Regioselective *cis,vic*-Dihydroxylation of α,β,γ,δ-Unsaturated Carboxylic Esters: Enhanced γ,δ-Selectivity by Employing Trifluoroethyl or Hexafluoroisopropyl Esters

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Abstract: The regioselectivity of Sharpless asymmetric dihydroxylation (AD) of α,β,γ,δ-unsaturated carboxylic esters was studied as a function of α-, β-, and δ-substituents and for fluorine-free versus fluorinated esters. The latter showed increased or complete γ,δ-selectivities: the hexafluoroisopropyl ester being superior to the trifluoroethyl ester. Olefinations of α,β-unsaturated aldehydes with phosphorus ylide **36** or phosphonate anion **41** provided α,β,γ,δ-unsaturated trifluoroethyl esters, leading *inter alia* to complete *trans* selectivity and to **31** with 94% *E* selectivity, respectively.

Key words: asymmetric dihydroxylation, hexafluoroisopropyl ester, regioselectivity, trifluoroethyl esters, α,β,γ,δ-unsaturated esters

The Sharpless catalytic asymmetric dihydroxylation (AD) is one of the key tools of organic synthesis.[1] While applicable to many monoolefins relatively independently from their substitution pattern, AD reactions of dienes may be problematic with respect to achieving chemo- and regioselectivity. It is common for conjugated dienes, though, that their ADs can be stopped at the stage of mono-ADs.[2–4] This is due to the increase of steric hindrance and the decrease of electron density once the first C=C bond has reacted. In contrast, AD reactions of 1,3-dienes often lack regiocontrol. For instance, the dienoic ester **1** can be monohydroxylated but undergoes α,β-AD ('proximal functionalization', disfavored) along with γ,δ-AD ('distal functionalization', favored; Scheme 1).[3] Likewise, distal rather than proximal functionalization is preferred in the mono-AD of 2,4,6-octatrienoates.[4] The conclusion at that time, that mono-ADs of polyenes occur preferentially at their most electron-rich double bond,[4] disagrees with the regioselectivity of the mono-AD **3** → **2** + *iso*-**2** observed later.[3] The ester-substituted C=C bond of **3** would be regarded as more electron-rich than the ketone-substituted C=C bond; nonetheless, the former reacts faster. Neither are the γ,δ-:α,β-AD ratios in a series of 5-phenyl-2,4-pentadienoic acid derivatives accommodated by the reactivity order 'electron-rich C=C bond reacts prior to electron-deficient C=C bond': These ratios are 2:1 for the dihydroxylation of the *tert*-butyl ester in the presence of $(DHQ)_2PHAL$, 6.5:1 for the ethyl ester, and >20:1 for the Weinreb amide.[5]

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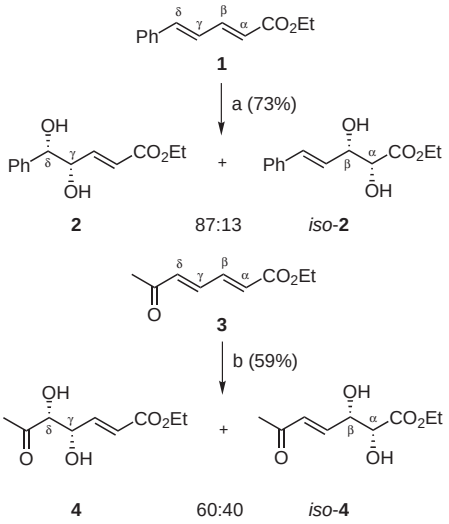
As described in the following we were able to shift the regioselectivity of the mono-AD of various α,β,γ,δ-unsaturated carboxylic esters from a given γ,δ:α,β ratio towards γ,δ or entirely to γ,δ by replacing methyl or ethyl esters by trifluoroethyl esters or in one case by the hexafluoroisopropyl ester. The dienoic esters of our substrates were the reportedly difficult cases **1**[3] and **3**[3] or dictated by a synthetic objective (**5**/**7**[6]) or contained δ-alkynyl substituents, a δ-acetyl group or an acetal.



