Facial-Selective Allylation of Methyl Ketones for the Asymmetric Synthesis of α-Substituted Tertiary Homoallylic Ethers

Lutz F Tietze,*[a] Ludwig Völkel,[a] Christian Wulff,[a] Berthold Weigand,[a] Christian Bittner,[a] Paul McGrath,[a] Keyji Johnson,[b] and Martina Schäfer[b]

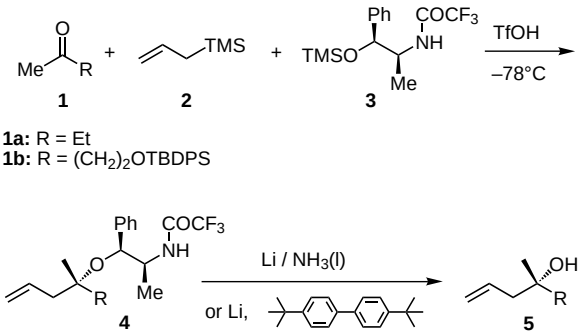
Dedicated to Professor Jean Francois Normant on the occasion of his 65th birthday

Abstract: The asymmetric synthesis of enantiomerically pure α-substituted tertiary homoallylic ethers **4a**, **11** and **12a–c** by the allylation of ethyl methyl ketone (**1a**) with γ-substituted allylsilanes **9a–h** is described. The allylsilanes were obtained by a nickel-catalysed Grignard cross-coupling reaction of (*E*)- and (*Z*)-(3-iodoallyl)trimethylsilane with various Grignard reagents. The reaction of the allylsilanes with **1a** in the presence of the trimethylsilyl ether of *N*-trifluoroacetylnorpseudoephedrine (**3**), and catalytic amounts of a mixture of trimethylsilyl triflate and trifluoromethanesulfonic acid led to the homoallylic ethers **4a**, **11** and **12a–c** with two new stereogenic centres, with a selectivity of 1:9 to >20:1 for the homoallylic and of 1:99 to >60:1 for the allylic centre. The facial selectivity does not depend on the configuration of the allylsilane, and in all reactions the *anti* product is preferentially formed. Interestingly, a pronounced switch of facial selectivity takes place with increasing length of the alkyl group of the allylsilane.

Keywords: allylation · amino alcohols · homoallylic alcohols · silanes

Introduction

A large number of natural products such as hydroxymyoporone,[1] cembranoids,[2] cineromycins[3] and erythrolids[4] contain an aliphatic tertiary alcohol moiety with a methyl group as one of the substituents. In Nature, this functionality is usually formed by an oxidative process of a methyl-substituted alkene. The chemical synthesis can easily be achieved by the allylation of an alkyl methyl ketone using allylsilanes, for example.[5] However, this transformation leads to a racemic mixture. In contrast, a facially selective allylation of alkyl methyl ketones is possible by the reaction of methyl ketone **1** with allyltrimethylsilane **2** in the presence of the norpseudoephedrine derivative **3**[6] and a catalytic amount of trifluoromethanesulfonic acid (TfOH) (Scheme 1). The homoallylic ethers **4** are the only products that are formed from the reaction of **1a**, with a diastereomeric ratio (d.r.) of 9:1 when the reaction is carried out at $-78\,^{\circ}C$, and with a d.r. of 24:1 at -104° C. Even more selective is the reaction of **1b**, which proceeds with a d.r. of 99:1 at $-78\,^{\circ}C$. The corresponding tertiary alcohols **5** can easily be obtained from **4** by reductive cleavage of the benzyl ether moiety either using lithium in liquid ammonia, or lithium in the presence of 4,4′-di-*tert*-butylbiphenyl. The described procedure is the only general method currently known for the facially selective addition to alkyl methyl ketones. All allylation methods employing either equimolar amounts of a chiral allyl reagent (such as allylbor-



Scheme 1. Allylation of alkyl methyl ketones **1a** and **1b** with allyltrimethylsilane **2** in the presence of **3**.

