# Claisen Rearrangement of Allyl Bromofluorovinyl Ethers

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A one-pot synthesis of α-bromo β-substituted γ-unsaturated acids via a diastereoselective Claisen rearrangement of allyl bromofluorovinyl ethers is described.

## Introduction

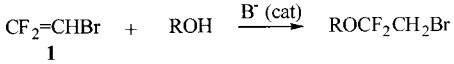
The Claisen rearrangement is considered as a useful synthetic transformation for the stereoselective construction of carbon-carbon bonds. Two new asymmetric centers may be created diastereoselectively with concomitant regio- and stereospecific formation of a new double bond. Moreover, because the most favorable transition-state geometry can ordinarily be predicted from principles of conformational analysis, the stereochemical outcome is subject to prediction and control. The effect of a fluorinated group on the Claisen rearrangement has already been described.[1] With regard to this subject, we have shown previously the use of fluoroalkenes as electrophiles for the synthesis of allyl fluorovinyl ethers, intermediaries in ulterior Claisen transpositions.[2–3]

## Results and Discussion

During the course of our current studies on the reactivity of fluoroalkenes leading to β-substituted γ-unsaturated acid derivatives via a Claisen transposition, we have chosen 2-bromo-1,1-difluoroethylene **(1)** as the electrophilic alkene. With regards to this reagent, two questions may be asked:

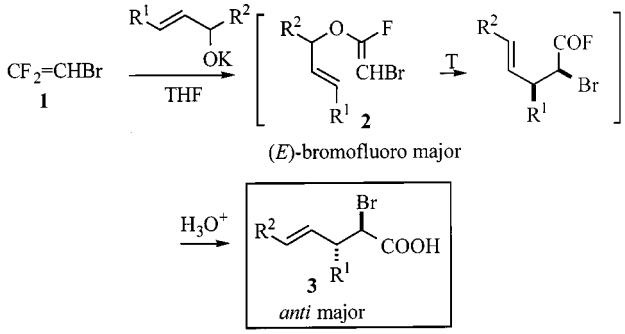
- Is the steric hindrance due to the bromine atom sufficient to influence the geometry of the vinyl group of the ether **2**, and thereby the diastereoselectivity of the acids **3**?
- Can the presence of potassium alkoxide in the medium make a β-elimination become competitive with the main reaction and then inhibit the formation of the desired product?

In the literature, only two references[4,5] report the addition of alcohols with **1** using the corresponding alkoxide as catalyst. The reaction takes place in protic medium and leads to a saturated fluorinated ether (Scheme 1).



Scheme 1. Addition reaction in protic medium

Herein, we describe the reaction of **1** with α-unsaturated alcohols in an anhydrous medium which makes it possible to obtain the allyl bromofluorovinyl ethers **2**. Claisen rearrangement of these ethers offers the advantage that it occurs at very low temperatures leading, with an internal asymmetric induction, to the α-bromo β-substituted γ-unsaturated acids **3** in good yields (Scheme 2). No known general and simple synthetic method is suitable for preparing these acids.[6–7]



Scheme 2. Synthesis of acids **3**

The acids **3** are obtained by a one-pot synthesis which includes three different steps: reaction between allyl potassium alkoxide and 2-bromo-1,1-difluoroethylene, selective Claisen rearrangement, and hydrolysis of acid fluoride. The results are summarized in Table 1.

The first step involves a selective fluorine substitution by a metal alkoxide. The alkoxide reacts according to an addition-elimination process[8] (via an intermediate carbanion) to give the vinyl ether **2** with the halogen atoms mainly in a *trans* geometry. It is the mesomeric effect of fluorine in the difluoromethylene group which determines the orientation of this addition[9] (Scheme 3).

This geometry has been shown with a saturated alkoxide (*n*heptOK, Scheme 4). In this case, since the ether **2** cannot undergo the transposition and, moreover, is very stable in

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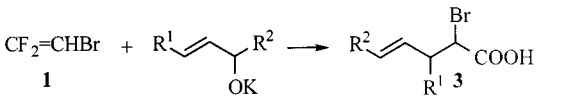
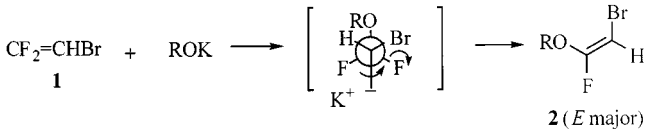
Table 1. Claisen rearrangement of allyl bromofluorovinyl ethers



