Communications to the Editor

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STEREOSELECTIVE SYNTHESIS OF TRIFLUOROMETHYLATED OLEFIN AND DIENE

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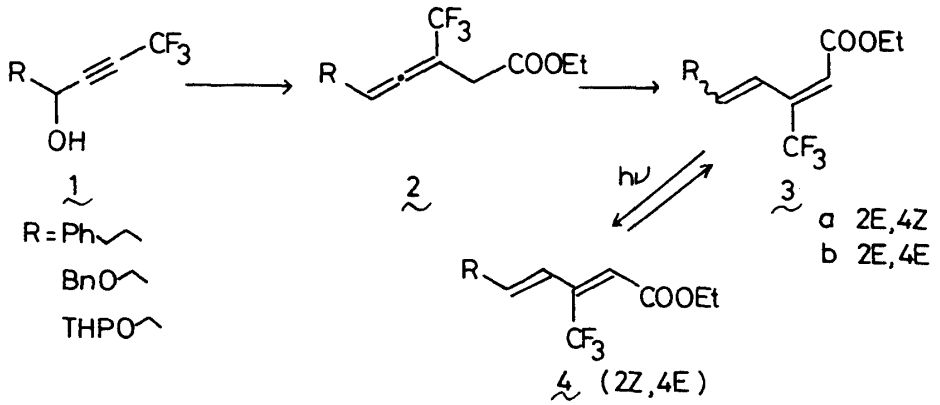
The stereoselective synthesis of trifluoromethylated Z-olefins (6) was achieved through the Claisen rearrangement of 1,1,1-trifluoropropenyl-2-carbinol derivatives (5 and 7). The olefins (6) were converted to trifluoromethylated diene, which was used as a key intermediate in the synthesis of trifluororetinal.

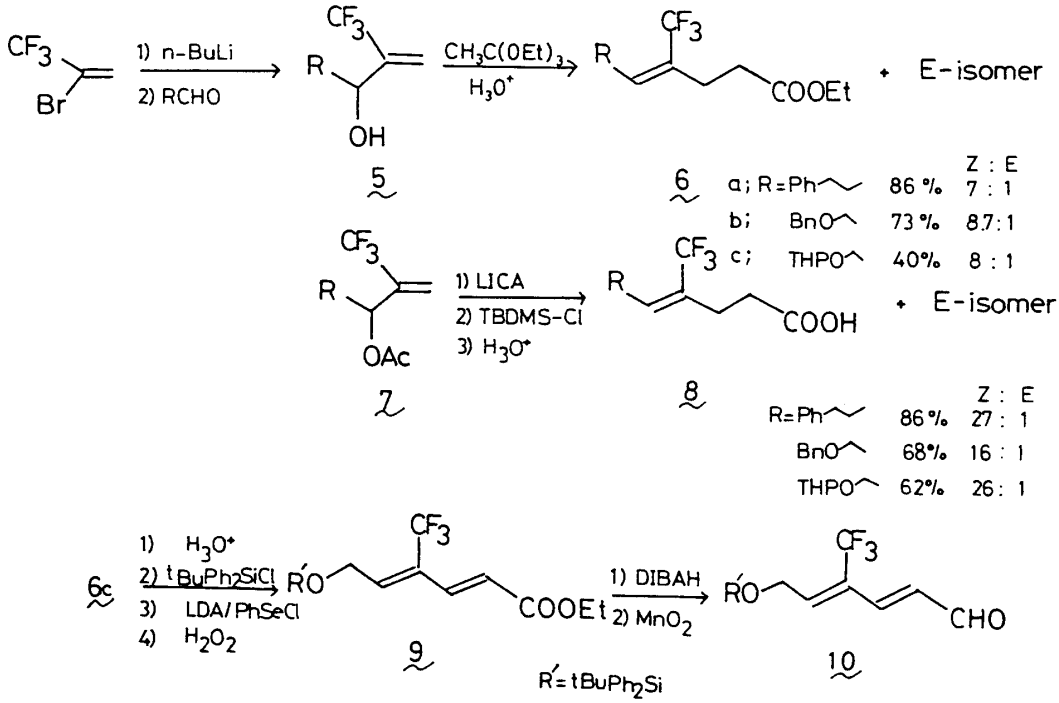
KEYWORDS —— Claisen rearrangement; 1,1,1-trifluoropropenyl-2-carbinol derivative; trifluoromethylated Z-olefin; 4-trifluoromethyl-2E,4Z-pentadienal derivative

