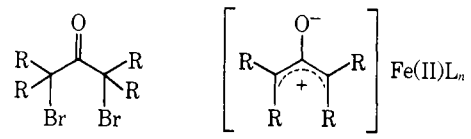
A Method for the Generation of a Synthetic Equivalent of Unsubstituted Oxyallyl via the Bromo Ketone–Iron Carbonyl Reaction. A New Route to Thujaplicins[1]

Summary: Iron carbonyl promoted reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and cyclic 1,3-dienes followed by Zn–Cu couple reduction formally corresponds to a [3 + 4 → 7] cycloaddition of unsubstituted oxyallyl and dienes; synthesis of α- and β-thujaplicins using the cyclocoupling reaction as key step has been achieved.

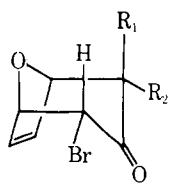
Sir: Reaction of α,α'-dibromo ketones **1** with $Fe_2(CO)_2$ generates the oxyallyl–Fe(II) species **2** (L = Br, CO, solvent,



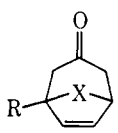
1 **2**

etc.) as reactive intermediate.[2] Its use in the synthesis of various cyclic systems has been demonstrated recently.[3] The limits were defined clearly by the type of the starting dibromides employable for the reaction. Secondary and tertiary dibromo ketones react with 1,3-dienes in a [3 + 4 → 7] manner to produce 4-cycloheptenones in good yields.[3a,d] However, attempted reactions with α,α'-dibromoacetone (**1**, R = H) were totally unsuccessful;[4] dibromides derived from other methyl ketones did not give satisfactory results either. Accordingly, for removal of this defect, thereby extending the use of the cyclocoupling reaction, discovery of suitable precursors which are synthetically equivalent to these methyl ketone dibromides would be required. This paper illustrates a simple two-step procedure surmounting this problem. The method consists of the generation of bromooxyallyls from polybromo ketones and removal of bromine atom(s) from the resulting cyclocoupling products.

For example, reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone (10 mmol) and $Fe_2(CO)_9$ (10 mmol) in dry furan (40 ml) (reflux, 38 hr) followed by the usual work-up gave a mixture of **3**, mp 119–120°, and **4**, mp 111–113°, in 57% combined



3, R_1 = H; R_2 = Br
4, R_1 = Br; R_2 = H



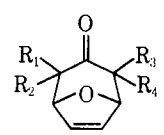
5, R = H; X = O
6, R = H; X = CH_2
12, R = $CH(CH_3)_2$; X = O

yield (after isolation, 9:1 ratio). These adducts were cleanly converted to the desired reduction product **5**, mp 37–39°, by exposure to 10 equiv of Zn–Cu couple[5] in methanol containing 5% of ammonium chloride (25°, 10 min) in >98% yield. Identity of **5** was established by comparison of the spectral data with reported ones.[6] The reaction of tetrabromoacetone (5 mmol) and excess cyclopentadiene with $Fe(CO)_5$ (6 mmol) in 1:5 tetrahydrofuran–benzene (80°, 45 min) followed by the Zn–Cu couple reduction led to the bicyclic ketone **6** in 60% yield.

Table I
Synthesis of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones from Polybromo Ketones and Furan[a]

Starting bromide	Product[b]	Yield, %[c]
$\alpha,\alpha,\alpha',\alpha'$-Tetrabromoacetone	**5**	60[d]
1,1,3,3-Tetrabromobutan-2-one	**7**	63[e]
1,1,3-Tribromo-3-methylbutan-2-one	**8**	87
2,4-Dibromopentan-3-one	**9**	90[f-h]
2,4-Dibromo-4-methylpentan-3-one	**10**	84[f,i]
2,4-Dibromo-2,4-dimethylpentan-3-one	**11**	96[f,g]

[a] The reaction was carried out in furan using polybromo ketones (a mixture of diastereomers, when possible) and $Fe_2(CO)_9$ in a mole ratio of 1:1–1.2. [b] All new compounds gave correct analytical and spectral (ir, NMR, and mass) data. [c] Isolated yield. [d] The product is very volatile, and the yield was determined by NMR. [e] A single isomer having an equatorial methyl group. [f] Result of the single-step procedure. [g] See ref 3d. [h] A 1:1 mixture of equatorial-equatorial and equatorial-axial isomers. [i] A single isomer in which R_3 methyl is equatorial.

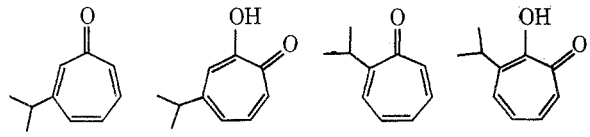


7, R_1 = CH_3; R_2 = R_3 = R_4 = H
8, R_1 = R_2 = CH_3; R_3 = R_4 = H
9, R_1 = R_3 = CH_3; R_2 = R_4 = H
10, R_1 = R_2 = R_3 = CH_3; R_4 = H
11, R_1 = R_2 = R_3 = R_4 = CH_3
15, R_1 = $CH(CH_3)_2$; R_2 = R_3 = R_4 = H

Since these products, **5** and **6**, are free from alkyl substituent at position α to carbonyl group, the two-step operation formally corresponds to a [3 + 4 → 7] cycloaddition involving an *unsubstituted* oxyallyl species as the three-carbon unit. 2-Methoxyallyl cation generated from 2-methoxyallyl halides and Ag(I) salts is known to cycloadd to these cyclic dienes, but only in lower yield.[6] Unsubstituted cyclopropanone, a molecule structurally related to oxyallyl, reacts with neither furan nor cyclopentadiene.[7]