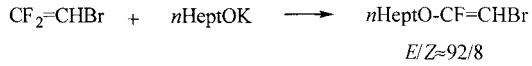
| $R^1$ | $R^2$ | Exp. cond n[a]/time (h)/T°C | Acid **3** | Yield[b] (%) | dr[c] *anti/syn* |
|---|---|---|---|---|---|
| Me | H | 1.5/2/-60 | **3a** | 80 | 87/13[e] |
| *n*Pr | " | 1.5/1/-55 | **3b** | 81 | 86/14 (94/6)[d] |
| *i*Pr | " | 2.0/3/-55 | **3c** | 68 | 84/16 (97/3)[d] |
| *t*Bu | " | 1.8/4/-55 | **3d** | 50 | 70/30 |
| Ph | " | 1.5/3/-90 | **3e** | 45 | 82/18 (100/0)[d] |
| Me | Me | 1.6/2/-90 | **3f** | 88 | 90/10 (99/1)[d] |

[a] Number of equivalents of allyl potassium alkoxide. – [b] Overall yields based on the starting bromodifluoroethylene, for products isolated from the reaction mixture by an acid-base treatment. – [c] Diastereomer ratio determined by $^1$H NMR. – [d] After purification. – [e] With commercial crotyl alcohol (*E*/*Z* = 94:6).



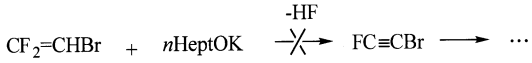
Scheme 3. Stereochemistry of addition-elimination reaction

acidic medium and does not hydrolyze, it can be isolated and its geometry can be determined by $^{19}$F and $^1$H NMR spectroscopy.[10]



Scheme 4. Substitution reaction by a saturated alkoxide

Note that the elimination reaction of hydrogen fluoride by the alkoxide (according to Scheme 5), if it takes place, does not seem to be substantial.

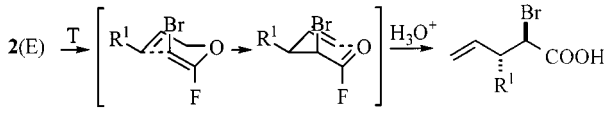


Scheme 5. Elimination reaction by a saturated alkoxide

Potassium alkoxides offer the advantage of reacting in THF with bromodifluoroethylene at very low temperatures (–90 °C), temperatures which are compatible with our Claisen rearrangement which occurs later at about –30 °C. Sodium alkoxides, however, only seem to react above 0 °C. Moreover, in these temperature conditions we have observed the presence of the saturated ether $ROCF_2CH_2Br$, sometimes in significant amounts. This can be explained either by the difficulty of obtaining anhydrous sodium alkoxide or by the fact that the intermediate carbanion, being more stable, can abstract a proton from the solvent before the β-elimination of the fluoride ion.

In a second step, by increasing the temperature of the reaction mixture to about –30 °C, the allyl fluorovinyl ethers quickly undergo Claisen rearrangement, giving the corresponding acid fluorides. We have already shown that the fluorine atom in the α position to the oxygen atom was responsible for a substantial decrease in the rearrangement reaction temperature, and that the greater the decrease in the electronegativity of the halogen atom in the β position, the more difficult the rearrangement.[3] Nevertheless, the influence of the halogen atom in the β position to the oxygen atom is lower than the one in the α position.[3]

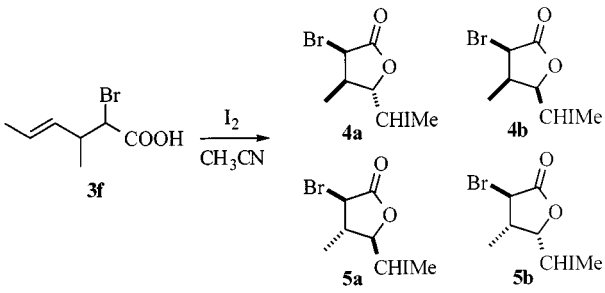
The Claisen rearrangement usually proceeds through a cyclic transition state with a favorable chair-like conformation. Thus, the *trans* bromofluorinated ether **2** (*E*) leads to the *anti* acid **3**, and the *cis* ether **2** (*Z*) to the *syn* acid **3** (Scheme 6). In Table 1 we can see a variable amount of *syn* product. This is probably due to the presence of a variable amount of *cis* bromofluorinated ether **2** (*Z*). The poor diastereoselectivity in the case of $R^1$ = *t*Bu has not been explained. In the case of $R^1 = R^2$ = Me, the high stereoselectivity (*E* > 98%) is demonstrated for the newly formed carbon-carbon double bond on the rearrangement.



