

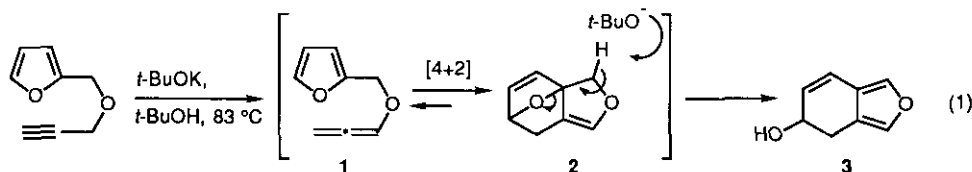
TOTAL SYNTHESIS OF EURYFURAN VIA TWO SEQUENTIAL FURAN RING TRANSFER REACTION

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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

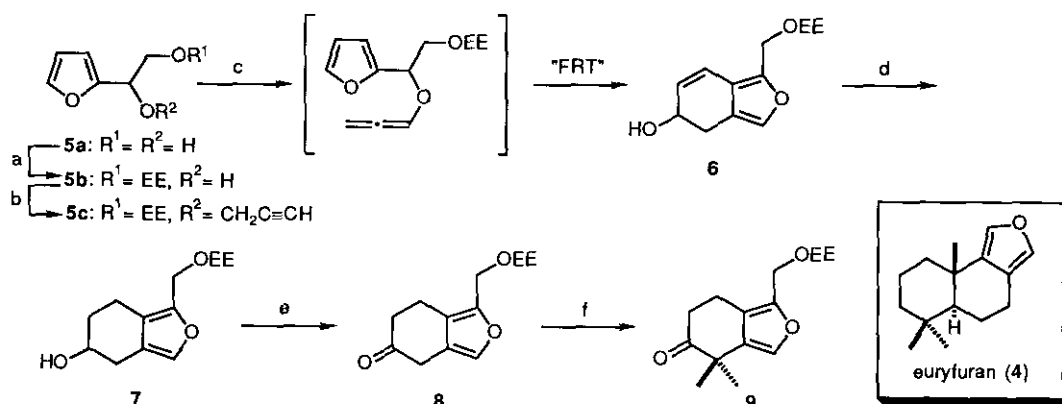


Scheme 1

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 nudibranchs *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 protocol¹¹ to give ketone (**8**) in 86% yield. Treatment of the ketone (**8**) with benzytrimethylammonium 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).

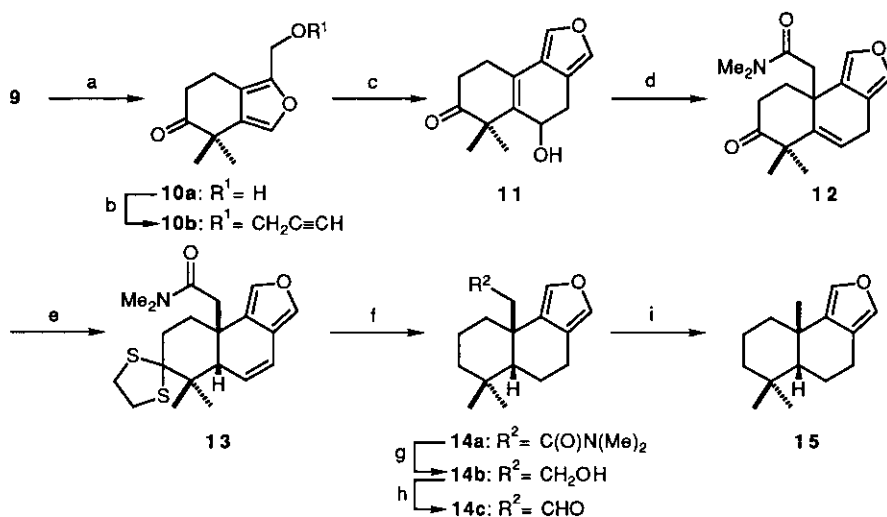


Reagents and reaction conditions: (a) ethyl vinyl ether, PPTS, CH_2Cl_2 , 0 °C; (b) propargyl bromide, *n*-Bu₄NHSO₄, aq. NaOH; (c) *t*-BuOK, *t*-BuOH, 83 °C; (d) H₂, Pd/C (5%), MeOH; (e) DMSO, TFAA, CH_2Cl_2 , -78 °C, then Et₃N; (f) Triton B, MeI, THF.

