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Trifluoromethyl *vs.* Methyl Ability to Direct Enantioselection in Microbial Reduction of Carbonyl Substrates.

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Abstract: The stereoselective reduction of 3-trifluoromethylcyclohexanone (**1a**), (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one (**3a**), and their unfluorinated analogues **1b** and **3b** has been performed with some growing microorganisms. Differences in the electronic and steric properties of the trifluoromethyl and methyl residues result in different chemo- and stereoselectivities in the microbial reduction of phenylbutenones **3a** and **3b** while cyclohexanones **1a** and **1b** showed strictly similar stereoselectivities. A new protocol based on ^{13}C NMR spectra of 2-phenylpropionic acid esters has been used to assign the absolute configuration of the obtained secondary alcohols.

The unique polar and electrostatic properties of the fluorine atom differ consistently from those of the hydrogen atom[1] so that it becomes apparent how the trifluoromethyl and methyl groups possess quite different electronic characteristics.[1,2] For instance, the electron density in the *ortho* and *para* positions of a phenyl ring is increased by a methyl and decreased by a trifluoromethyl, respectively, and the lipophilicity of methyl and trifluoromethyl differ significantly ($\pi_{CH3} = 0.50$; $\pi_{CF3} = 1.07$).[6]

From the steric point of view, while the substitution of a single fluorine for a hydrogen atom induces only small steric perturbation relative to the parent hydrocarbon,[7] the trifluoromethyl is commonly recognised as hardly comparable to the methyl. Physicochemical studies points to a size close to the *iso*-propyl[8] and remarkably smaller than the *tert*-butyl,[9] but different conclusions have sometimes been obtained by using different approaches. For instance, a trifluoromethyl group is capable of replacing statistically a methyl group in crystals[10] and at the same time it tends to behave like a *tert*-alkyl[11] in the kinetic resolution of some fluoroalkyl vinyl carbinols with lypases.[12]

While it is somehow arbitrary to separate electronic and steric effects in defining the ability of the trifluoromethyl group to direct the regio- and stereoselectivities of chemical and microbial processes, the gross diversity of the trifluoromethyl and methyl groups has often resulted in effectively controlling transformation selectivities. For instance, the α-hydroxylation of ethyl β-trifluoromethylbutyrate and the carbonyl reduction of ethyl α-oxo-β-trifluoromethylbutyrate both occurred with nearly complete stereoselection.[5] Moreover, only the carbonyl group in position 2 of 1,1,1-trifluoro-2,4-pentanedione was reduced by baker's yeast[17] and opposite enantioselectivities[16] were observed in the reduction of acetophenone and its 2,2,2-trifluoro analogue by (-)-DIP-Chloride™,[9a] Mosher's reagent,[18] Nasipuri's reagent,[19] CBS catalyst/BH_3,[20] CBS catalyst/catecholborane.[21]

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In order to further assess the stereodirecting ability of the trifluoromethyl relative to the methyl, we have reduced 3-trifluoromethylcyclohexanone **1a** and (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one **3a** as well as their parent unfluorinated analogues **1b** and **3b** with some growing microorganisms and we report here the obtained results. Cyclohexanones **1a,b** have been chosen as substrates due to the fact that while the reduction of various ketones with the trifluoromethyl bound directly to the carbonyl group has been compared with the reduction of their unfluorinated analogues by using several reagents, to the best of our knowledge no similar study has been performed with β-trifluoromethyl substituted ketones. Phenylbutenones **3a,b** have been investigated as they allowed assessment of the directing ability of the trifluoromethyl relative to the methyl both in chemo- and stereoselection (formation of unsaturated alcohols **4** *vs.* saturated alcohols **5** and formation of (*R*) *vs.* (*S*) enantiomers, respectively).

Results and Discussion

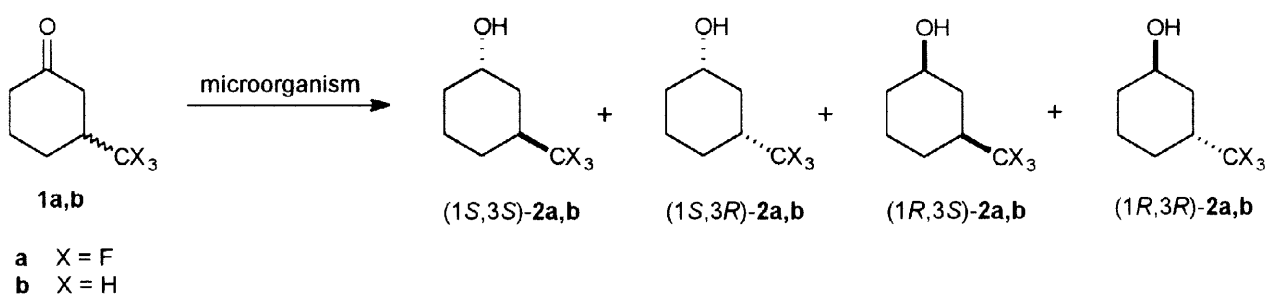
Microbial transformations. The reduction of cyclohexanones **1a,b** (Scheme 1) and of benzalacetones **3a,b** (Scheme 2) has been tried with growing cultures of several microorganisms and those affording fair amounts of alcohols **2**, **4**, and **5** with medium to high enantioselection are listed in Tables 1 and 2 where the diastereoisomer and enantiomer ratio of obtained products are also reported.

The two enantiomers of cyclohexanones **1a,b** were both accepted as substrates by the microorganisms[22] and trifluoromethylated ketone **1a** was reduced faster than methyl analogue **1b**. It is interesting to observe that baker's yeast has been reported to reduce various ketones bearing a trifluoromethyl residue directly bound to the carbonyl with higher rates compared to the corresponding hydrogenated analogues.[17a ,c; 23] The microbial reduction rate of cyclohexanones **1** showed the same sensitivity to the presence of fluorine atoms even if the trifluoromethyl residue is located far from the carbonyl site.