Scheme 6. Chair-like conformation in transition state

Finally, the hydrolysis of acid fluoride into acid is easy: it occurs in less than one hour at room temperature for the examples described here. It is interesting to emphasize that we have shown that, in a similar case,[11] an acid fluoride resulting from transposition is a reactive synthetic intermediary because it can lead to esters or amides if alcohols or amines are added instead of water.

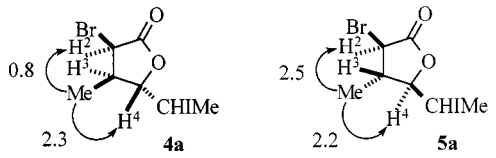
In order to confirm the configuration of the acids **3**, we have studied the $^1$H (NOE) NMR spectra of the lactones obtained after iodolactonization starting from the two diastereomers of **3f** ($R^1$ = Me, $R^2$ = Me) (separated by recrystallization). Thus, when **3f** as the mixture $D^1$:$D^2$ ≈ 99:1 ($D^1$ being the major diastereomer of **3f**) is treated with $I_2$ in $CH_3CN$ under ice-cooling, the reaction yields two iodolactones, **4a** and **4b** (**4a**:**4b** = 95:5); similarly, **3f** as the mixture $D^1$:$D^2$ ≈ 25:75 ($D^2$ being the minor diastereomer of **3f**) leads to **4a**, **5a** and **5b** (with **4a**:**5a**:**5b** ≈ 23:72:5; **4b** could not be detected) (Scheme 7).



Scheme 7. Iodolactonization reaction

The relative stereochemistry of the functional groups in **4a** and **5a** was determined by NOE analysis after irradiation

of the methyl protons at C-3 at 1.31 for **4a** or at 1.37 for **5a** (Scheme 8).




Scheme 8. $^1$H NMR NOE intensity changes, given as % value

We have observed for **4a** a significant effect on the 4-H proton and a slight effect on the 2-H proton and, for **5a**, about the same effect on the 2-H and 4-H protons (Scheme 8). These results allow us to conclude that **4** [**4a** + **4b**] is really the *cis*-2-bromo-3-methyl iodolactone with **4a** (Me and CHIMe in *trans* position) as the major isomer, and **5** [**5a** + **5b**] the *trans*-2-bromo-3-methyl iodolactone with **5a** (Me and CHIMe *trans*) as the major isomer.

As the iodolactonization is a stereoselective process, we may consider that $D^1$ is the *anti* isomer and $D^2$ the *syn* isomer.

## Conclusion

We have shown the very wide ranging reactivity of allylic potassium alkoxides with electrophilic fluoroalkenes. The allyl fluorovinyl ethers obtained rapidly undergo a rearrangement at very low temperatures which makes it possible to synthesize α-bromo β-substituted γ-unsaturated acid derivatives with *E* selectivity and in good yields. The reaction diastereoselectivity results from the predominant formation of **2** (*E*). Moreover, some acids can be obtained with high diastereoselectivity after purification.

## Experimental Section

$^1$H NMR and $^{13}$C NMR spectra were recorded on Varian VXR 300 and Bruker ARX 400 spectrometers, with $CDCl_3$ as solvent and TMS as internal standard. Infrared spectra were measured on a Perkin–Elmer 397 spectrometer. 2-Bromo-1,1-difluoroethylene was purchased from PCR-Lancaster.

**Preparation of the Acids 3a–f. General Procedure for 3f:** 3-Penten-2-ol (16 mmol) was added to KH (≈ 16 mmol) in THF (30 mL). After 1 h at +20 °C, this alkoxide solution was added to bromodifluoroethylene (10 mmol) in THF (40 mL) at –90 °C. The stirring was continued for 2 h, the mixture hydrolyzed with $H_2SO_4$ (10%) at –50 °C and then the temperature was allowed to rise to 20 °C. After 1 h at room temperature, the mixture was extracted with $Et_2O$. The product was isolated after an acid-base treatment (diluted $H_2SO_4$/$NaHCO_3$).

