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Di-2,2,2-trifluoro-1-(9-anthryl)ethyl fumarate, an easy starting point for the enantioselective preparation of *trans*-cyclohexene-4,5-dicarboxylate derivatives by Diels–Alder reaction

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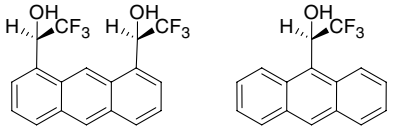
Abstract—Di-2,2,2-trifluoro-1-(9-anthryl)ethyl fumarate has been synthesized from fumaric acid and enantiopure Pirkle alcohol. The Diels–Alder reaction with different dienes employing different reaction conditions was assayed, with high diastereomeric excesses obtained. The structure and geometry of the cycloadducts was analyzed by NMR, molecular mechanics and X-ray diffraction. Hydrolysis made it possible to obtain the enantioenriched *trans*-cyclohexene-4,5-dicarboxylate derivatives and allow us to recover chiral auxiliary.

1. Introduction

Chiral solvating agents (CSAs) are widely used in NMR spectroscopy to determine enantiomeric purity in a fast and simple way. In recent years, a large number of different CSAs have been developed, achieving excellent results in the enantiodiscrimination of a variety of organic compounds.[1] CSAs have the ability to undergo specific non-convalent interactions with each enantiomer, forming differentiable diastereomeric complexes. This property has made it possible for them to be applied as chiral selectors in other analytical techniques, such as HLPC and gas chromatography with good levels in enantioseparation.[2]

However, little is known about the application of CSAs as chiral auxiliaries in asymmetric reactions, one of the most important subjects in modern organic synthesis.[3] Since the different chiral characters governing the enantiorecognition are of a similar nature to the interactions that are responsible for stereoselective synthesis, we expect good chiral induction capacity from CSA derivatives. Especially interesting would be the case where the CSA would induce stereoselectivity, and at the same time could be used for the determination of the enantiomeric purity of the product.

As has been shown in previous papers,[4] several arylalkylcarbinols, effective CSAs (Fig. 1), can be used as chiral templates in the catalyzed Diels–Alder reaction of acrylate with cyclopentadiene, obtaining satisfactory enantiomeric relations.[5] Recently, the synthesis of a chiral, macrocyclic dienophile based on a new, highly active CSA, α,α′-bis(trifluoromethyl)-1,8-anthracenedimethanol **1**, and fumaric acid has been reported.[6] Cycloaddition of cyclopentadiene leads to one predominant diastereosiomer (de = 80%). This result is especially interesting as there are very few studies in which an asymmetric Diels–Alder reaction of a chiral



1 **2**

Figure 1. α,α′-Bis(trifluoromethyl)-1,8-anthracenedimethanol **1** and 2,2,2-trifluoro-1-(9-anthryl)ethanol **2**.

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disubstituted fumaric chain occurs.[7] Nevertheless, the synthesis of CSA **1** occurs through a five-step route with 12% total yield, which makes it difficult to further generalize its application. In contrast, 2,2,2-trifluoro-1-(9-anthryl)ethanol **2** (Pirkle's alcohol), a widely used chiral solvating agent, is commercially available.

Herein we report the application of 2,2,2-trifluoro-1-(9-anthryl)ethanol **2** as a chiral auxiliary for the synthesis of chiral *trans*-cyclohexene-4,5-dicarboxylate derivatives, attaching two molecules of **2** to fumaric acid and studying cycloaddition with different dienes.

2. Results and discussion

The overall process takes place in three steps, as outlined in Figure 2 for the case of cyclopentadiene. First, the chiral dienophile is synthesized by esterification of commercially available fumaryl chloride and enantiopure 2,2,2-trifluoro-1-(9-anthryl)ethanol **2**. Next, the Diels–Alder reaction takes place, generating the cycloadduct with up to four new stereogenic centres. The final enantioenriched *trans*-cyclohexene-4,5-dicarboxylate derivate was obtained by the hydrolysis of the cycloadduct, at the same time making it possible to recover the chiral auxiliary.

