cipitate was filtered and washed with cold pentane several times. The separated liquid portion was hydrolyzed with 50 mL of 2 N HCl solution by stirring vigorously for 6 h at room temperature. The mixture was saturated with NaCl. The separated layer was subjected to fractional distillation, providing 4.2 g of caproaldehyde (84%): bp 130–131 °C; n^{20}_D 1.4034.

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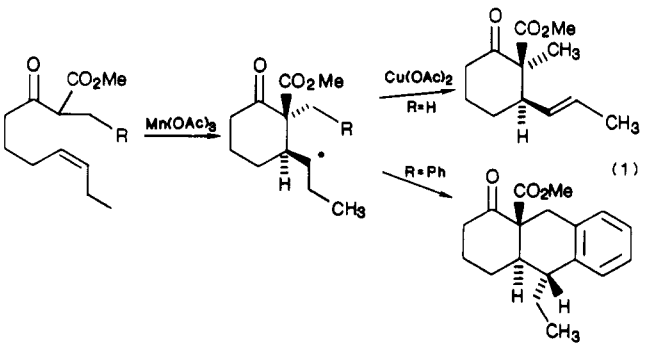
Manganese(III)-Based Oxidative Free Radical Cyclizations. 5. Termination of Polycyclization by Oxidative β-Hydride Elimination[1]

Summary: Oxidative free radical cyclization of β-keto esters such as **1a** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ leads to bicyclic products such as **6a** in excellent yield. The key steps are oxidation of **1a** to **2a** by $Mn(OAc)_3 \cdot 2H_2O$, two successive free radical cyclizations to give **4a**, and oxidative β-hydride elimination by $Cu(OAc)_2 \cdot H_2O$ to give **6a**.

Sir: Free radical cyclizations of alkenes have recently been developed into a powerful method for the synthesis of polycyclic compounds.[3] Typically these cyclizations are terminated reductively by hydrogen atom transfer. Development of methods for oxidative termination promises to increase the scope of these cyclizations since more highly functionalized products will be produced.[4,5] We have recently described manganese(III)-based oxidative free radical cyclizations which are initiated by oxidation of a β-dicarbonyl compound with $Mn(OAc)_3 \cdot 2H_2O$.[1] The resulting radical adds to a double bond to give a monocyclic radical which is either oxidized to an alkene by $Cu(OAc)_2 \cdot H_2O$[1a,c,d] or undergoes a second cyclization by adding to a proximate aromatic ring to give a cyclohexadienyl radical, which is oxidized and loses a proton to regenerate the aromatic ring.[1a,c] (see eq 1).

We report here a new class of oxidative cyclizations in which two sequential cyclizations to double bonds generate a bicyclic cyclopentylmethyl radical, which is then oxidized to generate an *exo*-methylenecyclopentane. Reaction of β-keto ester **1a**,[6a] as a 0.1 M solution in acetic acid, with



(1)

2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ for 26 h at room temperature gave an 86% yield of **6a**,[11] mp 71.8–72.5 °C. Oxidation of the β-keto ester of **1a** by $Mn(OAc)_3 \cdot 2H_2O$ gives the radical **2a** (Scheme I), probably as a manganese complex.[1d] Cyclization proceeds as expected for this class of stabilized radicals to give exclusively the tertiary cyclohexyl radical **3a**.[1] The primary cyclopentylmethyl radical **7a** is not formed. It is also possible that the double bond is involved in the rate-limiting oxidation of **1a**. If this were the case **3a** might be formed by the addition of the double bond to the manganese enolate of **1a** without the intermediacy of **2a**. Oxidative free radical cyclizations of β-keto esters with $Mn(OAc)_3 \cdot 2H_2O$ do not follow the cyclization rules developed for normal radical cyclizations.[12] Although the detailed mechanism is not known, these oxidative cyclizations are nevertheless quite predictable and consistent.

The monocyclic radical **3a** is a normal alkyl radical, not perturbed by stabilizing groups or manganese, which cyclizes, as expected,[3c,d,12] to give exclusively the cyclopentylmethyl radical **4a**. Cyclopentylmethyl radical **4a** undergoes the expected reaction[13] with $Cu(OAc)_2 \cdot H_2O$ to give organocopper intermediate **5a**, which undergoes facile β-hydride elimination to give **6a**. The success of this reaction depends upon the fact that cyclization of **3a** to give **4a** is faster than the oxidation of **3a** by either $Mn(OAc)_3 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$.