**2-Bromo-3-methyl-4-pentenoic Acid (3a):**[6] IR (neat): $\tilde{\nu}$ = 2960 cm$^{-1}$ (OH), 1715 (C=O), 1635 (C=C).

***anti*:** $^1$H NMR: δ = 1.20 [d, $J$ ($H^6$/$H^3$) = 6.7 Hz, 3 6-H], 2.84 [hex, $J$ ($H^3$/$H^4$) = 7.9 Hz, $J$ ($H^3$/$H^2$) = 7.7 Hz, $J$ ($H^3$/$H^6$) = 6.7 Hz, 3-H], 4.16 [d, $J$ ($H^2$/$H^3$) = 7.7 Hz, 2-H], 5.16 [dd, $J$ ($H^{5'}$/$H^4$) = 10.1 Hz, $J$ ($H^{5'}$/$H^5$) = 1 Hz, 5′-H], 5.17 [dd, $J$ ($H^5$/$H^4$) = 17.4 Hz, $J$ ($H^5$/$H^{5'}$) = 1 Hz, 5-H], 5.79 [ddd, $J$ ($H^4$/$H^5$) = 17.4 Hz, $J$ ($H^4$/$H^{5'}$) = 10.1 Hz, $J$ ($H^4$/$H^3$) = 7.9 Hz, 4-H], 10.07 (s, 1 H). – $^{13}$C NMR: δ = 18.1 (C-6), 41.4 (C-3), 51.5 (C-2), 117.2 (C-5), 138.3 (C-4), 174.8 (C-1).

***syn*:** $^1$H NMR: δ = 1.24 [d, $J$ ($H^6$/$H^3$) = 6.9 Hz, 3 6-H], 2.84 [hex, $J$ ($H^3$/$H^2$) = 8.6 Hz, $J$ ($H^3$/$H^4$) = 7.9 Hz, $J$ ($H^3$/$H^6$) = 6.9 Hz, 3-H], 4.12 [d, $J$ ($H^2$/$H^3$) = 8.6 Hz, 2-H], 5.13 [d, $J$ ($H^{5'}$/$H^4$) = 10.5 Hz, 5′-H], 5.19 [d, $J$ ($H^5$/$H^4$) ≈ 17 Hz, 5-H], 5.73 [ddd, $J$ ($H^4$/$H^5$) ≈ 17 Hz, $J$ ($H^4$/$H^{5'}$) = 10.5 Hz, $J$ ($H^4$/$H^3$) = 7.9 Hz, 4-H], 10.07 (s, 1-H). – $^{13}$C NMR: δ = 17.7 (C-6), 41.4 (C-3), 51.5 (C-2), 117.6 (C-5), 137.9 (C-4), 174.9 (C-1).

**2-Bromo-3-propyl-4-pentenoic Acid (3b):** After one recrystallization (hexane) of the mixture, the *anti* isomer could be obtained as a solid with a purity about 94%. IR (neat): $\tilde{\nu}$ = 2955 cm$^{-1}$ (OH), 1715 (C=O), 1640 (C=C).

***anti*:** $^1$H NMR: δ = 0.91 [t, $J$ = 7.1 Hz, 3 H], 1.20–1.50 [m, 4 H], 2.64 [m, $J$ ($H^3$/$H^4$) = 9.1 Hz, $J$ ($H^3$/$H^2$) = 7.1 Hz, 3-H], 4.25 [d, $J$ ($H^2$/$H^3$) = 7.1 Hz, 2-H], 5.14 [dd, $J$ ($H^5$/$H^4$) = 16.9 Hz, $J$ ($H^5$/$H^{5'}$) = 1.7 Hz, 5-H], 5.19 [dd, $J$ ($H^{5'}$/$H^4$) = 10.2 Hz, $J$ ($H^{5'}$/$H^5$) = 1.7 Hz, 5′-H], 5.59 [ddd, $J$ ($H^4$/$H^5$) = 16.9 Hz, $J$ ($H^4$/$H^{5'}$) = 10.2 Hz, $J$ ($H^4$/$H^3$) = 9.1 Hz, 4-H], 11.07 (s, 1-H). – $^{13}$C NMR: δ = 13.8 (C-8), 20.3 (C-7), 34.5 (C-6), 47.1 (C-3), 51.4 (C-2), 118.7 (C-5), 136.9 (C-4), 174.36 (C-1).

***syn*:** $^1$H NMR: δ = 0.92 [t, $J$ = 7.3 Hz, 3 H]; 1.20–1.50 [m, 4 H], 2.64 [m, $J$ ($H^3$/$H^2$) = 9.0 Hz, 3-H], 4.12 [d, $J$ ($H^2$/$H^3$) = 9.0 Hz, 2-H], 5.58 [ddd, 4-H], 11.07 (s, 1-H). – $^{13}$C NMR: δ = 13.8 (C-8), 19.9 (C-7), 33.9 (C-6), 47.1 (C-3), 50.6 (C-2), 119.4 (C-5), 136.5 (C-4), 174.45 (C-1). – $C_8H_{13}BrO_2$ (221.1): calcd. C 43.46, H 5.93; found C 43.37, H 6.09.

**2-Bromo-3-isopropyl-4-pentenoic acid (3c):** After one recrystallization (hexane) of the mixture, the *anti* isomer could be obtained as a solid with a purity of about 97%. IR (neat): $\tilde{\nu}$ = 2970 cm$^{-1}$ (OH), 1720 (C=O), 1645 (C=C).