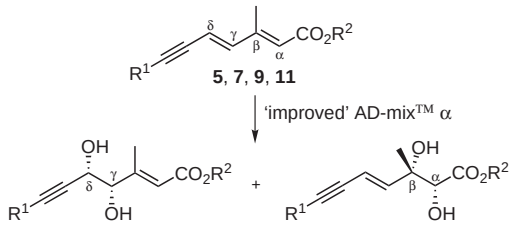
Scheme 1 ADs of ethyl esters of α,β,γ,δ-unsaturated carboxylic acids exhibiting incomplete regioselectivities (ref. 3). *Reagents and conditions*: a) Modified AD-mix™ α [namely $K_2OsO_2(OH)_4$ (1 mol%), $(DHQ)_2PHAL$ (1 mol%)], 0 °C; b) modified AD-mix™ α [$K_2OsO_2(OH)_4$ (1 mol%), $(DHQ)_2PHAL$ (2 mol%), $K_3Fe(CN)_6$ (2 equiv), K_2CO_3 (2 equiv), *t*-BuOH–*t*-BuOMe–H_2O (1:1:2)], 0 °C, no reductive workup.

The fluorinated esters of our study turned out to be considerably less reactive than their fluorine-free counterparts. Therefore, we employed higher-than-usual amounts of osmate (1–5 mol%) and enantiopure ligand (5–10 mol%) in their ADs. This measure is reminiscent of, but clearly preferable to, the use of 11 mol% of OsO_4 and 10 mol% of the ligand in the mentioned mono-AD of the dienoic Weinreb amide.[5]

Table 1 shows pairs of mono-ADs of 5-alkynylated 2,4-dienoic esters. Methyl 2,4-dienoate **5** with the *tert*-$BuMe_2SiC{\equiv}C$-substituent at C-5 showed a 85:15 preference for γ,δ- versus α,β-dihydroxylation. The analogous

trifluoroethyl ester **7** gave only γ,δ-dihydroxylation product **8**.[6] Similarly, methyl 2,4-dienoate **9** with the PhC≡C-substituent at C-5 gave a 70:30 mixture of the γ,δ- and α,β-dihydroxylation products **10**[8] and *iso*-**10** whereas the analogous trifluoroethyl ester **11** delivered the γ,δ-dihydroxylation product **12** selectively. In these AD reactions we used five times as much[9] osmate (namely 1 mol%) and AD-mix™ α ligand (namely 5 mol%) as routinely recommended[10] in order to achieve ca. 70% yields within ca. 24 hours.[11] Obviously, alkyne substituents slow down Os(VIII)-mediated *cis*,*vic*-dihydroxylations.[14,15]

Table 1 Regiocontrolled Dihydroxylations of δ-Alkynyl-β-methyl α,β,γ,δ-Unsaturated Esters with Trifluoroethoxy versus Alkoxy Moieties[a]



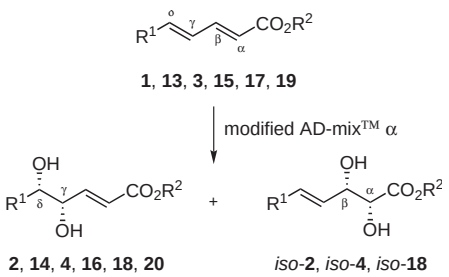
Substrate	R^1	R^2	Product(s)	Yield (%)	γ,δ-:α,β-attack
5[6]	TBS[c]	Me	**6**/*iso*-**6**[b]	65	85:15
7[6]		Tfe[d]	**8**	72	100:0
9	Ph	Me	**10**/*iso*-**10**[b]	79	70:30
11		Tfe[d]	**12**	65	100:0

[a] $K_2Os(OH)_4O_2$ (1 mol%), $(DHQ)_2PHAL$ (5 mol%), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–H_2O (1:1), 0 °C, 24 h; workup with $Na_2S_2O_3$.
[b] Inseparable by flash chromatography[7] on silica gel.
[c] TBS = *tert*-butyldimethylsilyl.
[d] Tfe = trifluoroethyl.

