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2-METHYL-6,6-BIS(TRIFLUOROMETHYL)CYCLOHEX-3-ENE-1-CARBALDEHYDE: REACTIVITY AND APPLICATION AS A MODEL FOR THE PREPARATION OF 16,16,16,17,17,17-HEXAFLUORORETINAL ANALOGS

Sarah Boichut, Cecile Boyer, Klaus Burger*, Alois Haas, Klaus Merz, Thierry Pages, Tilman Wallmichrath

Department of Chemistry, Ruhr University of Bochum, D-44780 Bochum
* Department of Organic Chemistry, University of Leipzig, D-04103 Leipzig

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New approaches to 16,16,16,17,17,17-hexafluororetinal and analogs,** via **2-methyl-6,6-bis(trifluoromethyl)cyclohexanone and 2-methyl-6,6-bis(trifluoromethyl)cyclohex-1-ene-1-carbaldehyde (7,7,7,8,8,8-hexafluoro-β-cyclocitral) are presented. An efficient synthesis for 2-methyl-6,6-bis(trifluoromethyl)-cyclohex-3-ene-1-carbaldehyde starting from hexafluoroacetone has been described and used for preparing reactive building blocks. The crystal structures of 6, 15 and 23 have been provided and the influence of the bis(trifluoromethyl)-group on bond lengths and angles have been discussed.

2-МЕТИЛ-6,6-БІС(ТРИФТОРОМЕТИЛ)ЦИКЛОГЕКС-3-ЕН-1-КАРБАЛЬДЕГИД: РЕАКЦІЙНА ЗДАТНІСТЬ ТА ВИКОРИСТАННЯ У ЯКОСТІ МОДЕЛІ ДЛЯ ОТРИМАННЯ 16,16,16,17,17,17-ГЕКСАФТОРОРЕТИНАЛЬНИХ АНАЛОГІВ

Сара Бойшу, Сесіль Бойєр, Клаус Бюргер, Алоїз Хаас, Клаус Мерц, Тьєррі Пейдж, Тільман Воллміхрат

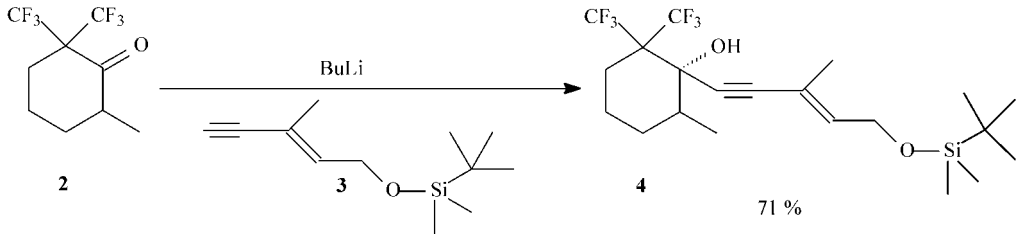
Представлені нові підходи до отримання 16,16,16,17,17,17-гексафтороретиналу та його аналогів** через **2-метил-6,6-біс(трифторометил)циклогексанон і 2-метил-6,6-біс(трифторометил) циклогекс-1-ен-1-карбальдегид (7,7,7,8,8,8-гексафторо-β-циклоцитрал). Описаний ефективний синтез 2-метил-6,6-біс(трифторометил)-циклогекс-3-ена-1-карбальдегіду з вихідного гексафтороацетону, який використовується для отримання будівельних блоків реакції. Наведені кристалічні структури 6, 15 и 23, а також обговорений вплив біс(трифторометил)-групи на довжину та кути зв'язків.

2-МЕТИЛ-6,6-БИС(ТРИФТОРОМЕТИЛ)ЦИКЛОГЕКС-3-ЭН-1-КАРБАЛЬДЕГИД: РЕАКЦИОННАЯ СПОСОБНОСТЬ И ПРИМЕНЕНИЕ В КАЧЕСТВЕ МОДЕЛИ ДЛЯ ПОЛУЧЕНИЯ 16,16,16,17,17,17-ГЕКСАФТОРОРЕТИНАЛЬНЫХ АНАЛОГОВ

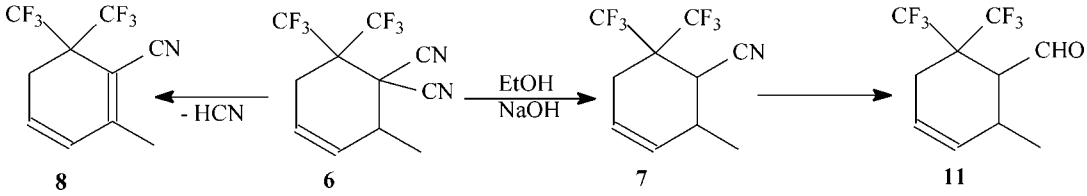
Сара Бойшу, Сесиль Бойер, Клаус Бюргер, Алоиз Хаас, Клаус Мерц, Тьерри Пейдж, Тильман Воллмихрат

Представлены новые подходы к получению 16,16,16,17,17,17-гексафтороретинала и его аналогов** через **2-метил-6,6- бис(трифторометил)циклогексанон и 2-метил-6,6-бис(трифторометил) циклогекс-1-эн-1-карбалдегид (7,7,7,8,8,8-гексафторо-β-циклоцитрал). Описан эффективный синтез 2-метил-6,6-бис(трифторометил)-циклогекс-3-эна-1- карбальдегида из исходного гексафтороацетона, применяемый для получения строительных блоков реакции. Приведены кристаллические структуры 6, 15 и 23, а также обсуждено влияние бис(трифторометил)-группы на длину и углы связей.

A world wide interest in fluorinated organic molecules is justified by their unpredictable biological properties mostly in a favourable way. Fluorinated retinals are active against some viral diseases and obstructions of the central nerve system; they are used in anaesthesia, as antibiotics and against diabetes [1-6]. In addition they are increasing metabolic stability and lipophilicity, enhancing *in vivo* absorption and transport rates, as well as improving permeability through certain body barriers [7, 8]. The trifluoromethyl group is attractive since it is relatively non-toxic and somewhat more stable than the difluoromethyl and the monofluoromethyl group [9, 10]. As far as retinals are concerned it was expected, especially by a bis(trifluoromethyl)-substitution in position 1, a reduction of the metabolism rate and hence an increase of their pharmacological activity. Recently, retinal was in the focus of some groups in industry and academia. The



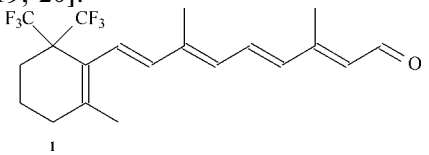
Scheme 1



Scheme 2

methyl groups in position 16 [11], 18 [12], 19 [13, 14] and 20 [15, 16] of retinal have been replaced by trifluoromethyl moieties.

Surprisingly the preparation of 16,16,16,17,17,17-hexafluororetinal (1) bearing a geminal pair of trifluoromethyl groups, is not described. A straight forward route was tested: the direct coupling of 2-methyl-6,6-bis(trifluoromethyl)-cyclohexanone (2) [17] with an O-silylated Nakanishi type alcohol 3 [18], which was added to the carbonyl group of 2 *via* a lithiated acetylene moiety to give adduct 4 as a 3:1 mixture of diastereomers in 73% yield (Scheme 1). Unexpectedly, the final step of the synthesis, the introduction of the CC double bond *via* elimination of water turned out to be highly problematic. We tested several standard protocols for H_2O elimination, so far without success [19, 20].



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Therefore, an alternative approach was started. From 2,2-bis(trifluoromethyl)ethylene-1,1-dicarbonitrile (5) [21] and (E)-1,3-pentadiene in a Diels-Alder reaction 1,1-bis(trifluoromethyl)-5-methyl-6,6-dicyano-cyclohexa-diene (6) was synthesized [22] and transferred via a 4 step synthesis (7 → 8 → 9) to 7,7,7,8,8,8-hexafluoro-β-cyclocitral (10), the ideal synthon for preparing 1 [23]. The weakness of this procedure was step 7 → 8, an allylic bromination with NBS providing 1,1-bis(trifluoromethyl)-5-methyl-6-cyano-cyclohex a-3,5-diene (8) only in low yields after a long lasting separation by MPLC. Therefore a more efficient route was demanded. Two routes were pursued: elimination of HCN from the 6 to 8 and the application of other halogensuccinimids. The first route, treating 6 in acidic media (conc. HCl, conc. H_2SO_4, CF_3SO_3H in CCl_4 at 20°C, 24h), did not provide 8. Under more drastic acidic conditions (refluxing in CF_3SO_3H) 6 decomposed in an uncontrolled way.