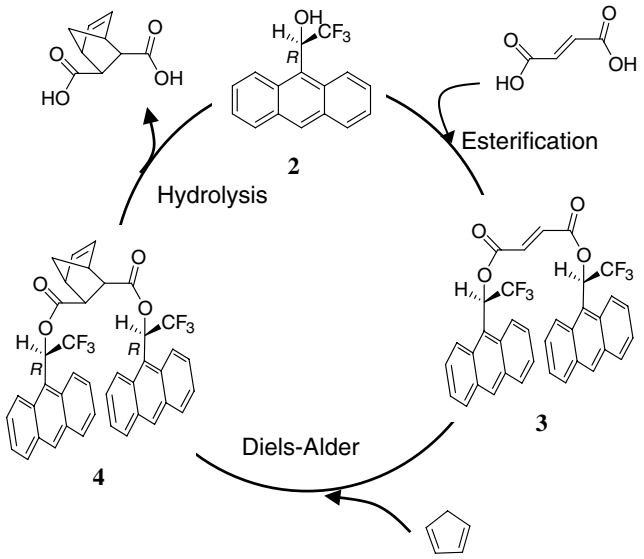

Figure 2. Asymmetric synthesis of *trans*-cyclohexene-1,2-carboxylic derivatives with 2,2,2-trifluoro-1-(9-anthryl)ethanol **2** as a chiral auxiliary.

2.1. Synthesis of the chiral dienophile

Di[1-(9-anthryl)-2,2,2-trifluoroethyl] fumarate **3** was easily prepared in both enantiomeric forms, (*RR*) and (*SS*), via a one step procedure from fumaryl dichloride and enantiopure alcohol **2**[8] in an 80% yield. Two approaches to dienophile **3** are possible: from either the *re–re* face or from the *si–si* face, leading to different diastereoisomers. C_2 symmetry makes both sides of the faces equivalent, leading to the same isomers.

A structural study of **3** was carried out by NMR and molecular mechanics. Exchange peaks (negative) were observed between the proton pairs H_1/H_8, H_2/H_7, H_3/H_6 and H_4/H_5 in the 2D NOESY/EXSY spectrum, which gives evidence of the existence of slow rotation around the sp^2–sp^3 bonds. A sharp singlet at 7.12 ppm in the ^1H NMR spectrum corresponds to the magnetically equivalent olefinic protons of **3**. The 2D IFSERF NMR experiment,[9] enabled us to measure the coupling constant between the equivalent protons H_{13}'s (15.9 Hz), corresponding to a *trans* position.

Molecular mechanics calculations (MacroModel package[10] with a MM3* force field[11]) using genetic algorithms[12] afforded four conformations of minimal energy for (*R*,*R*)-**3**, as depicted in Figure 3. **3A** is the predominant, most stable structure and it can be seen that the *si–si* face is clearly more accessible than the *re–re* face. The same happens with structure **3B**. In contrast, the minor conformations **3C** and **3D** allow attack from both faces. NOE experiments showed a major cross relaxation between the olefinic protons H_{13} and protons H_{11}, H_1 and H_8, which is coherent with geometries **3A** and **3B**. This analysis allows us to predict that *R*,*R*-**3** is predisposed for attack at the *si–si* face.

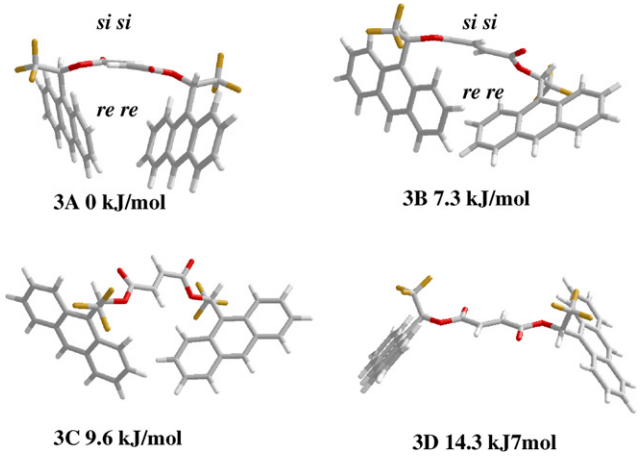

Figure 3. Lowest energy conformations of di-2,2,2-trifluoro-1-(9-anthryl)-ethylfumarate **3** with their relative energy values, obtained by molecular mechanics calculations.

2.2. Asymmetric Diels–Alder reaction

Diels–Alder reaction of *R*,*R*-**3** was first performed with cyclopentadiene, to give cycloadduct **4a**. Different catalysts and solvents were assayed (Table 1). Working at −78 °C, the best result was obtained using $EtAlCl_2$ as a catalyst in dry dichloromethane, obtaining a diastereomeric ratio of 80%. Diastereoselectivity was measured by integration of the olefinic signals in the ^1H NMR spectrum of the crude diastereomeric mixture, and corresponds to the enantioselectivity of the final product.

