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Trifluoromethylation of camphorquinone and its monoimine derivatives

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ABSTRACT

Treatment of (1*R*)-camphorquinone **2** with (trifluoromethyl)trimethylsilane in the presence of catalytic amounts of caesium fluoride in DME at room temperature yields two pairs of *exo*/*endo* isomers of trifluoromethylated silylated alcohols **5** and **6**. In this case, nucleophilic addition of the CF_3 anion occurs neither regio- nor stereoselectively. On the other hand, the analogous reaction with (1*R*)-camphorquinone 3-imines **3**, followed by hydrolysis with 5 M HCl in ethanol, leads stereoselectively to (1*R*,2*S*)-2-hydroxy-2-(trifluoromethyl)bornan-3-one **8**. The attempted reductions of the intermediate adducts with $NaBH_4$ in ethanol gave the corresponding (1*R*,2*S*)-3-imino-2-(trifluoromethyl)bornan-2-ols **9** as the sole isomers in high yield. The configuration of C(2), that is, the *endo* course of the nucleophilic CF_3 addition, was proven by X-ray crystallography. Furthermore, the reduction of the C=N bond in **9** with DIBAL-H leads stereoselectively to the *exo* amino derivatives **10**, which, by treatment with phosgene, smoothly form the fused 1,3-oxazolidin-2-ones **11**. In contrast, the reduction of ketone **8** yields a mixture of the *exo*,*exo*- and *exo*,*endo*-2,3-diols **12**.

1. Introduction

Camphor derivatives are important chiral auxiliaries and ligands for stereocontrolled reactions and organocatalysis.[1] Special attention has been focused on the enantiomerically pure 2,3-diols and 3-amino-2-ols derived from camphor.[2,3] A very important modification of the structure of organic molecules is the introduction of fluorine atoms or perfluoroalkyl residues, which in most cases results in significant changes in their physical and chemical properties.[4a–d] In spite of this obvious fact and rapidly growing interest in the chemistry of fluorinated compounds, relatively little is known about applications of fluorine-containing chiral auxiliaries and chiral ligands in asymmetric synthesis.[4e,f] To the best of our knowledge, recent reports are limited to the synthesis and successful exploration of chiral 2-trifluoromethyloxazolidines as chiral auxiliaries.[4g,h] Of special interest is the introduction of the CF_3 group, which can be conveniently introduced via nucleophilic addition using (trifluoromethyl)trimethylsilane (Me_3SiCF_3, Ruppert-Prakash reagent).[5] The trifluoromethylation of aldehydes and ketones with the Ruppert-Prakash reagent has been extensively studied, and along with classical procedures based on the application of an ether as the solvent and fluoride ion as a catalyst,[6] new variants with DMSO[7a] or DMF as the solvent and carbonates,[7b] as well as acetates,[7c] as catalyst, were reported. The enantioselective trifluoromethylation of aldehydes and ketones has been investigated, with the enantioselectivity resulting from the use of a catalyst containing either a chiral cation[8a–d] or anion.[8d] Another paper has reported the diastereoselective nucleophilic trifluoromethylation of some aromatic aldehydes, which contain a sulfinyl auxiliary at the *ortho*-position.[9]

Trifluoromethylations of imines are also known, although, in comparison with carbonyl compounds, the number of reports concerning this reaction is much smaller. In a recent paper, activated *N*-tosyl aldimines have been shown to undergo reaction with the Ruppert-Prakash reagent under fluoride catalysis.[10] The C=N bond in *N*-sulfinylimines is also sufficiently activated to undergo nucleophilic trifluoromethylation under typical conditions. In this case, the application of enantiomerically pure substrates led to the formation of trifluoromethylated products in a diastereoselective manner.[11] Subsequent desulfinylation under mild conditions provides convenient access to enantiomerically pure α-(trifluoromethyl)amines. The activation of the C=N bond by the strong electron withdrawing CF_3 substituents allows the addition of the CF_3 anion to ketimines derived from hexafluoroacetone.[12]

To the best of our knowledge, camphor derivatives, which bear trifluoromethyl groups, have scarcely been described,[13] and the fluoride catalyzed nucleophilic trifluoromethylation of camphor led to the adduct in less than 1% yield.[6,14] On the other hand, there is a report on the highly efficient reaction with norbornan-2-one, leading stereoselectively to the *exo*-trifluoromethyl norbornanole.[6]

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Herein, we report the introduction of the trifluoromethyl group into the camphor skeleton by using camphorquinone and its monoimines as substrates.