Reactions using fluoride ions, known as a strong base under certain conditions [24] gave, while refluxing with a mixture of 5 parts KF in CH_3CN (20h) in the presence of 18-Crown-6, a 37% yield of compound 7 (calculated by ^1H NMR).

These experiments confirm that both EtO^- and F^- act as nucleophiles and not as bases. The reaction using fluoride anion as a nucleophile in a non-protic solvent like CH_3CN probably implies a hydrogen transfer from the solvent.

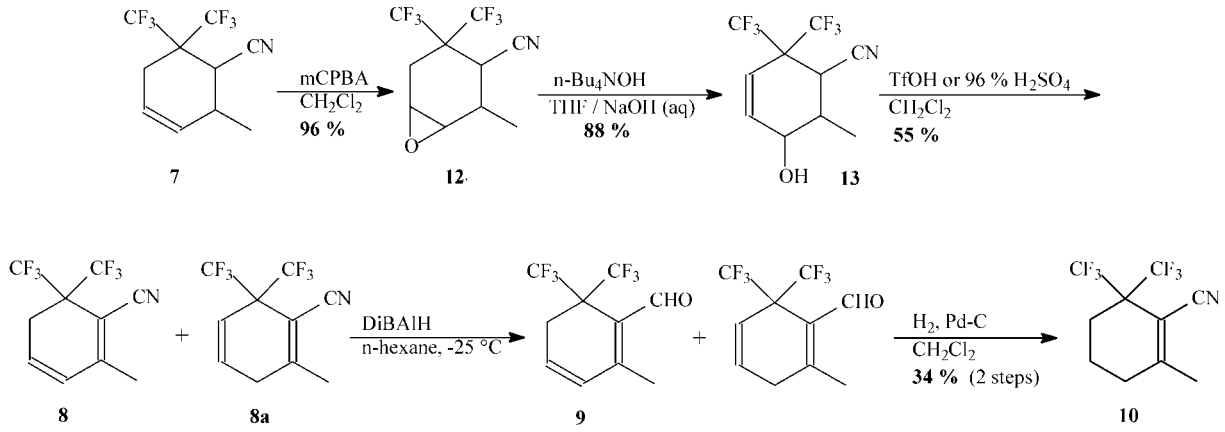
No reactions were observed investingating route two, between 1,1-bis(trifluoromethyl)-5-methyl-6-cyano-cyclohexa-3-ene (7) with NSCl or NSI.

Furthermore, allylic hydroxylation of 7 with SeO_2, isomerization of the double bond, to get the corresponding 8 failed. Similar attempts to isomerize 7 under basic or acidic conditions (DBU, ether; conc. sulfuric acid; excess of TfOH), were unsuccessful and the starting material was recovered.

A new pathway was tested, avoiding allylic halogenation and MPLC purification steps. The CC double bond of 7 was transformed by m-CPBA to give epoxide 12. Under basic conditions, allyl alcohol 13 was obtained and dehydrated in acidic media to give nitriles 8 and 8a, isolated as an isomeric mixture according to Scheme 3.

The different experiments, carried out to dehydrate 13 With P_4O_{10} in CH_2Cl_2 at 20°C (12h) were not satisfactory. Better results were obtained with conc. sulfuric acid or triflic acid in DCM providing the two isomers 8 and 8a in a 9:1 ratio, which were characterized by ^1H-NMR spectroscopy. The nitrile functions of the isomers were transformed into aldehyde moieties in low yields (30-50%). They were not isolated but directly hydrogenated to a mixture, which was purified by liquid chromatography (glass column, eluant: pentane / AcOEt, 98:2) giving the conjugated aldehyde 10, in 34% yield (calculated from the nitriles 8 and 8a). This corresponds to results published earlier [23], but the procedure is less time consuming.

An additional attempt elucidating a promising precursor was the preparation of 1,1-bis(trifluoromethyl)-5-methoxy-6,6-dicyanocyclohex-3-ene (14) from 5 and 1-methoxybutadiene. This route was not pursued. Instead 2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-



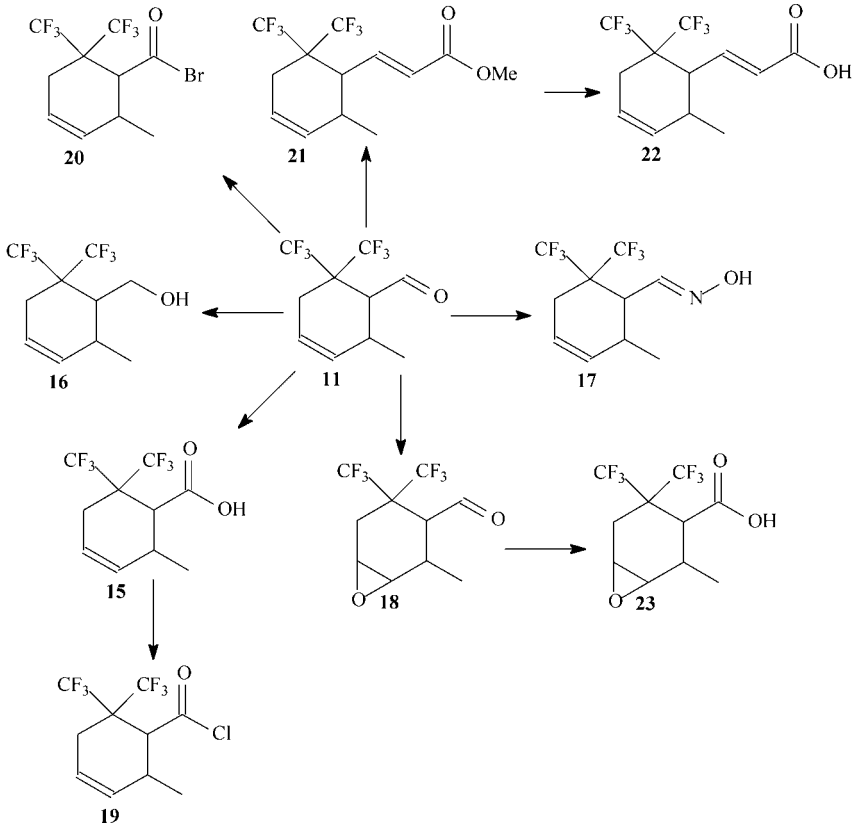
Scheme 3

ene-1-carbaldehyde (11) was made from 7 as shown in Scheme 2 in preparative amounts. The easy access made 11 the preferred synthon and was used as a model for studying the influence of the bis(trifluoromethyl) group on the reactivity of the aldehyde function. The compounds synthesized are summarized in Scheme 4. Only a mixture of $NaClO_2$, NaH_2PO_4 and H_2O_2 oxidized it to the acid 15 in 70% yield. With m-CPBA 11 was oxidized to give the epoxialdehyde 18 and the acid 23 was obtained from 18 similarly to the preparation of 15. With hydroxylamine 17 is formed and the reduction with $NaBH_4$ provided alcohol 16. The acid bromide 20 was obtained from 11 and bromosuccinimid in CCl_4. The corresponding acid chloride 19 was made by chlorinating 15 with oxalyl choride, PCl_5 or $SOCl_2$. A Wittig-Horner-Reaction of 11 with trimethyl-phosphonoacetate converted it into the corresponding methyl ester 21, which was hydrolyzed to give acid 22.

These compounds represent a substantial number of bis(trifluoromethyl) substituted cyclohexenes and provide an interesting class of building blocks.

The present structure determinations of 6, 15 and 23 were undertaken to investigate the influence of a geminal pair of trifluoromethyl groups on further substituents on the ratinal ring backbone.

The molecule 6 is shown in Fig. 1. A striking feature of 6 is the angle of the dicyano group with 105.9° which is different to the angle of 108.1° in the dicyano group of dicyano-2-ethoxy-6-isopropyl-4-methylcyclohex-3-ene. Within experimental error, the influence of the neighbouring trifluoromethyl group on the dicyanogen group in 6 is similar to the values in 2,3-dichloro-5,5-dicyano-6,6-bis(trifluoromethyl)norborane [25]. There



Scheme 4

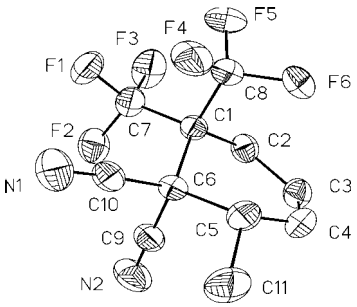


Fig. 1. The molecular structure of 6 with displacement ellipsoids for non-H atoms at the 50% probability level. Hydrogen atoms are omitted for clarity

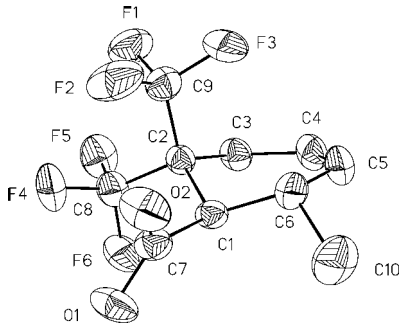


Fig. 2. The molecular structure of 15 with displacement ellipsoids for non-H atoms at the 50% probability level. Hydrogen atoms are omitted for clarity.

are slightly short CN bonds 1.137 A° and 1.140 A° than the observed distance of 1.143 A° and 1.145 A° in dicyano-2-ethoxy-6-isopropyl-4-methylcyclohex-3-ene [26].

