A Simple Route to Enantiopure Fluorocyclohexenones

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This paper is dedicated to Professor H.J. Bestmann on the occasion of his 70th birthday.

The 4-fluoro substituted cyclohexadienone **10** was shown to undergo a very efficient differentiation of enantiotopic double bonds in a Diels–Alder cycloaddition process. Epoxidation followed by thermal retro reaction generated the enantiopure fluorocyclohexenone **13**.

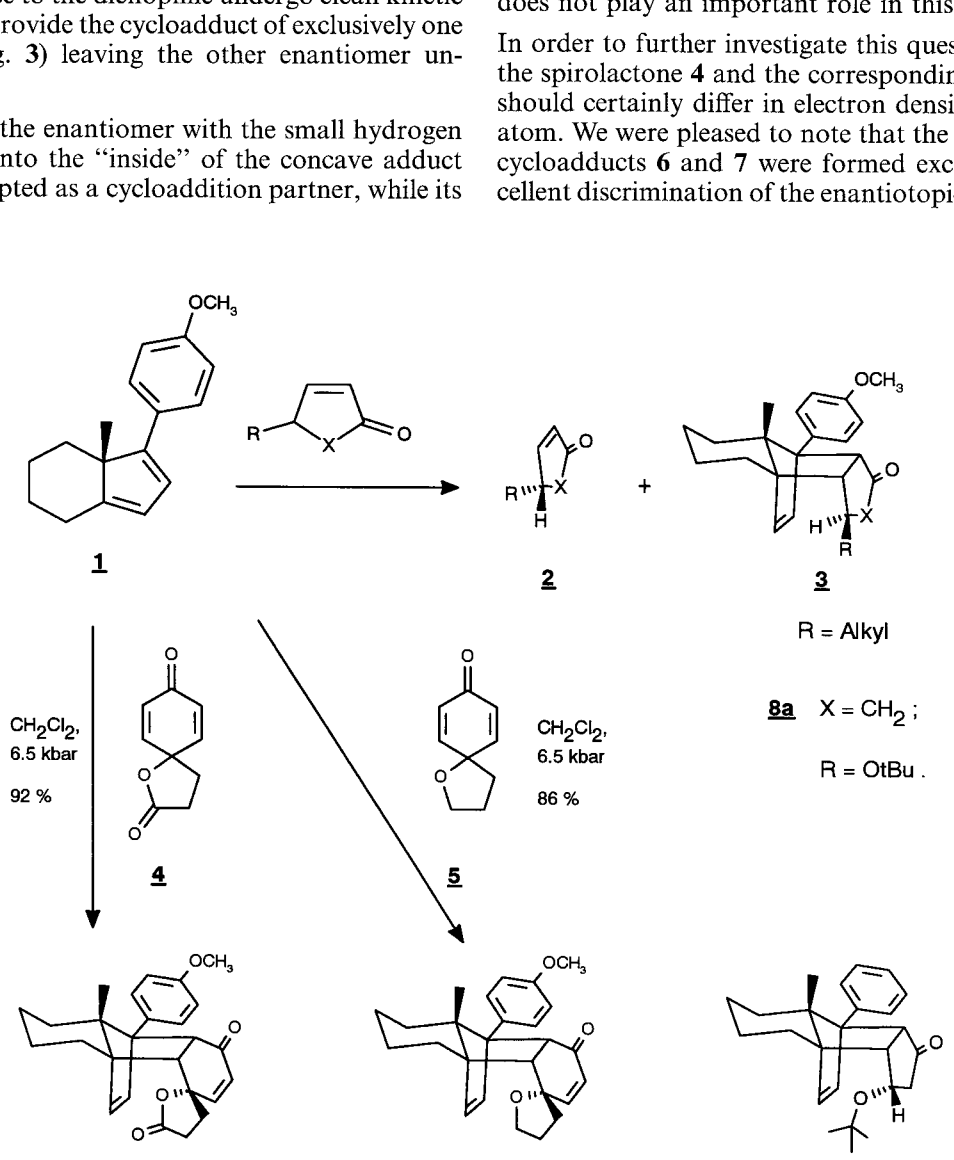
The excellent general selectivity observed with the enantiopure cyclopentadiene **1**,[1] lead us to investigate a few clear cut examples for chiral recognition and for kinetic resolution in particular.[2]

As communicated recently,[3] five- and six-membered unsaturated cyclic carbonyl compounds which bear alkyl substituents close to the dienophile undergo clean kinetic resolution and provide the cycloadduct of exclusively one enantiomer (e.g. **3**) leaving the other enantiomer untouched (see **2**).