In the absence of a catalyst, the diastereoselectivity dropped to 23% de and also the use of Lewis acids $TiCl_4$ and BF_3 led to a lower facial selectivity. Furthermore, the use of more polar solvents seems to prevent the forma-

Table 1. Yield and diastereomeric excess obtained from the cycloaddition of cyclopentadiene to dienophile **3** at −78 °C employing different reaction conditions

Catalyst	Solvent	Yield (%)	de[a] (%)
$EtAlCl_2$	CH_2Cl_2	100	80
$EtAlCl_2$	Toluene	50	25
$EtAlCl_2$	THF	75	29
$EtAlCl_2$	Ether	70	42
$EtAlCl_2$	Acetonitrile	80	44
$TiCl_4$	CH_2Cl_2	73	23
$BF_3{\cdot}OEt_2$	CH_2Cl_2	77	31
—	CH_2Cl_2	100	23

[a] In all cases, the same major diastereoisomer is obtained.

tion of the complex dienophile–$EtAlCl_2$, also resulting in lower diastereomeric excesses.

To see the effect of the reaction temperature, the cycloaddition was carried out in a range of −100 to 50 °C. We observed that if the temperature was increased, the reaction was faster, but with a lower diastereoselectivity: a low temperature favoured the formation of the activated complex between dienophile **3** and Lewis acid; at higher temperatures the reaction took place directly between the diene and dienophile, without the implication of the Lewis acid.

After having optimized the reaction conditions with cyclopentadiene, other dienes were tested, giving highly satisfactory results, as summarized in Table 2. In each case, diastereomeric excess, obtained by the integration of signals in the ^1H NMR spectrum, correspond to the enantiomeric excess of the final product. If the diastereomeric cycloadduct is purified by chromatography or crystallization, in all cases an ee of 100% can be achieved.

A complete NMR study of major cycloadducts **4a**–**4d** was performed after purification by column chromatography. The ^1H NMR spectrum of **4b** is shown in Figure 4. The signals of the anthracene ring at the *exo*-position can be differentiated from that at the *endo*-position. In all cases, the NOE effect was observed between the protons of the central cyclohexene ring and some protons of the chiral auxiliary, showing that they are close in space. This led us to conclude that the geometry of the cycloadducts is not linear, but folded enabling π-interaction between the anthracene rings.

Table 2. Diels–Alder reaction between (*R*,*R*)-**3** and several dienes

Cycloadduct	Diene	Conditions	Yield (%)	de (%)
4a		−78 °C, 1 h, 1 equiv $EtAlCl_2$	100	82
4b		−78 °C, 3 h, 1 equiv $EtAlCl_2$	80	95
4c		−78 °C, 2 h, 1 equiv $EtAlCl_2$	90	90
4d		−78 °C, 1 h, 1 equiv $EtAlCl_2$	95	90

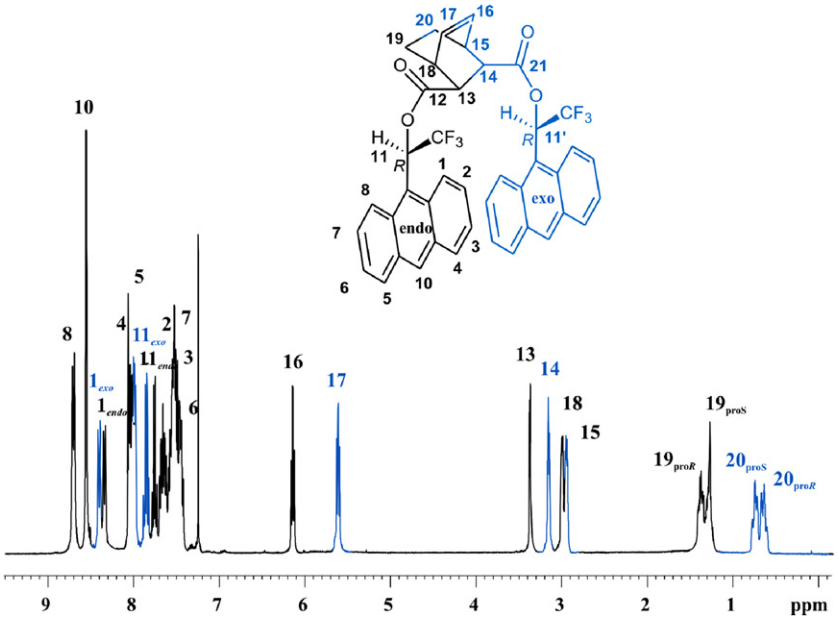

Figure 4. ^1H NMR spectrum at 500 MHz of cycloadduct **4b**.

The crystal structure of the 1:1 adduct of **4d** and chloroform was studied by X-ray diffraction. Compound **4d** appears as approximately symmetric around the C2 axis. Stacks of parallel anthracene molecules can be observed, providing stabilization by π-interactions. The absolute configuration of the new stereogenic centres was (*S*,*S*), if (*R*)-**2** was used as the chiral auxiliary, and this corresponds to reaction at the *si–si* face of the diene. These experimental results validated the previous hypothesis based on theoretical calculations (Fig. 5).