Table 2 documents how our 'fluorine-containing versus fluorine-free ester concept' allows to convey complete γ,δ-regioselectivity to the mono-AD of the α,β,γ,δ-unsaturated esters **13** versus **1** (Ph being the δ-substituent), **15** versus **3** (acetyl being the δ-substituent), and **19** versus **17** (a ketal being the δ-substituent). While the ethyl esters reacted with 65:35[16]–92:8[16] γ,δ- versus α,β-preferences, their trifluoroethyl analogues gave 100:0 ratios.

Some trifluoroethyl 2,4-dienoates were not *cis*,*vic*-dihydroxylated with complete γ,δ-selectivity (Tables 3 and 4). This concerned scaffolds where the fluorine-free substrates react at C-α and C-β preferentially (**21**, **25**) or almost as much as at C-γ and C-δ (**29**). In these cases, the fluorinated counterparts **23**, **27**, and **31** allowed to overcome this bias qualitatively but not completely. Accordingly, the latter substrates gave 50:50, 69:31, and 92:8 mixtures of the γ,δ- and α,β-diol isomers **24**/*iso*-**24**, **28**/*iso*-**28**, and **32**/*iso*-**32**, respectively. The 32% yields both of **24**/*iso*-**24** and **28**/*iso*-**28** could not be raised to the 73% which was the yield of the **32**/*iso*-**32** mixture, not even when employing, as we actually did, 5 mol% of $K_2Os(OH)_4O_2$ and 10 mol% of $(DHQ)_2PHAL$.

Table 2 Regiocontrolled Dihydroxylations of δ-Alkynyl α,β,γ,δ-Unsaturated Esters Containing Trifluoroethoxy versus Ethoxy Moieties

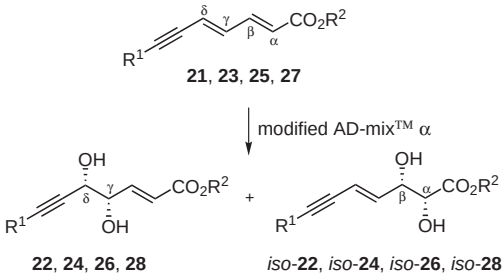


Substrate	R^1	R^2	Product(s)	Yield (%)	γ,δ-:α,β-attack
1[a]	Ph	Et	**2**/*iso*-**2**[b]	71	92:8
13[a]		Tfe[c]	**14**	63	100:0
3[d]		Tfe[c]	**4**/*iso*-**4**[e]	55	73:27
15[d]		Tfe[c]	**16**	44	100:0
17[f]		Et	**18**/*iso*-**18**[b]	45	65:35
19[f]		Tfe[c]	**20**	39	100:0

[a] Conditions same as in footnote a of Table 1.
[b] Inseparable by flash chromatography[7] on silica gel.
[c] Tfe = trifluoroethyl.
[d] Conditions same as in footnote a of Table 1 but less $K_3Fe(CN)_6$ (2.0 equiv), less K_2CO_3 (2.0 equiv), 0 °C, 4 d, no workup with $Na_2S_2O_3$.
[e] Compound **4** was isolated pure, *iso*-**4** in a mixture with $MeSO_2NH_2$.
[f] Conditions same as in footnote a of Table 1 but 48 h.

The last formula line of Table 4 illustrates how ADs of conjugated dienoic esters may be improved from an imperfect to a virtually perfect γ,δ-:α,β-regioselectivity based on the 'fluorine-containing versus fluorine-free

Table 3 Regioselectivity of Dihydroxylations of δ-Alkynyl α,β,γ,δ-Unsaturated Esters Containing Trifluoroethoxy versus Ethoxy Moieties