Obviously only the enantiomer with the small hydrogen atom pointing into the "inside" of the concave adduct molecule is accepted as a cycloaddition partner, while its mirror image cannot accomodate the bulky alkyl residue in this "inside" position. In comparison, dienophiles which carry an alkoxy group instead of an alkyl residue (e.g. *tert*-butoxycyclopent-2-enone) performed poorly: given a long reaction time a nearly 1:1 mixture of both diastereomers **8a** and **8** was obtained.[4]

Without any doubt, the *R* configuration reacts somewhat faster, but in contrast to carbon side chains the rate differences are much smaller in this case. It can therefore be concluded that there is less space demand for an alkoxy group, irrespective of the oxygen substitutent, compared to a CH_2 group and that free electron pair–π-repulsion does not play an important role in this cycloaddition.

In order to further investigate this question we checked the spirolactone **4** and the corresponding ether **5**, which should certainly differ in electron density at the oxygen atom. We were pleased to note that the two enantiopure cycloadducts **6** and **7** were formed exclusively with excellent discrimination of the enantiotopic double bonds.[5]



Scheme 1

Noticing this remarkable difference in space demand for oxygen and $-CH_2-$ and remembering the results summarized in Scheme 1 even larger effects can be expected between hydrogen and $-CH_2-$. Unfortunately, the corresponding cyclohexadienones (compare to **10**!) rearrange very rapidly into the corresponding phenols (compare **9**).

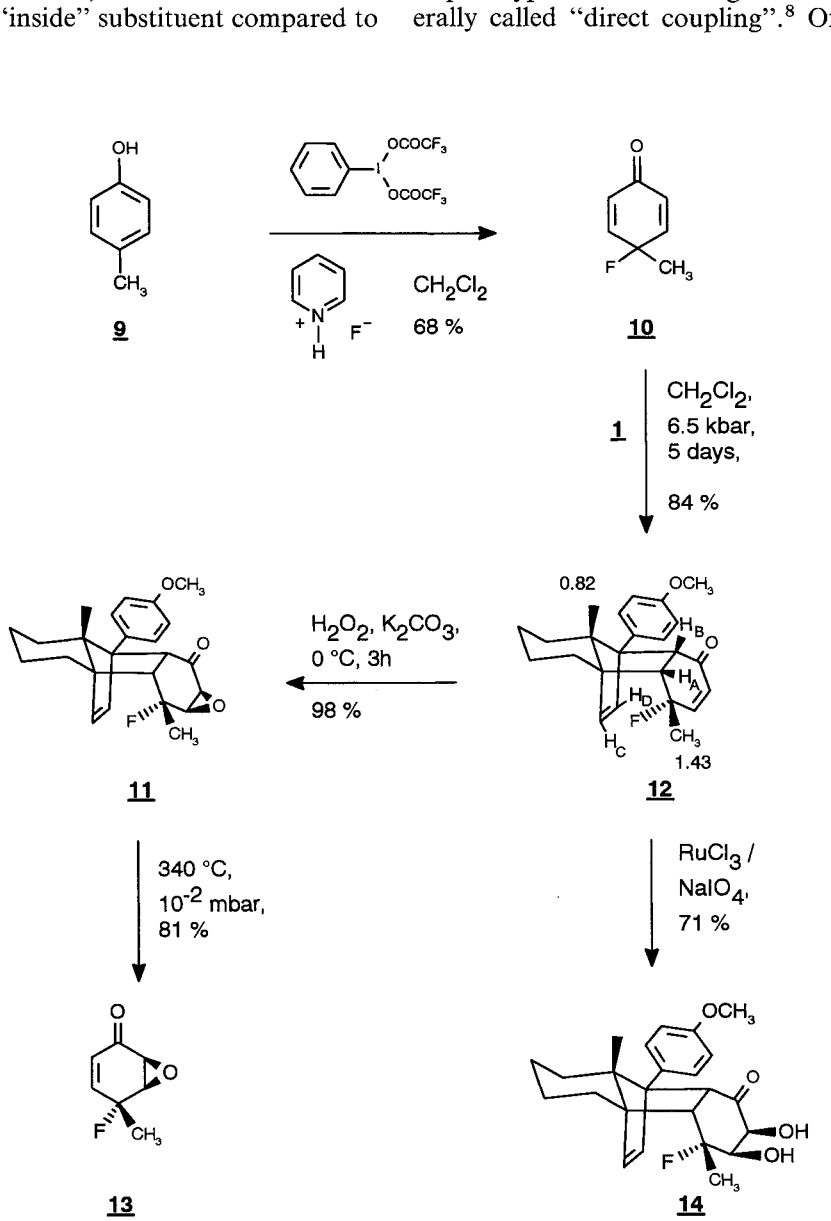
We therefore decided to replace a hydrogen with a fluoro atom, a trick which is well-established in medicinal chemistry or in connection with biologically active compounds in general.[6]