[a] Prof. Dr. DR. h.c. L. F Tietze, Dipl.-Chem. L. Völkel, Dr. C. Wulff, Dipl.-Chem. B. Weigand, Dipl.-Chem. C. Bittner, Dr. P. McGrath
Institut für Organische Chemie
der Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551 399476
E-mail: ltietze@gwdg.de

[b] Dr. K. Johnson, Dr. M. Schäfer
Institut für Anorganische Chemie
der Georg-August-Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)

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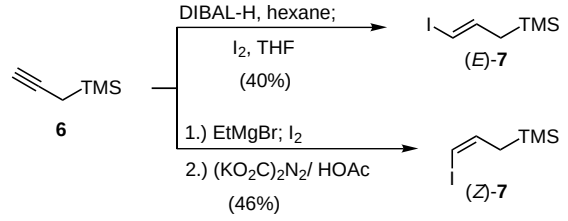
anes and allyltitanium compounds) or chiral catalysts (which gave excellent selectivities with aldehydes) failed when applied to alkyl methyl ketones.[7–10] Herein we describe the facially selective allylation of **1a** with γ-substituted allylsilanes to generate α-substituted tertiary homoallylic ethers with two new stereogenic centres.

Results and Discussion

Synthesis of γ-substituted allylsilanes: Several procedures are known for the selective synthesis of (*E*)- and (*Z*)-configured allylsilanes.[11] However, the Grignard cross-coupling of trimethylsilyl(TMS)-alkenyl halides, such as (*E*)-**7** and (*Z*)-**7**, with various alkyl Grignard reagents **8a–d** provided the most suitable access to a large number of substituted allylsilanes (Scheme 2).[12] Allylsilane (*Z*)-**7** was obtained as described by



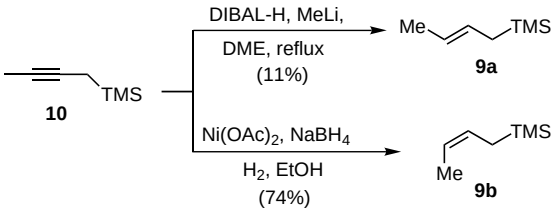
Scheme 2. Synthesis of γ-substituted allylsilanes **9c–j**.

Schinzer et al.,[13] and (*E*)-**7** was synthesized in 40% overall yield by hydroalumination of propargyl trimethylsilane with diisobutylaluminum hydride (DIBAL-H) followed by treatment with iodine. Coupling of (*E*)-**7** and (*Z*)-**7** with the alkyl Grignard reagents **8** in the presence of a catalytic amount of $Cl_2Ni(PPh_3)_2$ proceeded stereoselectively, and led to the formation of the isomerically pure allylsilanes **9c–j** in 58 to 87% yield (Table 1). Allylsilanes **9a** and **9b** were prepared starting with the methylation of propargyl trimethylsilane to give **10**, followed by reduction, using either DIBAL-H/MeLi or Ni-P2 (nickel boride catalyst)/H_2 (Scheme 3).[14–16] In the

Table 1. Cross-coupling of the vinylic halides **7** with various Grignard reagents.

R	Vinylic halide	Product[a]	*t* [h]	Yield [%]
Et	(*E*)-**7**	**9c**	4	70
Et	(*Z*)-**7**	**9d**	4.5	68
Pr	(*E*)-**7**	**9e**	2.5	69
Pr	(*Z*)-**7**	**9f**	6	69
Bu	(*E*)-**7**	**9g**	20	59
Bu	(*Z*)-**7**	**9h**	3.5	58
Bn	(*E*)-**7**	**9i**	3.5	74
Bn	(*Z*)-**7**	**9j**	24	87