The structures of 15 and 23 are presented in Fig. 2 and 3. Both retinal molecules consist of a carboxy group which is neighbouring to the bis(trifluoromethyl) group. In contrast to 15, a slight influence of the geminal pair of trifluoromethyl group on the carboxy function of 23 is observable. The C=O bonds in 23

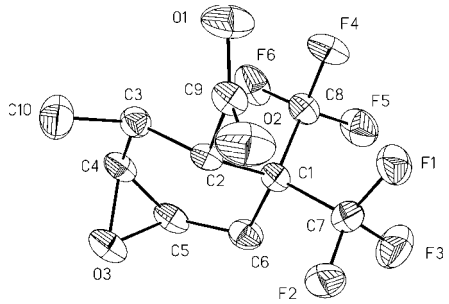
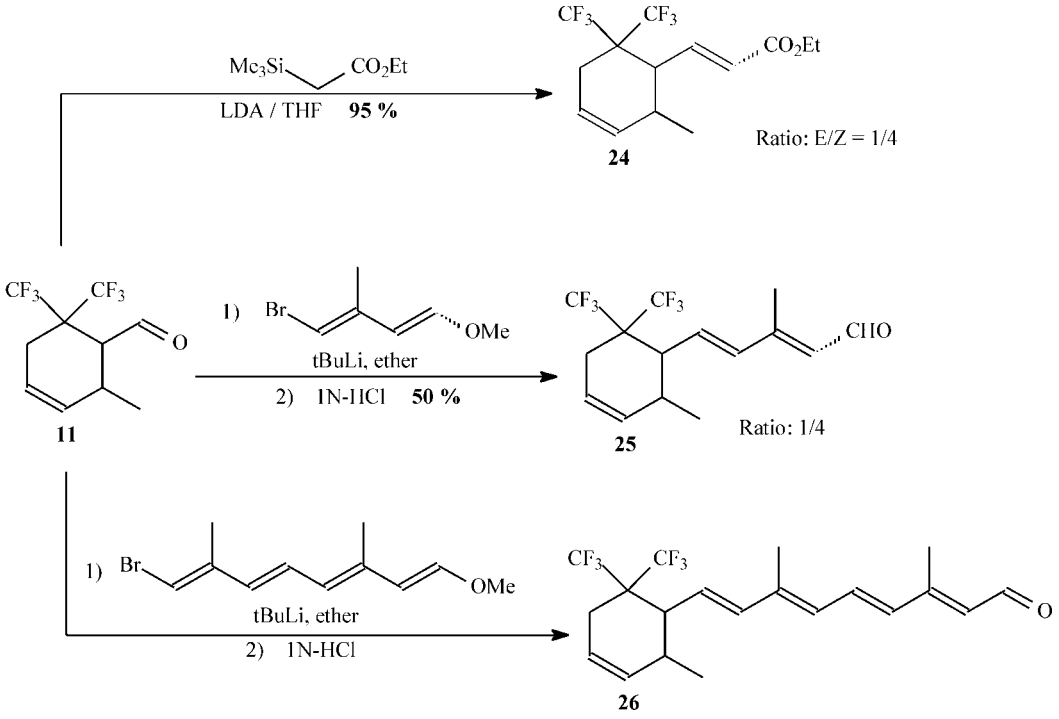


Fig. 3. The molecular structure of 23 with displacement ellipsoids for non-H atoms at the 50% probability level. Hydrogen atoms are omitted for clarity.

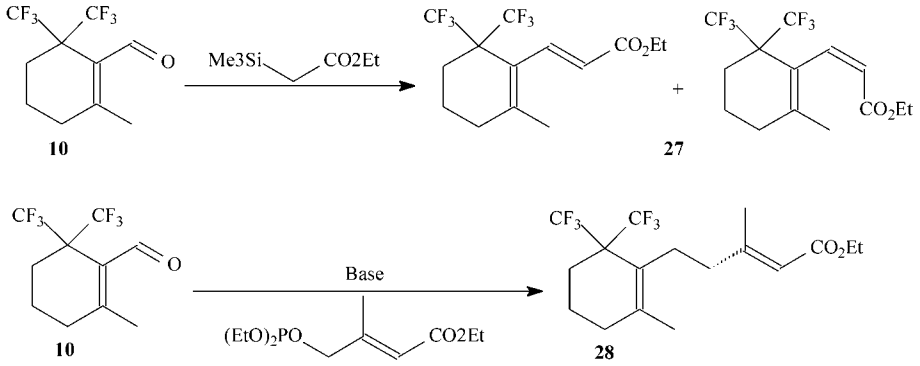
with 1.189 A° is slightly shorter than the C=O value observed for carboxylic acids in the literature [27]. Furthermore the C-O bond lengths of the epoxy group with 1.434 and 1.444 A° are shorter than the C-O bond lengths in a comparable epoxy substituted ring system [28]. There is no influence of the geminal pair of trifluoromethyl group on the retinal ring geometry observable. All of the bond lengths and bond angles in the ring backbone of the compounds 6, 15 and 23 are in the normal range.

Condensations leading to precursors of the target molecule 1

Target molecule 1 can be prepared from 10 in a number of ways [29]. A coupling reaction was chosen in order to have a convergent synthesis but also trying to minimize the ratio of the isomeric products usually obtained in such a synthesis. The synthons for building up the side chain are either commercially available or are readily prepared by literature methods [30]. Although the targeted part 10 of the bis(trifluoromethylated) vitamin A is available by two different routes the easier accessible aldehyde 11 was used to test some coupling methodology.



Scheme 5



Scheme 6

The first attempt was made with the commercially available ethyl 2-trimethylsilyl acetate in THF in the presence of LDA. The expected product 24 was obtained in 95% yield as a mixture of E/Z isomers in a ratio of 1:4. It was also formed as methylesters 24a from 11 and trimethylphosphono acetate in 72% yield. Condensation of 11 with lithiated $BrCH{=}C(CH_3)CH{=}CHOCH_3$, prepared *in situ* by halogen-metal exchange, led to the desired condensation products 25 characterized by ^1H-, ^{13}C NMR spectra and GC-MS data. Two isomers were obtained. However, by-products could not be removed completely by liquid chromatography (glass column). Therefore, the yield was determined spectroscopically. Analogously 11 reacted with the lithiated $BrCH{=}C(CH_3)CH{=}CHCH{=}C(CH_3)CH{=}CHOCH_3$ giving a mixture of products. After purification a single isomer 26 was obtained and characterised by ^1H NMR and ^{13}C NMR spectra, see Scheme 5.

When 10 reacted, under conditions described above, the expected compounds were obtained, as shown in Scheme 6, but in rather low yields. Based on practical experience made before, 10 is used as the appropriate synthon for building up the side chain. With ethyl 2-trimethylsilylacetate it reacted to the corresponding 27 consisting of two isomers (ratio 2:1) and characterised by GC-MS analysis. With ethyl-3-methyl-4-(diethylphosphonato)-but-2-enoate 10 formed 15% of 28 as a 1:1 mixture of two isomers. According to these results it can be concluded that 10 is less reactive than 11, forming with increasing chain length less stable retinal analogous.

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Experimental

The compounds 2 [17], 6 [22] and 7-10 [23] were synthesised according to literature methods. IR spectra were recorded in cm^{-1}, neat between KBr pellets, using a Bruker Vektor 22 and Bruker FT-IR-spectrometer IFS. NMR spectra were recorded, if not otherwise stated with a Bruker WP 80 PFT spectrometer (^{19}F), ^1H, and ^{13}C NMR spectra were obtained using an AM 400 PFT-NMR spectrometer. In general $CDCl_3$ was employed as a solvent at 25°C. As reference standards (δ in ppm, J in Hz), TMS was used for ^1H and ^{13}C (internal), and for ^{19}F NMR spectra $FCCl_3$ (internal). If not otherwise stated mass spectra m/z, (%) of liquids were obtained with a HP-gaschromatograph 5890 with a 12,5 m capillary column covered with OVI and an HP MS Engine 5989 A and an electron ionisation (EI, 70eV). Solids were recorded (EI, 70eV) with a Varian MAT-CH 7 instrument.