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 2E,4Z- and 2E,4E-dienes (3a and 3b), none of the 2Z,4Z-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 2Z,4E-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 ester-enolate Claisen rearrangement[8] 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; H_2O_2).[9] The stereochemistry of the newly formed double bond of 9 was confirmed by ^{1}H-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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7) The ratio was determined by integrating the ^{19}F-NMR signals. The stereochemistry was assigned by the chemical shift of olefinic proton and its small coupling with fluorine; the CF_3 group when cis to an adjacent olefinic proton provides a deshielding effect of approx. 0.50 ppm and a small coupling constant ($\sim J_{H\text{-}F}$=1.5Hz) which is not present in the stereoisomer. See the following references: A. E. Asato, D. Mead, M. Denny, T. T. Bopp and R. S. H. Liu, J. Am. Chem. Soc., 104, 4979 (1982); W. R. Cullen, D. S. Dawson and G. E. Styan, Can. J. Chem., 43, 3392 (1965).
Structures of the new compounds were determined by ^{1}H-NMR, IR and mass spectra. ^{1}H-NMR of 6a ($CDCl_3$)δ: 1.18 (t, J=7.2Hz, $CH_2\underline{CH_3}$), 2.25-2.83 (m, 8H, $Ph\underline{CH_2}\underline{CH_2}$ and $\underline{CH_2}\underline{CH_2}COOEt$), 4.05 (q, J=7.2Hz, $\underline{CH_2}CH_3$), 5.74 (t, J=7.5Hz, olefinic), 7.01-7.34 (m, 5H, ArH); 6b ($CDCl_3$)δ: 1.24 (t, J=7.2Hz, $CH_2\underline{CH_3}$), 2.52 (br s, 4H, $\underline{CH_2}\underline{CH_2}COOEt$), 4.15 (q, J=7.2Hz, $\underline{CH_2}CH_3$), 4.27 (m, 2H, $O\underline{CH_2}CH$=), 4.53 (s, 2H, $PhCH_2$), 6.00 (t, J=5.4Hz, olefinic), 7.39 (br s, 5H, ArH); 6c ($CDCl_3$)δ: 1.25 (t, J=7.2Hz, $CH_2\underline{CH_3}$), 1.41-1.91 (m, 6H, THP), 2.48 (br s, 4H, $\underline{CH_2}\underline{CH_2}COOEt$), 3.31-3.98 (m, 2H, THP), 4.12 (q, J=7.2Hz, $\underline{CH_2}CH_3$), 4.31 (m, 2H, $O\underline{CH_2}CH$=), 4.58 (br s, 1H, THP), 5.94 (t, J=5.7Hz, olefinic).

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^{1}H-NMR of 9 ($CDCl_3$)δ: 1.30 (t, J=7.2Hz, $CH_2\underline{CH_3}$), 1.43-1.95 (m, 6H, THP), 3.27-4.03 (m, 2H, THP), 4.22 (q, J=7.2Hz, $\underline{CH_2}CH_3$), 4.50 (m, 2H, $O\underline{CH_2}CH$=), 4.58 (br s, 1H, THP), 6.12 (d, J=17.1Hz, CH=$\underline{CH}$COOEt), 6.51 (t, 5.4Hz, $\underline{CH}$=CCF_3), 7.18 (d, J=17.1Hz, $\underline{CH}$=CHCOOEt); 10 ($CDCl_3$)δ: 1.08 (s, 9H, tBu), 4.54 (m, 2H, $\underline{CH_2}OSiPh_2tBu$), 6.31 (dd, J=15.0Hz and 7.5Hz, CH=$\underline{CH}$CHO), 6.67 (t, J=5.7Hz, CCF_3=$\underline{CH}CH_2$), 6.98 (d, J=15.0Hz, $\underline{CH}$=CHCHO), 7.37-7.76 (m, 10H, ArH), 9.57 (d, J=7.5Hz, CHO).

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