

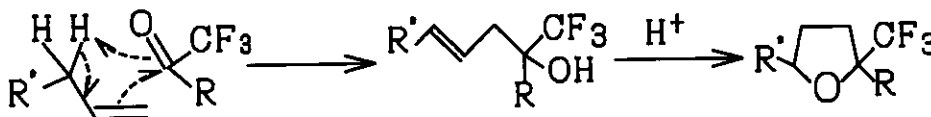
**SYNTHESIS OF TRIFLUOROMETHYLATED TETRAHYDROPYRANS
FROM ENE REACTION PRODUCTS OF TRIFLUOROMETHYL KETONES:
SYNTHESIS OF FLUORINE ANALOGS OF A SESQUITERPENE⁺**

Takabumi Nagai, Hiroshi Ohtsuka, Mayumi Koyama,
Akira Ando, Takuichi Miki, and Itsumaro Kumadaki^{*}

Faculty of Pharmaceutical Sciences, Setsunan University,
45-1, Nagaotoge-cho, Hirakata, Osaka, 573-01, Japan

Abstract -- As the extension of the ene reaction of trifluoromethyl ketones, α -trifluoromethylated tetrahydropyrans, including fluorine analogs of sesquiterpenes, were synthesized from trifluoromethylated homoallyl alcohols, the products of the ene reaction.

In the course of our study to find new reactions for syntheses of fluorine compounds, we reported ene reaction of trifluoromethyl ketones¹⁻⁴ and derivatization of the products to various trifluoromethyl compounds.⁵⁻⁷ Among these researches, α -trifluoromethylated homoallyl alcohols, the ene reaction products of trifluoromethyl ketones, were converted to α -(trifluoromethyl)tetrahydrofurans and fluorinated monoterpenes. (Scheme 1)



Scheme 1

In this paper, we present synthesis of α -(trifluoromethyl)tetrahydropyrans including fluorine analogs of sesquiterpenes. Some of sesquiterpenes have an α -methyltetrahydropyran as their skeleton, as shown in Figure 1.

⁺ This paper is dedicated to my revered Professor Masatomo Hamana on the occasion of his 75th birthday.

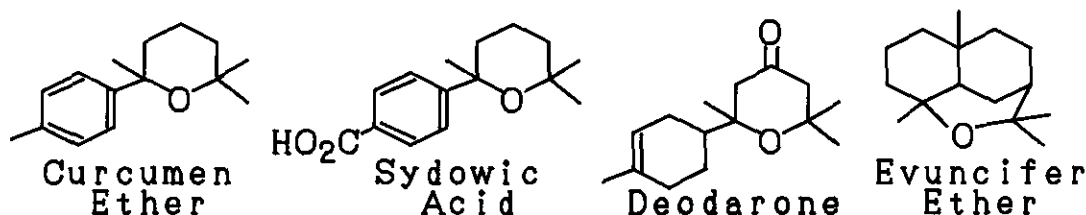
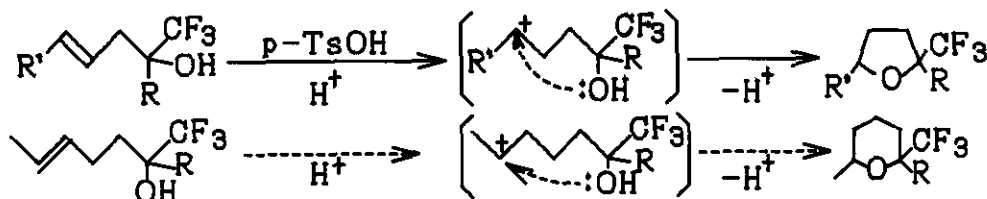


Figure 1. α -Methyltetrahydropyrans

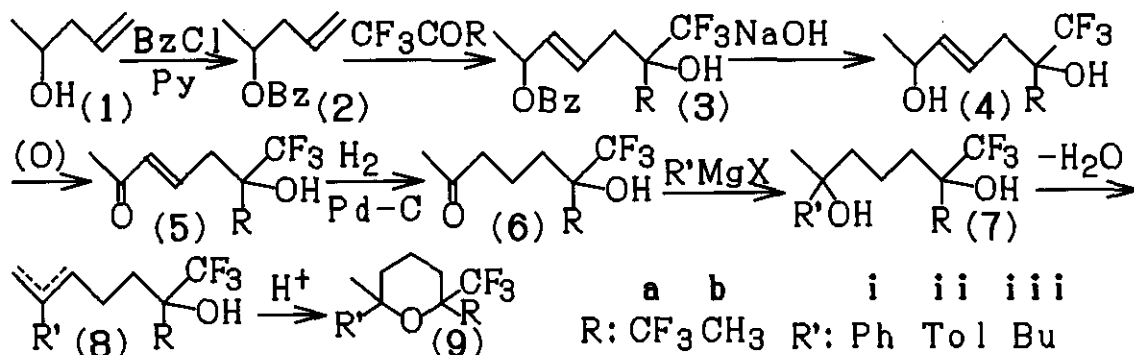
We expected that if the method used for the synthesis of α -(trifluoromethyl)tetrahydrofurans could be applied for a 4,5-unsaturated alcohol, an α -(trifluoromethyl)tetrahydropyran would be obtained. (See Scheme 2)