Crystal structure determinations The intensities were measured with a Bruker-axs-SMART diffractometer ($Mo_K\alpha$ radiation, λ = 0.71707 A°, ω-Scan, T = 213 K, the structures were solved by direct methods. Refinements were carried out with the SHELXL-97 package. All non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms were placed in calculated positions and refined isotropically in riding mode. All refinements were made by full-matrix least-squares on F^2. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 632394-632396. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; email: deposit@ccdc.cam.ac.uk).

Crystal data	6	15	23
Empirical formula	$C_{11}H_8F_6N_2$	$C_{10}H_{10}F_6O_2$	$C_{10}H_9F_6O_3$
Formula weight	282.19	276.18	291.17
Space group	$P2_1/c$	Pbca	$P2_1$
a (A°)	7.228(2)	11.965(2)	6.926(1)
b (A°)	13.312(4)	12.332(3)	10.305(2)
c (A°)	12.367(4)	15.342(3)	7.996(1)
β (°)	103.10(3)	90	104.707(4)
V ($A^{\circ 3}$)	1159.0(5)	2263.7(8)	552.06(16)
Z	4	8	2
μ (Mo-Kα) (mm^{-1})	1.617	1.621	1.752
2 θ Range (°)	50	50	50
Refl. coll.	4867	5202	2873
Ind. Refl.	2025 (R_{int}=0.0258)	1904 (R_{int}=0.0812)	1477(R_{int}=0.0202)
R_1 and wR_2 [I > 2σ (I)]	0.0358, 0.0917	0.0469, 0.0904	0.0335, 0.0920
R_1 and wR_2 [all data]	0.0420, 0.0964	0.1144, 0.1144	0.0347, 0.0932
Goodness-of-fit, S	1.025	0.906	1.104
Data-to-parameter ratio	2025/172	1904/167	1477/176

7,8-Dehydro-5,6-dihydro-6-hydroxy-β-ionyliden-ethanol-11-(tert.-butyl)-dimethyl)-silylether (4)

In a dry argon atmosphere to a 3-methyl-pent-4-inol-(tert.-butyl-dimethyl-silylether (0.5 g, 2.18 mmol), dissolved in THF (10 mL), cooled to 0°C, a solution

of 1.6 M butyllithium in n-hexane (1.5 mL, 2.4 mmol) were injected and stirred at 0°C (0.5 h). To this orange solution 1,1-bis(trifluoromethyl)- 3-methylcyclohexanon (0.4 g, 1.46 mmol) dissolved in THF (2 mL) was injected and stirred for 3 days. The procedure was stopped by adding a NH_4Cl solution. The mixture was extracted three times with ether; the combined organic phase was washed with water and dried over sodium sulfate. Volatile parts were removed by a rotating evaporator and the orange oil was purified by column chromatography (eluent: petrolether : chloroform 5:1). Yield: 0.49 g, (73.3%). The yellow oil consists of two isomers: ratio 3:1. They could not be separated and their configuration could not be elucidated. Bp 100°C/10^{-2} (dec), ^{1}H-NMR (80 MHz) δ: 0.05 (s, 6 H, Si(C<u>H</u>$_3$)$_2$; 0.88 (s, 9 H, C(C<u>H</u>$_3$)$_3$); 1.07 (s, 3 H, 14-C<u>H</u>$_3$); 1.74 (s, 3 H, 15-C<u>H</u>$_3$); 0.75-2.1 (m, 7 H, 2-C<u>H</u>$_3$, 3-C<u>H</u>$_3$, 4-C<u>H</u>$_3$, 5-C<u>H</u>); 4.23 (d, 2 H, l0-C<u>H</u>$_3$, ^{3}J(H,H) = 5.7); 5.94 (t,1H, 9-C<u>H</u>, ^{3}J(H,H) = 5.7).

^{13}C-NMR (62.86 MHz) δ: -5.36 (q, Si(CH$_3$)$_2$, ^{1}J(C,H) = 118.3); -3.73 (s, Si(CMe$_3$)); 16,62 (q, C-14, ^{1}J(C,H) = 127.8); 16.98 (q, C-15, ^{1}J(C,H) = 127.8) 18.28 (t, C-3, ^{1}J(C,H) = 127.8); 19.75 (t, C-4, ^{1}J(C,H) = 133.5); 25.78 (q, C(CH$_3$)$_3$ ^{1}J(C,H) = 120.1); 31.11 (t, C-2, ^{1}J(C,H) = 131.6); 38.48 (d, C-5, ^{1}J(C,H) = 133.5 Hz); 59.62 (sep, C-l, ^{2}J(C,F) = 20.8 Hz); 59.77 (t, C-11, ^{1}J(C,H) = 141.1 Hz);73.81 (s, C-6); 82.15 (s, C-7); 91.28 (s, C-8);117.08 (s, C-9); 124.59 (q, CF$_3$, ^{1}J(C,F) = 288.0); 125.07 (q, CF$_3$, J(C,F) = 288,0); 138.28 (d, C-l0, ^{1}J(C,H) = 160.2).

^{19}F-NMR I (75.26 MHz) δ: -58.98 (q, CF$_3$, ^{4}J(F,F) = 11.8); -65.56 (q, CF$_3$, ^{4}J(F,F) = 11.8). IR 3627(OH), 3460(OH), 2957, 2886, 2360, 2219, 1751, 1464, 1370, 1304, 1254, 1206, 1175, 1105, 953, 907, 837, 778, 727, 668, 541.

MS 458(M^+, 12); 402(7), 401(32); 309(21); 307(23), 267(6); 203(7); 147(7); 145(9); 107(57), 77(33); 75(100); 73(51).

2-Methyl-6,6-bis(trifluoromethyl)cyclohexa-1,3-diene-1-carbonitrile (8)

2-Methyl-6,6-bis(trifluoromethyl)cyclohexa-1,4-diene-1-carbonitrile (8a)

To a solution of 13 (5.6 g, 20.5 mmol) in DCM (400 mL), 96% H_2SO_4 (19.6 g, 10 eq.) or TfOH (18 mL, 10 eq.) were added at room temperature. The mixture was strirred for 1 d at room temperature. The organic phase was separated and neutralized with aqueous sodium hydroxide, then washed with water, dried with Na_2SO_4 and evaporated to dryness. The resulting solid was sublimed. Yield: 2.88 g (55%), white solid, mixture of two isomers.

^{1}H NMR Isomer 8 δ: 2.27 (s, 3H, CH$_3$); 2.88 (dd, 2H, J = 4.0, J = 2.0, CH$_2$); 6.05 (dt, 1H, J = 10.0, J = 2.0, H-3); 6.17 (dt, 1H, J = 10.0, J = 4.0, H-4). Isomer 8a δ: 2.29 (s, 3H, CH$_3$); 3.01 (br.t, 2H, J = 4.0; J = 2.5; CH$_2$); 5.87 (dt, 1H, J = 10.0, J = 2.0, H-5); 6.33 (dt, 1H, J = 10.0, J = 3.5, H-4).

2-Methyl-6, 6-bis(trifluoromethyl)cyclohex-3-ene-1-carbaldehyde (11)

To a cold (0°C) solution of 2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-1-carbonitrile (7) (5.0 g, 20 mmol) in ether (150 mL) DIBAlH (1 M in hexane, 43 mL) was added with stirring under inert gas. The mixture was stirred for 90 min at ambient temperature, then it was cooled to 0°C and diluted H_2SO_4 (10% in water; 100 mL) was added. After stirring for 2 h at room temperature, the organic phase was separated, washed with water (3x30 mL) and neutralized. After drying with Na_2SO_4, filtration and evaporation of the solvent i. vac. a slight yellow coloured oil was obtained, Which was purified chromatographically with a mixture of petrolether : acetic acidester = 60 : 1.

Yield: 4.8 g, (94.9%).

^{1}H-NMR δ: 1,01 (d, 3H, J = 6,6, CH$_3$); 2.46 (m, 2H, 6-CH/ 2-CH$_2$); 2,55 (d, 1H, 2-CH$_2$, J = 18,8); 2.74 (m, 1H, 5-C<u>H</u>); 5,59 (d, 1H, 3-CH/4-CH), J = 10,3); 5,64 (d, 1H, 3-CH/4-CH, J = 10,3); 9.73 (m, 1H, CHO). ^{13}C-NMR (62,86 MHz) δ: 19.87 (q, <u>C</u>H$_3$, J = 127,8); 26.36 (tr, 2-C, J = 131,6); 27.30 (d, 5-<u>C</u>, J = 124,0); 52.06 (sept, 1-<u>C</u>, J = 25,4); 54.22 (d, 6-<u>C</u>, <u>J = 129,4</u>); 120.03 (d, 4-C, J = 162,1); 124,68 (q, CF$_3$/CF$_3$, J = 286,1); 131.95 (d, 3-C, J = 162,1); 198.96 (d, CHO, J = 181,1). ^{19}F-NMR (75.26 MHz) δ: -65,5 (q, CF$_3$, J = 9.8,); -70,22 (q, CF$_3$, J = 9.8). MS m/z (%) 260 (M^+/17); 245(10); 231(100); 217(17); 163(55); 142(54); 127(40); 95(18); 69(17); 65(25). IR 2960, 2870, 1720, 1440, 1365, 1265, 1195, 1120, 705. Anal. calcd. for $C_{10}H_{10}F_6O$: C, 46,1%; H, 3,9%; Found: C, 44,4% (low value because of CF_4 formation); H, 4,0%.