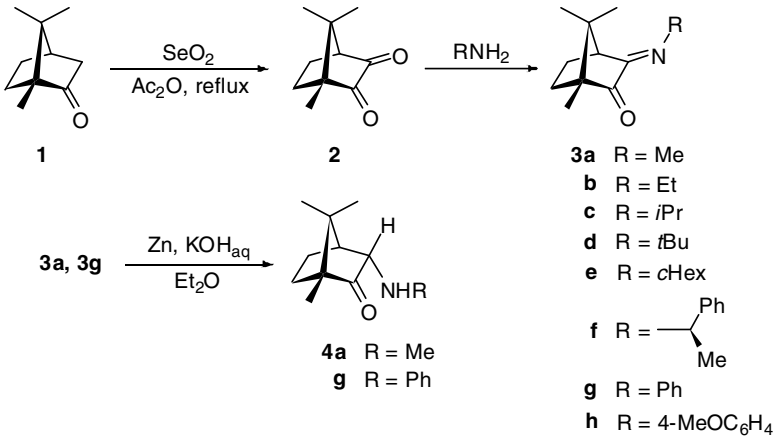
2. Results and discussion

The preparation of camphorquinone **2** was carried out by oxidation of (1*R*)-camphor **1** with SeO_2 in Ac_2O.[16] Subsequent reaction of **2** with primary amines led to the 3-monoimines **3** (Scheme 1).[17,18] Two imines **3a** and **3g** were stereoselectively converted to the 3-*endo*-amino camphor derivatives **4a** and **4g**, respectively, by reduction with Zn/KOH.[17a]

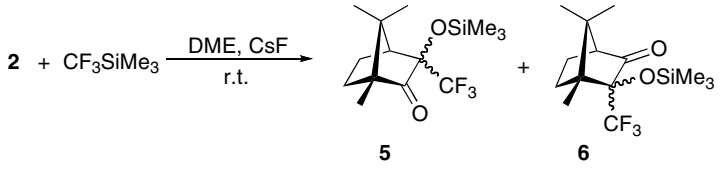
The first trifluoromethylations were attempted with **4a** and **4g** in 1,2-dimethoxyethane (DME) using CsF as the initiator. In both cases, after 24 h at room temperature, the starting amino ketones were recovered almost quantitatively, and no new product could be detected in the reaction mixture. Under the same conditions, quinone **2** reacted with CF_3SiMe_3, and, after typical workup, the crude mixture was examined by ^{19}F NMR spectroscopy. Four signals at −68.7, −69.5, −71.6 and −72.2 ppm in a ratio of 39:35:4:22 showed the formation of two pairs of *endo*/*exo*-isomers of the adducts **5** and **6** (Scheme 2).

The complex mixture was not separated, and therefore the configurations and the chemical shifts could not be correlated. Nevertheless, the result shows that there is no significant selectivity in the nucleophilic addition of CF_3 to camphorquinone.

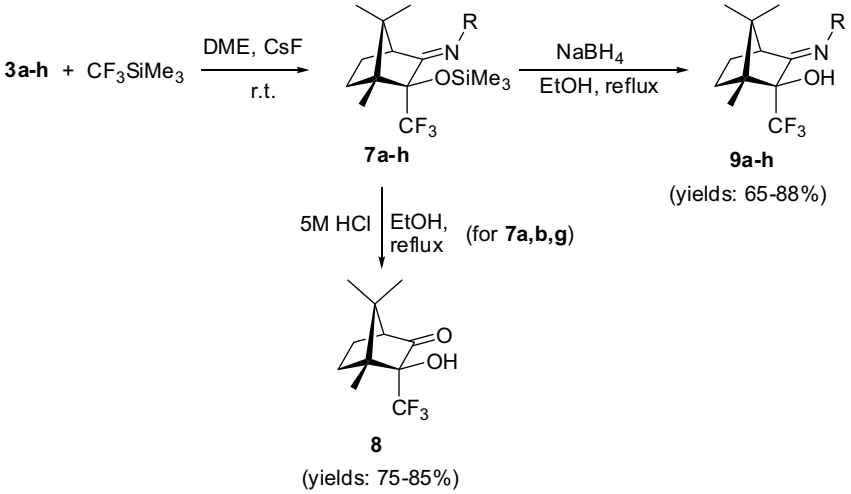
In contrast to **2**, imino ketone **3a** reacted with CF_3SiMe_3 to give only one product, which showed a ^{19}F NMR absorption at −68.5 ppm. According to the IR spectrum, the C=N group is preserved, but the product does not contain a C=O group. The ^1H NMR signal at 0.07 ppm confirmed the presence of an Me_3Si group. These data suggest the formation of a 1:1-adduct of type **7** (Scheme 3), and in analogy with the known reaction of MeLi with **3d**, which yields the product of the *endo*-attack (i.e., the *exo*-hydroxy