1a And **1b** were reduced by the different microbes with strictly similar face selectivities thus showing that, differently from the reduction rate, the reduction face selectivity is almost insensitive to the presence of fluorine. Specifically, *Hansenula anomala* and *Saccharomyces cerevisiae* delivered the hydride preferentially from the *Re* face of the carbonyl groups of **1a,b** and the formation of alcohols **2a,b** having the (1*S*) absolute configuration was favoured. An opposite face selectivity (and stereochemistry at the alcoholic stereogenic centre of prevailing products) was shown by *Streptomyces C53* and *Geotrichum candidum*. Stereoselectivities of 64% for the *Re* face, by *Saccharomyces cerevisiae*, and of 60% for the *Si* face, by *Geotrichum candidum*, were obtained (Table 1, runs 6 and 14, respectively) even if the face stereodifferentiating residue, namely the trifluoromethyl group, is β to the reacting carbonyl site.

Nearly the same enantiomeric excesses were obtained for both the *trans* and the *cis* diastereoisomers of cyclohexanols **2a** and **2b**.[24]

Scheme 1



1a,b

(1*S*,3*S*)-**2a,b** (1*S*,3*R*)-**2a,b** (1*R*,3*S*)-**2a,b** (1*R*,3*R*)-**2a,b**

a X = F
b X = H

Table 1.

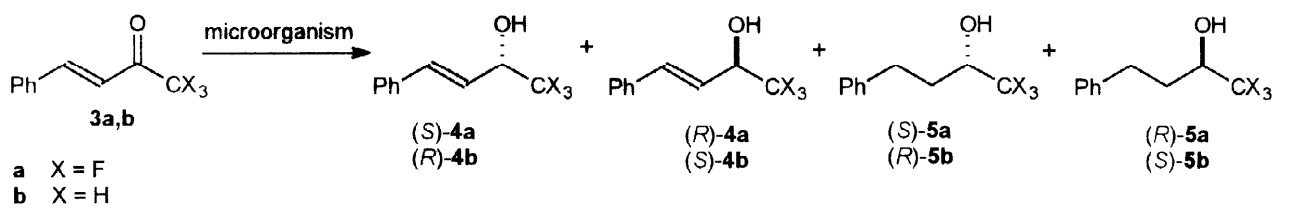
Run	Micro-organism	Substrate	Fermentation time (h)	Conversion (%)[a]	(1*S*)-**2** : (1*R*)-**2**[b]	% *trans* **2** (1*S*,3*S*) : (1*R*,3*R*)	% *cis* **2** (1*S*,3*R*) : (1*R*,3*S*)
1	*Hansenula anomala* CBS 110	**1a**	0.5	49	79 : 21	52 (79 : 21)	48 (79 : 21)
2			1.0	78	79 : 21	50 (77 : 23)	50 (81 : 19)
3			1.5	93	78 : 22	50 (77 : 23)	50 (81 : 19)
4	*Hansenula anomala* CBS 110	**1b**	2.0	42	79 : 21	53 (78 : 22)	47 (80 : 20)
5			7.0	90	78 : 22	50 (77 : 23)	50 (49 : 21)
6	*Saccharomyces cervisiae* NCYC 739	**1a**	0.5	60	82 : 18	68 (81 : 19)	32 (85 : 15)
7			1.0	91	80 : 20	56 (79 : 21)	44 (82 : 17)
8	*Saccharomyces cervisiae* NCYC 739	**1b**	2.0	61	85 : 15	65 (86 : 14)	35 (84 : 16)
9			7.0	83	81 : 19	54 (82 : 18)	46 (80 : 20)
10	*Streptomyces* C53	**1a**	7.0	63	34 : 66	45 (23 : 77)	55 (43 : 57)
11			24.0	94	36 : 64	45 (27 : 73)	55 (43 : 57)
12	*Streptomyces* C53	**1b**	24.0	52	24 : 76	40 (20 : 80)	60 (27 : 73)
13			48.0	89	29 : 71	49 (26 : 74)	51 (31 : 67)
14	*Geotrichum candidum* CBS 233.76	**1a**	2.0	86	20 : 80	56 (30 : 70)	44 (8 : 92)
15	*Geotrichum candidum* CBS 233.76	**1b**	7.0	47	25 : 75	59 (22 : 78)	41 (30 : 70)

([a]) Determined through the ratio of the ketone and alcohol peaks in GLC of organic extract of fermentations. ([b]) Ratio between the alcohols **2** having the (1*S*,3*R* and 3*S*) and (1*R*,3*S* and 3*R*) absolute configuration.

This shows that the differences in the electronic and steric properties of the trifluoromethyl and methyl residues were not particularly influential as far as enantioselectivity in product formation is concerned. The highest enantiomeric excesses in the formation of *cis*-3-trifluoromethylcyclohexanol **2a** were given by *Geotrichum candidum* and *Saccharomyces cerevisiae* which afforded the alcohols having the (1*R*,3*S*) absolute configuration and its (1*S*,3*R*) enantiomer in 84% and 70% e.e., respectively. As to the *trans* 3-trifluoromethylcyclohexanol **2a**, the (1*S*,3*S*) isomer was obtained in 72% e.e. by action of *Saccharomyces cerevisiae*.

Phenylbutenone **3b** and its trifluorinated analogue **3a** showed quite different patterns of reactivity towards the four microorganisms reported in Table 2. The crude fermentation extracts of phenylbutenone **3b** reduction contained variable amounts of 4-phenyl-2-butanone (**6b**) and of 4-phenyl-2-butanol (**5b**) and the

Scheme 2.