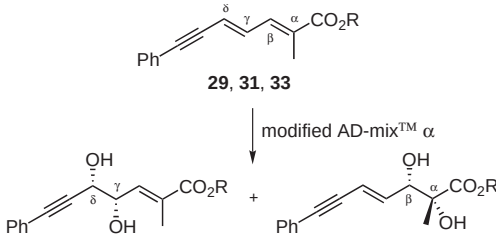


Substrate	R^1	R^2	Products[a]	Yield (%)	γ,δ-:α,β-attack
2[b]	TBS[c]	Et	**22**/*iso*-**22**	59	12:88
23[d]		Tfe[e]	**24**/*iso*-**24**	32	50:50
25[b]	Ph	Et	**26**/*iso*-**26**	53	23:77
27[d]		Tfe[e]	**28**/*iso*-**28**	32	69:31

[a] Inseparable by flash chromatography[7] on silica gel.
[b] Conditions same as in footnote a of Table 1 but more $K_2Os(OH)_4O_2$ (5 mol%), more $(DHQ)_2PHAL$ (10 mol%), 48 h.
[c] TBS = *tert*-butyldimethylsilyl.
[d] Conditions same as in footnote b but also $NaHCO_3$ (3.0 equiv).
[e] Tfe = trifluoroethyl.

ester concept': by dihydroxylating the respective hexafluoroisopropyl ester (specifically **33**[17]) – on grounds of expecting its $C^{\alpha}=C^{\beta}$ bond to be even electron-poorer than the $C^{\alpha}=C^{\beta}$ bond in the corresponding trifluoroethyl ester (specifically **31**). Under the forcing AD conditions which had provided the 92:8 mixture of γ,δ- and α,β-dihydroxy trifluoroethyl esters **32** and *iso*-**32**, we now obtained the γ,δ-dihydroxy hexafluoroisopropyl ester **34**[18] as a single isomer (40% yield).

Table 4 Regiocontrolled Dihydroxylation of an α-Methyl-δ-alkynyl α,β,γ,δ-Unsaturated Ester Containing Differently Fluorinated Alkoxy Moieties



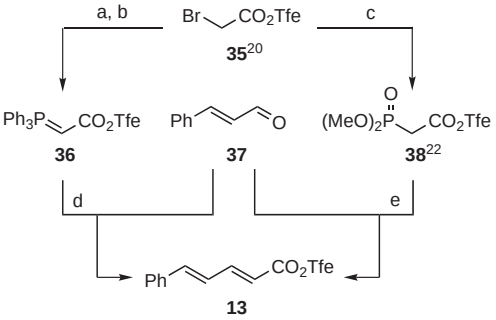
Substrate	R	Products	Yield (%)	γ,δ-:α,β-attack
29[a]	Et	**30**/*iso*-**30**[b]	70	56:44
31[c]	Tfe[d]	**32**/*iso*-**32**[b]	73	92:8
33[e]	Hf*ip*[f]	**34**	40	100:0

[a] Conditions same as in footnote a of Table 1.
[b] Separable by flash chromatography[7] on silica gel.
[c] Conditions same as in footnote a of Table 1 but more $K_2Os(OH)_4O_2$ (5 mol%), more $(DHQ)_2PHAL$ (10 mol%), 48 h.
[d] Tfe = trifluoroethyl.
[e] Conditions same as in footnote c but also $NaHCO_3$ (3.0 equiv).
[f] Hf*ip* = hexafluoroisopropyl.

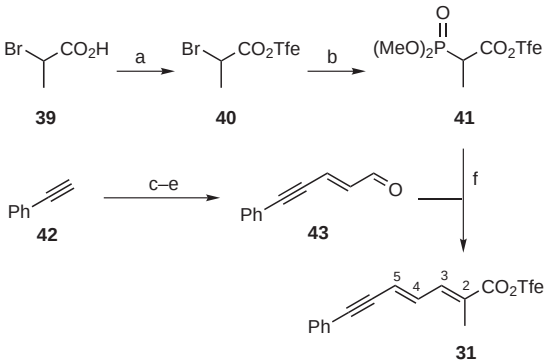
The α,β,γ,δ-unsaturated esters of the present study were prepared by Negishi, Heck or Stille couplings or by a Wittig or Horner–Wadsworth–Emmons (HWE) reaction.[19]