A very similar geometry was obtained for **4d** by molecular mechanics calculations, performing a conformational search with genetic algorithms. The obtained minimal energy conformation was also symmetric, but the distance between anthracene rings is smaller. NOE measurements in solution agree with the structure obtained by calculations and are different to the X-ray structure.

2.3. Hydrolysis and determination of the absolute configuration

The last step of the asymmetric reaction cycle was hydrolysis of the fumaryl adduct. For all cycloadducts **4a–d**, three different processes could be carried out: (i) the hydrolysis of the ester in basic aqueous solution generated, after acidification, the dicarboxylic acids; (ii) the methanolysis generated the methyl esters and (iii) the reductive hydrolysis by $LiAlH_4$[4] generated the corresponding primary diol. In all cases, it was possible to recover the chiral auxiliary quantitatively.

Especially interesting was the case of reduction with $LiAlH_4$ (Fig. 6). 2,2,2-Trifluoro-1-(9-anthryl)ethanol **2** is highly effective as a chiral solvating agent for alcohols and amines.[13] As we have tested with cyclopentadiene as the diene, the ^1H NMR spectrum of the crude mixture after the reduction reaction directly enables the determination of the enantiomeric excess. Enantiopure alcohol **2** forms diastereomeric complexes with the dialcohol product that can be differentiated with NMR. This means that in this kind of reaction it is possible to use a single chiral receptor for the asymmetric induction and for the measurement of the enantiomerical purity of the final product.

The absolute configuration of the final products was determined by comparison of the specific rotation with the literature value.[14–17] In all cases, the configuration obtained reveals a *si–si* face approach.

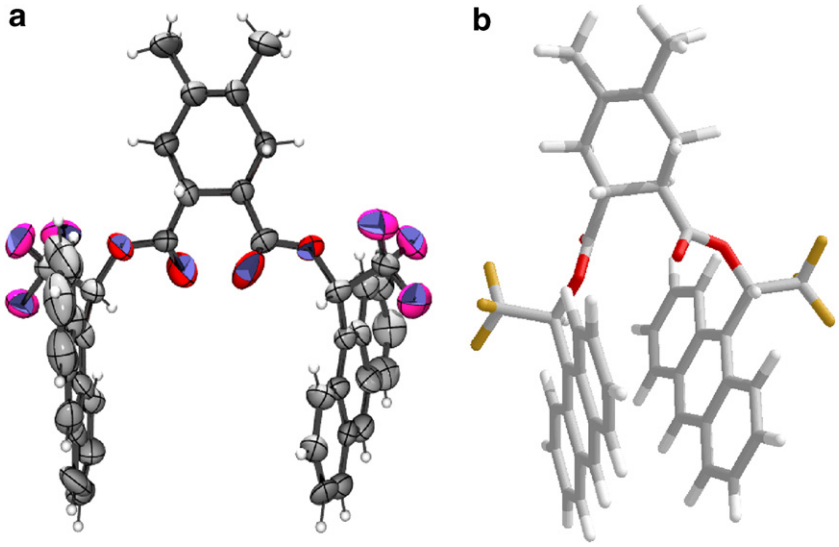

Figure 5. Geometry of cycloadduct **4d** obtained from (a) X-ray diffraction and (b) molecular mechanics calculations.

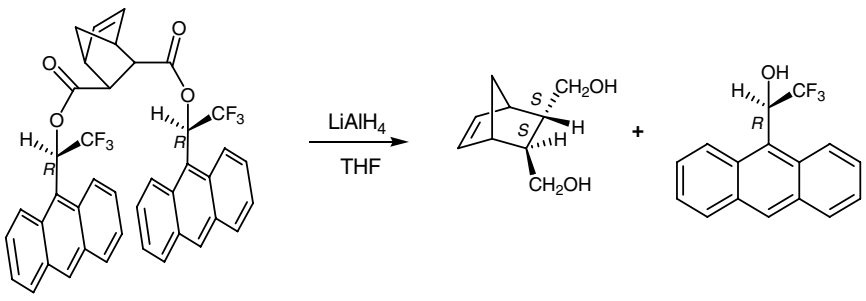

Figure 6. Reductive hydrolysis of adduct **4a**.

3. Conclusion

It has been shown that the easily available *Pirkles* alcohol can be used in a Diels–Alder reaction to obtain enantiopure *trans*-cyclohexene-4,5-dicarboxylate derivatives. The overall yield of the process is 80–90% with high enantiomeric relations. Moreover, the chiral auxiliary is recovered quantitatively, making it possible for it to be scaled-up and applied generally.