***anti*:** $^1$H NMR: δ = 0.90 [d, $J$ ($H^7$/$H^6$) = 6.8 Hz, 3 7-H], 0.98 [d, $J$ ($H^7$/$H^6$) = 6.8 Hz, 3 7-H], 1.82 [oct, $J$ ($H^6$/$H^7$) = 6.8 Hz, $J$ ($H^6$/$H^7$) = 6.7 Hz, $J$ ($H^6$/$H^3$) = 6.7 Hz, 6-H], 2.39 [dt, $J$ ($H^3$/$H^4$) = 9.6 Hz, $J$ ($H^3$/$H^2$) = 7.0 Hz, $J$ ($H^3$/$H^6$) = 6.7 Hz, 3-H], 4.47 [d, $J$ ($H^2$/$H^3$) = 7.0 Hz, 2-H], 5.12 [dd, $J$ ($H^5$/$H^4$) = 17.0 Hz, $J$ ($H^5$/$H^{5'}$) = 1.8 Hz, 5-H], 5.23 [dd, $J$ ($H^{5'}$/$H^4$) = 10.3 Hz, $J$ ($H^{5'}$/$H^5$) = 1.8 Hz, 5′-H], 5.62 [dt, $J$ ($H^4$/$H^5$) = 17.0 Hz, $J$ ($H^4$/$H^{5'}$) = 10.3 Hz, $J$ ($H^4$/$H^3$) = 9.6 Hz, 4-H], 11.77 (s, 1-H). – $^{13}$C NMR: δ = 18.6 (C-7), 21.1 (C-7), 29.8 (C-6), 50.7 (C-3), 53.9 (C-2), 119.9 (C-5), 134.7 (C-4), 175. 5 (C-1).

***syn*:** $^1$H NMR: δ: 0.83 [d, $J$ ($H^7$/$H^6$) = 7.0 Hz, 3 7-H], 0.93 [d, $J$ ($H^7$/$H^6$) = 6.8 Hz, 3 7-H], 2.27 [septd, $J$ ($H^6$/$H^7$) = 7.0 Hz, $J$ ($H^6$/$H^7$) = 6.8 Hz, 6-H], 2.54 [td, $J$ ($H^3$/$H^2$) = 10.8 Hz, $J$ ($H^3$/$H^4$) = 9.6 Hz, $J$ ($H^3$/$H^6$) = 3.8 Hz, 3-H], 4.19 [d, $J$ ($H^2$/$H^3$) = 10.8 Hz, 2-H], 5.17 [dd, $J$ ($H^5$/$H^4$) = 17.0 Hz, $J$ ($H^5$/$H^{5'}$) = 1.8 Hz, 5-H], 5.24 [dd, $J$ ($H^{5'}$/$H^4$) ≈ 10 Hz, $J$ ($H^{5'}$/$H^5$) = 1.8 Hz, 5′-H], 5.58 [dt, $J$ ($H^4$/$H^5$) = 17.0 Hz, $J$ ($H^4$/$H^{5'}$) ≈ 10 Hz, $J$ ($H^4$/$H^3$) = 9.6 Hz, 4-H], 11.77 (s, 1-H). – $^{13}$C NMR: δ = 15.8 (C-7), 21.4 (C-7), 28.2 (C-6), 48.3 (C-3), 52.5 (C-2), 121.3 (C-5), 132.3 (C-4), 175.7 (C-1). – $C_8H_{13}BrO_2$ (221.1): calcd. C 43.46, H 5.93; found C 43.21, H 6.15.

**2-Bromo-3-*tert*-butyl-4-pentenoic Acid (3d):** IR (neat): $\tilde{\nu}$ = 2950 cm$^{-1}$ (OH), 1710 (C=O), 1635 (C=C).

***anti*:** $^1$H NMR: δ = 0.99 [s, 9 7-H], 2.52 [dd, $J$ ($H^3$/$H^4$) = 9.8 Hz, $J$ ($H^3$/$H^2$) = 5.7 Hz, 3-H], 4.559 [d, $J$ ($H^2$/$H^3$) = 5.7 Hz, 2-H], 5.06 [dd, $J$ ($H^5$/$H^4$) = 16.9 Hz, $J$ ($H^5$/$H^{5'}$) = 1.9 Hz, 5-H], 5.20 [dd, $J$ ($H^{5'}$/$H^4$) = 10.2 Hz, $J$ ($H^{5'}$/$H^5$) = 1.9 Hz, 5′-H], 5.77 [dt,

$J$ ($H^4/H^5$) = 16.9 Hz, $J$ ($H^4/H^{5'}$) = 10.2 Hz, $J$ ($H^4/H^3$) = 9.8 Hz, 4-H], 11.70 (s, 1-H). – $^{13}$C NMR: δ = 28.3 (C-7), 34.1 (C-6), 48.8 (C-3), 55.6 (C-2), 119.35 (C-5), 135.6 (C-4), 176.1 (C-1).