3a,b

a X = F
b X = H

(*S*)-**4a**
(*R*)-**4b**

(*R*)-**4a**
(*S*)-**4b**

(*S*)-**5a**
(*R*)-**5b**

(*R*)-**5a**
(*S*)-**5b**

Table 2.

Run	Microorganism[a]	Substrate	Products		
			% satur. ketone **6**	% unsatur. alcohol **4** ((*S*) : (*R*))	% satur. alcohol **5** ((*S*) : (*R*))
1	*Geotrichum candidum* CBS 233.76	**3a**	n.d.[b]	73 (97 : 3)	27 (98 : 2)
2		**3b**	n.d.[b,c]	n.d.[b,c]	n.d.[b,c]
3	*Hansenula anomala* CBS 110	**3a**	n.d.[b]	10 (48 : 52)	90 (57 : 43)
4		**3b**	29	n.d.[b]	71 (2 : 98)
5	*Saccharomyces cervisiae* NCYC 739	**3a**	n.d.[b]	38 (26 : 74)	62 (18 : 82)
6		**3b**	92	n.d.[b]	8 (66 : 34)
7	*Kloechera saturnus* CBS 5761	**3a**	n.d.[b]	57 (17 : 83)	43 (63 : 37)
8		**3b**	38	n.d.[b]	62 (12 : 88)

([a]) Grown microorganisms were incubated for 27h with substrates **3**. After this time conversion was complete and product ratio was established by GLC of the crude extract. ([b]) The compound was less then 1% in the GLC analysis of the crude fermentation extract. ([c]) The substrate **3b** was transformed into unidentified products.

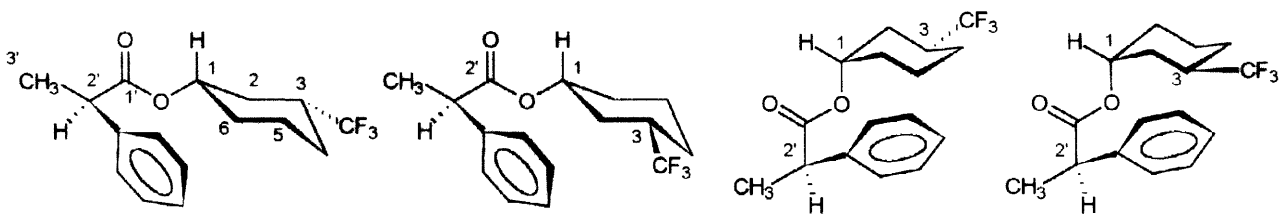
presence of butenol **4b** could not be detected (Scheme2). The product ratio changed in favour of the alcohol **5b** at the expense of the ketone **6b** on prolonging fermentation times. This suggests an easy microbial saturation of the olefinic double bond of **3b**, a behaviour already observed in the baker's yeast reduction of 4-(4-hydroxyphenyl)-2-butenone.[25] In contrast, extracts of trifluorobutenone **3a** fermentation contained both the unsaturated and saturated trifluoromethyl carbinols **4a** and **5a** and no saturated 1,1,1-trifluoro-4-phenyl-2-butanone (**6a**) was present thus showing that the microbial reduction of the carbon-carbon double bond in trifluorobutenone **3a** was not as easy as in **3b**.

Saccharomyces cerevisiae delivered the hydride preferentially from the *Si* face of the trifluoromethylated ketones and the formation of unsaturated and saturated alcohols **4a** and **5a** with the (*R*) absolute configuration was favoured (Table 2, run 5). The same face selectivity was shown with the unfluorinated analogue (run 6) and the (*S*) enantiomer of alcohol **5b** was formed preferentially.[14] The prevailing enantiomer of saturated alcohols **5a,b** formed by *Hansenula anomala* and *Kloechera saturnus* had configurations opposite to those obtained with *Saccharomyces cerevisiae* and the best enantioselection was given by *Geotrichum candidum*[26] which afforded (*S*)-**4a** and (*S*)-**5a** in 94% and 96% e.e., respectively (run 1).

In conclusion, differences in the electronic and steric properties of the trifluoromethyl and methyl residues affected the chemo- and stereoselectivity of the microbial reduction of phenylbutenones **3a,b** where the fluorination site is directly bound to the carbonyl group. In contrast, while the presence of the β substituent was clearly inducing stereodifferentiation in the microbial reduction of the cyclohexanones **1a,b**, the electronic and steric differences between the trifluoromethyl and methyl substituents seems less influential in determining different stereochemical outcomes in these reductions as cyclohexanols **2a** and **2b** were formed with strictly similar stereoselectivities.

Assignment of relative and absolute configurations. The assignment of the relative stereochemistries in cyclohexanols **2a,b** followed from the magnitude of the coupling constants exhibited by H-1 and H-3.

Scheme 3



(1*S*,3*R*,2'*R*)-**7a** (1*R*,3*S*,2'*R*)-**7a** (1*S*,3*S*,2'*R*)-**7a** (1*R*,3*R*,2'*R*)-**7a**

Specifically, in compounds (1*S*,3*R*)- and (1*R*,3*S*)-**2a,b** the substituents on C-1 and C-3 are *cis* diequatorially located as both H-1 and H-3 present, *inter alia*, coupling constants ranging between 10.7 and 11.2 Hz and are therefore axially disposed. In contrast, in the diastereoisomers **2a,b** having the (1*S*,3*S*) and (1*R*,3*R*) absolute configuration the substituents on C-1 and C-3 are *trans* disposed as H-3 is still in axial position (J = 10.1-11.2 Hz), but H-1 shows only smaller couplings (J = 3.4-3.7 Hz) as expected for equatorial protons.