Primary radicals are oxidized very slowly by $Mn(OAc)_3 \cdot 2H_2O$.[14] The unsaturated product **6a** is formed in only ≈20% yield in the absence of $Cu(OAc)_2 \cdot H_2O$. The major products are oligomer and a mixture of saturated products formed from **4a** by abstraction of a hydrogen atom from the medium.

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(6) Prepared by: (a) alkylation of the dianion[7] of methyl allylacetoacetate[8] with methallyl chloride in 49% yield; (b) alkylation of the dianion[7] of methyl allylacetoacetate[8] with allyl bromide in 43% yield; (c) alkylation of methyl 6-methyl-3-oxo-6-heptenoate[9] with crotyl bromide in 53% yield; (d) alkylation of the dianion[7] of methyl allylacetoacetate[8] with 1-bromomethylcyclohexene[10] in 47% yield; (e) alkylation of the dianion[7] of methyl allylacetoacetate[8] with *cis*-1-bromo-3-pentene[1c] in 42% yield.

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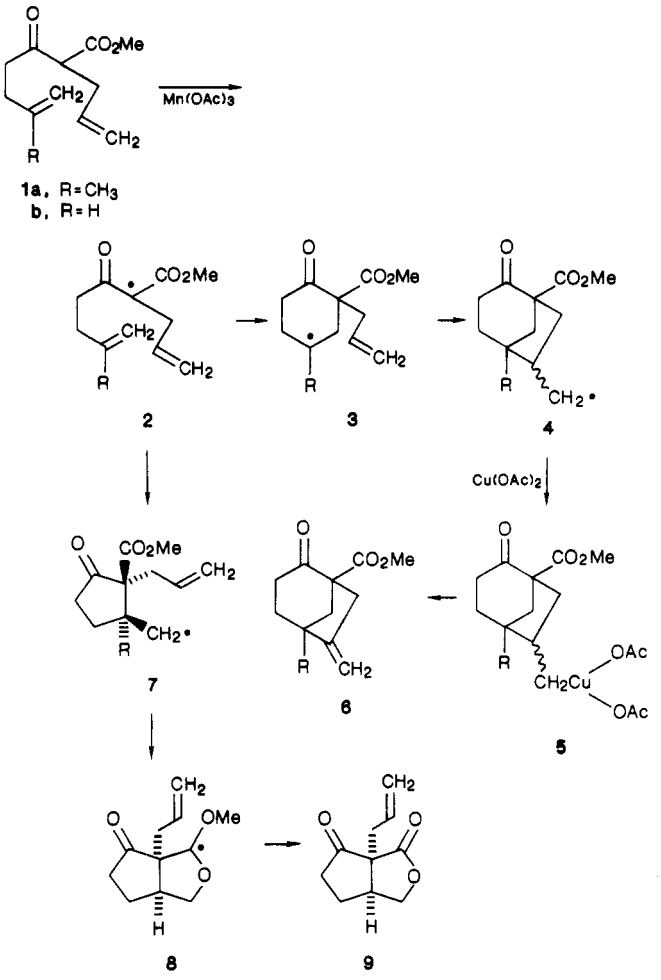
Scheme I

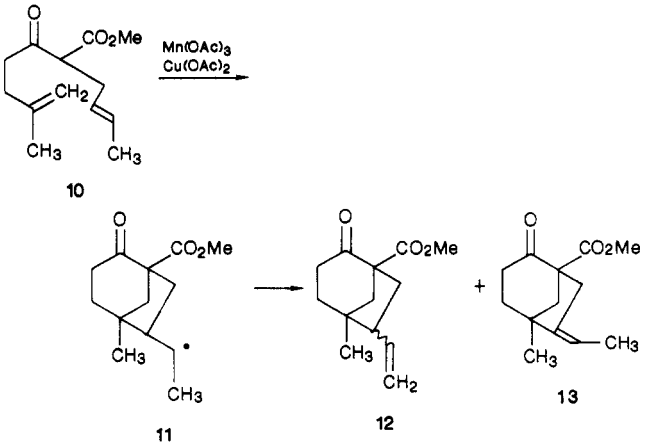


Reaction of **1b**[6b] as described above for 5 h at 25 °C gave a 48% yield of **6b**, mp 47.2–47.9 °C and a 18% yield of **9b**. As we have previously reported,[1c] oxidative cyclization to an unsubstituted terminal double bond gives a ≈ 9:4 mixture of secondary cyclohexyl radical **3b** and primary cyclopentylmethyl radical **7b**. Radical **3b** is converted to **6b** as described above for **6a**. Radical **7b** cannot add to the double bond since a trans-fused bicyclo[3.3.0]octane would be formed. Instead, the radical adds to the carbonyl group to give **8**, which is oxidized to give **9**.