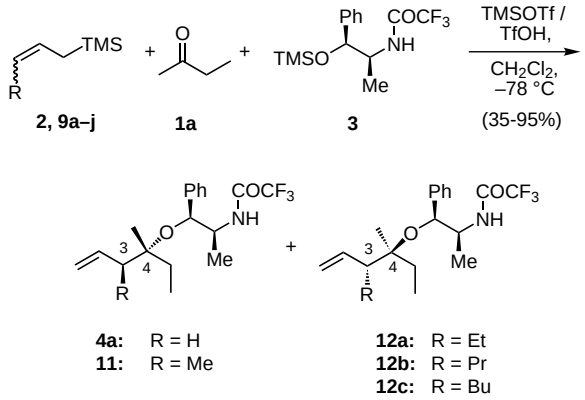
[a] *E*/*Z*-selectivity $\geq$ 99% in all cases.



Scheme 3. Synthesis of γ-substituted allylsilanes **9a** and **9b**.

first case, (*E*)-**9a** was obtained as a pure compound, albeit in a low yield. The second procedure led to the formation of the (*Z*)-configured crotylsilane **9b** in 74% yield.

Allylation of 1a: 2-Butanone is the methyl ketone that experiences the poorest facial differentiation, and was therefore chosen as the substrate for the allylation with different allyltrimethylsilanes **9**. The reaction was performed in a domino-type fashion[17] by adding catalytic amounts of a mixture of TfOH/TMSOTf (1:1) to a mixture of ketone **1a**, the γ-substituted allylsilane **9**, and the TMS ether **3** in dichloromethane at $-78\,^{\circ}C$, to give the homoallylic ethers **4a**, **11** and **12** (Scheme 4). Although allyltrimethylsilane **2** gave **4a** as the main product in 95% yield after 1 h, the γ-substituted allylsilanes **9a–h** are less reactive (Table 2). The reactivity of the allylsilanes **9**, and the diastereomeric ratios found for the



Scheme 4. Allylation of ethyl methyl ketone **1a** with γ-substituted allylsilanes **9a–j** in the presence of **3**.

Table 2. Allylations of ethyl methyl ketone (**1a**) with γ-substituted allylsilanes **2** and **9a–h** in the presence of **3**.

Allylsilane/ config.[a]	R	Main product	*t*	Yield [%][b]	*R*:*S* (C-3)[c]	*S*:*R* (C-4)[d]
2	H	**4a**	2 h	95	–	1:9
9a/*E*	Me	**11**	3 d	79	1:16	1:9
9b/*Z*	Me	**11**	5 d	73	1:>99	1:3
9c/*E*	Et	**12a**	6 d	64	23:1	2.2:1
9d/*Z*	Et	**12a**	5 d	46	>40:1	6.4:1
9e/*E*	Pr	**12b**	9 d	70	23:1	4.5:1
9f/*Z*	Pr	**12b**	8 d	35	>50:1	14:1
9g/*E*	Bu	**12c**	10 d	67	>25:1	5.6:1
9h/*Z*	Bu	**12c**	10 d	47	>60:1	>20:1

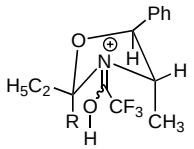
[a] In the case of **9i,j** no products were obtained. [b] Mixture of isomers. [c] Allylic centre by GC analysis. [d] Homoallylic centre by ^{13}C NMR analysis.