Scheme 2 illustrates Wittig reagent **36** in a completely *trans*-selective chain-extension of cinnamic aldehyde (**37**); it gave the trifluoroethyl dienoate **13** in quantitative yield.[24,25] A 65% yield of the same dienoate was obtained with 96:4 *trans* selectivity by an HWE reaction between cinnamic aldehyde (**37**) and deprotonated (NaH) trifluoroethyl phosphonylacetate **38**.[22]

The α-branched trifluoroethyl dienoate **31** stemmed from an HWE reaction in which we combined the lithium derivative of the α-branched trifluoroethyl phosphonylacetate **41** with enynal **43** (Scheme 3).[26] This reaction furnished **31** with 73% yield as a 2*E*,4*E*:2*Z*,4*E*:2*E*,4*Z* (90:6.4:3.6) mixture. This corresponds to 93.6% *E* selectivity with respect to the newly established $C^2=C^3$ bond and 3.6% loss of *trans* configuration at the previously present $C^4=C^5$ bond. HWE reagent **41**, which was not reported before, was obtained in 44% yield[27] from an Arbusov reaction between $P(OMe)_3$ and trifluoroethyl bromopropionate **40**.[28]



Scheme 2 Stereoselective synthesis of an α,β,γ,δ-unsaturated trifluoroethyl (Tfe) ester. *Reagents and conditions*: a) PPh_3 (1.0 equiv), toluene, r.t., 20 h, 100% (ref. 23 mentions no yield); b) NaOH (2 M, 1.0 equiv), H_2O, 0 °C, 100% (ref. 23 mentions no yield); c) $(MeO)_3P$ (1.3 equiv), 60–70 °C, 1 h; 4 h, 90 °C, 98%; d) **36** (3.0 equiv), CH_2Cl_2, r.t., 48 h, 100%, 2*E*,4*E*:2*E*,4*Z* (98.5:1.5) mixture; e) **38** (1.0 equiv), NaH (1.0 equiv), THF, 0 °C, 10 min; addition of **37**, –78 °C, THF, 90 min, 65%, 2*E*,4*E*:2*Z*,4*E* (96:4) mixture.



Scheme 3 Stereoselective synthesis of an α-methylated α,β,γ,δ-unsaturated trifluoroethyl (Tfe) ester. *Reagents and conditions*: a) F_3CCH_2OH (3.0 equiv), H_2SO_4 (cat.), benzene, reflux, 3 d, 78%; b) $(MeO)_3P$ (1.3 equiv), 180 °C, 4 h, 44%; c) CuCl (5 mol%), $NH_2OH{\cdot}HCl$ (cat.), *n*-$BuNH_2$ (30% in H_2O), 0 °C; then **42**, 3-bromo-2-propyn-1-ol (1.0 equiv), 0 °C → r.t., 2 h, 90%; d) $LiAlH_4$ (1.5 equiv), Et_2O, 0 °C → r.t., 3.5 h, 96%; e) MnO_2 (30 equiv), CH_2Cl_2, r.t., 4 h, 82%; f) **41** (1.2 equiv), *n*-BuLi (1.4 equiv), THF, -78 °C, 10 min; then **43**, 30 min; 0 °C, 2 h, 73% of a 2*E*,4*E*:2*Z*,4*E*:2*E*,4*Z* (90:6.4:3.6) mixture.

Acknowledgment

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References and Notes

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(8) All new compounds gave satisfactory ^{1}H NMR and ^{13}C NMR spectra and provided correct combustion analyses (**5**–**10**, **13**–**15**, **17**, **21**, **22**, **25**, **27**, **29**, **30**) or high-resolution mass spectra (**16**, **18**–**20**, **23**, **24**, **26**, **28**, *iso*-**30**, **31**–**35**, *iso*-**32**, **41**).