4. Experimental

4.1. Theoretical calculations

The conformational search was carried out with the genetic algorithm GACK, which can be downloaded from the Cambridge Chemistry Department www server at URL: http://www.ch.cam.ac.uk/. This program works in tandem with MacroModel, which handles the structural minimization using, in our case, the MM3* force field. The poolsize and the number of generations are important parameters. These were both set to 32, obtaining 1240 final structures, of which 382 were different. The cross over rate was set to 1.0 and the mutation rate per molecule to 0.4. Selection and replacement temperature were 10,000 K and 1000 K, respectively. The conformational search was repeated five times with different input structures, obtaining equivalent results in all cases.

NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H. The temperature was controlled to 0.1 °C. The NMR signals were identified completely with the aid of several 1D (NOE) and 2D (COSY, NOESY, HMQC and HMB) spectra.

4.2. (*R*,*R*)-Di[1-(9-anthryl)-2,2,2-trifluoroethyl] fumarate 3

A solution of (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol (2.6 g, 9.42 mmol), DMAP (574 mg, 4.71 mmol) and freshly distilled Et_3N (1.31 ml, 9.42 mmol) in dry CH_2Cl_2 (250 ml) was stirred under argon in a 500 ml round-bottomed flask, and fumaryl chloride (0.51 ml, 4.71 mmol) was added dropwise. After 1 h, the reaction mixture was successively washed with 200 ml portions of aqueous HCl (10%), a saturated bicarbonate solution and a saturated sodium chloride solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography over 150 mg of silica gel (CH_2Cl_2:hexane 1:3) to provide 2.42 g of **3** (81%) as yellow crystals: mp 125–127 °C; $[\alpha]_D^{20} = -80$ (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3054–2986 (OH), 2305 (C=H), 1740 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 1H, H_{13}), 7.51 (dd, $J = 7.3$ Hz, $J = 7.5$ Hz, 1H, H_6), 7.55 (dd, $J = 7.3$ Hz, $J = 7.5$ Hz, 1H, H_3), 7.60 (dd, $J = 8.9$ Hz, $J = 7.3$ Hz, 1H, H_7), 7.69 (dd, $J = 9.0$ Hz, $J = 7.3$ Hz, 1H, H_2), 7.92 (q, $J = 7.8$, 1H, H_{11}), 8.04 (d, $J = 8.5$ Hz, 1H, H_5), 8.07 (d, $J = 8.4$ Hz, 1H, H_4), 8.39 (d, $J = 9.0$ Hz, 1H, H_1), 8.59 (s, 1H, H_{10}), 8.69 (d, $J = 8.9$ Hz, 1H, H_8). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.0 (C_{11}), 120.1 (C_9), 122.3 (C_1), 124.1 (CF_3), 125.1 (C_3 and C_6), 125.8 (C_8), 126.8 (C_7), 128.0 (C_2), 129.4 (C_5), 129.6 (C_4), 130.7 (C_{1a}), 131.0 (C_{4a}), 131.5 (C_{5a}), 131.6 (C_{10}), 131.7 (C_{8a}), 133.7 (C_{13}), 162.5 (C_{12}). HRMS (ESI$^-$) *m*/*z* 632.1409 (M^-, δ −1.2 ppm).

4.3. General procedure for asymmetric Diels–Alder reaction of fumarate 3

The reaction with cyclopentadiene and $EtAlCl_2$ is typical. A solution of $EtAlCl_2$ (1 M in hexane, 3.16 ml, 3.16 mmol) was added to a solution of fumarate **3** (1 g, 1.58 mmol) in dry CH_2Cl_2 at −78 °C followed by freshly distilled cyclopentadiene (529 μl, 7.91 mmol). The resulting mixture was stirred for 60 min and then filtered over SiO_2. To obtain the major diastereoisomer, the crude material was purified by flash column chromatography on 100 mg of silica gel (EtOAc/hexane 1:50).