The absolute configurations of **2b** were assigned through comparison with authentic (1*S*,3*R*)-**2b** and (1*R*,3*R*)-**2b** obtained from $NaBH_4$ reduction of (*R*)-(+)-3-methylcyclohexanone (Aldrich). The absolute configurations at the alcoholic stereogenic centres of **2a**, **4a**, and **5a,b** were assigned by using (*S*)- and (*R*)-2-phenylpropionic acids as derivatizing agents.[27] Esters derived from secondary alcohols and 2-phenylpropionic acid adopt a preferred conformation in which the methyl group of the acid residue (CH_3-2') and the proton on the hydroxylated carbon of the alcoholic residue are eclipsed to the carbonyl group of the ester (Scheme 3). In this preferred conformation the phenyl ring of the esterifying acid shields the facing protons of the alcoholic portion and the chemical shift differences between the corresponding diastereotopic protons allow the absolute configuration at the alcoholic stereogenic centre to be established moving from the absolute configuration of the acid stereogenic centre.

The exact chemical shifts of single protons of trifluoromethylcyclohexyl esters **7a** were established through HETCOR experiments, ^{13}C resonances being easily assigned by chemical shift criteria and C,F coupling constants. Accurate inspection of ^{13}C NMR shifts in these esters showed that the shielding effect

Table 3.

cis-**7a**[a]		*trans*-**7a**[b]		**8a**[c]		**8b**[d]	
$\Delta\delta_C$	$\Delta\delta_H$	$\Delta\delta_C$	$\Delta\delta_H$	$\Delta\delta_C$	$\Delta\delta_H$	$\Delta\delta_C$	$\Delta\delta_H$
-0.24 (C-6)	-0.11 (H_{eq}-6)	-0.32 (C-6)	n.d. (H_{eq}-6)	-1.10 (C-4)	-0.32 (H-4)	-0.69 (C-4)	-0.22 (H-4)
-0.08 (C-5)	-0.08 (H_{ax}-6)	-0.32 (C-5)	n.d. (H_{ax}-6)	-0.49 (C-3)	-0.11 (H-3)	-0.12 (C-3)	-0.14 (H-3)
0.00 (C-1)	0.00 (H-1,-3,H_2-5)	+0.05 (C-1)	+0.40 (H_{ax}-3)	+0.10 (C-1)	+0.09 (F_3-1)	+0.28 (C-1)	+0.08 (H_3-1)
+0.23 (C-2)	+0.11 (H_{eq}-2)	+0.31 (C-3)	+0.09 (H_{eq}-2)				
+0.06 (C-3)	+0.05 (H_{ax}-2)	+0.39 (C-2)					

(a) $\Delta\delta_{C,H} = \delta_{C,H\,(1S,3R,2'R)} - \delta_{C,H\,(1R,3S,2'R)}$; (b) $\Delta\delta_{C,H} = \delta_{C,H\,(1S,3S,2'R)} - \delta_{C,H\,(1R,3R,2'R)}$; (c) $\Delta\delta_{C,H,F} = \delta_{C,H,F\,(2R,2'S)} - \delta_{C,H,F\,(2S,2'S)}$; (d) $\Delta\delta_{C,H} = {}_{C,H\,(2S,2'S)} - \delta_{C,H\,(2R,2'S)}$

exerted by the phenyl ring of the acid part on the facing residue of the alcoholic portion affects not only proton but also carbon nuclei.[28] This effect was also observed in ^{13}C NMR spectra of esters **8a,b** formed by 2-phenylpropionic acid and butenols **4a,b** and the chemical shift differences between corresponding diastereotopic carbon and protons, in couples of esters are reported in Table 3. These data clearly indicate that the phenyl ring of the esterifying acid shields the facing carbons of the secondary alcohol ($\Delta\delta_C$ values as high as 1.10 ppm have been observed),[29] the effects being consistent with those observed in proton spectra.

For the first time it has therefore been shown that a sensible and significative chemical shift difference exists between the corresponding diastereotopic carbons in ^{13}C NMR spectra of pairs of diastereoisomeric 2-phenylpropionic acid esters and these differences can be used to assign the absolute configuration at the alcoholic stereogenic centre when the absolute configuration of the acid is known. The use of differences in ^{13}C NMR spectra complements the well-established employment of differences in ^{1}H NMR spectra.[27] Other pairs of diastereoisomeric esters will be studied to demonstrate that such a use is of general applicability. This methodology can be particularly attractive whenever it is difficult to sort out the diagnostic chemical shifts in complex proton spectra (as in esters **7a**).

Acknowledgements. The European Union is gratefully acknowledged for financial support (Network INTAS-95-95).

Experimental Section

NMR spectra were recorded on a Bruker AC 250 or ARX 400 spectrometer in $CDCl_3$ solution with TMS as internal standard for ^{1}H and ^{13}C and $CFCl_3$ for ^{19}F, chemical shifts are reported in ppm and *J* are in Hz. In the ^{13}C NMR signal assignment capital letters refer to the pattern resulting from directly bonded (C, H) couplings and small letters to the one from (C, F) couplings. Flash chromatographies were performed with silica gel 60 F_{254} (60-200 μm, Merck). Columns used for GLC analyses: (A) 25 m x 0.25 mm i.d. fused silica capillary column coated with OV-1 (d_f = 0.25 μm), (B) 25 m x 0.25 mm i.d. fused silica capillary column coated with DAcTBSil βCDX (d_f = 0.25 μm), (C) 25 m x 0.25 mm i.d. fused silica capillary column coated with MEGADEX 1 (d_f = 0.25 μm), (D) 2 m x 2 mm i.d. pyrex column packed with 5% LAC 728 on Chromosorb W-DMCS. Apparata used for GLC analyses: Dani mod. 3800 for packed column, Dani mod. 6500 and 8610 for capillary columns.