products **4a** and **11** strongly depend on the length of R and, to some extent, also on their double-bond configuration. Most surprising, however, was the finding, that a change in the facial selectivity was observed with an increasing length of the alkyl chain of the allylsilane. The facial selectivities ranged from 1: > 99 to > 60:1 for the allylic centre at C-3 and from 1:9 to > 20:1 for the homoallylic centre C-4. Thus, reaction of **1a** with **2**, and **9a** and **9b** gave the homoallylic ethers **4a** and **11**, respectively, as the main products, with the *R* configuration at C-4 and the *S* configuration at C-3. On the contrary, the reaction of **1a** with **9e–h** led to **12a–c** as the main products, with the *S* configuration at C-4 and the *R* configuration at C-3. The change in facial selectivity at C-4 using the methyl- and the ethyl-substituted allylsilane (*E*)-**9a** and (*E*)-**9c**, as well as (*Z*)-**9b** and (*Z*)-**9d**, proceeded gradually from 1:9 to 2.2:1, and from 1:3 to 6.4:1, respectively. However, the total opposite is found for C-3 in which the facial selectivity went from 1:16 to 23:1, and from 1: > 99 to > 60:1.[18] In the reactions, the selectivity for C-4 is usually higher when using (*Z*)-allylsilanes. The yields range from 35–95%, depending on the substituent and on the configuration of the allylsilane. Therefore the yields are always slightly better for the (*E*)-allylsilanes. In all cases, no by-products were formed, except for small amounts of the desilylated norpseudoephedrine derivative **3**, which could be recovered by chromatography. All products were crystalline, and therefore the diastereomerically pure homoallylic ethers were obtained by recrystallisation from pentane. The benzyl-substituted allylsilanes **9i** and **9j** did not give the corresponding homoallylic ethers when reacted with ethyl methyl ketone (**1a**) under the described conditions, probably for steric reasons. Similarly, a reaction did not take place when alkenyl iodide (*E*)-**7** was used. In both cases, starting material was recovered.

To shorten the reaction time, the allylation was carried out at higher temperatures (e.g. $-40\,^{\circ}C$). However, the resulting yields and selectivities were significantly lower in all cases. An important point to take into consideration is the quality of the catalyst. During the optimisation of the allylation reaction, it was shown that the catalytically active species in the allylation of ketones is TfOH. The reproducibility of the allylation and of the yield strongly depends on the purity of the acid. We therefore produced the acid for these investigations by partial hydrolysis of TMSOTf. Under these conditions, constant and reproducible results were obtained. In the meantime, we also use high-quality TfOH, which is available in glass ampoules from Fluka and Aldrich.

Structure elucidation: The structures of the homoallylic ethers were determined by X-ray analysis (for **11**, **12a** and **12c**) as well as by ^1H and ^{13}C NMR spectroscopy.[19] As an example, the characteristic signals in the ^1H NMR spectrum of **12a** are discussed in detail. The signals for the norpseudoephedrine moiety are quite similar for all homoallylic ethers. The aromatic hydrogen atoms resonate as a multiplet at $\delta =$ 7.17–7.38. The signal of the benzylic proton is found at $\delta =$ 4.54 as a doublet with $J = 4.0$ Hz, and the neighbouring proton gives rise to multiplet centred at $\delta = 4.06$. The methyl group resonates as a doublet at $\delta = 1.20$ with $J = 6.8$ Hz. The signal for the amide proton is found at $\delta = 6.40$ as a broad doublet with $J = 8.0$ Hz. The methyl group at the homoallylic centre gives rise to a singlet at $\delta = 0.98$, while the two other methyl groups both appear as triplets with $J = 7.3$ Hz at $\delta = 0.63$ and 0.88. The signals for the diastereotopic hydrogen atoms of the methylene groups are found as multiplets centred at $\delta = 1.15$ and 1.48 (CH_2 of the side chain) and $\delta = 1.62$ (C_q-CH_2CH_3). The secondary vinylic proton resonates as a doublet of doublets of doublets with $J = 9.9$, 10.0 and 16.7 Hz at $\delta = 5.61$. The signals for the vinylic CH_2 group appear as doublets of doublets at $\delta = 4.97$ ($J = 2.2$ and 16.7 Hz) for H_{trans} and at $\delta =$ 5.11 ($J = 2.2$ and 9.9 Hz) for H_{cis}. The allylic CH group resonates as a doublet of doublets of doublets at $\delta = 1.87$ with $J = 2.0$, 10.0, and 10.0 Hz.