***syn*:** $^1$H NMR: δ = 1.00 [s, 9 7-H], 2.38 [dd, $J$ ($H^3/H^4$) = 10.4 Hz, $J$ ($H^3/H^2$) = 4.9 Hz, 3-H], 4.562 [d, $J$ ($H^2/H^3$) = 4.9 Hz, 2-H], 5.12 [dd, $J$ ($H^5/H^4$) = 16.9 Hz, $J$ ($H^5/H^{5'}$) = 2.0 Hz, 5-H], 5.26 [dd, $J$ ($H^{5'}/H^4$) = 10.2 Hz, $J$ ($H^{5'}/H^5$) = 2.0 Hz, 5′-H], 6.00 [dt, $J$ ($H^4/H^5$) = 16.9 Hz, $J$ ($H^4/H^{5'}$) = 10.2 Hz, $J$ ($H^4/H^3$) = 10.4 Hz, 4-H], 11.70 (s, 1-H). – $^{13}$C NMR: δ = 28.5 (C-7), 34.3 (C-6), 46.0 (C-3), 59.9 (C-2), 120.4 (C-5), 133.5 (C-4), 176.0 (C-1). – $C_9H_{15}BrO_2$ (235.1): calcd. C 45.97, H 6.43; found C 46.44, H 6.90.

**2-Bromo-3-phenyl-4-pentenoic Acid (3e):** The *anti* isomer was obtained as an oil with a purity of 100% after silica gel chromatography (cyclohexane/AcOEt = 80:20 + 1% AcOH). The *syn* isomer could be obtained as a solid with a purity of 90% after one recrystallization (hexane) from the remaining mixture. IR (neat): $\tilde{\nu}$ = 3020 cm$^{-1}$ (OH), 1710 (C=O), 1635 (C=C).

***anti*:** $^1$H NMR: δ = 3.92 [dd, $J$ ($H^3/H^2$) = 10.4 Hz, $J$ ($H^3/H^4$) = 8.2 Hz, 3-H], 4.47 [d, $J$ ($H^2/H^3$) = 10.4 Hz, 2-H], 5.16 [dd, $J$ ($H^5/H^4$) = 17.0 Hz, $J$ ($H^5/H^{5'}$) = 1.0 Hz, 5-H], 5.23 [dd, $J$ ($H^{5'}/H^4$) = 10.2 Hz, $J$ ($H^{5'}/H^5$) = 1.0 Hz, 5′-H], 6.06 [ddd, $J$ ($H^4/H^5$) = 17.0 Hz, $J$ ($H^4/H^{5'}$) = 10.2 Hz, $J$ ($H^4/H^3$) = 8.2 Hz, 4-H], 7.15–7.35 [m, 5 H], 10.72 (s, 1-H). – $^{13}$C NMR: δ = 49.1 (C-2), 53.2 (C-3), 118.6 (C-5), 127.7, 128.1, 128.9 (3 arom. C), 136.9 (C-4), 139.0 (C-6), 173.7 (C-1).

***syn*:** $^1$H NMR: δ = 3.90 [dd, $J$ ($H^3/H^2$) = 11.0 Hz, $J$ ($H^3/H^4$) = 8.4 Hz, 3-H], 4.43 [d, $J$ ($H^2/H^3$) = 11.0 Hz, 2-H], 5.14 [dd, $J$ ($H^5/H^4$) = 17.0 Hz, $J$ ($H^5/H^{5'}$) = 1.0 Hz, 5-H], 5.16 [dd, $J$ ($H^{5'}/H^4$) = 10.2 Hz, $J$ ($H^{5'}/H^5$) = 1.0 Hz, 5′-H], 5.94 [ddd, $J$ ($H^4/H^5$) = 17.0 Hz, $J$ ($H^4/H^{5'}$) = 10.2 Hz, $J$ ($H^4/H^3$) = 8.4 Hz, 4-H], 7.15–7.35 [m, 5 H], 10.72 (s, 1-H). – $^{13}$C NMR: δ = 48.7 (C-2), 53.7 (C-3), 118.7 (C-5), 127.6, 128.1, 128.8 (3 arom. C), 136.2 (C-4), 139.3 (C-6), 174.3 (C-1). – $C_{11}H_{11}BrO_2$ (255.1): calcd. C 51.79, H 4.35; found C 51.95, H 4.12.