With its small van der Waal's radius (1.35 Å) fluorine compares closely to hydrogen (1.20 Å) and its bond length to carbon (1.39 Å) compares quite nicely to the C–O bond (1.43 Å). In comparison to the adducts from Scheme 2, there would consequently be a substituent of the size of a hydrogen atom sitting in the position normally held by an oxygen atom.

In terms of space demand an ideal situation for very efficient face selectivity is met, with the fluorine atom readily accepted as an "inside" substituent compared to $-CH_2-$ or $-CH_3$ (see **12** in Scheme 2). Additionally, the higher electronegativity (4.0) of the fluoro substituent compared to oxygen (3.5) should certainly decrease the electron density at the cyclohexadienone double bonds. Since diene **1** operates as an electron rich 4π system smooth cycloadditions with high reaction rates are predicted.

For the synthesis of an appropriate starting material we were fortunately able to take advantage of a recent fluorination technique described by J.C. Jacquesy et al.[7] It makes use of an iodoso-bistrifluoroacetate and HF–pyridine complex and provided a 68% yield of cyclohexadienone **10** (see Scheme 2).

According to our expectations this material underwent a very efficient Diels–Alder process. At room temperature and 6.5 kbar it gave one single cycloadduct **12** in 84% yield. A first indication of the configuration given in Scheme 2 was taken from a 6 Hz through-space coupling of proton H_C with the α-fluoro atom, a phenomenon that is quite typical for fluoroorganic compounds and is generally called "direct coupling".[8] Of course the spatial



Scheme 2

arrangement necessary for this interaction demands the "inside" orientation for the fluoro atom. In order to unambigously prove this assignment NOE experiments were performed on H_A and H_B. In both cases satisfactory effects with the two methyl groups resonating at $\delta = 0.82$ and 1.43 were observed. Further NOE experiments were done on these two methyl groups. The NOE for $H_A \leftrightarrow CH_3$ ($\delta = 1.43$) was 7.3% and for $H_B \leftrightarrow CH_3$ ($\delta = 1.43$) was 6.9%.

Although these are relative and uncorrected data they showed very clearly that the single isomer formed had been generated with excellent face selectivity in a flawless *endo* addition process, thus transforming the complete material into just one enantiomer. This result is of value for the preparation of enantiopure fluoroorganic compounds. In a very recent compilation of this work[9] just one direct enantioselective introduction of fluoro atoms is mentioned, in which only ee values of about 70% can be achieved. However, the alternatives published are characterized by even lower enantiomeric excesses.

In contrast to this, the procedure described here does provide enantiopure fluoro compounds with ee values always around 99% (*vide infra*). As various fluorinated cyclohexadienones are readily prepared by the Jacquesy technique there are many options for either kinetic resolution (chiral cyclohexadienones) or differentiation of enantiotopic groups (prochiral cyclohexadienones).

To finally arrive at enantiopure fluorinated cyclohexenones, diastereoselective transformations at the six-membered ring were mandatory. As epoxidations and hydroxylations had proven to be particularly useful with the spiro derivatives **6** and **7**,[5] we initially concentrated our efforts on these oxidations.

One major reason to investigate these processes first was the fact that at this particular stage, in contrast to the Diels–Alder step the lower π electron density caused by the fluoro atom could easily be detrimental to the planned reactions. It was, therefore, necessary to use a nucleophilic epoxidation protocol, in order to make sure that the cyclopentene double bond was left untouched. To our great delight, treatment with hydrogen peroxide in the presence of potassium carbonate gave rise to a practically quantitative yield of epoxide **11**. In addition, an oxidation with $RuCl_3$ and sodium periodate[10] was successfully conducted. Although this cis-hydroxylation took 40 minutes in contrast to the 5 minutes necessary for spirolactone **7**, one could easily secure a 71% yield using this method.