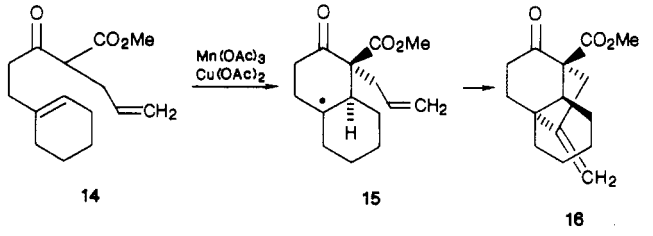
Keto ester **6b** contains the *exo*-methylenebicyclo-[3.2.1]octane moiety of the gibberellane and kaurane diterpenes. With suitable modification, this method should provide a very direct and efficient approach to these natural products.

Radical **4** is presumably formed as a mixture of isomers which are both converted to **6** by oxidative elimination. The cyclization of **10**[6c] was carried out to determine the stereochemistry of the second cyclization and to determine the nature of the oxidation products obtained from a secondary radical such as **11**. Oxidative cyclization of **10** gave a 65% yield of **12** as an inseparable 2:1 mixture of stereoisomers and a 5% yield of **13**. As we have previously observed, loss of a primary rather than tertiary hydrogen is highly preferred in the $Cu(OAc)_2 \cdot H_2O$ oxidation.[1a] The cyclization leading to **11** is almost stereorandom.

Oxidative cyclization of **14**[6d] as described above gave a 73% yield of **16**, mp 72.9–73.4 °C. The stereochemistry of **16** was assigned based on analysis of the ^1H and ^{13}C NMR spectra. The aliphatic carbon of the two-carbon bridge absorbs at the same frequency in **6a** (δ 39.9) and **16** (δ 40.5), which indicates that the cyclohexane of **16** is



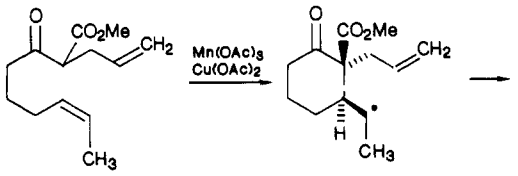
on the side of the three-carbon bridge. This assignment was confirmed by NOE experiments. Irradiation of the allylic methylene group at δ 2.80–2.95 leads to an NOE enhancement of the methine proton on the one-carbon bridge. The initial cyclization must therefore give the monocyclic radical **15** stereospecifically which then cyclizes normally to give **16**. The stereospecificity of the initial cyclization of **14** to give **15** is identical with that observed in the synthesis of podocarpic acid,[1a] although the origins of this selectivity are still obscure.



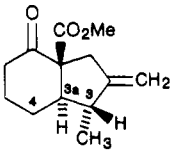
Oxidative cyclization of **17**[6e] for 13 h at 25 °C gave a 67% yield of **19** as a single stereoisomer. The stereochemistry of **19** was established by analysis of the 300-MHz ^1H NMR spectrum. H-3a at the ring fusion absorbs at δ 1.35 (ddd, J = 11.8, 11.7, 4.2 Hz). The two large vicinal coupling constants between H-3a and H-3 and H-3a and H-4_a require that the ring-fusion hydrogen be axial on the cyclohexane and pseudoaxial on the cyclopentane. Furthermore the methyl group must be α on the cyclopentane so that there can be a large dihedral angle between H-3a and H-3. The isomer shown is the only one of the four that can adopt a conformation which will give rise to two large vicinal coupling constants for H-3a.

The cyclization of **17** leads selectively to monocyclic radical **18**. The ethyl side chain is cis to the ester as previously observed.[1c] Cyclization of **18** leads exclusively to **19** to avoid severe steric repulsion between the carbomethoxy and methyl groups, which would be in a 1,3-diaxial relationship in the stereoisomer.

Oxidative polycyclization with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ should be generally useful in organic synthesis. Its power results from four important features. First, polycyclization followed by oxidative termination proceeds in high yield with good control of both the stereochemistry and the oxidative termination process. Second, initiation by oxidation of a β-dicarbonyl compound leads to a more highly functionalized product than initiation by treatment of an alkyl halide with R_3SnH. Third, oxidative termination inserts a double bond regiospecifically into the product. Fourth, the substrates are prepared remarkably easily, usually by alkylation of mono- or dianions of β-dicarbonyl compounds. We are continuing to explore the scope and limitations of this reaction and are



17 18



19

applying it to total synthesis.