Mechanistic considerations: It is well known that the allylation of aldehydes and ketones using either (*E*)- or (*Z*)-allylsilanes lead to the same stereochemistry of the main product in both cases.[20] However, the Lewis acid catalysed crotylations give mainly the *syn* products, whereas in the described reactions, the products with an *anti* orientation of the relevant substituents at the stereogenic centres were formed nearly exclusively. Recently, we were able to give a clear mechanistic explanation for the highly selective allylation of aldehydes, which proceeds with a d.r. > 99:1, by using our procedure based on on-line NMR spectroscopy.[21] It was shown that an oxazolidinium ion **13a** is formed as an intermediate, which then reacts in a stereoselective way with allyltrimethylsilane. In contrast, the surprisingly high facial selectivity found in the allylation of ketones, and especially the change in facial selectivity with an increase in the bulkiness of the substituent R of the allylsilane, cannot as yet be rationalised consistently. Contrary to what was found in the allylation of aldehydes, an oxazolidinium ion **13b** is not an intermediate. However, as is the case in the reaction of aldehydes, the $NHCOCF_3$ moiety in **3** is necessary for a high selectivity. Thus, the reaction of **1a** and allylsilane **2** in the presence of TfOH and the TMS ether of 1-phenylethanol proceeds with a low diastereoselectivity (d.r. = 1:1.8).



13a: R = H
13b: R = CH_3

Conclusion

The allylation of ethyl methyl ketone **1a** with γ-substituted *E*- and *Z*-allylsilanes was studied, and was found to give α-substituted homoallylic ethers with two new stereogenic centres. In the presence of the norpseudoephedrine derivative **3**, homoallylic ethers **11**, **12a**, **12b**, and **12c** were obtained with excellent selectivities of 1: > 99 for C-3 and > 20:1 for C-4. The resulting functionality was not accessible either by other allylation procedures, or by an aldol-type reaction. In contrast to the Lewis acid induced allylation of aldehydes and ketones, the *anti* products were formed nearly exclusively in this case. The most surprising feature of this reaction, however, is the reversal of facial selectivity with increasing bulkiness of the

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substituent of the allylsilane. The high facial selectivity, and the change in the selectivity when bulkier allylsilanes were used, is explained by an enzyme-like model in which the formation of a pocket is assumed, due to hydrogen bonding of **1** and **3**.

Experimental Section

(*E*)-(3-Iodoallyl)trimethylsilane ((*E*)-7): DIBAL-H (200 mmol, 20 % solution in hexane) was added to a solution of propargyl trimethylsilane (200 mmol) in hexane (80 mL) at 25 °C. The reaction mixture was stirred at 50 °C for 3.5 h, and was then concentrated in vacuum. The residue was dissolved in THF (100 mL) and iodine (200 mmol, solution in THF (100 mL)) was added at −50 °C. The mixture was warmed up to 25 °C, hydrolysed by adding water (100 mL), and treated with saturated aqueous $Na_2S_2O_3$ solution to remove the remaining iodine. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated in vacuum. Distillation (Vigreux, 10 cm, ≈5 mbar) gave (*E*)-**7** (21.2 g, 40 %) as a colorless, light-sensitive liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.02$ (s, 9H), 1.54 (dd, $J = 1.2$ and 8.5 Hz, 2H), 5.69 (dt, $J = 1.2$ and 14.2 Hz, 1H), 6.45 (dt, $J = 8.5$ and 14.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -2.03$, 27.50, 69.98, 143.0; HR-MS: calcd for $C_6H_{13}ISi$ 239.9831, found 239.9831.

Cross-coupling: general procedure: Alkylmagnesium bromide (≈2 M diethyl ether solution, 30 mmol) was added to a mixture of bis(triphenylphosphane)nickel dichloride (15.0–45.0 μmol) and (3-iodo-2-propenyl)trimethylsilane ((*E*)-**7** or (*Z*)-**7**, 15.0 mmol) in diethyl ether (50 mL) at −35 °C. The mixture was stirred at this temperature for 3–24 h (see Table 1), and then hydrolysed with saturated aqueous NH_4Cl. The organic layer was washed with saturated NH_4Cl solution, and combined with the pentane extracts (2 × 20 mL) of the aqueous layer. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the products were obtained as colourless liquids (purification by distillation or chromatography). The isomeric purities were analysed by GC.