4.4. Cycloadduct (11*R*,13*S*,14*S*,15*R*,18*S*,11′*R*)-4a

The above procedure provided 993 mg (85%) of **4a** as a white solid: mp 152–154 °C; $[\alpha]_D^{20} = -62$ (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 2303 (C=H), 1753 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, $J = 9.1$ Hz, 1H, $H_{19pro\,R}$), 1.36 (d, $J = 9.1$ Hz, 1H, $H_{19pro\,S}$), 2.94 (m, 2H, H_{14endo}, H_{15}), 3.30 (s, 1H, H_{18}), 3.67 (dd, $J = 4.5$ Hz, $J = 4.5$ Hz, 1H, H_{13exo}), 5.15 (dd, $J = 5$ Hz, $J = 2.8$ Hz, 1H, H_{17}), 6.00 (dd, $J = 5$ Hz, $J = 3$ Hz, 1H, H_{16}), 7.53 (m, 2H, H_{6endo}, H_{6exo}), 7.55 (m, 2H, H_{3endo}, H_{3exo}), 7.63 (m, 1H, H_{7endo}), 7.60 (m, 2H, H_{7exo}), 7.69 (m, 2H, H_{2exo}, H_{2endo}), 7.80 (q, $J = 7.8$ Hz, 1H, H_{11endo}), 7.87 (q, $J = 7.8$ Hz, 1H, H_{11exo}), 8.05 and 8.04 (d, $J = 8.5$ Hz, 2H, H_{5endo}, H_{5exo}), 8.08 (d, $J = 8.4$ Hz, 2H, H_{4endo}, H_{4exo}), 8.39 (d, $J = 9$ Hz, 1H, H_{1endo}), 8.41 (d, $J = 9$ Hz, 1H, H_{1exo}), 8.60 (s, 2H, H_{10endo}, H_{10exo}), 8.77 (d, $J = 8.9$ Hz, 1H, H_{8exo}), 8.79 (d, $J = 8.9$ Hz, 1H, H_{8endo}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.7 (C_{18}), 47.0 (C_{14endo}, C_{15}), 172.2 (C_{20}), 47.3 (C_{19}), 47.9 (C_{13exo}), 69.3 (C_{11exo}), 69.5 (C_{11endo}), 121.0, 120.9 (C_{9endo}, C_{9exo}), 122.4 (C_{1endo}, C_{1exo}), 124.3 (CF_3), 125.1 (C_{3endo}, C_{6endo}, C_{3exo}, C_{6exo}), 126.3, 126.2 (C_{8endo}, C_{8exo}), 126.5, 126.4 (C_{7endo}, C_{7exo}), 127.8 (C_{2endo}, C_{2exo}), 129.3 (C_{5endo}, C_{5exo}), 129.6, 129.5 (C_{4endo}, C_{4exo}), 130.6, 130.5 ($C_{1a\,endo}$, $C_{1a\,exo}$), 131.1, 131.0 ($C_{4a\,endo}$, $C_{4a\,exo}$), 131.1, 131.4 ($C_{5a\,endo}$, $C_{5a\,exo}$), 131.4 (C_{10endo}, C_{10exo}), 131.7, 131.6 ($C_{8a\,endo}$, $C_{8a\,exo}$), 134.6 (C_{17}), 137.3 (C_{16}), 171.0 (C_{12}). HRMS (ESI$^-$) *m*/*z* 698.1868 (M^-, δ −2.7 ppm).

4.5. Cycloadduct (11*R*,13*S*,14*S*,15*R*,18*S*,11′*R*)-4b

The above procedure provided 1.34 g (80%) of **4b** as white solid: mp 158–156 °C; $[\alpha]_D^{20} = -95$ (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3054–2985 (OH), 2359 (C=H), 1747–1712 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, $J_{5,6} = 8.5$ Hz, 2H, H_5), 1.36 (d, $J = 8.5$ Hz, 2H, H_5), 1.60 (d, $J = 8.5$ Hz, 2H, H_5), 1.84 (d, $J = 8.5$ Hz, 2H, H_5), 1.93 (t, $J = 8.5$ Hz, 2H, H_5), 2.51 (s broad, 1H, H_{18}), 4.91 (s broad, 1H, H_{17}), 7.45 (m, 2H, H_6), 7.52 (m, 2H), 7.55 (m, 2H, H_7), 7.65 (m, 2H, H_2), 7.78 (2 × q, $J_{11,F} = 7.8$ Hz, 2H, H_{11}), 8.02, 7.99 (d, $J = 8.5$ Hz, 2H, H_5), 8.05 (d, $J = 8.4$ Hz, 2H, H_4), 8.33, 8.18 (2 × d, $J = 9.0$ Hz, 2H, H_1), 8.54 (s, 2H, H_{10}), 8.69, 8.63 (2 × d, $J = 8.9$ Hz, 2H, H_8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (C_{20}), 23.8 (C_{19}), 31.9 (C_{15}), 32.0 (C_{18}), 45.4 (C_{13exo}), 45.9

(C_{14endo}), 70.0, 69.4 (C_{11}), 121.0 (C_9), 122.5 (C_1), 124.3 (CF_3), 125.0 (C_3, C_6), 126.2 (C_8), 126.4 (C_7), 127.8, 127.7 (C_{2endo}, C_{2exo}), 129.2 (C_5), 129.6, 129.5 (C_{4endo}, C_{4exo}), 130.5 (C_{1a}), 131.1 (C_{4a}), 131.4, 131.3 (C_{10endo}, C_{10exo}), 131.4 (C_{5a}), 131.7 (C_{8a}), 132.2 (C_{17}), 134.2 (C_{16}), 171.9 (C_{21}), 171.9 (C_{12}). (MALDI-TOF, *m*/*z*, %, THF-cca): 712.0 (M, 100), 713.0 (90), 714.0 (30).