The present modification possesses wide applicability. Tribromides of methyl ketones have also proved to serve as a simple and practical precursor of the reactive oxyallyl intermediates. Several examples of the reaction with furan are given in Table I. Thus, we are apparently in a position to be capable of generating 2-oxyallyls with no substitution as well as mono-, 1,1-di-, 1,3-di-, tri-, and tetraalkylation patterns, in a formal sense, via the bromo ketone–iron carbonyl reaction.[8]

With this versatile method now available, further application for the synthesis of troponoids should be stimulated. Firstly, the synthesis of β-thujaplicin (hinokitiol, **14**) has been accomplished by use of the bicyclic ketone **12** obtained from tetrabromoacetone and 2-isopropylfuran. Hydrogenation of **12** (10% Pd/C, C_2H_5OH, 96%), ether cleav-



13 14 16 17

age [$BF_3 \cdot OEt_2$–$(CH_3CO)_2O$, −10°, three products in 70%], bromination (1 equiv of NBS, 98%), and dehydrobromination (LiCl–DMF, 130°, 77%) gave the tropone **13**.[9] 3-Isopropylcyclohepta-2,6-dienone, one of the ether cleavage products, was also converted to **13** by treatment with DDQ–*p*-TsOH (benzene, 100°) in 80% yield. The tropone **13** was transformed to the tropolone **14** by the usual procedure ($NH_2NH_2 \cdot H_2O$ at 25° and then 2 *N* KOH at 80°, 100%).[10] The product was identical in all respects with the naturally occurring material.[11]

2-Isopropyltropone (**16**) has been prepared from **15** (derived from 1,1,3,3-tetrabromo-4-methylpentan-2-one and furan) by sequential treatments with H_2 over 10% Pd/C in C_2H_5OH (96%), BBr_3 in CH_2Cl_2 at −78–25° (giving 6-bromo-2-isopropylcyclohept-2-enone as major product in 70%), 1 equiv of Br_2 in CCl_4 (100%), and LiCl in DMF at 150° (20%). The tropone **16** can be converted to α-thujaplicin (**17**) by the known method.[12,13]

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Supplementary Material Available. Illustrative experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-806.

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(4) Although dibromoacetone was consumed by treatment with $Fe_2(CO)_9$, no product arising from the desired intermolecular cyclocoupling reactions could be obtained. The most prevalent reasons for the failure would be the instability of the oxyallyl intermediate **2** (R = H) bearing no carbocation-stabilizing substituents, and/or the high reactivity of the precursory enolate species, $[CH_2{=}C(O^-)CH_2Br]Fe(II)L_n$.[2] In this context, the reaction of oxyallyls could be effected by introducing appropriate substituents which can modify, either electronically or sterically, the stability–reactivity relationship.
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Direct Ring Fluorination of Aryl Oxygen Compounds with Xenon Difluoride

Summary: In the absence of hydrogen fluoride initiation, anisole, phenol, 2-naphthol, veratrole, catechol, and resorcinol react with xenon difluoride in methylene chloride or ether to give monofluoro substituted products in yields of 37–71%. Veratrole and catechol give the corresponding 4-fluoro compounds almost exclusively, while 2-naphthol is readily converted to 1-fluoro-2-naphthol.

Sir: In the course of our studies on the synthesis of fluoro analogs of pharmacologically active compounds, we have examined the reaction of xenon difluoride with a variety of aryl oxygen compounds. The pioneering studies of Filler, Hyman, and Shaw[1–4] have demonstrated the utility of XeF_2 as a selective fluorinating reagent for aromatic hydrocarbons. In extending the scope of this reaction to include functionally substituted aryl compounds, we report here our results with methoxy- and hydroxy-substituted benzenes.

Xenon difluoride was prepared photochemically by a modification of Matheson's procedure.[5] The solvents dichloromethane and ether (Baker AR) were used without further purification. Anisole and veratrole were distilled before use, while phenol, catechol, resorcinol, and 2-naphthol were of reagent grade and used without further purification.

The procedure was adapted from that previously described.[1]

In a typical experiment, 4 g (37 mmol) of anisole (3-fold excess) dissolved in 12 ml of methylene chloride in a 30-cc Kel-F bottle was degassed to 5×10^{-6} Torr and poured onto 2.1 g (12.2 mmol) of xenon difluoride contained in an evacuated (5×10^{-6} Torr) Kel-F bottle at −196°. The resulting mixture was warmed gradually until the reaction commenced (as evidenced by the evolution of xenon gas and accompanying color change of the solution). Reactions usually occurred in the range of −10 to 25° and were complete within a matter of minutes for the monosubstituted benzenes and several hours for the disubstituted compounds. A small portion of the reaction mixture was treated with NaF pellets to remove the hydrogen fluoride produced and then analyzed by gas chromatography or mass spectrometry. For the remainder of the mixture, the solvent and HF were removed under reduced pressure (5–10 Torr) and the pure compounds were isolated by crystallization or fractional distillation. The results of these reactions are listed in Table I. In all cases, satisfactory yields (37–71%) of monofluorinated products were obtained. Mass spectral analysis failed to reveal any products due to fluorine addition. These reactions occur spontaneously upon warming to 25°. This behavior is in contrast to the reaction of XeF_2 and benzene which requires initiation by hydrogen fluoride. Presumably, the function of the HF is to polarize the Xe–F bond.[3] It is possible that this polarization can