3,4-Epoxy-2-methyl-6,6-bis(trifluoromethyl)cyclohexane-1-carbonitrile (12)

To a solution of 7 (33.0 g, 128 mmol) in DCM (450 mL) m-CPBA (47.0 g, 70% w/w 1.5 eq.) was added at room temperature. After two days the white precipitated solid was filtered off and washed with DCM. The sample was neutralized with aqueous sodium hydroxide. The organic phase was separated, washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. Yield: 33.8 g (96%), white solid, mp 70°C.

^{19}F NMR (75.26 MHz) δ: -68.0 (q, J_{FF} = 9.8, CF$_3$); -71.6 (q, J_{FF} = 9.8, CF$_3$). ^{1}H NMR (200 MHz, resolved with HMQC correlation) δ: 1.46 (d, 3H, J = 7.0, CH$_3$); 2.23 (dq, 1H, J = 16.6, J = 2.0; CH$_2$); 2.47 (dd, 1H, J = 16.6, J = 5.5, CH$_2$); 2.51 (m, 1H, C<u>H</u>CH$_3$); 2.91 (d, 1H, J = 12.0, CHCN); 3.28 (dd, 1H, J = 4.0, J = 1.5, CHO); 3.36 (m (looks like dd), 1H; CHO). ^{13}C NMR δ: 16.1 (C<u>C</u>H$_3$); 24.1 (CH$_2$); 29.4 (CH$_2$); 29.5 (<u>C</u>CN); 48.8 (CO); 49.5 (sept, J_{CF} = 26.2, C(CF$_3$)$_2$); 55.0 (CO); 115.1 (CN); 122.6 (q, J = 286.7, CF$_3$); 123.2 (q, J = 286.7, CF$_3$). MS 272 [M — H]$^+$ (4); 257 (82); 218 (4); 204 (15); 186 (5); 176 (5); 166 (8); 145 (7); 127 (6); 109 (9); 95 (11); 84 (16); 75 (12); 69 (66); 55 (34); 41 (100); 39 (68).

3-Hydroxy-2-methyl-6,6-bis(trifluoromethyl)cyclohex-4-ene-1-carbonitrile (13)

To a solution of epoxide 12 (31.0 g, 110 mmol) in THF (225 mL), aqueous sodium hydroxide (70 mL; 16.6 N; 10 eq.) and n-Bu$_4$NOH (70 mL; 40% w/w; 0.25 eq.) were added. The solution was refluxed for 2 h. The dark red solution formed was neutralized with 5N HCl and evaporated *in vacuo*, The remaining

product was extracted with DCM (3x100 mL). The organic phase was dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by silica gel filtration (eluent: DCM).Yield: 26.4 g (88%), white solid, mp 74°C.

^{19}F NMR (75.26 MHz) δ: -68.0 (q, J_{FF} = 9.8, CF_3); -71.6 (q, J_{FF} = 9.8, CF_3). ^{1}H NMR (200 MHz) δ: 1.34 (d, 3H, J = 7.0, CH_3); 2.31 (m, 1H, C<u>H</u>CH_3); 3.35 (d, 1H, J = 12.0, CHCN); 4.13 (dd, 1H, J = 5.5, J = 3.0 Hz, CHOH); 5.79 (d, 1H, J = 10.5, H-5); 6.51 (dd, 1H, J = 10.5, J = 5.5, H-4).

^{13}C NMR (Resolved with HMQC correlation) δ: 14.9 (CH_2); 28.0 (<u>C</u>CN); 32.5 (<u>C</u>CH_3); 52.5 (m, <u>C</u>$(CF_3)_2$); 62.9 (COH); 116.0 (CN); 118.0 (C-5); 122.15 (q, J = 286.1 , CF_3); 122.3 (q, J = 286.1, CF_3); 137.1 (C-4). MS 273 $[M]^+$ (1); 258 (2); 244 (9); 216 (4); 204 (100); 186 (9); 177 (10); 166 (14); 158 (6); 149 (13); 127 (7); 117 (19); 109 (14); 84 (49); 83 (31); 69 (45); 55 (28); 39 (29).

2-Methoxy-6,6-bis(trifluoromethyl)-cyclohex-3-ene-1,1-carbodinitrile (14)

To a cold solution (0°C) of 5 (2.55 g, 119 mmol) in dry pentane (60 mL), a solution of 1.0 g of 1-methoxybutadiene (1 eq.) in dry pentane (100 mL) was slowly added. The solution was stirred for 1 h at 0°C, then for 3 h at room temperature. The resulting white solid was filtered at 0°C and washed with cold pentane (3x 20 mL) Yield: 3.45 g (97%), white solid, mp 70°C.

^{19}F NMR (75.26 MHz) δ: -65.8 (q, J_{FF}= 12.2, CF_3); -68.0 (q, J_{FF}= 12.2, CF_3). ^{1}H NMR (200 MHz) δ: 5.94 (br, s, 2H, olefinic protons); 4.39 (br. s, 1H, C<u>H</u>OCH_3); 3.76 (s, 3H, OCH_3); 2.90 (d, 1H, J = 19.1, CH_2); 2.73 (d, 1H, J = 19.1, CH_2). ^{13}C NMR δ: 27.4 (CH_2); 41.5 (<u>C</u>$(CN)_2$); 58.0 (<u>C</u>$(CF_3)_2$); 62.1 (OCH_3); 80.5 (<u>C</u>HOCH_3); 112.4 (CN); 113.3 (CN); 126.7, 127.6 (CH=CH); 124.7 (q, J = 287.8, CF_3); 125.2 (q, J = 287.8, CF_3).

2-Methyl 6-bis(trifluoromethyl)cyclohex-3-ene-1-carbonic acid (15)

A buffer solution of NaH_2PO_4 (0.32 g, 2.2 mmol) in water (2 mL) was added to a solution of 11 (2.6 g, 10 mmol) in acetonitrile (10 mL). The mixture was added to a solution to hydrogen peroxide (30% in water; 1.1 mL, 10.4 mmol). After cooling to 10°C a solution of $NaClO_2$ (to 80% is 1.6 g, 14 mmol) in water (14 mL) was added slowly. After stirring for 15 h at ambient temperature, the reaction mixture was treated with Na_2SO_3 (~1.0 g) to destroy HOCl and H_2O_2. After neutralization with 10% HCl, the mixture was extracted with ether, the organic phase was separated and dried with Na_2SO_4. After filtration and evaporation of the solvent *in vacuo* a white solid was obtained. Yield: 2.4 g (86.9%), mp 84-87°C.

^{1}H-NMR (200 MHz) δ: 1.03 (d, 3H, J = 6.8); 2.41 (d, 1H, J = 20.0); 2.50 (d, 1H, J = 16.0); 2.53-2.63 (m, 1H); 2.77 (s, 1H); 5.47-5.61 (m, 2H); 9.85 (s, 1H, COOH). ^{13}C-NMR (200MHz) δ: 20.31 (CH-<u>C</u>H_3); 27.17 (CH_2); 31.28 (<u>C</u>H-CH_3); 48.64 (<u>C</u>H-COOH); 52.4 (sept, J = 25.0, <u>C</u>$(CF_3)_2$); 119.87, 132.05 (C=C); 122.05, 127.72 (2 CF_3); 176.98 (COOH). ^{19}F —NMR (235.3 MHz) δ: —66.7 (6 F, d, J_{HF} = 8.5, CH$(CF_3)_2$).

6,6-Bis(trifluoromethyl)-2-methyl-1-hydroxymethyl-cyclohex-3-en (16)

To a solution of 11 (0.25 g, 0.96 mmol) in 10 ml ether $LiAlH_4$ (0.05 g, 1.31 mmol) was slowly added. Reaction took place with slight foam up. After 20 min dil. sulfuric acid (5 mL) was added and the mixture continuously stirred for additional 15 min. The organic phase was separated and the aqueous solution was extracted twice with ether (10 ml each). The combined phase was washed with water and dried afterwards with sodium sulphate. Ether was removed with the aid of a rotational vaporizer providing 20 (0.235 g, 93.4%) as a colourless liquid.