2-Butynyltrimethylsilane (10): Methyllithium (133 mmol, 1.6 M solution in diethyl ether) was added dropwise to a mixture of propargylsilane (111 mmol) in THF (150 mL) at −78 °C. The solution was stirred for 3 h, and then iodomethane (222 mmol) was added at −78 °C. After warming up to 25 °C over a period of 3 h, the reaction mixture was stirred for 5 h at this temperature. Water (100 mL) and pentane (100 mL) were then added. The organic layer was washed with water (10 × 250 mL) and dried over Na_2SO_4. Distillation (30 cm Vigreux) led to the alkyne **10** (11.9 g, 85 %, 86 % solution in THF) as a colourless liquid. V.p. 110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.06$ (s, 9H), 1.24 (q, $J = 3.0$ Hz, 2H), 1.62 (t, $J = 3.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = -2.18$, 3.45, 6.82, 73.68, 76.23.

(*E*)-2-Butenyltrimethylsilane (9a): Methyllithium (1.6 M in diethyl ether, 100 mmol) was added to a solution of DIBAL-H (1 M in hexane, 100 mmol) in DME (30 mL) at 25 °C. The mixture was stirred for 1 h. Hexane and diethyl ether were then removed under vacuum at 25 °C (DME remained), and the alkyne **10** (50.0 mmol) was added. The mixture was heated at reflux for 24 h, and then water (100 mL) and pentane (100 mL) were added. The organic layer was washed with water (7 × 100 mL), and the alkene **9a** (5.50 mmol, 11 %) was isolated by distillation as a colourless 50 % solution in pentane. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.02$ (s, 9H), 1.14 (d, $J = 7.5$ Hz, 2H), 1.66 (d, $J = 6.0$ Hz, 3H), 5.15–5.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = -2.01$, 18.03, 22.59, 123.08, 127.02.

(Z)-2-Butenyltrimethylsilane (9b): A solution of $NaBH_4$ (4.20 mmol, 159 mg) in EtOH (10 mL), ethylenediamine (8.40 mmol, 505 mg), and the alkyne **10** (42.0 mmol) were added to a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (4.20 mmol, 1.05 g) in EtOH (20 mL). The mixture was stirred vigorously under a hydrogen atmosphere for 24 h (1 atm, 25 °C) and filtered through silica gel (pentane). The organic layer was then washed with water (5 × 100 mL), and dried over Na_2SO_4. Distillation (20 cm Vigreux) led to the alkene **9b** (3.98 g, 31.0 mmol, 74 %) as a colourless liquid. V.p. 120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.08$ (s, 9H), 1.48 (d, $J = 7.5$ Hz, 2H), 1.55 (d, $J = 6.0$ Hz, 3H), 5.26–5.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = -1.78$, 12.59, 18.06, 121.16, 126.42.

Allylation with substituted allylsilanes: general procedure: The catalyst (30 μL, TfOH/TMSOTf 1:1) was added dropwise to a mixture of auxiliary **3** (0.50 mmol, 1.0 equiv), ethyl methyl ketone (1.00 mmol, 2.0 equiv), and allylsilane (1.00 mmol, 2.0 equiv) in CH_2Cl_2 (2.5 mL) at −78 °C. The mixture was stirred at this temperature for 5–10 days, and triethylamine (0.15 mL) was then added at −78 °C. The reaction mixture was washed with water (2 mL) and dried over $MgSO_4$. *tert*-Butylammonium fluoride (TBAF; 0.50 mmol) was added, and the solution was stirred for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by chromatography (silica gel, petroleum ether/*tert*-butyl methyl ether 10:1–20:1). The crystals for X-ray analysis were obtained by recrystallisation from pentane at −20 °C.