General procedure for microbial reductions. Each microorganism was grown for the given time (see below) at 30 °C in shaken Erlenmeyer flasks (300 cm^3) containing the given culture medium (50 cm^3). The carbonyl compound **1** or **3** (in standard procedure 50 mg per flask) dissolved in ethanol (0.5 cm^3) was added to the grown culture and incubation was continued for the time reported in Tables 1 and 2. Each resulting mixture was extracted twice with ethyl acetate, the combined organic phases were dried over sodium sulfate and evaporated under reduced pressure. The composition of the crude residue was determined by GLC analyses. *Geotrichum candidum* CBS 233.76 was grown for three days at 120 rev^{-1} on a medium containing glucose (50 g L^{-1}), peptone (10 g L^{-1}), and yeast extract (10 g L^{-1}) in deionized water and adjusted to pH 7. *Hansenula anomala* CBS 110, *Kloechera saturnus* CBS 7661 and *Saccharomyces cerevisiae* NCYC 739 were grown for three days at 120 rev^{-1} on a medium containing glucose (30 g L^{-1}), malt extract (10 g L^{-1}), and yeast extract (10 g L^{-1}) in deionized water and extracted to pH 7. *Streptomyces* C53 was grown for one day at 120 rev^{-1} on a medium containing glucose (30 g L^{-1}), malt extract (10 g L^{-1}), and yeast extract (10 g L^{-1}) in deionized water and extracted to pH 7.

Gas-chromatographic analyses. 3-Trifluoromethylcyclohexanone **1a** and 3-trifluoromethylcyclo-

hexanols **2a**: the fermentation extracts were analysed as follows: column (D), 4 min at 100 °C, then 4 °C min^{-1} to 200 °C (order of elution: **1a**, *trans*-**2a**, *cis*-**2a**); column (B), 1 min at 40 °C, then 20 °C min^{-1} to 95 °C, 2 min at 95 °C and finally 1.5 °C min^{-1} to 130 °C [order of elution: (1*S*,3*S*)-**2a**, (1*R*,3*R*)-**2a**, (1*R*,3*S*)-**2a**, and (1*S*,3*R*)-**2a**]; the esters **7a** between 3-trifluoromethylcyclohexanols **2a** and (*R*)-(-)-2-phenylpropionic acid were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 130 °C, 2 min at 130 °C and finally 2 °C min^{-1} to 150 °C [order of elution: (1*R*,3*R*,2'*R*)-**7a**, (1*S*,3*S*,2'*R*)-**7a**, (1*R*,3*S*,2'*R*)-**7a**, (1*S*,3*R*,2'*R*)-**7a**]. 3-Methylcyclohexanone **1b** and 3-methylcyclohexanols **2b**: the fermentation extracts were analysed as follows: column (D), 4 min at 90 °C, then 4 °C min^{-1} to 200 °C (order of elution: **1b**, *trans*-**2b**, *cis*-**2b**); column (B), 1 min at 40 °C, then 20 °C min^{-1} to 65 °C, 2 min at 65 °C and finally 1 °C min^{-1} to 100 °C [order of elution: (1*R*,3*R*)-**2b**, (1*S*,3*R*)-**2b**, (1*R*,3*S*)-**2b**, (1*S*, 3*S*)-**2b**]. (*E*)-1,1,1-Trifluoro-4-phenyl-3-buten-2-one **3a**, (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ols **4a**, and 1,1,1-trifluoro-4-phenyl-2-butanols **5a**: the fermentation extracts were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 80 °C, 2 min at 80 °C, 3 °C min^{-1} to 110 °C, 1 min at 110 °C and finally 10 °C min^{-1} to 230 °C (order of elution: **3a**, **5a**, **4a**); column (C), 1 min at 70 °C, then 20 °C min^{-1} to 120 °C, 2 min at 120 °C and finally 1 °C min^{-1} to 150 °C [order of elution: (*R*)-**5a**, (*S*)-**5a**, (*S*)-**4a**, (*R*)-**4a**]; the esters **8a** between (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ols **4a** and (*S*)-(+)-2-phenylpropionic acid were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 130 °C, 2 min at 130 °C, 3 °C min^{-1} to 175 °C, 1 min at 175 °C and finally 10 °C min^{-1} to 250 °C [order of elution: (2*R*,2'*S*)-**8a**, (2*S*,2'*S*)-**8a**]; the esters **9a** between 1,1,1-trifluoro-4-phenyl-2-butanols **5a** and (*S*)-(+)-2-phenylpropionic acid were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 130 °C, 2 min at 130 °C, 3 °C min^{-1} to 175 °C, 1 min at 175 °C and finally 10 °C min^{-1} to 250 °C [order of elution: (2*R*, 2'*S*)-**9a**, (2*S*, 2'*S*)-**9a**]. (*E*)-4-Phenyl-3-buten-2-one **3b** and 4-phenyl-2-butanols **5b**: the fermentation extracts were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 80 °C, 2 min at 80 °C, 2 °C min^{-1} to 100 °C, 1 min at 100 °C and finally 10 °C min^{-1} to 150 °C (order of elution: **3b**, **5b**), column (C), 1 min at 70 °C, then 20 °C min^{-1} to 110 °C, 2 min at 110 °C and finally 1 °C min^{-1} to 140 °C [order of elution: (*S*)-**5b**, (*R*)-**5b**]; the esters **9b** between 4-phenyl-2-butanols **5b** and (*S*)-(+)-2-phenylpropionic acid were analysed as follows: column (A), 1 min at 40 °C, then 20 °C min^{-1} to 150 °C, 2 min at 150 °C, 3 °C min^{-1} to 195 °C, 1 min at 195 °C and finally 10 °C min^{-1} to 220 °C [order of elution: (2*S*, 2'*S*)-**9a**, (2*R*, 2'*S*)-**9a**].