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(11) It is interesting to note that while we mono(dihydroxylated) methyl dienoate **5** asymmetrically (see text) we could not realize its racemic dihydroxylation at identical substrate concentration using $K_2Os(OH)_4O_2$ (10 mol%) and $NMO{\cdot}H_2O$[12] (1.2 equiv) in *t*-BuOH–H_2O (1:1) over the course of 4 d. This seems to imply that the asymmetric dihydroxylation of compound **5** benefits from a considerable ligand accelerating effect by the added amine.[13] It was only for this reason that all *cis*,*vic*-dihydroxylations of our study were undertaken as asymmetric dihydroxylations and their ee values considered unimportant and thus undetermined [except for compounds **14** (99% ee) and **34** (84% ee)]. All asymmetric dihydroxylations of our study were performed with the AD-mix α ligand, for example, with $(DHQ)_2PHAL$, and never with the AD-mix β ligand, for example, with $(DHQD)_2PHAL$. The reason is that Sharpless et al. (ref. 3) found decreased γ,δ:α,β dihydroxylation ratios employing AD-mix β instead of AD-mix α for the dihydroxylation of α,β,γ,δ-unsaturated esters **1** (→ **2**:*iso*-**2** = 83:17 instead of 87:13) or **3** (→ **4**:*iso*-**4** = 56:44 instead of 60:40).

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(15) An ancillary observation of the same effect was our failure to dihydroxylate *trans*-1,6-bis(trimethylsilyl)-3-hexene-1,5-diyne with $K_2OsO_2(OH)_4$–NMO, $K_2OsO_2(OH)_4$–$(DHQ)_2PHAL$–$K_3Fe(CN)_6$ or $KMnO_4$: Schmidt-Leithoff J.; *Ph.D. Dissertation*; Universität Freiburg, **2006**.

(16) We observed 5% more γ,δ- and 5% less α,β-dihydroxylation in the mono-ADs of dienoates **1** and **3** than in the hands of Sharpless et al.[3] (see Scheme 1). This might be due to our catalyst/ligand ratio being 1:5 and Sharpless' being 1:1 and 1:2, respectively.

(17) **1,1,1,3,3,3-Hexafluoroisopropyl (2*E*,4*E*)-2-Methyl-7-phenyl-2,4-heptadien-6-ynoate (33)**: ^{1}H NMR (400.1 MHz, $CDCl_3$, TMS; 4% 2*Z*,4*E*-isomer): δ = 2.07 (dd, $^4J_{2\text{-Me},3}$ = 1.4 Hz, $^5J_{2\text{-Me},4}$ = 0.5 Hz, 2-CH_3), 5.88 (sept, $J_{1'',F}$ = 6.2 Hz, 1″-H), 6.28 (br d, $J_{5,4}$ = 15.3 Hz, 5-H), 6.97 (dd, $J_{4,5}$ = 15.4 Hz, $J_{4,3}$ = 11.7 Hz, 4-H), 7.32–7.38 (m, 3′-H, 4′-H, 5′-H), partly superimposed by 7.38 (ddq, $J_{3,4}$ = 11.7 Hz, $^4J_{3,5}$ = 1.4 Hz, $^4J_{3,2\text{-Me}}$ = 0.9 Hz, 3-H), 7.43–7.52 (m, 2′-H, 6′-H). HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{17}H_{12}F_6O_2$: 362.0741; found: 362.0735.

