TOTAL SYNTHESIS OF EURYFURAN *VIA* TWO SEQUENTIAL FURAN RING TRANSFER REACTION

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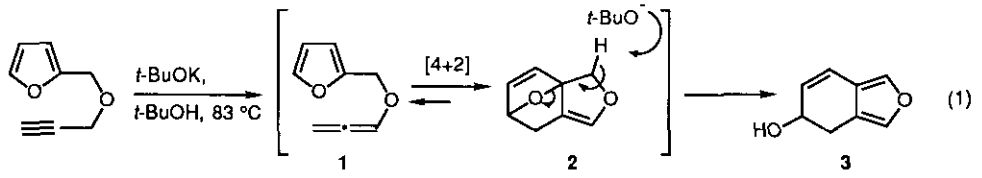
Abstract-Total synthesis of the marine natural product euryfuran (**4**) *via* two sequential furan ring transfer reaction is presented. Key elements of the reaction pathway include as follows; 1) the preparation of propargyl ethers (**5c**), (**10b**), and (**17c**), and its transformation to allylic alcohols (**6**), (**11**) and (**18**), 2) introduction of the angular alkyl group *via* [3,3] sigmatropic rearrangement.

The intramolecular Diels-Alder Reaction has become one of the most useful synthetic protocols in modern organic synthesis.[1,2] Previously we found that the allene unit is a versatile synthon as a dienophile in the intramolecular Diels-Alder reaction due to the absence of unfavorable nonbonded interactions in the transition state.[3] From this point of view, we have developed a new method for the transformation of 2-substituted furans to 3,4-fused furans (*furan ring transfer* (**FRT**) reaction) *via* the intramolecular Diels-Alder reaction of allenyl furfuryl ether (**1**) followed by base catalyzed ring opening of the resulting adduct (**2**).[4]

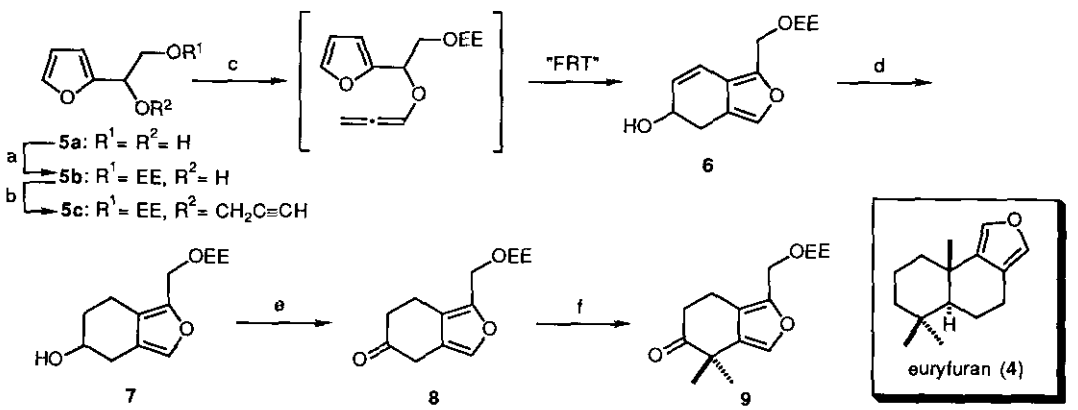


Scheme 1

The methodology for the preparation of furans has been well adopted, but few general strategies for 3,4-fused furans have been developed because of the poor nucleophilic character of the C-3 position of furan. Although the synthesis of fused furans has generally been approached by a careful stereocontrolled construction of a parent carbocycle upon which the furan ring is appended, there remains a need for the truly general methodology, which facilitates the preparation of 3,4-fused furan ring systems.

Euryfuran (**4**) is one of the drimane sesquiterpene having the 3,4-fused furan skeleton, and is isolated in (-)-form from the nudibranches *Hypselodoris californiensis* and *H. porterae*,[5] and also in (+)-form from the sponges *Dysidea herbacea*[6] and *Euryspongia* species.[5] Several sesquiterpenes of the drimane class exhibit important biological activities including insect antifeedant, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties.[7] Although a number of syntheses of euryfuran have been reported,[8] most of them are nothing but with regard to the assembly of the

furan ring. In this paper, we describe the total synthesis of euryfuran *via* two sequential furan ring transfer reaction. Treatment of **5a**[9] with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) afforded 1-ethoxyethyl ether (**5b**) in 76% yield with based on recovery. The alcohol (**5b**) was converted to propargyl ether (**5c**) in quantitative yield by treatment with propargyl bromide using the phase transfer catalyst.[10] Treatment of propargyl ether (**5c**) with excess of *t*-BuOK in *t*-BuOH (83 °C, 30 min) resulted in a smooth FRT reaction to give bicyclic allylic alcohol (**6**), which was converted to alcohol (**7**) by selective hydrogenation in 64% yield from the propargyl ether (**5c**). The alcohol (**7**) was oxidized according to Swern's protocol[11] to give ketone (**8**) in 86% yield. Treatment of the ketone (**8**) with benzyltrimethylammonium hydroxide (Triton B) and iodomethane gave *gem*-dimethylated product (**9**) in 75% yield. The reaction cleanly proceeded and no regio-isomer was detected (Scheme 2).