Esters 7a from (*R*)-(-)-2-phenylpropionic acid and *trans*- and *cis*-3-trifluoromethylcyclohexanols (2a). 15 Erlenmeyer flasks containing grown cultures of *Hansenula hanomala* were incubated with trifluoromethylcyclohexanone **1a** as described in the general procedure, then the flasks were extracted and the obtained crude oil was flash chromatographed (eluting system: *n*-hexane/Et_2O = 80 : 20) to give 313 mg (41% yield) of *trans*-3-trifluoromethylcyclohexanol (**2a**) and 298 mg (39% yield) of *cis*-**2a**. *Trans*-**2a**: ^1H NMR δ_H: 4.23 (1H, brtt, J = 3.5 and 3.0 Hz, H-1_{eq}), 2.62 (1H, dtt, J = 8.8, 11.2, and 3.5 Hz, H-3_{ax}), and 2.2-1.0 (9H, m, remaining H); ^{19}F NMR δ_F: -74.90 (brd, J = 8.8 Hz, CF_3-3). *Cis*-**2a**: ^1H NMR δ_H: 3.60 (1H, tt, J = 10.7 and 4.2 Hz, H-1_{ax}), 2.52 (1H, dtt, J = 8.8, 11.2, and 3.5 Hz, H-3_{ax}), and 2.2-1.0 (9H, m, remaining H); ^{19}F NMR δ_F: -74.86 (brd, J = 8.8 Hz, CF_3-3). The esterification of the alcohols **2a** with (*R*)-(-)-2-phenylpropionic acid was performed as described in ref. 27 and obtained compounds **7a** were analysed by GLC and NMR (^1H, ^{19}F, ^{13}C). (1*S*,3*S*,2'*R*)-**7a**: ^1H NMR δ_H: 7.4-7.2 (5H, m, ArH), 5.15 (1H, brtt, J = 3.3 and 3.0 Hz, H-1_{eq}), 3.73 (1H, brq, J = 6.8 Hz, H-2'), 2.21 (1H, dtt, J = 8.5, 12.1, and 3.4 Hz, H-3_{ax}), 2.01 (1H, brd, J = 13.9 Hz, H-2_{eq}), 1.51 (3H, d, J = 6.8 Hz, Me-2'), and 2.10-1.10 (7H, m, remaining H); ^{19}F NMR δ_F: -75.19 (brd, J = 8.5 Hz, CF_3-3); ^{13}C NMR δ_C: 173.51 (S, C-1'), 140.57 (S), 128.63, 127.36, 127.17 (D) (Ar C), 127.68 (Sq, $J_{C,F}$ = 278.4 Hz, CF_3-3), 66.28 (D, C-1), 45.76 (D, C-2'), 36.88 (Dq, $J_{C,F}$ = 27.0 Hz, C-3), 28.70 (T, C-6), 28.94 (Tq, $J_{C,F}$ = 2.8 Hz, C-2), 24.13 (Tq, $J_{C,F}$ = 2.8 Hz, C-4), 18.88 (T, C-5), and 17.94 (Q, C-3'). (1*R*,3*R*,2'*R*)-**7a**: ^1H NMR δ_H: 7.4-7.2 (5H, m, ArH), 5.15 (1H, brtt, J = 3.3 and 3.0 Hz, H-1_{eq}), 3.71 (1H, brq, J = 6.8 Hz, H-2'), 1.92 (1H, brd, J = 13.9 Hz, H-2_{eq}), 1.81 (1H, dtt, J = 8.4, 12.2, and 3.6 Hz, H-3_{ax}), 1.51 (3H, d, J = 6.8 Hz, Me-2'), and 2.1-1.1 (7H, m, remaining H); ^{19}F NMR δ_F: -75.35 (brd, J = 8.4 Hz, CF_3-3); ^{13}C NMR δ_C:

173.51 (S, C-1'), 140.69 (S), 128.63, 127.36, 127.17 (D) (Ar C), 127.68 (Sq, $J_{C,F}$ = 278.4 Hz, CF_3-3), 66.23 (D, C-1), 45.76 (D, C-2'), 36.57 (Dq, $J_{C,F}$ = 27.0 Hz, C-3), 29.02 (t, C-6), 28.55 (tq, $J_{C,F}$ = 2.8 Hz, C-2), 24.13 (tq, $J_{C,F}$ = 2.8 Hz, C-4), 19.20 (t, C-5), and 17.88 (q, C-3'). (1*S*,3*R*,2'*R*)-**7a**: ^{1}H NMR δ_H: 7.4-7.2 (5H, m, ArH), 4.69 (1H, tt, J = 11.2 and 4.2 Hz, H-1), 3.70 (1H, brq, J = 7.1 Hz, H-2'), 2.18 and 1.30 (2H, m, H-2_{eq} and H-2_{ax}), 2.11 (1H, dtt, J = 8.1, 12.2 and 3.4 Hz, H-3), 1.89 and 1.17 (2H, m, H-6_{eq} and H-6_{ax}), 1.88 and 1.30 (2H, m, H-5_{eq} and H-5_{ax}), 1.86 and 1.20 (2H, m, H-4_{eq} and H-4_{ax}), and 1.49 (3H, d, J = 7.1 Hz, Me-2'); ^{19}F NMR δ_F: -74.84 (brd, J = 8.1 Hz, CF_3-3); ^{13}C NMR δ_C: 173.82 (S, C-1'), 140.53 (S) and 128.61, 127.39, 127.11 (D) (Ph-2'), 126.98 (Dq, $J_{C,F}$ = 278.5 Hz, CF_3-3), 71.55 (D, C-1), 45.61 (D, C-2'), 40.75 (Dq, $J_{C,F}$ = 27.3 Hz, C-3), 30.74 (T, C-6), 30.35 (Tq, $J_{C,F}$ = 2.7 Hz, C-2), 23.96 (Tq, $J_{C,F}$ = 2.7 Hz, C-4), 22.46 (T, C-5), and 18.40 (Q, C-3'). (1*R*,3*S*,2'*R*)-**7a**: ^{1}H NMR δ_H: 7.4-7.2 (5H, m, ArH), 4.69 (1H, tt, J = 11.2 and 4.2 Hz, H-1), 3.70 (1H, brq, J = 7.1 Hz, H-2'), 2.11 (1H, dtt, J = 8.1, 12.2 and 3.4 Hz, H-3), 2.07 and 1.25 (2H, m, H-2_{eq} and H-2_{ax}), 2.00 and 1.25 (2H, m, H-6_{eq} and H-6_{ax}), 1.88 and 1.30 (2H, m, H-5_{eq} and H-5_{ax}), 1.86 and 1.20 (2H, m, H-4_{eq} and H-4_{ax}), and 1.49 (3H, d, J = 7.1 Hz, Me-2'); ^{19}F NMR δ_F: -74.83 (brd, J = 8.1 Hz, CF_3-3); ^{13}C NMR δ_C: 173.82 (S, C-1'), 140.48 (S), and 128.61, 127.39, 127.11 (D) (Ph-2'), 126.95 (Dq, $J_{C,F}$ = 278.5 Hz, CF_3-3), 71.55 (D, C-1), 45.66 (D, C-2'), 40.69 (Dq, $J_{C,F}$ = 27.3 Hz, C-3), 30.98 (T, C-6), 30.12 (Tq, $J_{C,F}$ = 2.7 Hz, C-2), 23.96 (Tq, $J_{C,F}$ = 2.7 Hz, C-4), 22.54 (T, C-5), and 18.49 (Q, C-3').

Esters 8a from (*S*)-(+)-2-phenylpropionic acid and (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol (4a). 10 Erlenmeyer flasks containing grown cultures of *Saccharomyces cerevisiae* were incubated with **3a** as described in the general procedure, then the flasks were extracted and the obtained crude oil was flash chromatographed (eluting system: *n*-hexane/ethyl acetate 7 : 3) to give 156 mg (31% yield) of (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol (**4a**)[30] and 258 mg (51% yield) of 1,1,1-trifluoro-4-phenyl-2-butanol (**5a**).[30] The esterification of butenol **4a** with (*S*)-(+)-2-phenylpropionic acid was performed as described in ref. 27 and obtained compounds **8a** were analysed by GLC and NMR (^{1}H, ^{19}F, ^{13}C). (2*S*,2'*S*)-**8a**: ^{1}H NMR δ_H: 7.4-7.2 (10H, m, ArH), 6.76 (1H, brd, J = 15.9 Hz, H-4), 6.09 (1H, brdd, J = 15.9 and 7.5 Hz, H-3), 5.80 (1H, m, H-2), 3.87 (1H, brq, J = 7.1 Hz, H-2'), and 1.57 (3H, d, J = 7.1 Hz, Me-2'); ^{19}F NMR δ_F: -77.73 (brd, J = 6.6 Hz, F_3-1); ^{13}C NMR δ_C: 172.48 (S, C-1'), 139.85, 134.99 (S) and 128.89, 128.72, 128.61, 127.49, 127.45, 126.91 (D) (Ar C), 138.50 (D, C-4), 123.05 (Sq, $J_{C,F}$ = 280.8 Hz, C-1), 117.14 (D, C-3), 71.13 (Dq, $J_{C,F}$ = 33.5 Hz, C-2), 45.39 (D, C-2'), and 18.10 (Q, C-3'). (2*R*,2'*S*)-**8a**: ^{1}H NMR δ_H: 7.4-7.2 (10H, m, ArH), 6.44 (1H, brd, J = 15.9 Hz, H-4), 5.98 (1H, brdd, J = 15.9 and 6.7 Hz, H-3), 5.82 (1H, m, H-2), 3.85 (1H, brq, J = 7.1 Hz, H-2'), and 1.57 (3H, d, J = 7.1 Hz, Me-2'); ^{19}F NMR δ_F: -77.64 (brd, J = 6.6 Hz, F_3-1); ^{13}C NMR δ_C: 172.39 (S, C-1'), 139.85, 134.99 (S) and 129.02, 128.82, 128.72, 127.59, 127.49, 127.00 (D) (Ar C), 137.40 (D, C-4), 123.15 (Sq, $J_{C,F}$ = 280.8 Hz, C-1), 116.65, (D, C-3), 70.69 (Dq, $J_{C,F}$ = 33.5 Hz, C-2), 45.29 (D, C-2'), and 18.32 (Q, C-3').