(18) **1,1,1,3,3,3-Hexafluoroisopropyl (*E*,4*S*,5*S*)-4,5-Dihydroxy-2-methyl-7-phenyl-2-hepten-6-ynoate (34)**: $K_3Fe(CN)_6$ (273 mg, 828 μmol, 3.0 equiv), $(DHQ)_2PHAL$ (21.5 mg, 27.6 μmol, 10 mol%), K_2CO_3 (114 mg, 828 μmol, 3.0 equiv), and $MeSO_2NH_2$ (26.3 mg, 276 μmol, 1.0 equiv) were suspended in *t*-BuOH–H_2O (4 mL:5 mL) at 0 °C. $K_2Os(OH)_4O_2$ (5.1 mg, 13.8 μmol, 5 mol%) and a solution of **33** (100 mg, 276 μmol) in *t*-BuOMe (2 mL) were added to the reaction mixture. After stirring at 0 °C for 2 d sat. aq $Na_2S_2O_3$ (10 mL) was added. The resulting mixture was stirred at r.t. for 30 min, the organic phase separated and extracted with EtOAc (4 × 15 mL). The combined organic phases were dried with Na_2SO_4. After evaporation of the solvent the residue was purified by flash chromatography[7] (eluent: cyclohexane–EtOAc, 3:1) giving the title compound [43.5 mg, 40% of an inseparable *E*:*Z* mixture (95.4:4.6)] as a colorless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$, TMS; 4.6% 2*Z*-isomer): δ = 2.07 (d, $^4J_{2\text{-Me},3}$ = 1.5 Hz, 2-CH_3), 2.66, 2.81 (2 × br s, 4-OH, 5-OH), 4.58 (d, $J_{5,4}$ = 7.0 Hz, 5-H), 4.66 (incompletely resolved dd, $J_{4,3}$ = 8.3 Hz, $J_{4,5}$ = 7.0 Hz, 4-H), 5.85 (sept, $J_{1'',F}$ = 6.1 Hz, 1″-H), 6.94 (dq, $J_{3,4}$ = 8.4 Hz, $^4J_{3,2\text{-Me}}$ = 1.4 Hz, 3-H), 7.29–7.40 (m, ArH). HRMS (EI, 70 eV, fragment 1): *m*/*z* $[M - C_9H_6O]^+$ calcd for $C_8H_8F_6O_3$: 266.0377; found: 266.0373. HRMS (EI, 70 eV, fragment 2): *m*/*z* $[M - C_8H_7F_6O_3]^+$ calcd for C_9H_7O: 131.0497; found: 131.0495.

(19) The only exception was hexafluoroisopropyl ester **33**.[17] It was obtained in 96% yield by a carbodiimide-mediated esterification of hexafluoroisopropanol with the carboxylic acid obtained from the saponification of ethyl ester **29**.

(20) Trifluoroethyl bromoacetate(**35**) was obtained in 75% yield by an H_2SO_4-catalyzed esterification from bromoacetic acid and trifluoroethanol (2.0 equiv). Previously, **35** was obtained by trifluoroethanolysis of ethyl bromoacetyl chloride in 81% yield.[21]

(21) Morphy, J. R.; Rankovic, Z.; York, M. *Tetrahedron* **2003**, *59*, 2137.

(22) Trifluoroethyl(dimethylphosphonyl)acetate(**38**) has not been previously described and was prepared by the Arbusov reaction (Scheme 2).[20] This reaction is higher yielding (98%) than the synthesis of the analogous trifluoroethyl(diethylphosphonyl)acetate by treatment of (diethylphos-phono)

acetic acid first with $SOCl_2$ and then with trifluoro-ethanol (Σ = 58%): Birnbaum, J. C.; Busche, B.; Lin, Y.; Shaw, W. J.; Fryxell, G. E. *Chem. Commun.* **2002**, 1374.

(23) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387.

(24) The phosphonium bromide precursor of ylide **36** was prepared from PPh_3 and 2,2,2-trifluoroethyl bromoacetate (**35**)[20] in two steps and 100% overall yield. The same ylide was similarly obtained by Kwon et al.[23] but used *en route* to allenic carboxylic esters and not in a Wittig reaction.

(25) Trifluoroethyl dienoate **13** was obtained as a mixture of 2*E*,4*E*-**13** and 2*E*,4*Z*-**13** isomers (98.5:1.5), which was inseparable by flash chromatography on silica gel.[7] The formation of 2*E*,4*Z*-**13** can be explained by an isomerization of the C^3=C^4 bond.