Scheme 2

For this purpose, an ene reaction product, an α -trifluoromethylated homo-allyl alcohol, must be converted to a 4,5-unsaturated alcohol. Another problem is that a 4,5-unsaturated alcohol might cyclize not only to a tetrahydro-pyran but also to a tetrahydrofuran. For selective cyclization to a tetra- hydropyran, disubstitution at the 5-position seemed to be necessary, since a tertiary cation is more stable than a secondary one. On the basis of these considerations, 4-penten-2-ol (1) was chosen as a starting material. Thus, the ene reaction of the benzoate (2) of 1 with hexafluoroacetone gave an adduct (3a)⁸ in 86 % yield. Attempted hydrogenation of the double bond of 3a in the presence of 5 % Pd-C resulted in hydroge-nolysis of the benzoyloxy group. Thus, 3a was hydrolyzed to 4a. Catalytic reduction of 4a resulted in dehydroxylation. Therefore, 4a was oxidized first with Jones reagent to an enone (5a). This was hydrogenated in the presence of 5 % Pd-C to a keto alcohol (6a). The ene reaction of 2 with trifluoroacetone in the presence of aluminum chloride at -78°C afforded an ene reaction product (3b, 52 %). This was converted similarly to 6b through hydrolysis, oxidation with PCC and hydrogenation in a good yield.

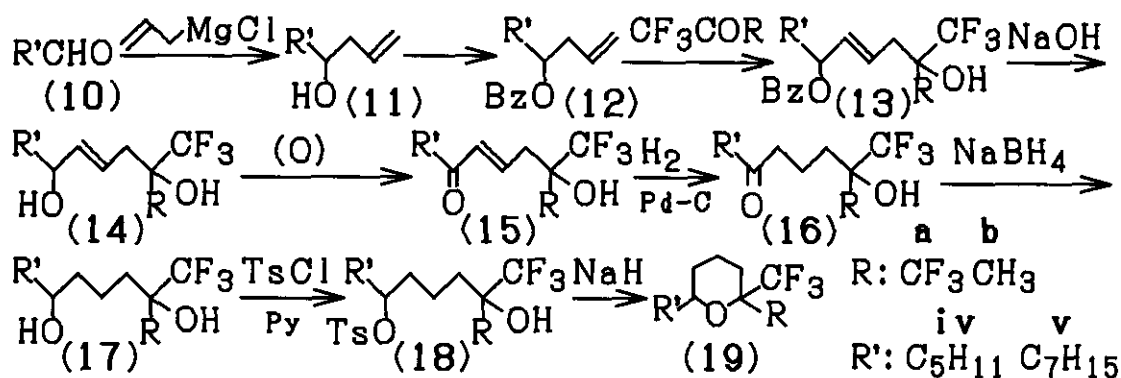
Treatment of the ketones (6) with $R'MgX$, where R' was phenyl, *p*-tolyl or butyl, gave diol compounds (7), dehydration of which with phosphoryl chloride in pyridine gave a mixture of enol compounds (8). A main product was a *trans*-4,5-unsaturated alcohol, but small amounts of a *cis* isomer and a 5,6-unsaturated alcohol were formed. When R' was butyl, another isomer of the double bond was formed. However, we treated the mixtures with *p*-TsOH without separation, expecting that the most stable tertiary cation would be formed. Tetrahydropyran compounds (9) were formed exclusively, as expected. Overall yields from 6 to 9 are about 20-30 % for these substituents. The products (9a-ii) and (9b-ii), which have a *p*-tolyl group, are hexafluoro and trifluoro analogs of curcumen ether. (See Scheme 3)



Scheme 3

This method provides a general route for preparation of a trifluoromethylated α -tetrasubstituted tetrahydropyran, but would not give a good result for the synthesis of α -trisubstituted tetrahydropyrans, since the cation is not tertiary and cyclization to a tetrahydrofuran or an oxepane might occur. A trisubstituted tetrahydropyran was synthesized as follows: Hexanal (10-iv) or octanal (10-v) was treated with allylmagnesium chloride to give corresponding homoallyl alcohols (11). Compounds (11) were converted with benzoyl chloride and pyridine to benzoates (12), the ene reaction of which with hexafluoroacetone or trifluoroacetone gave compounds (13). These benzoates were hydrolyzed with sodium hydroxide to diols (14). Catalytic hydrogenation of the double bond of (13) or (14) was unsuccessful.

ful, since hydrogenolysis of the carbon-oxygen bond occurred before reduction of the double bond. Thus, the compounds (14) were first oxidized with PCC to unsaturated keto alcohols (15), which were hydrogenated in the presence of 5 % Pd-C to give saturated keto alcohols (16). Reduction of the compounds (16) with NaBH₄ afforded diols (17). They were tosylated in pyridine to tosylates (18) of the secondary hydroxyl group. Treatment of 18 with sodium hydride in an aprotic solvent afforded objective tetrahydropyran compounds (19). (See Scheme 4)



Scheme 4

In conclusion, we could obtain two types of trifluoromethylated tetrahydropyrans starting from the ene reaction products of trifluoromethyl ketones.

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8. All the new compounds gave spectral data consistent with the assigned structures. Compounds (9) and (19) are mixtures of diastereoisomers.

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