Formation of the catalyst: Trimethylsilyl trifluormethanesulfonate (TMSOTf, 1 mL, 7.48 mmol) was poured into a Schlenk flask. Water (33.6 μL, 1.87 mmol) was then added to the TMSOTf. After three days, the hydrolysis was complete and a catalytically active mixture of $(TMS)_2O$, TfOH and TMSOTf (1:2:2) was formed.

(3*S*,4*R*,1′*S*,2′*S*)-3,4-Dimethyl-4-(1′-phenyl-2′-trifluoracetamido-1′-propoxy)-hex-1-ene (11): M.p. 67 °C; $[\alpha]_D^{20} = -36.0$ ($c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.62$ (t, $J = 7.5$ Hz, 3H), 1.06 (d, $J = 7.0$ Hz, 3H), 1.13 (s, 3H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.28 (q, $J = 7.5$ Hz, 2H), 2.44 (dq, $J = 7.0$ Hz, 1H), 4.08 (m_c, 1H), 4.55 (d, $J = 3.5$ Hz, 1H), 5.03–5.10 (m, 2H), 5.96 (ddd, $J = 18.0$, 9.5, and 8.0 Hz, 1H), 6.42 (d, $J = 8.0$ Hz, 1H), 7.17–7.38 (m, 5H); minor diastereomer (distinguishable signals): $\delta = 0.89$ (t, $J = 7.5$ Hz, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 2.33 (dq, $J = 7.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 8.08$, 14.89, 16.90, 20.31, 30.26, 44.71, 51.95, 73.87, 81.14, 114.79, 115.89 (q, $^1J_{C,F} = 288$ Hz), 126.69, 127.72, 128.19, 140.78, 141.42, 156.41 (q, $^2J_{C,F} = 37$ Hz); elemental analysis calcd (%) for $C_{19}H_{26}F_3NO_2$: C 63.85, H 7.33; found: C 64.02, H 7.45.

(3*R*,4*S*,1′*S*,2′*S*)-3-Ethyl-4-methyl-4-(1′-phenyl-2′-trifluoracetamido-propoxy)-hex-1-ene (12a): M.p. 90.1 °C; $[\alpha]_D^{20} = -21.4$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.63$ (t, $J = 7.3$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.98 (s, 3H), 1.15 (m_c, 1H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.48 (m_c, 1H), 1.62 (m_c, 2H), 1.87 (ddd, $J = 2.0$, 10.0, 10.0 Hz, 1H), 4.06 (m_c, 1H), 4.54 (d, $J = 4.0$ Hz, 1H), 4.97 (dd, $J = 2.2$, 16.7 Hz, 1H), 5.11 (dd, $J = 2.2$, 9.9 Hz, 1H), 5.61 (ddd, $J = 9.9$, 10.0, 16.7 Hz, 1H), 6.40 (d_{br}, $J = 8.0$ Hz, 1H), 7.17–7.38 (m, 5H); minor diastereomer (distinguishable signals): $\delta = 0.90$ (t, $J = 7.3$ Hz, 3H), 1.10 (s, 3H), 1.22 (d, $J = 6.8$ Hz, 3H), 2.06 (ddd, $J = 2.0$, 10.0, and 10.0 Hz, 1H), 4.05 (dd, $J = 2.2$, 16.7 Hz, 1H), 5.13 (dd, $J = 2.2$, 9.9 Hz, 1H), 5.70 (ddd, $J = 9.9$, 10.0, 16.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 8.08$, 12.13, 16.86, 21.00, 21.58, 28.90, 51.89, 53.89, 73.90, 80.93, 115.84 (q, $^1J_{C,F} = 288.4$ Hz), 116.73, 126.80, 127.69, 128.17, 138.78, 141.36, 156.39 (q, $^2J_{C,F} = 37$ Hz); elemental analysis calcd (%) for $C_{20}H_{28}F_3NO_2$: C 64.67, H 7.60; found: C 64.45, H 7.67.