4.6. Cycloadduct (11*R*,13*S*,14*S*,11′*R*)-4c

The above procedure provided 1.1 g (90%) of **4c** as yellow needles: mp 147–149 °C; $[\alpha]_D^{20} = -80$ (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 2304 (C═H), 1753 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (d, 1H, $J = 17$ Hz, H_{15proR}), 1.99 (d broad, 1H, $J = 17$ Hz, H_{18proR}), 2.27 (dd, 1H, $J = 17$ Hz, $J = 5$ Hz, H_{15proS}), 2.37 (d broad, 1H, $J = 17$ Hz, H_{18proS}), 3.19 (dt, $J = 10$ Hz, $J = 5.8$ Hz, 1H, H_{13exo}), 3.19 (dt, $J = 10$ Hz, $J = 5.8$ Hz, 1H, H_{14endo}), 7.49 (m, 2H, H_6, $H_{6'}$), 5.28 (s broad, 1H, H_{17}), 7.54 (m, 2H, H_3, $H_{3'}$), 7.55 (m, 2H, H_7, $H_{7'}$), 7.65 (m, 2H, H_2, $H_{2'}$), 7.76, 7.74 (2 × q, $J_{11,F} = J = 7.8$ Hz, 2H, H_{11}, $H_{11'}$), 8.00, 7.99 (d, $J = 8.5$ Hz, 2H, H_5, $H_{5'}$), 8.05 (d, $J = 8.4$ Hz, 2H, H_4, $H_{4'}$), 8.32, 8.20 (2 × d, $J = 9.0$ Hz, 2H, H_1, $H_{1'}$), 8.54 (2 × s, 2H, H_{10}, $H_{10'}$), 8.67, 8.65 (2 × d, $J = 8.9$ Hz, 2H, H_8, $H_{8'}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8 ($C_{16'}$), 27.4 (C_{18}), 31.7 (C_{15}), 40.6 (C_{13exo}), 41.2 (C_{14endo}), 69.175 (C_{11}), 120.9 (C_9, $C_{9'}$), 122.6 (C_1, $C_{1'}$), 124.2 (CF_3), 124.9 (C_6, $C_{6'}$), 125.0 (C_3, $C_{3'}$), 126.2 (C_8, $C_{8'}$), 126.3 (C_7, $C_{7'}$), 127.7, 127.6 (C_2, $C_{2'}$), 129.2 (C_5, $C_{5'}$), 129.5 (C_4, $C_{4'}$), 130.5 (C_{1a}, $C_{1a'}$), 131.0 (C_{4a}, $C_{4a'}$), 131.2 (C_{10}, $C_{10'}$), 131.4 (C_{5a}, $C_{5a'}$), 131.6 (C_{8a}, $C_{8a'}$), 131.9 (C_{17}), 172.34 (C_{12}), 172.5 (C_{19}). HRMS (ESI^-) *m*/*z* 700.2028 (M^-, δ −2.1 ppm).

4.7. Cycloadduct (11*R*,13*S*,14*S*,11′*R*)-4d

The above procedure provided 910 mg (95%) of **4d** as yellow needles: mp 145–148 °C; $[\alpha]_D^{20} = -86$ (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3055–2994 (OH), 2359 (C═H), 1749–1704 (C═O). ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (d, $J = 16.3$ Hz, 2H, H_{15proS}, H_{15proR}), 2.32 (d, $J = 14.4$ Hz, 2H, H_{18proS}, H_{18proR}), 3.18 (m, 1H, H_{14exo}), 3.19 (m, 1H, H_{13endo}), 7.46 (m, 2H, H_3, H_6), 7.47 (m, 1H, H_7), 7.57 (dd, $J = 8.0$ Hz, $J = 7.3$ Hz, 1H, H_2), 7.73 (q, $J = 7.8$, 1H, H_{11}), 8.24 (d, $2 \times J = 8.4$ Hz, 2H, H_4, H_5), 8.24 (d, $J = 9.0$ Hz, 1H, H_1), 8.47 (s, 1H, H_{10}), 8.56 (d, $J = 8.9$ Hz, 1H, H_8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (C_{16}, C_{17}), 32.8 (C_{15}, C_{18}), 41.5 (C_{14endo}, C_{13exo}), 68.8 (C_{11}), 120.7 (C_9, $C_{9'}$), 122.4 (C_1, $C_{1'}$), 123.8 (C_{16a}, C_{17a}), 124.1 (CF_3), 124.8 ($C_{3'}$, C_6, $C_{6'}$), 126.1 (C_8, $C_{8'}$), 126.3 (C_7, $C_{7'}$), 127.5 (C_2, $C_{2'}$), 129.2 (C_5, $C_{5'}$), 129.4 (C_4, $C_{4'}$), 130.7 (C_{1a}, $C_{1a'}$), 130.9 (C_{4a}, $C_{4a'}$), 131.2 (C_{10}, $C_{10'}$), 131.3 (C_{5a}, $C_{5a'}$), 131.6 (C_{8a}, $C_{8a'}$), 172.0 (C_{12}, C_{20}). (MALDI-TOF, *m*/*z*, %, THF-cca): 714.1 (M, 100), 715.1 (MH^+, 43).