These highly chemo- and diastereoselective transformations clearly show that the selective introduction of additional stereogenic centers does not pose any particular problem in a very rigid cycloadduct, but the scope of these reactions remains to be determined.

Since in the spirolactone series (see **6**, Scheme 1) succesful retro reactions had been run with the epoxide, as well as with the acetonide protected diol, we were quite confident that similar reactions could also be expected from **11** and **14**. Since **11** could be used in this thermolysis directly without the introduction of any protecting groups, epoxide **11** was the first substrate to be pyrolyzed.

At a reaction temperature of 340 °C and 10^{-2} mbar adduct **11** underwent a clean retro-Diels–Alder cleavage to provide the pure diene along with an 81% yield of fluoro epoxide **13**. The product **13** crystallized very nicely and was purified by recrystallization from dichloromethane and hexanes.

NMR measurements with the (+)-Eu(hfc)$_3$ shift reagent on the pure compound showed epoxide **13** to be enantiopure within the limits of error (ee > 98%).

From these results the conclusion can be drawn that the by no means trivial enantioselective fluorination can be replaced by a chemoselective and regioselective version if reactive prochiral compounds like **10** can be prepared, which can be selectively attacked by a chiral 4π-system. It should be mentioned in passing that compounds like **13** can of course be readily converted into acyclic, multifunctionalized fluoroorganic compounds by oxidative cleavage of the double bond or by reaction at the diol or epoxide moiety.

The preparation of epoxide **13** demonstrates the general feasibility of this approach. Further experiments to broaden the scope of this procedure are under way in our laboratory.

Melting points were determined on a Büchi melting point microscope and are uncorrected. IR spectra were measured on a Perkin Elmer 581 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP 200 and WP 300. δ Values are given relative to TMS; J values in Hz. In the APT-spectra (+) means a positive signal for C and CH_2 and (−) a negative signal for CH and CH_3. MS were determined with a Finnigan MAT 312 instrument and VG Autospec at 70 eV. For flash chromatography silica gel (30–60 mesh) (Baker) was used at 0.3 bar. All solvents were dried by the usual methods. The high pressure reactions were performed in a Nova Swiss apparatus. For the retro-Diels–Alder reaction a special flash vacuum pyrolysis apparatus was used.[11] Cyclohexadienone **10** was prepared according to the procedure described by J.C. Jacquesy et al.[7].

(4*S,4a*S**,4b*S**,8a*S**,9a*R**)-4-Fluoro-9-(4-methoxyphenyl)-4,8a-dimethyl-4b,5,6,7,8,9a-hexahydro-4b,9-etheno-4b*H*-fluoren-1,4(*H*)-one (12):**

A solution of 4-fluoro-4-methylcyclohexa-2,5-dienone (**10**, 0.5 g, 3.97 mmol) and diene **1** (1.0 g, 4.20 mmol) in CH_2Cl_2 (3 mL) was brought into a Teflon hose and was pressurized over 5 d at 6.5 kbar in a high pressure autoclave. Purification of the raw material by flash chromatography (Et_2O/hexanes, 1:4); yield: 1.22 g (3.33 mmol; 84%); white foam; $[\alpha]_D$ −169.6 ($c = 1$, $CHCl_3$).