Scheme 1.



Scheme 2.



Scheme 3.

compound),[17c] the same orientation of substituents can be proposed for **7**.

The attempted desilylation of **7a** by heating with aqueous 5 M HCl in ethanol led to the removal of the Me_3Si group and to the hydrolysis of the imino group to yield the corresponding 2-hydroxyketone **8**. The same product was obtained from **7b** and **7g**. The structure of the crystalline product **8** was unambiguously confirmed by X-ray crystallography (Fig. 1a), which proved the proposed *endo*-addition of the CF_3 group.

The hydroxy group of molecule **8** forms an intermolecular hydrogen bond with the carbonyl O-atom of a neighbouring molecule. The interaction links the molecules into extended chains, which run parallel to the [100] direction and can be described by a graph set motif[20] of $C(5)$.

The selective desilylation of **7a**–**h** was smoothly performed by treatment with $NaBH_4$ in methanolic or ethanolic solution.[21a] Under these conditions, the imino group was preserved, and the products obtained are imino alcohols of type **9** (Scheme 3). In the case of **9a**, the structure of the racemate was determined by X-ray crystallography (Fig. 1b).[21b]

The hydroxy group of the molecule *rac*-**9a** forms an intermolecular hydrogen bond with the N-atom of a neighbouring molecule, which in turn forms an identical hydrogen bond with the original molecule. These interactions link pairs of the molecules into centrosymmetric dimers and generate a graph set motif[20] of $R_2^2(10)$.

The same product **9a** was obtained when adduct **7a** was hydrolyzed by treatment with 5 M HCl in ethanol for 20 days at room temperature. It is worth mentioning that the attempted reduction of adducts of type **7** with $LiAlH_4$ in diethyl ether failed, and neither desilylation nor reduction of the C=N group was observed.

The imino alcohols **9** are promising starting materials for the preparation of trifluoromethylated amino alcohols.[22] Widely applied methods for the conversion of imines into the corresponding amines are treatment with $NaBH_4$ or $LiAlH_4$.[24] In the case of the silylated imino alcohols **7**, the attempted reaction with $NaBH_4$ in ethanol failed. Furthermore, the imino alcohols **9** were resistant towards the reaction with $LiAlH_4$. Another powerful reducing agent is diisobutyl aluminium hydride (DIBAL-H).[24] In the case of **9a** and **9g**, heating with DIBAL-H in refluxing THF solution for 30 min yielded the desired amino alcohols **10a** and **10g** (Scheme 4).

In each case, the ^{19}F NMR spectra of the crude mixture revealed the presence of only one signal of the CF_3 group. Pure products **10** were obtained as single stereoisomers by column chromatography on alumina. Based on the fact that nucleophiles attack the camphor derivatives from the *endo* side, we attribute the 2-*exo*-OH, 3-*exo*-NHR configuration to products **10a** and **10g**. This preliminary assumption was confirmed by the cyclization of isolated amino alcohol **10a** to the 1,3-oxazolidin-2-one derivative **11a** by treatment with phosgene in toluene solution. The absorption band of the C=O group appeared in the IR spectrum at 1765 cm^{-1}.

The hydroxy ketone **8** was reduced with $NaBH_4$ as well as with DIBAL-H. In both cases, mixtures of stereoisomeric 2,3-diols **12** were obtained (Scheme 5). The selectivity of these reactions was determined by using ^{19}F NMR spectroscopy. The major isomer exhibited a signal for the CF_3 group at −73.7 ppm and a minor one at −69.2 ppm. The comparison of the intensities of these signals showed that the selectivity of the reactions with $NaBH_4$ in methanol at 0 °C was ca. 9:1 (de 79%). The selectivity slightly increased to 10:1 (de 91%) with DIBAL-H in dichloromethane at −5 to 0 °C, but decreased to 4:1 (de 63%) at −30 °C.