^{1}H-NMR (80 MHz) δ: 1.25 (d, 3 H, C<u>H</u>$_3$, ^{3}J(H,H) = 8.7); 1.61-2.01 (m, 1 H, 6-C<u>H</u>); 2.23-2.65 (m, 3 H, 2-C<u>H</u>$_2$/5-C<u>H</u>); 3.62-3.91 (m, 2 H, C<u>H</u>$_2$OH); 3.95-4.16 (br, 1 H, O<u>H</u>); 5.45-5.79 (m, 2 H, 3-C<u>H</u>/4C<u>H</u>). ^{13}C-NMR (62.86 MHz) δ: 20.17 (q, CH_3 ^{1}J(C,H) = 127.8); 27.94 (t, C-2, ^{1}J(C,H) = 135.4); 32.09 (d, C-5, ^{1}J(C,H) = 131.6); 46.31 (d, C-6, ^{1}J(C,H) = 127.8); 51.92 (sep, C-l, ^{2}J(C,F) = 22.9); 61.41 (t, CH_2OH, ^{1}J(C,H) = 143.1); 119.60 (d, C-4, ^{1}J(C,H) = 164.0), 125.58 (q, CF_3, ^{1}J(C,F) = 284.2); 133.95 (q, C-3, ^{1}J(C,H) = 160.2). ^{19}F-NMR (75.26 MHz) δ: -66.51 (qu, CF_3/CF_3, ^{4}J(F,F) = 9,8); -68.76 (q, CF_3/CF_3, ^{4}J(F,F) 9.8).

IR 3410, 3037, 2984, 2925, 1446, 1374, 1346, 1263, 1203, 1160, 1125, 1090, 1061, 990, 964, 884, 711, 694, 608, 545, 458, 418. MS (m/z, %): <u>244 (M^+-H_2O, 37)</u>, 232(70), 217(17), 183(8), 175(100), 163(48), 155(49), 127(34), 91(13), 65(23), 51(17). (PCI) <u>245((M^+-H_2O+H,100)</u>, 233(57), 223(10), 195(7), 175(5).

2-Methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-1-carbaldehydeoxime (17)

To a mixture of hydroxylamine hydrochloride (0.17 g, 2.5 mmol) and pyridine (0.3 ml) in dry ethanol (0.6 ml) 11 (0.52 g, 2 mmol) was added, (the temperature should not exceed 45°C). Stirring was maintained at 20°C (12h). Then the ethanol was evaporated i. vac. to dryness. The residue was extracted with DCM. The organic phase was washed with 3N HCl (10 mL), with water, with sat. $NaHCO_3$ solution, again with water and finally with brine. After drying with Na_2SO_4, filtration and evaporation to dryness, a yellow oil was obtained. Yield: 0.5 g (90.9%). ^{1}H-NM δ: 0.95 (d, 3H, J = 6.8, CH_3); 2.45 (2d, 2H, J = 16.9, CH_2); 2.54 (m, 1H, <u>C</u>H-CH_3); 2.24 (m, 1H, <u>C</u>H-CH=NOH); 5.57 (m, 2H, CH=CH); 7.36, 7.38 (d, 1H, <u>C</u>H=NOH, J = 8.47); 8.65 (s, 1H, NOH). ^{13}C-NMR δ: 18.77 (CH-<u>C</u>H_3); 25.71 (CH_2); 29.3 (<u>C</u>H-CH_3); 43.0 (<u>C</u>H-C=N); 51.0 (sept, J = 24.2, <u>C</u>$(CF_3)_2$); 119.3, 131.4 (<u>C</u>=C); 122.68, 125.53 (2q, 2 CF_3); 148.5 (C=NOH). ^{19}F-NMR (75.26 MHz) δ: -65.75 (q, J = 9.8, CF_3); -70.67 (q, J = 9.8, CF_3).

3,4-Epoxy-2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-1-carbaldehyde (18)

m-CPBA (70% are 0.7 g, 2.9 mmol) was added to a solution of 2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-1-carbaldehyde (11) (0.5 g, 1.9 mmol) in DCM (8 mL). After 5 h of stirring at ambient temperature, the reaction mixture is neutralized with a 1 M solution NaOH in water. The organic phase was separated, washed with water and dried with Na_2SO_4.

After filtration and evaporation under reduced pressure a beige solid was obtained. Yield: 0.4 g (75.3%). ^{1}H-NMR (200 MHz) δ: 1.12 (d, 3H, J = 7.3 Hz, CH_3); 2.0-2.6 (m, 4H, CH_2, C<u>H</u>-CH_3, C<u>H</u>-CHO); 3.1 (m, 1H, CH=CH); 3.2 (m, 1H, CH=CH); 9.7 (s, 1H, CHO).

2-Methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-acid chloride (19)

To a suspension of 15 (1.38 g, 5 mmol) in DCM (5 mL) DMF (0.54 mL) was added. The solution was cooled to 0°C and oxalyl chloride (0.5 mL, 5.75 mmol) was added. Stirring was continued at ambient temperature for 2 h. The solvent was removed i. vac. providing a yellow oil. Yield: 0.9 g (61.1%). The acid chloride was also obtained by reacting 15 with an excess of thionyl chloride. ^{1}H-NMR (200 MHz) δ: 1.26 (d, 3H, J = 6.8, CH_3); 2.59 (d, 1H); 2.63 (d, 1H); 2.58-2.65 (m, 1H); 2.87 (s, 1H); 3.24 (d, 1H, J = 11.0, CH(C=O)Cl,); 5.66 (m, 2H, CH=CH). ^{13}C-NMR (100.6 MHz) δ: 20.3 (CH_3); 27.1 (CH_2); 39.5 (CH); 52.7 (hept, <u>C</u>$(CF_3)_2$, J = 25.7); 60.3 (CH); 121.2 (CH); 124.4, 124.73 (2q, J = 286.8, 2x CF_3,); 131.6 (CH); 173.2 ((C=O)Cl). ^{19}F-NMR (235.36 MHz) δ: -64.7. (q, J = 11.3, CF_3); -70.1 (q, J = 11.0, CF_3).

2-Methyl-6,6-bis(trifluoromethyl)cyclohex-3-ene-acid bromide (20)

N-Bromosuccinimide (0.82 g, 4.6 mmol) and AIBN (catalytic amounts) were added to a solution of 11 (1.0 g, 3.8 mmol) in carbon tetrachloride (10 mL). The solution was kept at 100°C for 3h. After cooling, the solution was filtered and the solvent evaporated. The yellow liquid crystallizes on standing and was recrystallized from pentane. Yield: 0.54 g (38.9%).

^{13}C-NMR (50.3 MHz) δ: 20.11 (CH_3); 27.0 (CH_2); 31.12 (CH); 52.8 (sept, J = 25.7, <u>C</u>$(CF_3)_2$,); 65.0 (CH); 119.3, 131.6 (C=C); 124.7 (q, J = 285.5, 2 CF_3); 174.7 (C=OBr).

Methyl 3-[2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-enyl]-2-propenoate (21)

Trimethylphosphonoacetate (0.35 mL, 2 mmol) was added to a solution of NaH (0.05 g, 2 mmol) in THF (3 mL) followed by 11 (0.4 g, 1.5 mmol) in THF (3 mL). The mixture was refluxed for several h, quenched with ice/water and extracted with ether. The organic phase was dried with Na_2SO_4. After filtration and evaporation to dryness an orange oil was obtained. Yield: 0.35 g (72%). Yield: 2.9 g, (52.6%). ^{1}H-NMR δ: 0.90 (d, 3H, J = 6.5, CH_3); 2.34 (m , 4H, CH_2, C<u>H</u>-CH_3,C_6<u>H</u>); 3.68 (s, 3H, CH_3, OCH_3); 5.55 (m, 2H, CH=CH); 5.84 (d, 1H, C<u>H</u>COOCH_3 (E), $^3J_{vin}$ = 15.5); 6.85 (dd, 1H, CH-C<u>H</u>=CH (E), $^3J_{vin}$ = 14.1, J_{all} = 11.5). ^{13}C-NMR δ: 20.54 (CH-<u>C</u>H_3); 27.28 (CH_2); 31.51 (<u>CH</u>-CH_3); 47.36 (<u>CH</u>-C=C); 52.04 (COO<u>C</u>H_3); 53.18 (sept, J = 24.0, <u>C</u>$(CF_3)_2$); 120.80, 132.84 (C=C); 126.15 (C=<u>C</u>(=O)OCH_3); 145.29 (<u>C</u>=C(=O)OCH_3). ^{19}F-NMR (235.3 MHz) δ: -65.55 (q, J_{FF} = 8.8, CF_3); -70.2 (q, J_{FF} = 8.8, CF_3).