Scheme 2

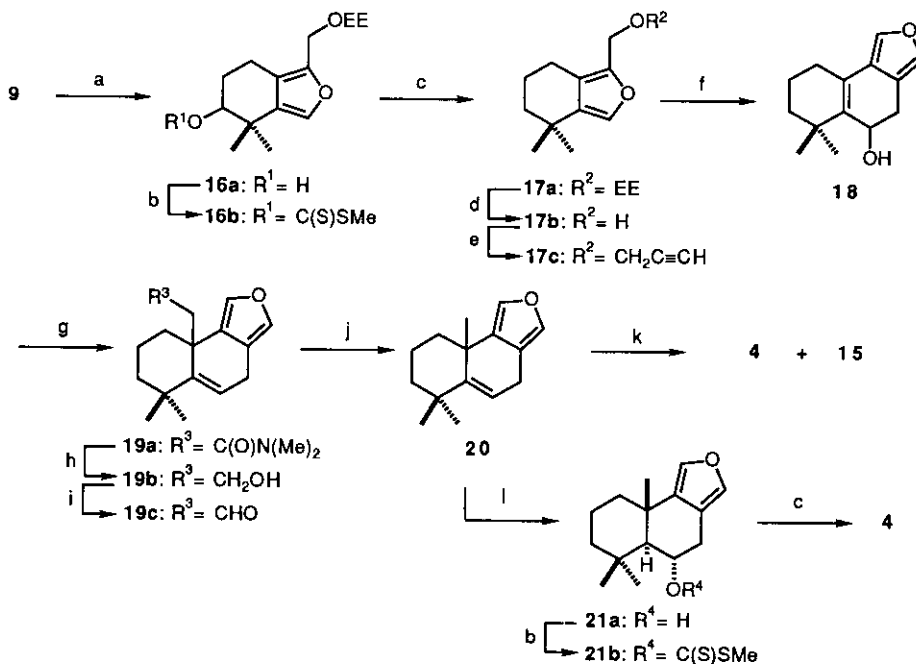
Deprotection of the 1-ethoxyethyl group of the ketone (**9**) by treatment with PPTS in ethanol gave alcohol (**10a**) in quantitative yield, which was converted to propargyl ether (**10b**) in 80% yield with based on recovery. The propargyl ether (**10b**) was led to tricyclic allylic alcohol (**11**) 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 triflate¹³ 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 triethylborohydride¹⁴ and DMSO oxidation.¹⁵ Decarbonylation using Wilkinson's complex¹⁶ 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 ¹H-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 NaBH₄, 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, $n\text{-Bu}_4\text{NHSO}_4$, aq. NaOH; (c) $t\text{-BuOK}$, $t\text{-BuOH}$, 83°C ; (d) $\text{Me}_2\text{NC(OMe)}_2\text{Me}$, $o\text{-xylene}$, 143°C ; (e) $\text{HS(CH}_2)_2\text{SH}$, Zn(OTf)_2 , CH_2Cl_2 , 40°C ; (f) Raney Ni(W-2), EtOH; (g) LiBHET_3 , THF; (h) DMSO, $\text{SO}_3\cdot\text{Py}$, Et_3N , CH_2Cl_2 ; (i) $(\text{Ph}_3\text{P})_3\text{RhCl}$, benzene, 78°C .

Scheme 3



Reagents and reaction conditions: (a) NaBH_4 , EtOH; (b) $n\text{-BuLi}$, CS_2 , THF, -78°C , then MeI; (c) $n\text{-Bu}_3\text{SnH}$, AIBN, toluene, 90°C ; (d) PPTS, EtOH; (e) propargyl bromide, $n\text{-Bu}_4\text{NHSO}_4$, aq. NaOH; (f) $t\text{-BuOK}$, $t\text{-BuOH}$, 83°C ; (g) $\text{Me}_2\text{NC(OMe)}_2\text{Me}$, $o\text{-xylene}$, 143°C ; (h) LiBHET_3 , THF; (i) DMSO, $\text{SO}_3\cdot\text{Py}$, Et_3N , CH_2Cl_2 ; (j) $(\text{Ph}_3\text{P})_3\text{RhCl}$, benzene, 78°C ; (k) H_2 , Pd/C (5%), EtOAc, EtOH; (l) $\text{BH}_3\cdot\text{THF}$, 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 ¹H-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 hydride 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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