Esters 8b from (*S*)-(+)-2-phenylpropionic acid and (*E*)-4-phenyl-3-buten-2-ol (4b). The esterification of racemic butenol **4b** with (*S*)-(+)-2-phenylpropionic acid was performed as described in ref. 27 and obtained compounds **8b** were analysed by ^{1}H and ^{13}C NMR. (2*S*,2'*S*)-**8b**: ^{1}H NMR δ_H: 7.4-7.1 (10H, m, ArH), 6.31 (1H, brd, J = 15.8 Hz, H-4), 6.03 (1H, dd, J = 15.8 and 6.0 Hz, H-3), 5.53 (1H, m, H-2), 3.75 (1H, brq, J = 7.3 Hz, H-2'), 1.52 (3H, d, J = 7.3 Hz, Me-2'), and 1.38 (3H, d, J = 6.6 Hz, H_3-1); ^{13}C NMR δ_C: 173.66 (S, C-1'), 140.69, 136.36, (S) and 128.60, 128.46, 127.71, 127.62, 127.06, 126.47, (D) (Ar C), 130.74 (D, C-4), 128.60 (D, C-3), 70.81 (D, C-2), 45.76 (D, C-2'), 20.39 (Q, C-1), 18.48 (Q, C-3'). (2*R*,2'*S*)-**8b**: ^{1}H NMR δ_H: 7.4-7.1 (10H, m, ArH), 6.53 (1H, brd, J = 16.0 Hz, H-4), 6.17 (1H, dd, J = 16.0 and 6.7 Hz, H-3), 5.53 (1H, m, H-2), 3.74 (1H, brq, J = 7.3 Hz, H-2'), 1.52 (3H, d, J = 7.3 Hz, Me-2'), and 1.30 (3H, d, J = 6.5 Hz, H_3-1); ^{13}C NMR δ_C: 173.76 (S, C-1'), 140.62, 136.36 (S) and 128.56, 127.87, 127.57, 127.06, 126.55 (D) (Ar C), 131.43 (D, C-4), 128.72 (D, C-3), 71.21 (D, C-2), 45.73 (D, C-2'), 20.11 (Q, C-1), 18.48 (Q, C-3').

Esters 9a from (*S*)-(+)-2-phenylpropionic acid and 1,1,1-trifluoro-4-phenyl-2-butanol (5a). The

esterification of trifluorobutanol **5a**, obtained as described above from incubation with *Saccharomyces cerevisiae*, with (*S*)-(+)-2-phenylpropionic acid was performed as described in ref. 27 and obtained compounds **9a** were analysed by GLC and NMR (^{1}H and ^{19}F). (2*R*,2'*S*)-**9a**: ^{1}H NMR δ_H: 7.4-6.8 (10H, m, ArH), 5.28 (1H, m, H-2), 3.76 (1H, brq, J = 7.0 Hz, H-2'), 2.26 (2H, m, H_2-4), 1.91 (2H, m, H_2-3), 1.57 (3H, d, J = 7.0 Hz, Me-2'); ^{19}F NMR δ_F: -78.20 (brd, J = 6.6 Hz, F_3-1). (2*S*,2'*S*)-**9a**: ^{1}H NMR δ_H: 7.4-6.8 (10H, m, ArH), 5.28 (1H, m, H-2), 3.79 (1H, brq, J = 7.0 Hz, H-2'), 2.56 (2H, m, H_2-4), 2.02 (2H, m, H_2-3), 1.57 (3H, d, J = 7.0 Hz, Me-2'); ^{19}F NMR δ_F: -78.31 (brd, J = 6.5 Hz, F_3-1).

Esters 9b from (*S*)-(+)-2-phenylpropionic acid and 4-phenyl-2-butanol (5b). 10 Erlenmeyer flasks containing grown cultures of *Kloechera saturnus* were incubated with **3b** as described in the general procedure, then the flasks were extracted and the obtained crude oil was flash chromatographed (eluting system: *n*-hexane/ethyl acetate 7 : 3) to give 294 mg (58% yield) of 4-phenyl-2-butanol (**5b**) which was reacted with (*S*)-(+)-2-phenylpropionic acid as described in ref. 27 to give two diastereoisomeric esters **9b** which were analysed by GLC and ^{1}H NMR. (2*R*,2'*S*)-**9b**: ^{1}H NMR δ_H: 7.4-7.0 (10H, m, ArH), 4.91 (1H, m, H-2), 3.67 (1H, brq, J = 7.2 Hz, H-2'), 2.56 and 2.54 (2H, m, H_2-4), 1.87 ad 1.80 (2H, m, H_2-3), 1.49 (3H, d, J = 7.2 Hz, H_3-3), and 1.11 (3H, d, J = 6.3 Hz, H_3-1). (2*S*,2'*S*)-**9b**: ^{1}H NMR δ_H: : 7.4-6.9 (10H, m, ArH), 4.91 (1H, m, H-2), 3.66 (1H, brq, J = 7.2 Hz, H-2'), 2.34 and 2.31 (2H, m, H_2-4), 1. 76 ad 1.71 (2H, m, H_2-3), 1.49 (3H, d, J = 7.2 Hz, H_3-3), and 1.21 (3H, d, J = 6.3 Hz, H_3-1).

References and Notes

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28. It is interesting to observe that a low non-equivalence was observed for the chemical shifts of C-1, C-1', C-2', and C-3' in couples of diastereoisomeric esters **7a** ($\Delta\delta_C \leq 0.05$ ppm) so that the preference for the eclipsed conformation described above and depicted in Scheme 3 is further supported.
29. The effect is highly dependent on the phenyl-ring/shielded-carbon distance. For instance, in *trans*-**7a** the ester moiety is axially disposed (namely the conformation of the alcoholic precursor *trans*-**2a** is retained in the ester as in this compound too the alcoholic proton H-1 exhibits only small coupling constants, consistent with an equatorial position) so that the phenyl ring is quite near C-3 (≈ 5.2 Å; Scheme 3) which thus shows a $\Delta\delta_C = 0.31$ ppm. Differently, in *cis*-**7a** the ester moiety is equatorial (as proven by the large coupling constants shown by H-1 which indicate axial-axial interactions), so that the phenyl ring is less near C-3 (≈ 6.7 Å) which consequently presents a lower $\Delta\delta_C$ (0.06 ppm).
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