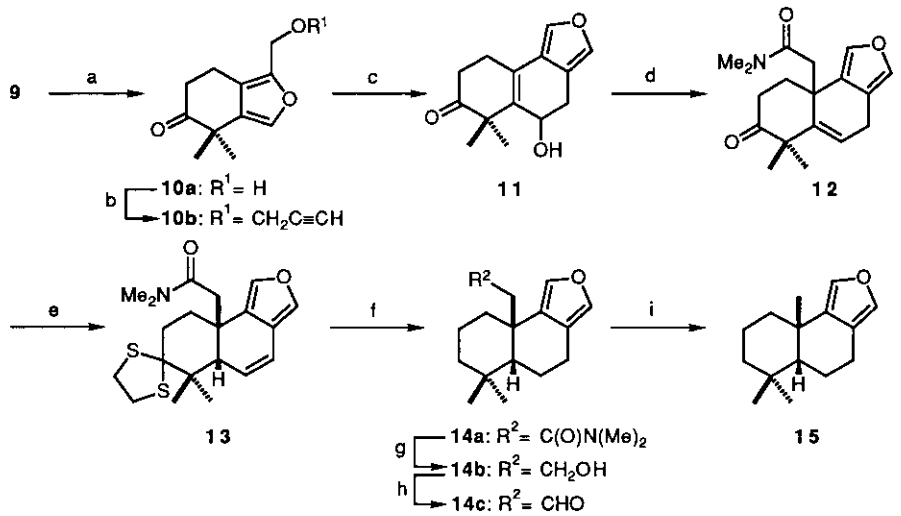


Reagents and reaction conditions: (a) ethyl vinyl ether, PPTS, CH_2Cl_2, 0 °C; (b) propargyl bromide, *n*-Bu_4NHSO_4, aq. NaOH; (c) *t*-BuOK, *t*-BuOH, 83 °C; (d) H_2, Pd/C (5%), MeOH; (e) DMSO, TFAA, CH_2Cl_2, -78 °C, then Et_3N; (f) Triton B, MeI, THF.

Scheme 2

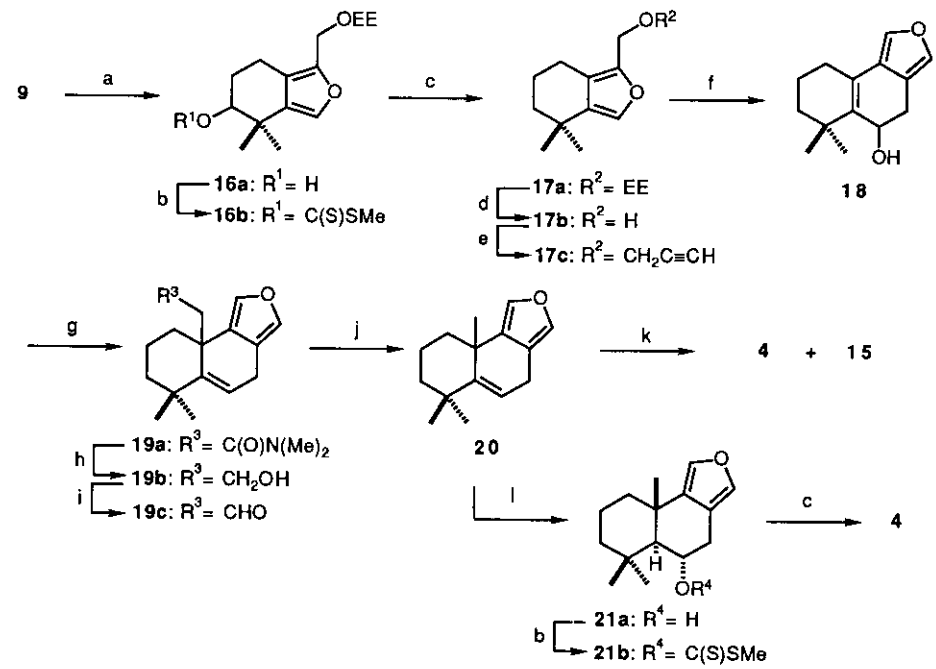
Deprotection of the 1-ethoxyethyl group of the ketone (**9**) by treatment with PPTS in ethanol gave alcohol (**10a**) in quantitative yield, which was converted to propargyl ether (**10b**) in 80% yield with based on recovery. The propargyl ether (**10b**) was led to tricyclic allylic alcohol (**11**) *via* FRT reaction in 73% yield. The next phase of synthesis was introduction of the methyl group into the angular position. After many trials, we applied Eschenmoser's protocol.[12] Heating of the allylic alcohol (**11**) and *N*, *N*-dimethylacetamide dimethyl acetal in refluxing *o*-xylene (143 °C) smoothly proceeded to a [3,3] sigmatropic rearrangement leading to amide (**12**) in 40% yield.