IR ($CHCl_3$): ν = 2928 (m), 2864 (w), 1668 (s), 1612 (w), 1516 (s), 1248 (s), 1180 (m), 988 (w), 824 cm^{-1} (w).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.56$ (bd, $J = 13$ Hz, 1 H), 0.82 (s, 3 H), 1.0–1.46 (m, 5 H), 1.43 (d, $J = 21$ Hz, 3 H), 1.85 (dt, $J = 4/12$ Hz, 1 H), 2.29 (bd, $J = 10$ Hz, 1 H), 2.81 (dd, $J = 2/8$ Hz, 1 H), 3.7–3.85 (m, 4 H), 5.75 (dd, $J = 1/10$ Hz, 1 H), 5.85 (d, $J = 5$ Hz, 1 H), 6.05 (dd, $J = 5/6$ Hz, 1 H), 6.53 (dd, $J = 10/11$ Hz, 1 H), 6.87 (d, $J = 9$ Hz, 2 H), 7.30 (d, $J = 9$ Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): $\delta = 15.3$ (−); 2.1 (+); 23.8 (+); 27.5 (+) d, $J_{CF} = 8$ Hz; 28.5 (+); 32.8 (−) d, $J_{CF} = 28$ Hz; 50.4 (−) d, $J_{CF} = 4$ Hz; 50.7 (−) d, $J_{CF} = 18$ Hz; 55.1 (−); 61.2 (+); 62.4 (+) d, $J_{CF} = 4$ Hz; 71.4 (+); 92.9 (+) d, $J_{CF} = 172$ Hz; 113.0 (−); 129.0 (+); 129.1 (−); 130.4 (−) d, $J_{CF} = 10$ Hz; 135.3 (−); 139.0 (−); 148.9 (−) d, $J_{CF} = 29$ Hz; 158.2 (+); 198.6 (+) d, $J_{CF} = 2$ Hz.

MS (100 °C): m/z (%) = 367 (4/M$^+$ + 1), 366 (8/M$^+$), 346 (3), 266 (3), 251 (3), 241 (100), 225 (12), 197 (11), 181 (5), 165 (7), 153 (4), 121 (9), 106 (7), 76 (6).

HRMS: m/z calc. for $C_{24}H_{27}O_2F_1$: 366.1995; found: 366.1994.

(2*S,3*R**,4*R**,4a*S**,4b*S**,8a*S**,9a*R**)-2,3-Epoxy-4-fluoro-9-(4-methoxyphenyl)-4,8a-dimethyl-octahydro-4b,9-etheno-4b*H*-fluoren-1(4*H*)-one (11):**

To a solution of fluorocyclohexadienone adduct **12** (40 mg, 0.109 mmol) in THF (3 mL) was added at 0 °C 30 % H_2O_2 (0.3 mL) in water (1 mL) and aq K_2CO_3 (0.2 mL). After 3 h the reaction mixture was washed with brine (10 mL) and 5 % $FeSO_4$ (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave **11**; yield: 41 mg (0.107 mmol; 98 %); white solid; mp 138 °C; $[\alpha]_D$ −85.4 ($c = 1$, $CHCl_3$).

IR ($CHCl_3$): ν = 2928 (s), 2859 (m), 1718 (s), 1615 (w), 1517 (s), 1251 (s), 1182 (m), 1037 (m), 822 cm^{-1} (w).

^1H NMR (200 MHz, $CDCl_3$): δ = 0.55 (bd, J = 13 Hz, 1 H), 0.75 (s, 3 H), 1.1–1.7 (m, 5 H), 1.88 (d, J = 21 Hz, 3 H), 1.98 (dt, J = 3/12 Hz, 1 H), 2.15 (d, J = 12 Hz, 1 H), 2.76 (dd, J = 10/30 Hz, 1 H), 3.32 (d, J = 4 Hz, 1 H), 3.36 (dd, J = 1/4 Hz), 3.79 (s, 3 H), 3.90 (dd, J = 1/10 Hz, 1 H), 5.93 (dd, J = 6/14 Hz, 1 H), 6.12 (dd, J = 1/6 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.13 (d, J = 9 Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 15.8 (−); 21.0 (+); 23.5 (+); 25.6 (+); 27.1 (−) d, J_{CF} = 27 Hz; 27.9 (+) d, J_{CF} = 22 Hz; 51.7 (−) d, J_{CF} = 16 Hz; 52.7 (−); 55.1 (−), 55.9 (−); 60.2 (+) d, J_{CF} = 3 Hz; 60.9 (+); 61.8 (−) d, J_{CF} = 40 Hz; 63.8 (+); 68.0 (+); 113.4 (−); 127.7 (−); 130.7 (−); 135.5 (−); 138.9 (−); 158.0 (+); 205.2 (+).

MS (100 °C): m/z (%) = 382 (3/M^+), 366 (7), 252 (2), 242 (18), 240 (100), 225 (7), 197 (6), 165 (3), 149 (3), 121 (5), 91 (3).

HRMS: m/z calc. for $C_{24}H_{27}O_3F_1$: 382.1944; found: 382.1947.