(3*R*,4*S*,1′*S*,2′*S*)-3-Propyl-4-methyl-4-(1′-phenyl-2′-trifluoracetamido-propoxy)-hex-1-ene (12b): M.p. 65.9 °C; $[Ga]_D^{20} = -27.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.60–0.67$ (m, 4H, 6-H_3), 0.89 (t, $J = 7.3$ Hz, 3H), 0.90 (s, 3H), 1.08–1.38 (m, 5H), 1.21 (d, $J = 1.5$, 10.0 Hz, 3H), 4.06 (m_c, 1H), 4.53 (d, $J = 5.0$ Hz, 1H), 4.96 (dd, $J = 2.0$, 17.0 Hz, 1H), 5.09 (dd, $J = 2.0$, 10.0 Hz, 1H), 5.62 (ddd, $J = 10$, 10, 17 Hz, 1H), 6.42 (d_{br}, $J = 8.0$ Hz, 1H), 7.20–7.36 (m, 5H); minor diastereomer (distinguishable signals): $\delta = 0.62$ (t, $J = 7.5$ Hz, 3H), 1.11 (s, 3H), 2.18 (dt, $J = 1.5$ and 10.0 Hz, 1H), 5.72 (ddd, $J = 10.0$, 10.0, and 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 7.95$, 13.88, 16.58, 20.58, 21.50, 28.70, 30.33, 51.70, 51.79, 73.90, 80.81, 115.81 (q, $^1J_{C,F} = 288$ Hz), 116.24, 126.80, 127.69, 128.17, 138.78, 141.36, 156.39 (q, $^2J_{C,F} = 36$ Hz); elemental analysis calcd (%) for $C_{21}H_{30}F_3NO_2$: C 65.43, H 7.84; found: C 65.24, H 7.85.

(3*R*,4*S*,1′*S*,2′*S*)-3-Butyl-4-methyl-4-(1′-phenyl-2′-trifluoracetamido-propoxy)-hex-1-ene (12c): M.p.66.4 °C; $[\alpha]_D^{20} = -24.0$ (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), $\delta = 0.64–0.74$ (m, 1H), 0.79 (t, $J = 7.5$ Hz, 3H), 0.89 (t, $J = 7.0$ Hz, 3H), 0.91 (s, 3H), 1.08–1.43 (m, 5H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.62 (m_c, 2H), 1.96 (dt, $J = 1.6$, 10.0 Hz, 1H), 4.54 (d, $J = 4.0$ Hz, 1H), 4.96 (dd, $J = 2.0$, 17.0 Hz, 1H), 5.08 (dd, $J = 2.0$, 10.0 Hz, 1H), 5.61 (ddd, $J = 10.0$, 10.0, 17.0 Hz, 1H), 6.42 (d_{br}, $J = 8.0$ Hz, 1H), 7.24–7.35 (m, 5H); minor diastereomer (distinguishable signals): $\delta = 0.62$ (t, $J = 7.5$ Hz, 3H), 1.12 (s, 3H), 5.73 (ddd, $J = 10.0$, 10.0, and 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 8.03$, 14.00, 16.75, 21.57, 22.71, 27.98, 28.76, 29.86, 51.85, 52.01, 73.89, 80.96, 115.84 (q, $^1J_{C,F} = 288$ Hz), 116.43, 126.85, 127.67, 128.15, 139.29, 141.30, 156.39 (q, $^2J_{C,F} = 37$ Hz); elemental analysis calcd (%) for $C_{22}H_{32}F_3NO_2$: C 66.14, H 8.07; found: C 66.17, H 7.99.

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[19] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-151421 (**11**), CCDC-151422 (**12a**) and CCDC-151423 (**12c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). The two stereogenic centres of the norpseudoephedrine moiety are known, therefore a heavy atom in the molecule is not necessary to calculate the absolute configuration.

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