Treatment of **12** with 1,2-ethanedithiol in the presence of zinc triflate[13] gave 1,3-dithiolane compound (**13**) with migration of the double bond in 45% yield. Further treatment of **13** with Raney® Ni (W-2) gave **14a** in 61% yield, which was converted into aldehyde (**14c**) in 65% yield by successive reduction using lithium triethylborohydride[14] and DMSO oxidation.[15] Decarbonylation using Wilkinson's complex[16] gave angular methylated compound (**15**) in a moderate yield (Scheme 3). This compound (**15**) proved to have *cis*-fused configuration instead of *trans*-fused euryfuran (**4**), since the ^{1}H-nmr signals of *gem*-dimethyl protons appear at δ 0.63 and 0.95, different from the data reported for euryfuran (δ 0.91 and 0.94).[8] To avoid the migration to *cis*-fused compound, we examined the carbonyl reduction before second FRT reaction (Scheme 4). The ketone (9) was reduced with $NaBH_4$, yielding alcohol (**16a**) in 97% yield, which was then converted to the xanthate (**16b**) in 96% yield.



Reagents and reaction conditions: (a) PPTS, EtOH; (b) propargyl bromide, n-Bu_4NHSO_4, aq. NaOH; (c) t-BuOK, t-BuOH, 83 °C; (d) $Me_2NC(OMe)_2Me$, o-xylene, 143 °C; (e) $HS(CH_2)_2SH$, $Zn(OTf)_2$, CH_2Cl_2, 40 °C; (f) Raney Ni(W-2), EtOH; (g) $LiBHEt_3$, THF; (h) DMSO, SO_3•Py, Et_3N, CH_2Cl_2; (i) $(Ph_3P)_3RhCl$, benzene, 78 °C.

Scheme 3



Reagents and reaction conditions: (a) $NaBH_4$, EtOH; (b) n-BuLi, CS_2, THF, -78 °C, then MeI; (c) n-Bu_3SnH, AIBN, toluene, 90 °C; (d) PPTS, EtOH; (e) propargyl bromide, n-Bu_4NHSO_4, aq. NaOH;(f) t-BuOK, t-BuOH, 83 °C; (g) $Me_2NC(OMe)_2Me$, o-xylene, 143 °C; (h) $LiBHEt_3$, THF; (i) DMSO, SO_3•Py, Et_3N, CH_2Cl_2; (j) $(Ph_3P)_3RhCl$, benzene, 78 °C; (k) H_2, Pd/C (5 %), EtOAc, EtOH; (l) BH_3•THF, THF, 0 °C, then NaOH, H_2O_2.

Scheme 4

The xanthate (**16b**) was next reduced with *n*-tributyltin hydride to give the desired compound (**17a**) in 72% yield. After deprotection of the 1-ethoxyethyl group of **17a** in quantitative yield, the resulting alcohol (**17b**) was converted to propargyl ether (**17c**) in 89% yield. The FRT reaction of **17c** followed by [3,3] sigmatropic rearrangement gave the amide (**19a**) in 30% yield. The amide (**19a**) was then converted into aldehyde (**19c**) by successive reduction and DMSO oxidation in 77% yield. Decarbonylation of **19c** using Wilkinson's complex gave **20** in 67% yield. Hydrogenation of **20** yielded an inseparable mixture of **15** and euryfuran (**4**) in a ratio of 3:5, which was integrated by the ^{1}H-nmr signals of methyl groups. On the other hand, hydroboration of **20** yielded only *trans*-fused alcohol (**21a**) in 30% yield, which was then converted to xanthate (**21b**) in 62% yield. The xanthate (**21b**) was next reduced with *n*-tributyltin hydrid to give the desired euryfuran (**4**) in 40% yield, which was identical with the authentic sample in all spectral aspects.[8]

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