(4*R,5*R**,6*S**)-5,6-Epoxy-4-fluorocyclohex-2-enone (13):**

Epoxide adduct **11** (115 mg, 0.301 mmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 185 °C–220 °C and 10^{-2} mbar through a pyrolysis tube heated to 340 °C. After 15 min the whole starting material was sublimed off and a 1:1 mixture of diene **1** and epoxide **13** was trapped on a cooling finger. Two recrystallizations from CH_2Cl_2/hexanes gave **13**; yield: 34.6 mg (0.244 mmol, 81 %); colorless crystals; mp 38 °C. After separation of the epoxide **13** by crystallization, the diene **1** can be isolated in quantitative yield from the CH_2Cl_2/hexanes soln by flash chromatography (Et_2O/hexanes, 1:10); $[\alpha]_D$ −77.8 (c = 0.38, $CHCl_3$).

ee > 98 % [determined by ^1H NMR; (+)-Eu(hfc)$_3$/$CDCl_3$]

IR ($CHCl_3$): ν = 2988 (w), 1696 (s), 1376 (w), 1256 (w), 1164 (w), 1140 (w), 1112 (m), 1088 (m), 904 (m), 820 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.74 (d, J = 22 Hz, 3 H), 3.52 (dd, J = 2/4 Hz, 1 H), 3.73 (ddd, J = 1/3/6 Hz, 1 H), 6.02 (ddd, J = 1/2/11 Hz, 1 H), 6.46 (ddd, J = 2/3/11 Hz, 1 H).

MS (25 °C): m/z (%) = 143 (6/M^+ + 1), 142 (70/M^+), 127 (2), 113 (100), 107 (6), 99 (68), 87 (41), 85 (80), 82 (39), 79 (4), 71 (20).

HRMS: m/z calc. for $C_7H_7O_2F_1$: 142.0430; found: 142.0410.

(2*S,3*R**,4*R**,4a*S**,4b*S**,8a*S**,9a*R**)-4-Fluoro-2,3-dihydroxy-9-(4-methoxyphenyl)-4,8a-dimethyloctahydro-4b,9-etheno-4b*H*-fluoren-1(4*H*)-one (14):**

Fluorocyclohexadienone adduct **12** (30 mg, 0.082 mmol) was dissolved in a mixture of EtOAc (2 mL) and MeCN (2 mL) at 0 °C. With vigorous stirring a solution of $RuCl_3 \cdot xH_2O$ (1 mg, 0.005 mmol) and $NaIO_4$ (25 mg, 0.117 mmol) in deionized water (0.5 mL) was added. The reaction mixture was stirred for 40 min and then quenched with sat. aq $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with EtOAc (20 mL). The extracts were dried ($MgSO_4$). Evaporation of the solvent and purification by flash chromatography (EtOAc/hexanes 1:1) gave **14**; yield: 23 mg (0.058 mmol, 71 %); white solid; $[\alpha]_D$ −23.3 (c = 0.82, $CHCl_3$).

IR ($CHCl_3$): ν = 3489 (br, s), 2926 (s), 2856 (m), 1710 (s), 1614 (w), 1516 (s), 1250 (s), 1183 (m), 1103 (m), 1058 (m), 1041 (m), 825 cm^{-1} (w).

^1H NMR (200 MHz, $CDCl_3$): δ = 0.52 (bd, J = 13 Hz, 1 H), 0.79 (s, 3 H), 1.1–2.8 (m, 5 H), 1.65 (d, J = 23 Hz, 3 H), 1.92 (dt, J = 3/9 Hz, 1 H), 2.23 (d, J = 11 Hz, 1 H), 2.57 (bs, 1 H), 2.70 (dd, J = 9/24 Hz, 1 H), 3.58 (bs, 1 H), 3.80 (s, 3 H), 3.81–3.95 (m, 2 H), 4.15 (bs, 1 H), 5.93 (d, J = 6 Hz, 1 H), 6.27 (dd, J = 6/14 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.30 (d, J = 9 Hz, 2 H).

MS (120 °C): m/z (%) = 401 (1/M^+ + 1), 400 (3/M^+), 266 (1), 251 (1), 241 (20), 240 (100), 225 (12), 197 (8), 165 (4), 149 (4), 128 (10), 100 (8), 91 (4).

HRMS: m/z calc. for $C_{24}H_{29}O_4F_1$: 400.2050; found: 400.2050.

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