**2-Bromo-3-methyl-4-hexenoic Acid (3f):** After one recrystallization (hexane) of the mixture, the *anti* isomer could be obtained as a solid (m.p. 67 °C) with a purity of 99% and the *syn* isomer as an oil with a purity about 75%. IR (neat): $\tilde{\nu}$ = 2960 cm$^{-1}$ (OH), 1710 (C=O).

***anti*:** $^1$H NMR: δ = 1.17 [d, $J$ ($H^7/H^3$) = 6.7 Hz, 3 7-H], 1.69 [dd, $J$ ($H^6/H^5$) = 6.4 Hz, $J$ ($H^6/H^4$) = 1.5 Hz, 3 6-H], 2.78 [hex, $J$ ($H^3/H^4$) = 7.9 Hz, $J$ ($H^3/H^2$) = 7.6 Hz, $J$ ($H^3/H^7$) = 6.7 Hz, 3-H], 4.13 [d, $J$ ($H^2/H^3$) = 7.6 Hz, 2-H], 5.37 [ddq, $J$ ($H^4/H^5$) = 15.2 Hz, $J$ ($H^4/H^3$) = 7.9 Hz, $J$ ($H^4/H^6$) = 1.5 Hz, 4-H], 5.59 [dq, $J$ ($H^5/H^4$) = 15.2 Hz, $J$ ($H^5/H^6$) = 6.4 Hz, 5-H], 11.59 (s, 1-H). – $^{13}$C NMR: δ = 18.0, 18.5 (C-6, C-7), 40.6 (C-2), 52.3 (C-3), 128.0, 131.0 (C-4, C-5), 175.3 (C-1).

***syn*:** $^1$H NMR: δ = 1.20 [d, $J$ ($H^7/H^3$) = 6.7 Hz, 3 7-H], 1.66 [dd, $J$ ($H^6/H^5$) = 6.5 Hz, $J$ ($H^6/H^4$) = 1.5 Hz, 3 6-H], 2.78 [hex, $J$ ($H^3/H^2$) = 8.9 Hz, $J$ ($H^3/H^4$) = 8.1 Hz, 3-H], 4.04 [d, $J$ ($H^2/H^3$) = 8.9 Hz, 2-H], 5.31 [ddq, $J$ ($H^4/H^5$) = 15.3 Hz, $J$ ($H^4/H^3$) = 8.1 Hz, $J$ ($H^4/H^6$) = 1.5 Hz, 4-H], 5.62 [dq, $J$ ($H^5/H^4$) = 15.3 Hz, $J$ ($H^5/H^6$) = 6.5 Hz, 5-H], 11.59 (s, 1-H). – $^{13}$C NMR: δ = 18.0, 18.3 (C-6, C-7), 40.55 (C-2), 51.9 (C-3), 128.8, 130.5 (C-4, C-5), 175.4 (C-1). – $C_7H_{11}BrO_2$ (207.1): calcd. C 40.60, H 5.36; found C 40.66, H 5.44.

**Preparation of Iodolactones 4 and 5:** A mixture of compound **3f** (0.21 g, 1 mmol) and solid iodine (0.8 g, 3 mmol) in 5 mL of acetonitrile was stirred in the dark, under argon, at 0 °C for 5 h. After addition of $Et_2O$, the reaction mixture was successively washed with saturated aqueous $NaHSO_3$, $NaHCO_3$ and NaCl solutions. It was dried over $MgSO_4$ and concentrated in vacuo.

If the **3f** used was *anti*/*syn* ≈ 99:1, the iodolactonization led to a mixture of **4a** and **4b** with **4a**/**4b** ≈ 95:5. Compounds **4a** and **4b** were separated by silica gel chromatography (cyclohexane/AcOEt = 80:20). If the **3f** used was *anti*/*syn* = 25:75, the iodolactonization gave a mixture of **4a**, **5a** and **5b** with **4a**/**5a**/**5b** ≈ 23:72:5. Compound **5b** was separated from the mixture by silica gel chromatography (cyclohexane/AcOEt = 80:20). Compound **5a** was obtained with a purity of 95% from the mixture of **4a** and **5a** by recrystallization ($Et_2O$).

