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STERESELECTIVE SYNTHESIS OF TRIFLUOROMETHYLATED OLEFIN AND DIENE

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The stereoselective synthesis of trifluoromethylated *Z*-olefins (6) was achieved through the Claisen rearrangement of 1,1,1-trifluoropropenyl-2-carbinol derivatives (5 and 7). The olefins (6) were converted to trifluoromethylated diene, which was used as a key intermediate in the synthesis of trifluororetinal.

KEYWORDS — Claisen rearrangement; 1,1,1-trifluoropropenyl-2-carbinol derivative; trifluoromethylated *Z*-olefin; 4-trifluoromethyl-2*E*,4*Z*-pentadienal derivative

In connection with our recent synthesis of trifluororetinals,¹⁾ we reported the synthesis of trifluoromethylated diene derivatives (3) through the Claisen rearrangement of trifluoromethylated propargyl alcohols (1) and the following isomerization of allenic compounds (2) under basic conditions.²⁾ Although the isomerization of 2 to 3 was effectively carried out to yield 2*E*,4*Z*- and 2*E*,4*E*-dienes (3a and 3b), none of the 2*Z*,4*Z*-isomer (4) was isolated. To obtain 4, photoisomerization of 3a and 3b has been employed. This photoisomerization gave a photo-stationary state of a mixture of 3b and 4 and a laborious separation of the desired 2*Z*,4*E*-isomer (4) from 3b was required. Here we report the stereoselective synthesis of trifluoromethylated olefin (*Z*-form) and the following conversion to the fully functionalized diene derivative, which has already proven to be an important intermediate for the preparation of all-trans 20,20,20-trifluororetinal.¹⁾ At this time, only one method is known for the preferential formation of trisubstituted *Z*-trifluoromethyl olefin.³⁾ It is significant that most of the known procedures for the preparation of trifluoromethylated olefin gives the *E*-isomer as a major product.⁴⁾

By considering the nature of the highly ordered transition state of the Claisen rearrangement,⁵⁾ we have chosen the trifluoromethylated allylic alcohols (5) as starting materials. These can be easily obtained from 1,1,1-trifluoro-2-bromopropene.⁶⁾

Heating of a mixture of alcohol (5) and ethyl orthoacetate (large excess) at 140°C in the presence of propionic acid (catalytic amount) gave 4-trifluoromethyl-4-pentenoate derivative (6) in 40-86% yields. The ratio of the stereoisomer (Z/E) was 7:1 to 8:1.⁷⁾ Formation of the Z-isomer as a major product revealed that the substituent R in allylic alcohols (5) preferentially occupies the equatorial position in the cyclic transition state.⁵⁾ In order to improve the Z/E ratio of the rearranged products, the escer-enolate Claisen rearrangement⁸⁾ was applied. The ketene silyl acetal was generated by treating the acetate of 5 with lithium isopropylcyclohexylamide at -78°C, followed by the addition of t-butyldimethylsilyl chloride and hexamethylphosphoramide (HMPA). Subsequent heating of the reaction mixture at 70°C (2h) gave the rearranged 4-trifluoromethyl-4-pentenoic acid derivative (8) in 62-86% yields. A higher Z/E ratio (16:1-27:1) than that of the ethyl orthoacetate Claisen rearrangement was obtained. Conversion of the Z-olefin (6c) to diene (9) was accomplished by simple procedures (i; LDA, ii; PhSeCl, iii; H₂O₂).⁹⁾ The stereochemistry of the newly formed double bond of 9 was confirmed by ¹H-NMR and the conversion to dienal (10), which is identical with the reported one.¹⁰⁾ This procedure for the preparation of trifluoromethylated Z-olefin (6) and conversion of 6c to 10 made it possible to synthesize trifluororetinal in a large scale. We are now extending the utility of this stereoselective synthesis of 6 and 9 to the preparation of the trifluoromethylated analog of biologically active compounds.

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Structures of the new compounds were determined by ^1H -NMR, IR and mass spectra. ^1H -NMR of 6a (CDCl_3) δ : 1.18 (t, $J=7.2\text{Hz}$, CH_2CH_3), 2.25-2.83 (m, 8H, PhCH_2CH_2 and $\text{CH}_2\text{CH}_2\text{COOEt}$), 4.05 (q, $J=7.2\text{Hz}$, CH_2CH_3), 5.74 (t, $J=7.5\text{Hz}$, olefinic), 7.01-7.34 (m, 5H, ArH); 6b (CDCl_3) δ : 1.24 (t, $J=7.2\text{Hz}$, CH_2CH_3), 2.52 (br s, 4H, $\text{CH}_2\text{CH}_2\text{COOEt}$), 4.15 (q, $J=7.2\text{Hz}$, CH_2CH_3), 4.27 (m, 2H, $\text{OCH}_2\text{CH=}$), 4.53 (s, 2H, PhCH_2), 6.00 (t, $J=5.4\text{Hz}$, olefinic), 7.39 (br s, 5H, ArH); 6c (CDCl_3) δ : 1.25 (t, $J=7.2\text{Hz}$, CH_2CH_3), 1.41-1.91 (m, 6H, THP), 2.48 (br s, 4H, $\text{CH}_2\text{CH}_2\text{COOEt}$), 3.31-3.98 (m, 2H, THP), 4.12 (q, $J=7.2\text{Hz}$, CH_2CH_3), 4.31 (m, 2H, $\text{OCH}_2\text{CH=}$), 4.58 (br s, 1H, THP), 5.94 (t, $J=5.7\text{Hz}$, olefinic).
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 ^1H -NMR of 9 (CDCl_3) δ : 1.30 (t, $J=7.2\text{Hz}$, CH_2CH_3), 1.43-1.95 (m, 6H, THP), 3.27-4.03 (m, 2H, THP), 4.22 (q, $J=7.2\text{Hz}$, CH_2CH_3), 4.50 (m, 2H, $\text{OCH}_2\text{CH=}$), 4.58 (br s, 1H, THP), 6.12 (d, $J=17.1\text{Hz}$, CH=CHCOOEt), 6.51 (t, 5.4Hz, CH=CCF_3), 7.18 (d, $J=17.1\text{Hz}$, CH=CHCOOEt); 10 (CDCl_3) δ : 1.08 (s, 9H, tBu), 4.54 (m, 2H, $\text{CH}_2\text{OSiPh}_2\text{tBu}$), 6.31 (dd, $J=15.0\text{Hz}$ and 7.5Hz , CH=CHCHO), 6.67 (t, $J=5.7\text{Hz}$, $\text{CCF}_3=\text{CHCH}_2$), 6.98 (d, $J=15.0\text{Hz}$, CH=CHCHO), 7.37-7.76 (m, 10H, ArH), 9.57 (d, $J=7.5\text{Hz}$, CHO).

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