(26) **2,2,2-Trifluoroethyl (2*E*,4*E*)-2-Methyl-7-phenyl-2,4-heptadien-6-ynoate (31)**: At –78 °C *n*-BuLi (2.5 M in hexane, 1.23 mL, 3.07 mmol, 1.4 equiv) was added to a solution of **41** (694 mg, 2.63 mmol, 1.2 equiv) in THF (15 mL). After 10 min a solution of **43** (342 mg, 2.19 mmol) in THF (10 mL) was added. Stirring was continued at –78 °C for 30 min and at 0 °C for another 2 h. Quenching by adding aq NH_4Cl (10 mL), phase separation, extraction of the aq phase with Et_2O (3 × 15 mL), drying of the combined organic phases with Na_2SO_4, and purification of the crude product by flash chromatography[7] (eluent: cyclohexane–EtOAc, 5:1) furnished the title compound (73%) as a 2*E*,4*E*:2*Z*,4*E*:2*E*,4*Z* (90:6.4:3.6) mixture. ^{1}H NMR (400.1 MHz, $CDCl_3$, TMS): δ = 2.04 (dd, $^4J_{2\text{-Me},3}$ = 1.4 Hz, $^5J_{2\text{-Me},4}$ = 0.5 Hz, 2-CH_3), 4.56 (q, $J_{1'',F}$ = 8.5 Hz, 1″-H_2), 6.22 (ddd, $J_{5,4}$ = 15.4 Hz, $^4J_{5,3}$ = $^6J_{5,2'/6'}$ = 0.7 Hz, 5-H), 6.97 ($J_{4,5}$ = 15.4 Hz, $J_{4,3}$ = 11.8 Hz, 4-H), 7.31 [dqd, in part superimposed by m (3′-H, 4′-H, 5′-H), $J_{3,4} \approx$ 11.8 Hz, $^4J_{3,2\text{-Me}}$ = 1.4 Hz, $^4J_{3,5}$ = 0.9 Hz, 3-H], 7.32–7.37 (m, 3′-H, 4′-H, 5′-H), 7.44–7.51 (m, 2′-H, 6′-H). HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{16}H_{13}F_3O_2$: 294.0868; found: 294.0867.

(27) **2,2,2-Trifluoroethyl 2-(Dimethoxyphosphonyl)propionate (41)**: Neat 2,2,2-trifluoroethyl 2-bromopropionate (4.58 g, 19.5 mmol) was heated at 60 °C while trimethyl phosphite (2.99 mL, 3.14 g, 25.3 mmol, 1.3 equiv) was added slowly. The resulting solution was then heated at 180 °C for 4 h. Distillation (bp 25–30 °C/0.45 mbar) afforded the title compound (2.27 g, 44%). ^{1}H NMR (400.1 MHz, $CDCl_3$, TMS): δ = 1.48 (dd, $J_{3,P}$ = 17.7 Hz, $J_{3,2}$ = 7.3 Hz, 3-H_3), 3.15 (dq, $^2J_{2,P}$ = 23.8 Hz, $J_{2,3}$ = 7.3 Hz, 2-H), 3.79, 3.80 (2 × d, $J_{OMe,P}$ = 11.0 Hz, 2 × OCH_3), AB signal (δ_A = 4.49, δ_B = 4.55, J_{AB} = 12.7 Hz, A and B peaks in addition split to q by $J_{1',F}$ = 8.3 Hz, B peaks further split to d by unassigned *J* = 0.5 Hz, 1′-H_2). HRMS (EI, 70 eV, fragment 1): *m*/*z* $[M - OC_3H_3]^+$ calcd for $C_4H_9F_3O_4P$: 209.0190; found: 209.0187. HRMS (EI, 70 eV, fragment 2): *m*/*z* $[M - CH_2CF_3]^+$ calcd for $C_5H_{10}O_5P$: 181.0266; found: 181.0263. HRMS (EI, 70 eV, fragment 3): *m*/*z* $[M - OCH_2CF_3]^+$ calcd for $C_5H_{10}O_4P$: 165.0317; found: 165.0316.

(28) Compound **40** was obtained in 78% yield by esterification of 2-bromopropionic acid. A two-step synthesis of **40** via acid chloride formation from 2-bromopropionic acid followed by trifluoroethanolysis yielded 83% of **40**: Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939.