**2-Bromo-4-hydroxy-4-[iodo-1-ethyl]-3-methyl Butanoic Acid Lactone (4, 5):**

**4a:** $^1$H NMR: δ = 1.31 [d, $J$ ($H^5/H^3$) = 6.6 Hz, 3 5-H], 1.96 [d, $J$ ($H^7/H^6$) = 7.1 Hz, 3 7-H], 2.59 [dquint, $J$ ($H^3/H^4$) = 7.6 Hz, $J$ ($H^3/H^2$) = 6.8 Hz, $J$ ($H^3/H^5$) = 6.6 Hz, 3-H], 4.06 [dd, $J$ ($H^4/H^3$) = 7.6 Hz, $J$ ($H^4/H^6$) = 4.2 Hz, 4-H], 4.43 [qd, $J$ ($H^6/H^7$) = 7.1 Hz, $J$ ($H^6/H^4$) = 4.2 Hz, 6-H], 4.61 [d, $J$ ($H^2/H^3$) = 6.8 Hz, 2-H]. – $^{13}$C NMR: δ = 15.9 (C-5), 23.2 (C-7), 24.4 (C-6), 39.7 (C-3), 47.7 (C-2), 87.9 (C-4), 170.9 (C-1).

**4b:** $^1$H NMR: δ = 1.13 [d, $J$ ($H^5/H^3$) = 7.0 Hz, 3 5-H], 2.09 [d, $J$ ($H^7/H^6$) = 6.6 Hz, 3 7-H], 3.06 [quintd, $J$ ($H^3/H^5$) = 7.0 Hz, $J$ ($H^3/H^2$) = 6.7 Hz, $J$ ($H^3/H^4$) = 4.0 Hz, 3-H], 3.97 [dq, $J$ ($H^6/H^4$) = 11.0 Hz, $J$ ($H^6/H^7$) = 6.6 Hz, 6-H], 4.50 [dd, $J$ ($H^4/H^6$) = 11.0 Hz, $J$ ($H^4/H^3$) = 4.0 Hz, 4-H], 4.89 [d, $J$ ($H^2/H^3$) = 6.7 Hz, 2-H]. – $^{13}$C NMR: δ = 9.7 (C-5), 21.4 (C-7), 25.4 (C-6), 40.0 (C-3), 48.3 (C-2), 84.6 (C-4).

**5a:** $^1$H NMR: δ = 1.37 [d, $J$ ($H^5/H^3$) = 7.0 Hz, 3 5-H], 1.99 [d, $J$ ($H^7/H^6$) = 7.0 Hz, 3 7-H], 2.80 [quintd, $J$ ($H^3/H^5$) = 7.0 Hz, $J$ ($H^3/H^2$) = 6.9 Hz, $J$ ($H^3/H^4$) = 5.9 Hz, 3-H], 4.09 [dd, $J$ ($H^4/H^6$) = 7.3 Hz, $J$ ($H^4/H^3$) = 5.9 Hz, 4-H], 4.15 [d, $J$ ($H^2/H^3$) = 6.9 Hz, 2-H], 4.43 [pent, $J$ ($H^6/H^4$) = 7.3 Hz, $J$ ($H^6/H^7$) = 7.0 Hz, 6-H]. – $^{13}$C NMR: δ = 18.1 (C-5), 24.0 (C-7), 25.5 (C-6), 44.6 (C-3), 45.7 (C-2), 88.9 (C-4), 171.1 (C-1).

**5b:** $^1$H NMR: δ = 1.20 [d, $J$ ($H^5/H^3$) = 6.4 Hz, 3 5-H], 2.09 [d, $J$ ($H^7/H^6$) = 7.2 Hz, 3 7-H], 2.49 [dquint, $J$ ($H^3/H^4$) = 8.8 Hz, $J$ ($H^3/H^2$) = 6.4 Hz, $J$ ($H^3/H^5$) = 6.4 Hz, 3-H], 3.36 [dd, $J$ ($H^4/H^3$) = 8.8 Hz, $J$ ($H^4/H^6$) = 1.9 Hz, 4-H], 4.32 [qd, $J$ ($H^6/H^7$) = 7.2 Hz, $J$ ($H^6/H^4$) = 1.9 Hz, 6-H], 4.50 [d, $J$ ($H^2/H^3$) = 6.4 Hz, 2-H]. – $^{13}$C NMR: δ = 13.7 (C-5), 26.1 (C-7), 26.2 (C-6), 43.2 (C-3), 47.2 (C-2), 86.9 (C-4), 171.1 (C-1).

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[10] (*n*-heptOCF=CHBr) $^1$H NMR: (*E*) isomer δ = 4.04 (t, *J* = 6.3 Hz, 2 H), 4.99 (d, *J* = 1.7 Hz, 1 H); (*Z*) isomer δ = 3.85 (t, *J* = 6.5 Hz, 2 H), 4.56 (d, *J* = 23.2 Hz, 1 H). – $^{19}$F NMR [referenced to $CFCl_3$]: (*E*) isomer δ = –85.3 (br. s, 1 F); (*Z*) isomer δ = –79.7 (d, *J* = 23.2 Hz, 1 F]).
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