3-[(2-Methyl-6.6-bis(trifluoromethyl)cyclohex-3-enyl)]-2-propenoic acid (22)

A mixture of 21 (0.33 g, 1 mmol) and K_2CO_3 (0.3 g, 2 mmol) in methanol / water (10:1, 11 mL) was stirred at 45°C for 5 h. Then the solution was quenched with ice and neutralized with dil. HCl. After extraction with ether, the organic phase was dried with Na_2SO_4. After evaporating the i. vac., a slightly orange oil was obtained. Yield: 0.25 g (79.3%).

^{1}H-NMR (300 MHz) δ: 0.92 (d, 3H, J = 6.52, CH_3); 2.2-2.5 (m, 4H, $CHCH_3$, CH, CH_2) ; 5.57 (m, 2H, CH=CH); 5.86 (d, 1H, J = 15.55, CH=CH); 6.9 (m, 1H, CH=CH). ^{13}C-NMR (75.47 MHz) δ: 19.14 (CH_3); 28.35 (CH_2); 30.07 (<u>C</u>HCH_3); 45.96 (<u>C</u>H); 51.82 (sept, J = 24.15, <u>C</u>$(CF_3)_2$); 119.45 (CH=CH); 124.33, 123.71 (2 q, J = 287.5, 2x CF_3); 124.61 (CH=CH); 131.38 (CH=CH); 146.4 (CH=CH), 170.1 (COOH).

3,4-Epoxy-2-methyl-6,6-bis(trifluoromethyl)cyclohexan-1-carboxylate (23)

A buffer solution of NaH_2PO_4 (0.04 g, 0.25 mmol) in water (0.4 ml) is added to 18 (0.3 g, 1.1 mmol) dissolved in acetonitrile (1 ml). This mixture is added to a solution of hydrogen peroxide (30%, 0.1 ml, 1.14 mmol). The unit is cooled to 10°C and a solution of $NaClO_2$ (80%, 0.14 g, 1.5 mmol) in water (1.3 mL) was added dropwise. After 3 h stirring, the mixture was treated at 20°C with Na_2SO_3 to destroy HOCl and H_2O_2 which remained in excess. After neutralisation with 10% of hydrochloric acid, the mixture is extracted with ether. The organic phase wws separated, dried with sodium sulfate, filtered and evaporated to dryness. Beige solid (0.2 g, 63%).

^{1}H-NMR (200 MHz, DMSO) δ: 1.12 (d, 3H, <u>C</u>H_3-CH, ^{3}J = 6.1); 2.20 (d, 1H , C<u>H</u>$_2$, J = 16.6); 2.50 (2d (superimpose), 2H, <u>CH</u>-COOH, <u>CH</u>-CH_3); 2.63 (dd, 1H, CH_2 , J = 16.6); 5.7); 13.18 (s, br, 1H COOH) ^{13}C-NMR (100 MHz, DMSO) δ: 40.8 (several signals, superimposed by DMSO)°; 49.9 (oxirane C); 51.31 (<u>CH</u>$(CF_3)_2$); 56.7 (oxirane C); 125.0 (q, CF_3, J = 283.2); 125.2 (q, CF_3, J = 285.3); 171.3 (<u>CO</u>OH). ^{19}F-NMR (235.36 MHz, DMSO): δ: -63.8 (q, J = 11.1); -68.9 (q, J = 11.0).

Ethyl- (24) and Methyl-(2E/2Z)-3-[2',2'-bis(trifluoromethyl)-6'-methylcyclohex-4'-enyl]-prop-2-enoat (24a)

24: In an Argon protected atmosphere 1.l g (6.89 mmol) 2-trimethylsilyl acetic acid ethylester, dissolved in THF (10 mL), were cooled to -75°C. Then an equivalent lithiumdiisopropyl amide suspended in THF was injected at -75°C and stirred for 15 min. After dropwise adding of 1.28 g (4.92 mmol) 11, dissolved in THF, (5 mL) and stirring at -75°C (3 h), then warming to -35°C (1 h) while stirring, the clear solution turns slowly yellowish. After warming to about -10°C, a saturated solution of NH_4Cl (5 mL) was added. The mixture was extracted three times with ether (20 mL each), washed with water and dried with sodium sulfate. The solvents were removed with a rotating evaporator providing a red-brown oil, which was purified by column chromatography (eluent petrol ether : chloroform 4:1. The isomers formed could not be separated. Total yield 1.54 g (4.66 mmol, 94.8%); the two isomers E and Z were formed in a 1.4 ratio. bp 89,198C/10^{-2}.

^{1}H-NMR δ: 0.95 (d, 3 H, C<u>H</u>, ^{3}J(H,H) = 7.0); 1.19 (t, 3 H, OCH_2C<u>H</u>$_3$, ^{3}J(H,H) = 7.5); 2.15-2.24 (m, 1 H, 5-C<u>H</u>); 2.34-2.42 (m, 1 H, 6-C<u>H</u>); 2.41-

2.45 (m, 2 H, 2-C$\underline{H_2}$); 4,08 (qu, 2 H, OC$\underline{H_2}$CH$_3$, ^{3}J(H,H) = 7.5); 5.48- 5.61 (m, 3C$\underline{H}$/4C$\underline{H}$); 5.83 (d, 1 H, 8-C$\underline{H}$(E), ^{3}J(H,H) = 15.6); 5.92 (d, 1 H, 8-C$\underline{H}$ (Z), ^{3}J(H,H) = 11.5); 6.18 (t, 1 H, 7-C$\underline{H}$ (Z), ^{3}J(H,H)vin = 11.5, ^{3}J(H,H)all = 11,5 Hz); 6.85 (t, 1 H, 7-C$\underline{H}$ (E), ^{3}J(H,H) vin = 15.6 Hz, ^{3}J(H,H) all = 11.0). ^{13}C-NMR (62,86 MHz) δ: 13.15 (q, CH$_2$C$\underline{H}$$_3$, ^{1}J(CH) = 128.0); 18.90 (q, CH$_3$ (2), ^{1}J(C,H) = 126.5); 20.01 (qu, CH$_3$ (E), ^{1}J(C,H) = ?); 26.76 (1, C-2, ^{1}J(C,H) = 125.1); 31.76 (d, C-6, ^{1}J(C,H) = 128.0 Hz); 40.46 (d, C-5, ^{1}J(C,H) = 137.0); 52.51 (sep, C-l, ^{2}J(C,F) = 23.8); 59.96 (t, C$\underline{H_2}$CH$_3$ (Z), ^{1}J(C,H) = 147.4); 60.41 (t, (E), ^{1}J(C,H) = 147.4); 120.07 (d, C-4 (Z), ^{1}J(C,H) = 162.3); 120.29 (d , C-4 (E)); 123.44 (d, C-8 (E)); 123.70 (d, C-8 (Z), ^{1}J(C,H) = 165.2); 132.38 (d, C-3 (E)); 132.64 (d, C-3 (Z), ^{1}J(C,H) = 159.3); 144.35 (d, C-7, ^{1}J(C,H) = 159.1); 165.56 (s, C-9). ^{19}F-NMR (75,26 MHz) δ: -64.42 (qu, CF$_3$ (Z), ^{4}J(F,F) = 9.8); -65.31 (qu, CF$_3$ (E), ^{4}J(F,F) = 9.8); -70.04 (q, CF$_3$ (E), ^{4}J(F,F) = 9.8); -70.30 (q, CF$_3$ (Z), ^{4}J(F,F) = 9.8. IR 2977, 1722 (C=O), 1445, 1374, 1265, 1218, 1192, 1124, 1098, 1039, 858, 697, 630, 540, 432. MS (m/z, %) (Z) 330 (M$^+$, 50), 315(16), 301(19), 285(26), 257(32), 241(10), 215(8), 187(11), 145(9), 127(8), 91(10), 68(100), 55(28). (E- isomer) 330 (M+, 8), 315(1), 301(2), 285(10), 257(30), 235(5), 217(3), 187(9), 161(11), 101(15), 73(8), 68(100), 55(49).

24a: Trimethylphosphonoacetic acid methylester (0.35 ml, 2 mmol) is added dropwise to a suspention of NaH (0.05 g, 2 mmol) in THF (3 mL). A solution of 11 (0.4 g, 1.5 mmol) in THF (3 mL) was added dropwise and the mixture was refluxed for 3 h. The content was then crashed on ice, extracted three times with ether the organic phase was dried with Na_2SO_4. After filtration and evaporation 24a (0.35 g, 72%) was provided as an orange oil. E,Z isomers could not be separated.

