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FORMAL TOTAL SYNTHESIS OF XESTOQUINONE *VIA* FURAN RING TRANSFER REACTION STRATEGY

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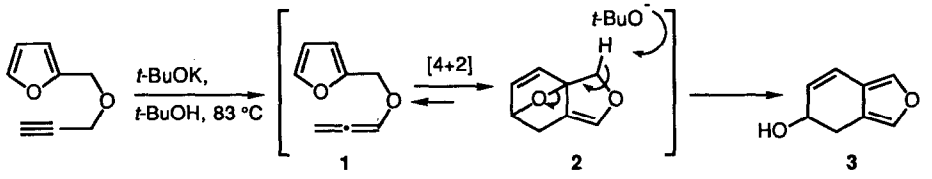
Key words: xestoquinone; fused furan; furan ring transfer reaction; cycloaddition; Friedel-Crafts acylation

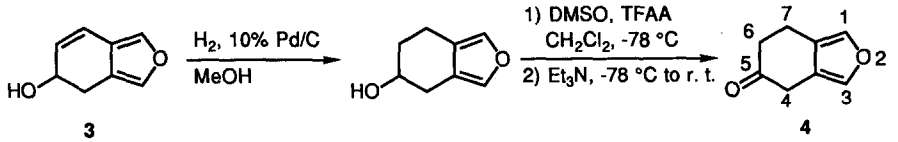
Abstract: *A formal total synthesis of the marine natural product xestoquinone (**5**) based upon FRT reaction strategy is accomplished by preparation of the pentacyclic furan **6**, an advanced key intermediate in Harada's previous total synthesis of this target.*

Previously, 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** as shown in Scheme 1.[1]

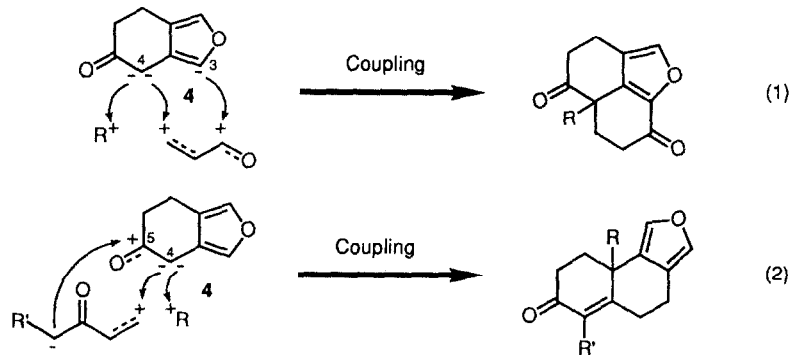


Scheme 1

Moreover in recent studies with a model system, we have successfully examined the feasibility of FRT reaction.[1c,e,f] These efforts have led to the general strategy for the preparation of functionalized polycyclic furan ring systems. For example, ketone **4**, derived from FRT reaction product **3** (Scheme 2),[1e] is useful for the introduction of quaternary carbon at C_4 and for the annelation *via* Michael addition reaction at C_4 followed by Friedel-Crafts acylation at C_3 (eq. 1) or followed by Aldol condensation at C_5 (eq. 2).

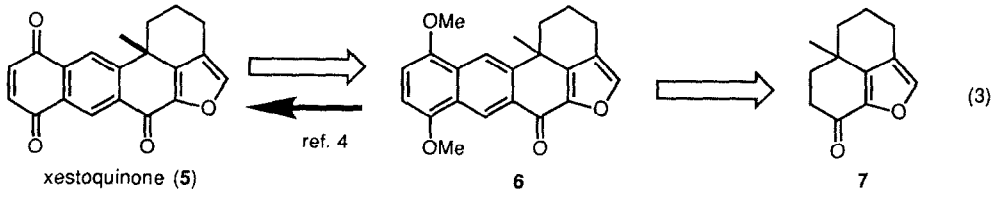


Scheme 2



As part of our effort to develop the synthetic methods for the fused furans based on this strategy, we describe here the total synthesis of biologically active natural fused furan xestoquinone (**5**).

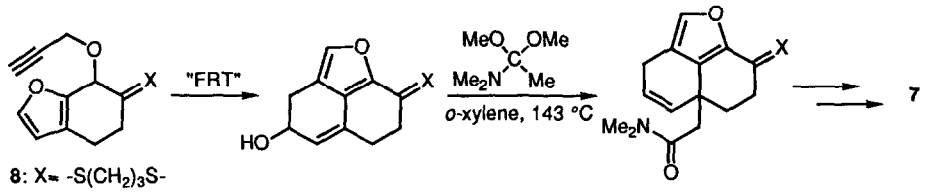
Xestoquinone (**5**) is a polyketide isolated from the Okinawan marine sponge *Xestospongia sapra* as a powerful cardiotonic constituent.[2] It was also isolated from an *Adocia sp.* sponge from Truk Lagoon.[3] Recently, the first total synthesis of xestoquinone was achieved by Harada.[4] We investigated a formal total synthesis of xestoquinone *via* the key intermediates **6** and **7** as shown in eq. 3.