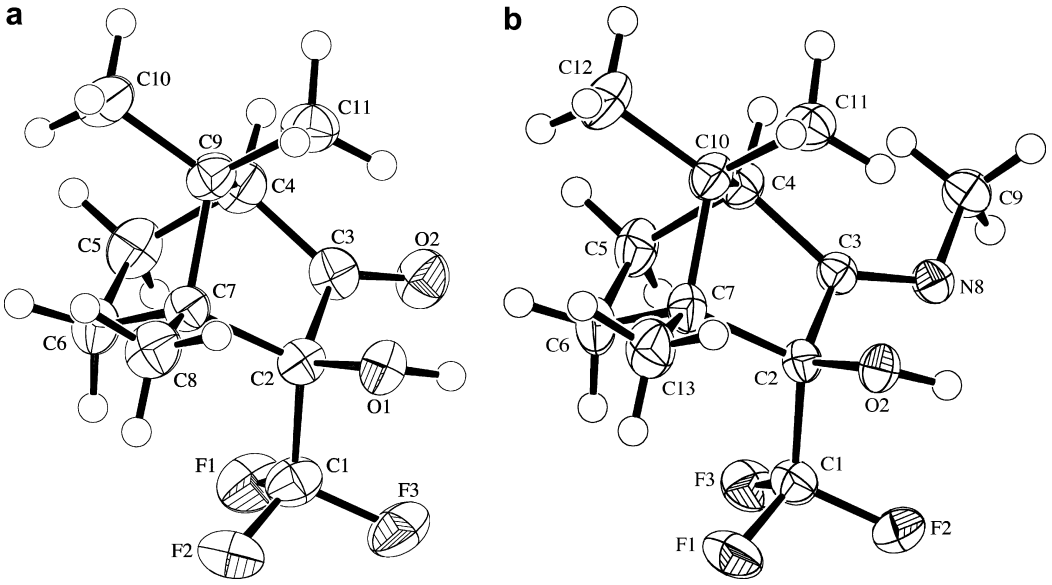
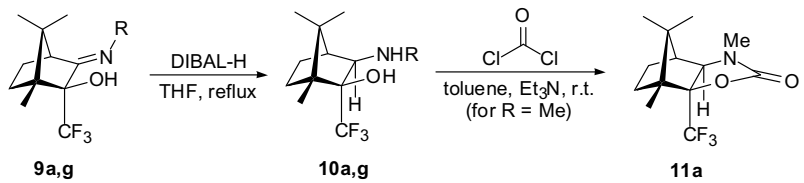
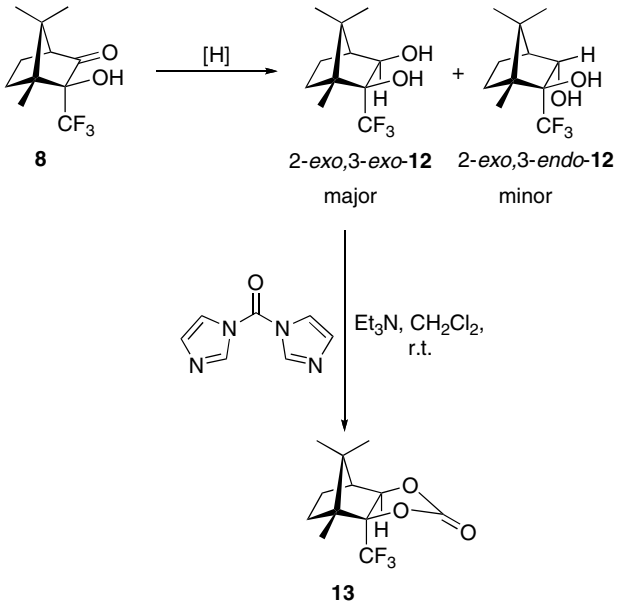


Figure 1. ORTEP plots[19] of the molecular structures of (a) **8** and (b) *rac*-**9a** (arbitrary numbering of the atoms, 50% probability ellipsoids).



