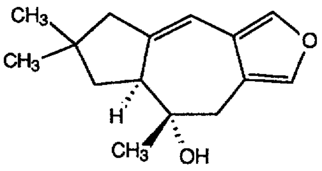
Annulation of the furan ring directly onto bicyclic ketone **2**[7] utilized a modified literature sequence beginning with regiospecific formylation (HCO_2Et, NaOEt, C_6H_6, 18h, rt, 84%) to give **3** followed by preparation of the stereoisomeric thiomethylene derivatives **4** and **5** (^{n}BuSH, *p*-TsOH, C_6H_6, 3h, 80°C, 74%, **4**:**5** = 69:31) (Scheme).[8] Subsequently both **4** and **5** were transformed into furan **6** using a procedure worked out in our laboratories (Me_3S^+ $MeSO_4^-$, CH_2Cl_2, 50% NaOH, 44h, 48°C, 24h, rt; 2N HCl, THF, 3h, rt, total yield 45%).[9] Pauson-Khand cycloaddition[10] of **6** with propyne ($Co_2(CO)_8$, CO, C_6H_6, 44h, 64°C, 64%) provided regioisomers **7a** and **7b** in a 2:1 ratio. The newly formed ring fusion possessed exclusively *exo* stereochemistry as required, and no degradation of the furan ring was detected during this transformation.[11] This mixture was carried through the remainder of the steps since both isomers result in the same final product.

The presence of the furan required care in selection of a reagent for 1,4-reduction. As expected, neither dissolving metal reduction nor catalytic hydrogenation were suitable: catalytic hydrogenation of the enone was somewhat faster than reduction of the furan, but not by enough to be useful in a practical sense.

Using a modified hydride reagent previously shown to be selective for 1,4-reduction of cyclohexenones,[12] reduction to the saturated ketones **8a** and **8b** was achieved (LiAl(O^{t}Bu)$_3$H , THF, 30h, 5°C, then PCC, CH_2Cl_2, 45m, 62%). Alkylation to give **9a** and **9b** proceeded (CH_3I, 2 eq KO^{t}Bu, ^{t}BuOH, C_6H_6, 5m, rt, 20m, 35°C, 45%), but not without an unexpected side reaction.[13] A significant amount (ca. 25%) of a more polar product was consistently observed in these alkylations, tentatively identified as ring-opened alcohol **10**. Although not useful here, **10** should be valuable for the preparation of other lactarane sesquiterpenes such as Furoscrobiculin B (**11**).[1] Reduction of **9a** and **9b** ($LiAlH_4$, ether, 30m, 0°C, 1h, rt, 75%) provided a mixture of alcohols **12a-c**. Deoxygenation of this mixture using Barton's procedure (NaH, CS_2, CH_3I; ^{n}Bu$_3$SnH, toluene, 30m, 110°C) gave a 71% yield of very clean Furanether B.[14,15]



10



11

This short (9 steps from 2-methylfuran, and 5 steps from the previously prepared **6**) synthesis illustrates the efficacy of transition metal based methodology in providing stereocontrolled access to polycyclic systems of moderate complexity, and extends our knowledge of the functional group tolerance of the furan moiety. The ease with which this methodology allows the introduction of all the necessary structural elements for the lactarane system, as well as the versatility of the furan moiety in further oxidative transformations (e.g., as a lactone precursor) should be readily adapted to efficient syntheses of additional examples of this relatively lightly studied class of compounds. Such studies will be reported in due course.[16]

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[15] Satisfactory IR, NMR, and high-resolution MS data were obtained for all new compounds, and C/H analyses for compounds **7**, **8**, and **9**.

[16] This is dedicated to the memory of Allan R. Day, Professor of Chemistry, University of Pennsylvania, who was an innovator in education and an inspiration in research.

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