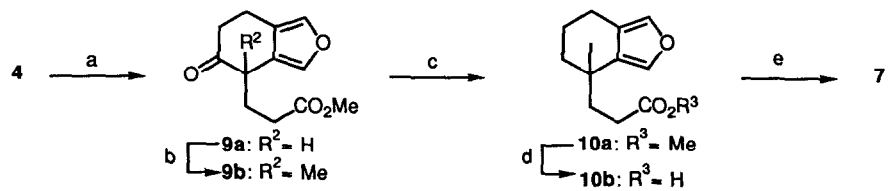
xestoquinone (**5**) **6** **7**

Tricyclic furan **7** was already synthesized *via* FRT reaction of **8** followed by [3,3] sigmatropic rearrangement in our laboratory (Scheme 3).[1c]

We now report the alternative route to **7** as shown in scheme 4. Treatment of **4** with lithium hexamethyldisilazide (LHMDS) and methyl acrylate gave monoalkylated compound **9a** in 63% yield, which was then converted to **9b** *via* methylation by treatment with Triton B and iodomethane in 85% yield. Formation of tosylhydrazone followed by reduction with $NaBH_3CN$[5] gave **10a** in 72% yield, which was converted to carboxylic acid **10b** in quantitative yield. The cyclization step was easily achieved in a single step by treatment of **10b** with 3.0 equiv of triphenyl phosphine in refluxing carbon tetrachloride[6] for 30 min to yield **7** in 38% yield. The structure of **7** was secured after a comparison of spectral data with those previously synthesized from another route.[1c]



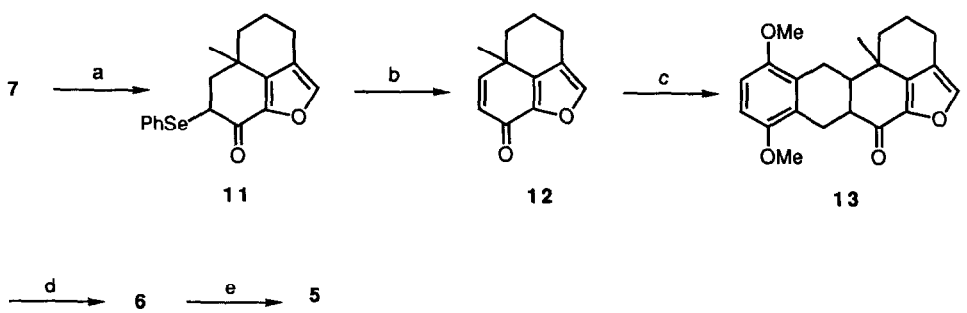
Scheme 3



Reaction conditions: (a) LHMDS, CH_2=$CHCO_2Me$, THF; (b) Triton B, MeI, THF; (c) $TsNHNH_2$, TsOH, DMF-sulfolane, 105 °C, then $NaBH_3CN$; (d) aq. NaOH, MeOH-THF; (e) Ph_3P, CCl_4, 77 °C.

Scheme 4

Having shown that the synthetic plan had effectively produced the versatile advanced intermediate ketone **7**, we accomplished the conversion of ketone **7** to pentacyclic ketone **6** as shown in Scheme 5.



Reaction conditions: (a) LHMDS, PhSeCl, THF, -78 °C (b) H_2O_2, Py, CH_2Cl_2, 0 °C;
(c) 2,3-bis(bromomethyl)-1,4-dimethoxybenzene, $CrCl_2$, HMPT; (d) DDQ, benzene, 80 °C; (e) ref. 4.

Scheme 5

Phenylselenylation of the ketone **7** followed by oxidative elimination yielded enone **12** in 57% yield. Treatment of **12** with 2,3-bis(bromomethyl)-1,4-dimethoxybenzene[7] in the presence of chromium(II) chloride,[8] proceeding Diels-Alder reaction yielded **13** in 77% yield, which was converted to **6** *via* dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 30% yield. The identity of **6** was secured after a comparison of spectral data with those previously reported.[4] Thus, conversion of **6** to xestoquinone was recently accomplished by Harada,[4] we also achieved the formal total synthesis of xestoquinone *via* FRT reaction strategy.

Our results clearly demonstrate the utility and potential of FRT reaction. Further synthetic application of this strategy is currently underway in our laboratory.

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