9a,g **10a,g** **11a**

Scheme 4.



Scheme 5.

Chromatographic separation of the mixture afforded the major product in pure form in 83% yield. Based on the same argumentation as in the case of the imino alcohols **10**, we attribute the 2-*exo*-OH, 3-*exo*-OH configuration to this product (2-*exo*,3-*exo*-**12**). The postulated structure was proved by the reaction with carbonyl diimidazole in dichloromethane in the presence of triethylamine at room temperature. Under these conditions, carbonate **13** was obtained in 91% yield. This result confirms the proposed structure of the major isomer 2-*exo*,3-*exo*-**12**.

3. Conclusions

The presented results show that, in contrast to camphor, both camphorquinone **2** and its monoimines **3** undergo nucleophilic trifluoromethylation to give the corresponding silylated alcohols. Whereas the reaction with **2** leads to a mixture of regio- and stereoisomeric adducts, the analogous reaction with **3** occurs chemo- and diastereoselectively from the *endo* side to exclusively give the silylated imino alcohols **7**. Hydrolysis of the latter opens up access to the hydroxy ketone **8**, which cannot be prepared directly from **2**, as a sole product.

The desilylation of adducts **7** with $NaBH_4$ in alcoholic solution leads to imino alcohols **9**, which subsequently could be reduced stereoselectively to the amino alcohols **10**. The hydroxy ketone **8**, upon treatment with $NaBH_4$ reacts to give the 2-*exo*,3-*exo*-diol **12** as the major product, which was isolated in pure form. Taking into account that β-amino alcohols and diols derived from camphor are important building blocks for the synthesis of chiral auxiliaries[2a,3b] and in organocatalysis,[1,25] the trifluoromethylated derivatives **10** and 2-*exo*,3-*exo*-**12** can find further applications in organic synthesis.

4. Experimental

4.1. General

Melting points were determined on a Melt-Temp. II apparatus (Aldrich) in capillary, and are uncorrected. The ^1H, $^{13}C\{^1H\}$ and ^{19}F NMR spectra were recorded using a Bruker AC-200 or Bruker Avance II Plus 700 spectrometer in $CDCl_3$ with TMS as an internal standard. Assignments of signals in ^{13}C NMR spectra were made on the basis of DEPT 135 experiments. The IR spectra were measured using an NEXUS FT-IR spectrophotometer. The MS spectra (CI, EI) were obtained using a LKB-2091, Finnigan MAT-95 or Finnigan MAT-90 spectrometer. Optical rotations were measured on Perkin–Elmer 241 MC spectropolarimeter for $\lambda = 589$ nm. Elemental analyses were performed in the Microanalytical Laboratory of Centre of Molecular and Macromolecular Studies PAS in Łódź.

4.2. Materials

Commercial (1*R*)-camphor **1**, 1,1′-carbonyldiimidazol, sodium borohydride and a solution of diisobutylaluminium hydride (DIBAL-H) in dichloromethane (1 M) were purchased from Sigma–Aldrich. A commercial solution of *phosgene* in toluene (20%) was purchased from Fluka. (1*R*)-Camphorquinone **2**,[16] iminoketones **3a** and **3b**,[17a] **3c**,**e**,**f**,[3b] **3d**[17b] **3g**,**h**[17c] and aminoketones **4a** and **4b**[17a] were prepared according to known protocols. Dimethoxyethane (DME) and tetrahydrofuran (THF) were dried over sodium with benzophenone and dichloromethane over sodium hydride, and they were freshly distilled prior to use.

4.3. Reactions of iminoketones 3 with (trifluoromethyl)trimethylsilane—a general procedure

In a dry two-necked flask equipped with a septum and a tube filled with anhydrous calcium chloride, 1 mmol of the corresponding iminoketone **3a**–**h** dissolved in 1.5 ml of anhydrous DME was placed. Then, a catalytic amount of freshly dried caesium fluoride and 157 mg (0.17 ml, 1.1 mmol) Ruppert-Prakash reagent were added. The mixture was stirred at room temperature and, after ca. 1 h (TLC control), the reaction was quenched by the addition of water (1 ml). The solution was extracted three times with dichloromethane. The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated and the crude oily products **7a**–**h** were used for further reactions without purification.