^{1}H-NMR δ: 0.90 (d, 3H, CH$_3$, J = 6.44); 2.34 (m, 4H, CH$_2$, C$\underline{H}$-CH$_3$,C$_6\underline{H}$); 3.68 (s, 3H, CH$_3$, COOCH$_3$); 5.55 (m, 2H, cyclohexene CH=CH); 5.84 (d, 1H, $\underline{CH}$COOCH$_3$ (E), ^{3}J$_{vin}$ = 15.5); 6.85 (dd, 1H, CH-$\underline{CH}$=CH (E), ^{3}J$_{vin}$ = 14.07, J$_{all}$ = 11.5); ^{13}C-NMR δ: 20.54 (CH-$\underline{C}$H$_3$); 27.28 (CH$_2$); 31.51 ($\underline{CH}$-CH$_3$); 47.36 ($\underline{CH}$-C=C); 52.04 (COO$\underline{CH}$$_3$); 53.18 (hept, $\underline{C}$(CF$_3$)$_2$, ^{2}J = 24.03 Hz); 120.80, 132.84 (C=C, cyclohexene); 126.15 (C=$\underline{C}$(=O)OCH$_3$); 145.29 ($\underline{C}$=C(=O)OCH$_3$); 126.76, 125.14 (2q, 2 CF$_3$, ^{1}J = 287.1), ^{1}J = 284.73); 166.11 ($\underline{C}$OOCH$_3$). ^{19}F-NMR: (235.3 MHz) δ: -65.55 (q, ^{4}J$_{F-F}$ = 8.6); -70.2 (q, ^{4}J$_{F-F}$ = 9.0).

3-Methyl-5-(2-methyl-6,6-bis(trifluoromethyl)cyclohex-3-enyl)-penta-2,4-dienal (25)

Freshly prepared BrCH=C(CH$_3$)C=CHOCH$_3$ (0.345 g, 1.94 mmol.) dissolved in dry ether, was cooled to -70°C under Argon atmosphere followed by slow injecting (syringe) tert.-butyllithium (1.7 M) to the solution, which was stirred at -70°C (1.5 h). Aldehyde 11 (0.7 eq.) dissolved in 1.5 mL of dry ether was slowly added at -70°C with stirring (1 h) under Argon and then warmed to 0°C (3 h). The solution was cooled to -40°C, quenched *slowly* with 10 mL 1N HCl and stirred at 20°C (12 h). The organic phase was decanted and the product was extracted with 3x10 mL ether. The combined organic phases were washed with 3x10 mL water, dried over $MgSO_4$ and evaporated to dryness i. vac. Yield 0.8 g of a yellow oil. The resulting oil was purified by liquid chromatography (glas column, 35 g silica gel, diameter = 1.5 cm) providing 0.2 g of a mixture of products, which could not be purified further (part of the product was lost on the column). Recrystallization failed as the product is not stable at 20°C. Purification step including ^{1}H NMR and ^{13}C NMR taken a few hours after GCMS data.

^{1}H NMR major isomer, 80%; [minor isomer, 20%] δ: 0.99d, H-11, 3H, J = 7.0 [1.02d, H-11, 3H, d, J = 6.5]. 2,29d, H-10, 3H, J = 1.0[2.31d, H-10,3H, J = 1.0]; 2.39-2.61m, H-1,2,5, 4H[identical]; 5.60-5.63m, H-4,3, 1H [identical]; 5.67-5.70m, H-3,4, 1H [identical]; 5.95dd, H-6,7,8, 1H, J = 8.0, J = 1.0 [5.91d, H-6,7,8, J = 8.0]; 6.24br,d, H-6,7,8, 1H [6.10br,d, H-6,7,8, 1H, J = 7.5]; 6.26br,s, H-6,7,8, 1H [6.29br,s, H-6,7,8, 1H]; 10.14d, H-9, 1-H, J = 8.0 [10.16d, H-9, 1-H, J = 7.5]. ^{13}C NMR (Resolved with HMQC correlation, major isomer only)δ: 18.18 (C-11); 24.93 (C-10); 25.12 (C-5); 29.73 (C-2); 46.10 (C-1); 118.43 (C-3, 4); 127.76 (C-6, 7, 8); 130.70 (C-3, 4); 132.81 (C-6, 7, 8); 135.91 (C-6, 7, 8); 189.33 (C-9). MS 326 (M$^+$, 2); 308 (1); 258 (4); 243 (3); 230 (5); 211 (3); 189 (5); 161 (27); 145 (5); 141 (10); 133 (2); 127 (3); 115 (3); 95 (100); 68 (69); 53 (14); 41 (19); 39 (19).

3,7-Dimethyl-9-[2-methyl-6,6-bis(trifluoromethyl) cyclohex-3-enyl]-nona-2,4,6,8-tetraenal (26)

This procedure is identical with the preparation of 25. Ratio of all reactants, solvent were based on Br(CH=C(CH$_3$)C=CH)$_2$OCH$_3$ (0.33 g°; 1.43 mmol). The product was purified by liquid chromatography (glass column, 25 g silcal gel, diameter = 1.5 cm; solvent: S1) 300 mL CH_2Cl_2; S2) CH_2Cl_2 / Pentane gradient S3); 150 mL pentane; S4) pentane / AcOEt: 90/10) Off column, the following crops were obtained:

S1): Product A (150 mg); S4): Product C (260 mg); both fractions were mixtures of non identified products

S3): Product B (140 mg) was according to ^{1}H- and ^{13}C-NMR spectra pure. However, interpretation of the resulting spectra was difficult and is therefore tentative. Note: Product B was stored at -30°C. Degradiation or isomerisation occurred after a few days at 20°C.

^{1}H NMR δ: 9.46 (s, 1H, CHO) ; 6.90 (d, J = 8.0); 6.69 (d, J = 8.2); 5.93 (d, J = 8.8); 5.56-5.66 (m, 2H); 5.25 (d, J = 8.5); 2.82 (br. signal, CHCH$_3$); 2.61 (d, 1H, J = 19.5, CH$_2$); 2.41 (d, 1H, J = 19.5; CH$_2$); 2.03 (d, 1H, J = 9.8); 1.95 (s, 3H, CH$_3$ of the side chain); 1.90 (s, 3H, CH$_3$ of the side chain); 1.84 (d, 3H, J = 3.8). ^{13}C NMR δ: 8.59; 11.44; 21.37; 26.55; 28.03; 46.81; 51.45; 64.42; 117.72. MS (direct inlet): 396 (M$^+$ = 392.38, 8), 231 (24), 165 (33), 147 (9), 137 (43), 122 (100), 109 (76), 95 (93), 77 (16), 67 (22), 55 (3), 43 (51).

Ethyl-(2E/2Z)-3-[2'.2'-bis(trifluoromethyl)-6'-methylcyclohex-5'-enyl]-prop-2-enoate (27)

The preparation was carried out as described for 24. Analogously 2-trimethylsilylaceticacid ethylester (0.025 g, 0.15 mmol) was reacted with 10 (0.02 g, 0.75 mmol) providing two isomers of 31, separated and analysed by GC/MS spectroscopy. They were

tentatively assigned to E and Z (ratio 2:1) as already reported for 24, 24a (see also 28).

MS (m/z, %) Isomer I: 370 (27, M^+), 315 (17), 287 (46), 285 (48), 257 (80) 256 (100), 254 (55), 217 (10), 215 (13), 187 (49), 145 (20), 127 (30), 77 (33), 55 (50); Isomer II: 370 (12, M^+), 315 (3), 287 (3), 285 (6), 257 (24), 256 (23), 254 (100), 217 (2), 215 (1), 187 (9), 145 (3), 127 (54), 77 (23), 55 (13).

Ethyl-(2E,4E,4Z)-5-[6',6'-bis(trifluoromethyl)-2'-metylcyclohex-1-enyl]-3-methyl-penta-2,4-dienoate (28)

To a solution of ethyl-3-methyl-4-(diethylphosphonato)-but-2-enoate (0.150 g, 0,57 mmol) in hexane (4 mL) under Argon n-butyllithium (0.356 mL, 0.57 mmol, 1.6 M solution) are injected and stirred at 0°C until a clear yellow solution (about 0.5 h) was formed. 10 (0.1 g, 0.385 mmol), dissolved in 1 mL hexane was dropped with stirring at 22°C (3h). By adding a mixture of ether (4 mL) and dil. HCl (2 mL) the reaction was stopped. The organic phase was isolated and analysed by GC/MS spectroscopy. The product mixture contained two new substances (about 7 and 8%), which were tentatively assigned by 2 independent mass spectra which provided identical fragmentation pattern with M+ but significant different intensities for two isomers.

MS-Spectrum (m/z, %) Isomer I: 370(51, M^+), 325(16), 283(13), 256(13), 246(39), 218(100), 162(96), 134(85), 111(18), 81(91). Isomer II: 370(100, M^+), 325(56), 283(50), 256(39), 246(31), 218(49), 162(41), 134(27), 111(32), 81(53).

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