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Supplementary Material Available: Experimental procedures for the preparation of **1a** and **6a** and spectral data for **6b**, **9**, **16**, and **19** (3 pages). Ordering information is given on any current masthead page.

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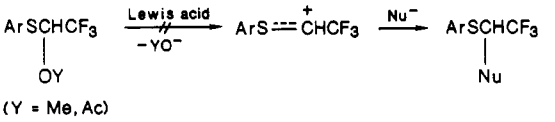
Electrolytic Transformation of Fluoroorganic Compounds. 3.[1] Highly Regioselective Anodic Methoxylation of *N*-(2,2,2-Trifluoroethyl)amines

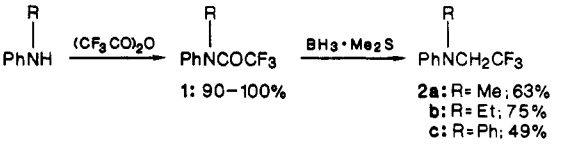
Summary: Anodic methoxylation of *N*-alkyl-*N*-(2,2,2-trifluoroethyl)anilines and *N*-(2,2,2-trifluoroethyl)diphenylamine places the methoxy group in the α-position (toward the trifluoromethyl group); these products are useful building blocks for the construction of a carbon–carbon bond at this α-position.

Sir: Although a great deal of recent interest has been focused on trifluoromethylated compounds because of their remarkable biological activities,[2] their preparative methods are limited in many cases.[3] For example, nucleophilic or electrophilic substitution at the α-positions of trifluoromethylated compounds generally occur with difficulty. Since the generation of a carbenium ion adjacent to a trifluoromethyl group is particularly difficult due to its strong electron-withdrawing effect,[4] attempts to prepare desired compounds bearing a trifluoromethyl group by S_N1 reaction via a trifluoroethyl carbenium ion have been unsuccessful so far.[5] Therefore, construction of a carbon–carbon bond α to the trifluoromethyl group is of current importance.

Scheme I



Scheme II



Scheme III

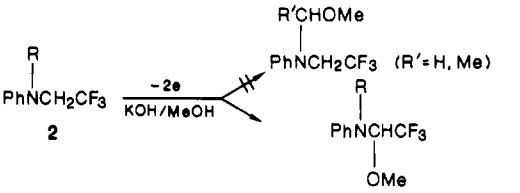


Table I. Oxidation Potentials (Half-Peak Potentials, $E^{ox}_{p_{1/2}}$) of *N*-(2,2,2-Trifluoroethyl)amines 2[a]

(trifluoroethyl)-amine 2	R	$E^{ox}_{p_{1/2}}$, V vs SCE
2a	Me	0.96
2b	Et	0.96
2c	Ph	1.05

[a] 2 mM of 2 in 0.1 M Et_4NOTs/MeCN. Sweep rate: 100 mV s^{-1}.

In our previous paper,[6] we reported the successful anodic methoxylation and acetoxylation of aryl 2,2,2-trifluoroethyl sulfides to give the corresponding α-methoxy and α-acetoxy sulfides, respectively, together with their synthetic utilization for fluoroorganic compounds. It was also found that nucleophilic substitution of these sulfides via cationic intermediates did not occur in the presence of Lewis acid (Scheme I), although nonfluorindated α-methoxy or α-acetoxy sulfides are known to easily generate cationic intermediates which can be trapped with various nucleophiles.[7]

In this paper, we wish to report highly regioselective anodic methoxylation of *N*-alkyl-*N*-(2,2,2-trifluoroethyl)-anilines **2a,b** and *N*-(2,2,2-trifluoroethyl)diphenylamine (**2c**) together with the first example of the generation of an α-trifluoromethylated iminium cation, which can be trapped with various carbon nucleophiles to give useful trifluoromethylated compounds.

The starting compounds **2** for the electrolysis were prepared by trifluoroacetylation of *N*-alkylanilines or diphenylamine followed by reduction with borane–dimethyl sulfide complex.[8] Trifluoroacetoanilides **1a,b** gave the corresponding *N*-(2,2,2-trifluoroethyl)aniline derivatives **2a,b** in good yields, while *N*-(trifluoroacetyl)diphenylamine (**1c**) provided the trifluoroethyl derivative **2c** in low yield

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