4.3.1. Hydrolysis of adducts 7—a general procedure

To a solution of crude **7a**, **7b** or **7g** in 2 ml of ethanol, 1 ml of a 5 M solution of hydrochloric acid was added and the mixture was refluxed for 15 h. Then, the mixture was basified with aqueous sodium hydroxide (20%). The mixture was diluted with water and extracted with dichloromethane. The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated. The crude product was purified by column chromatography on silica gel using hexane with an increasing amount of dichloromethane (0–50%) as an eluent. Product **8** was isolated as a yellowish solid. Yields: 180–200 mg (75–85%). Analytically pure product **8** was obtained by crystallization.

4.3.1.1. (1*R*,2*S*)-2-Hydroxy-2-(trifluoromethyl)bornan-3-one 8. Colourless crystals, mp 140–142 °C (Et_2O/hexane). ^1H NMR (200 MHz): δ 1.01, 1.07, 1.10 (3s, 3H each, $3CH_3$), 1.57–2.03 (m, 4H, $2CH_2$), 2.34 (d, $^3J_{H,H} = 4.8$ Hz, 1H, CH),[26] 3.22 (br s, 1H, OH) ppm. ^{13}C NMR (50 MHz): δ 9.5, 18.2, 22.0 ($3CH_3$), 20.8; 28.6 ($2CH_2$), 46.2, 59.4 ($2C_q$), 59.1 (CH), 79.2 (q, $^2J_{C,F} = 27.1$ Hz, C_q), 124.3 (q, $^1J_{C,F} = 287.3$ Hz, CF_3), 211.2 (C=O) ppm. ^{19}F NMR (188 MHz): δ −70.5 (s, CF_3) ppm. IR (KBr): ν 3402s (br, OH), 3017w, 2998w, 2948w, 2884w, 1754vs (C=O), 1636w, 1463w, 1403w, 1376w, 1365w, 1265m, 1173s, 1159vs, 1120s, 986w, 968w, 825w, 741w, 607w cm^{-1}. MS (CI, isobutane): *m*/*z* 237 (100, $[M+1]^+$), 69 (9, $[CF_3]^+$). Anal. Calcd for $C_{11}H_{15}F_3O_2$ (236.24): C, 55.93; H, 6.40. Found: C, 55.96; H, 6.41. $[\alpha]_D = -119.2$ (*c* 1.0, $CHCl_3$).

4.3.2. Desilylation of adducts 7 with sodium borohydride—a general procedure

To a solution of the corresponding adduct **7** in 2 ml of methanol (or ethanol), 190 mg (5 mmol) of sodium borohydride was added in small portions while cooling the reaction flask in an ice-bath. When the evolution of hydrogen ceased, the mixture was heated at reflux for 18 h. Then, the mixture was cooled to room temperature and the solvent evaporated. The semisolid residue was dissolved in water and extracted with dichloromethane. The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated and the crude products were purified by column chromatography on silica gel using hexane with an increasing amount of dichloromethane (0–90%) as an eluent. In some cases, analytically pure samples were obtained after crystallization.

4.3.2.1. (1*R*,2*S*)-3-Methylimino-2-(trifluoromethyl)bornan-2-ol 9a. Yield: 200 mg (80%). Colourless crystals, mp 166–168 °C (Et_2O/hexane). ^{1}H NMR (200 MHz): δ 0.95, 0.99, 1.07 (3s, 3H each, $3CH_3$), 1.32–1.92 (m, 4H, $2CH_2$), 2.74 (d, $^3J_{H,H}$ = 4.8 Hz, 1H, CH), 3.20 (s, 3H, CH_3N), 3.67 (br s, 1H, OH) ppm. ^{13}C NMR (50 MHz): δ 9.9, 18.7 ($2CH_3$), 21.8 (CH_2, CH_3), 29.0 (CH_2), 40.1 (CH_3N), 48.9 (CH), 47.5, 51.6 ($2C_q$), 79.9 (q, $^2J_{C,F}$ = 26.3 Hz, C_q), 125.4 (q, $^1J_{C,F}$ = 287.8 Hz, CF_3), 178.4 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.7 (s, CF_3) ppm. IR (KBr): ν 3405s (br, OH), 2995s, 2983m, 2970s, 1698s (C=N), 1636w, 1496w, 1458w, 1394m, 1339m, 1287s, 1272s, 1159vs, 1121s, 1030m, 966s, 830m, 741m cm^{-1}. MS (EI): *m*/*z* 249 (21, M$^{+\cdot}$), 109 (12), 96 (13), 69 (100, $[CF_3]^+$), 59 (10), 42 (32). Anal. Calcd for $C_{12}H_{18}F_3NO$ (236.24): C, 57.82; H, 7.28, N, 5.62. Found: C, 57.78; H, 7.14; N, 5.60. $[\alpha]_D$ = −3.7 (*c* 0.9, $CHCl_3$).