4.8. Crystal data

A suitable crystal of **4d** was selected for X-ray single crystal diffraction experiment and mounted at the tip of a glass fibre on an Enraf-Nonius CAD4 diffractometer producing graphite monochromated Mo Kα radiation. After the random search of 25 reflections, the indexation procedure gave rise to the cell parameters. Data were collected in the ω–2θ scan mode. Absorption correction was performed following the empirical PSI-scan method. The structural resolution procedure was made using the WinGX package.[18] Solving for structure factor phases was performed by SHELXS86, and the full-matrix refinement by SHELXL97.[19] Non-H atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parent atoms. Crystallographic data have been deposited with the CCDC as supplementary material with the deposition number CCDC 623129.

Refinement parameters and crystal data for **4d**

Empirical formula	$C_{43}H_{33}Cl_3F_6O_4$
Formula weight	834.04
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P*21
Unit cell dimensions	$a = 12.841(3)$ Å $b = 9.314(4)$ Å $c = 16.811(5)$ Å $\alpha = 92.62(2)°$
Volume	2008.5 $Å^3$
Z	2
Density (calculated)	1.379 Mg/m^3
Absorption coefficient	0.298 mm^{-1}
F(000)	856
Crystal size	$0.43 \times 0.24 \times 0.15$ mm^3
Theta range for data collection	2.43–25.64°
Index ranges	$-15 \leqslant h \leqslant 15$, $0 \leqslant k \leqslant 11$, $-20 \leqslant l \leqslant 0$
Reflections collected	4180
Independent reflections	4040 [R(int) = 0.0637]
Completeness to theta	25.64°, 99.5%
Refinement method	Full-matrix least-squares on F_2
Data/restraints/parameters	4040/1/508
Goodness-of-fit on F_2	0.899
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0636$, $wR_2 = 0.1592$
R indices (all data)	$R_1 = 0.3575$, $wR_2 = 0.2476$
Absolute structure parameter	0.1(4)
Largest diff. peak and hole	0.343 and −0.291 e $Å^{-3}$

4.9. General procedure for hydrolysis in aqueous solution

To a solution of cycloadduct (11*R*,13*S*,14*S*,15*R*,18*S*,11′*R*)-**4a** (90 mg, 0.13 mmol) in THF (10 ml) an aqueous solution of KOH (70 mg, 1.28 mmol) was added. After 4 h, the THF was evaporated under reduced pressure, the crude diluted with water and extracted with several portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give 67 mg (95%) of pure (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol **4**, after crys-

tallization in $CHCl_3$. The remaining basic aqueous solution was acidified with concentrated HCl until pH = 1 and extracted with ether. The combined organic phases were dried over $MgSO_4$, filtered, concentrated and crystallized in hexane to recover 22 mg (95%) of pure (1*S*,2*S*,3*S*,4*R*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid.

4.10. General procedure for methanolysis

To a solution of cycloadduct (11*R*,13*S*,14*S*,15*R*,18*S*,11′*R*)-**4a** (200 mg, 0.29 mmol) in THF (5 ml) K_2CO_3 (396 mg, 2.8 mmol) was added following by methanol (5 ml). After stirring for 4 h, the solution was acidified with HCl (10%) until pH = 7, and extracted with several portions of ether and CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on 20 mg of silica gel (CH_2Cl_2:toluene 1:1) to furnish 150 mg (95%) of pure (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol and 57 mg (95%) of pure dimethyl (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxilate.

4.11. General procedure for reduction

To a solution of cycloadduct (11*R*,13*S*,14*S*,15*R*,18*S*,11′*R*)-**4a** (185 mg, 0.27 mmol) in dry THF (12 ml) $LiAlH_4$ (45 mg, 1.18 mmol) was added at 0 °C under argon. After stirring for 2 h, the solution was acidified with HCl (10%) until pH = 1, and extracted with several portions of ether and CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on 20 mg of silica gel (CH_2Cl_2/toluene 1:1) to furnish 137 mg (95%) of pure (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol and 39 mg (95%) of pure (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dimethanol.

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