Analogously, *rac*-**9a** was prepared from *rac*-**3a** (mp 60–62 °C, hexane) in 78% yield. Colourless crystals; mp 153–155 °C (Et_2O/hexane).

4.3.2.2. (1*R*,2*S*)-3-Ethylimino-2-(trifluoromethyl)bornan-2-ol 9b. Yield: 220 mg (83%). Colourless crystals; mp 58–60 °C (hexane). ^{1}H NMR (200 MHz): δ 0.98, 1.02, 1.14 (3s, 3H each, $3CH_3$), 1.18 (t, 3H, $^3J_{H,H}$ = 7.3 Hz, CH_3CH_2), 1.37–1.96 (m, 4H, $2CH_2$), 2.74 (d, $^3J_{H,H}$ = 4.8 Hz, 1H, CH), 3.20 (br s, 1H, OH), 3.46 (q, 2H, $^3J_{H,H}$ = 7.3 Hz, CH_3CH_2) ppm. ^{13}C NMR (50 MHz): δ 9.7, 15.1, 18.5, 21.9 ($4CH_3$), 22.0, 28.8 ($2CH_2$), 47.1, 51.2 ($2C_q$), 47.3 (CH_2N), 48.9 (CH), 79.7 (q, $^2J_{C,F}$ = 26.4 Hz, C_q), 125.3 (q, $^1J_{C,F}$ = 288.2 Hz, CF_3), 176.4 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.6 (s, CF_3) ppm. IR (KBr): ν 3416vs (br, OH), 2984s, 2971s, 2938m, 2833m, 1689m (C=N), 1496w, 1459w, 1395w, 1395w, 1356w, 1286m, 1270s, 1227w, 1161vs, 1145s, 1119s, 1094m, 1042w, 1011w, 970m, 848w, 741w cm^{-1}. MS (EI): *m*/*z* 263 (28, M$^{+\cdot}$), 248 (13), 110 (17), 82 (10), 69 (92, $[CF_3]^+$), 56 (100), 41 (16). Anal. Calcd for $C_{13}H_{20}F_3NO$ (263.31): C, 59.30; H, 7.66; N, 5.32. Found: C, 59.24; H, 7.69; N, 5.23. $[\alpha]_D$ = +11.4 (*c* 1.1, $CHCl_3$).

4.3.2.3. (1*R*,2*S*)-3-(Isopropyl)imino-2-(trifluoromethyl)bornan-2-ol 9c. Yield: 230 mg (82%). Isolated after chromatography as a pale yellow oil. ^{1}H NMR (700 MHz): δ 0.95, 1.00, 1.08 (3s, 3H each, $3CH_3$), 1.11, 1.13 (2d, $^3J_{H,H}$ = 6.3 Hz, 3H each, $(CH_3)_2CH$), 1.41–1.43, 1.64–1.71, 1.78–1.88 (3m, 4H, $2CH_2$), 2.70 (d, $^3J_{H,H}$ = 4.9 Hz, 1H, CH), 3.21 (br s, 1H, OH), 3.59–3.63 (m, 1H, $(CH_3)_2CH$) ppm. ^{13}C NMR (175 MHz): δ 10.1 (q, $^4J_{C,F}$ = 1.4 Hz, CH_3), 18.9, 22.3, 23.3, 23.8 ($4CH_3$), 22.5 (CH_2), 29.2 (q, $^4J_{C,F}$ = 2.6 Hz, CH_2), 47.08 (q, $^3J_{C,F}$ = 1.4 Hz, C_q), 49.6, 53.1 (2CH), 51.5 (C_q), 80.1 (q, $^2J_{C,F}$ = 26.4 Hz, C_q), 125.7 (q, $^1J_{C,F}$ = 286.9 Hz, CF_3), 174.3 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.6 (s, CF_3) ppm. IR (film): ν 3393s (br, OH), 2970vs, 2940vs, 2881s, 1692vs (C=N), 1605w, 1497m, 1459s, 1395s, 1380s, 1364s, 1345m, 1282vs, 1271vs, 1228m, 1166vs, 1145vs, 1102vs, 1011s, 996s, 967s, 836s, 742s cm^{-1}. MS (CI, NH_3): *m*/*z* 279 (14), 278 (100, $[M+1]^+$). Anal. Calcd for $C_{14}H_{22}F_3NO$ (277.33): C, 60.63; H, 8.00. Found: C, 60.53; H, 7.96. $[\alpha]_D$ = +5.4 (*c* 1.0, $CHCl_3$).

4.3.2.4. (1*R*,2*S*)-3-(*tert*-Butyl)imino-2-(trifluoromethyl)bornan-2-ol 9d. Yield: 230 mg (79%). Colourless crystals, mp 46–49 °C (hexane, dry ice). ^{1}H NMR (200 MHz): δ 0.97, 1.03, 1.10 (3s, 3H each, $3CH_3$), 1.26 (s, 9H, $(CH_3)_3C$), 1.43–1.90 (m, 4H, $2CH_2$), 2.79 (d, $^3J_{H,H}$ = 5.0 Hz, 1H, CH), 3.21 (br s, 1H, OH) ppm. ^{13}C NMR (50 MHz): δ 9.8, 18.5, 22.2 ($3CH_3$), 21.9, 28.7 ($2CH_2$), 30.0 ($(CH_3)_3C$), 47.6, 50.1, 55.0 ($2C_q$, $(CH_3)_3C$), 52.8 (CH), 80.3 (q, $^2J_{C,F}$ = 25.6 Hz, C_q), 125.4 (q, $^1J_{C,F}$ = 288.2 Hz, CF_3), 172.9 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.5 (s, CF_3) ppm. IR (KBr): ν 3388s (br, OH), 3017w, 2971s, 2883w, 1685m (C=N), 1656w, 1474w, 1460w, 1398w, 1391w, 1364w, 1283m, 1266s, 1214m, 1199m, 1161vs, 1154vs, 1101s, 998w, 968s, 923w, 850w, 828w, 747w, 688w cm^{-1}. MS (EI): *m*/*z* 291 (20, M$^{+\cdot}$), 235 (26, $[(M+1-C_4H_9)]^+$), 166 (20), 109 (16), 69 (47, $[CF_3]^+$), 57 (100, $[C_4H_9]^+$), 41 (18). Anal. Calcd for $C_{15}H_{24}F_3NO$ (291.36): C, 61.84; H, 8.30; N, 4.81. Found: C, 61.83; H, 8.36; N, 4.87. $[\alpha]_D$ = +13.0 (*c* 1.3, $CHCl_3$).

4.3.2.5. (1*R*,2*S*)-3-(Cyclohexyl)imino-2-(trifluoromethyl)bornan-2-ol 9e. Yield: 210 mg (65%). Colourless crystals, mp 98–102 °C (pentane, dry ice). ^{1}H NMR (700 MHz): δ 0.95, 1.00, 1.08 (3s, 3H each, $3CH_3$), 1.25–1.33, 1.42–1.46, 1.56–1.68, 1.77–1.87 (4m, 14H, $7CH_2$), 2.70 (d, $^3J_{H,H}$ = 4.9 Hz, 1H, CH), 3.23–3.27 (m, 2H, CH, OH) ppm. ^{13}C NMR (50 MHz): δ 9.7, 18.4, 21.9 ($3CH_3$), 22.3, 24.3, 25.3, 28.8, 32.9, 33.4 ($7CH_2$), 47.3, 51.1, ($2C_q$), 49.3, 60.8 (2CH), 79.7 (q, $^2J_{C,F}$ = 26.1 Hz, C_q), 125.3 (q, $^1J_{C,F}$ = 288.0 Hz, CF_3), 174.6 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.6 (s, CF_3) ppm. IR (KBr): ν 3300s (br, O–H), 3002m, 2987m, 2934vs, 2858m, 1751w, 1686m, 1680m, 1655w, 1496w, 1477m, 1406w, 1397w, 1352m, 1284m, 1272s, 1227w, 1163vs, 1147vs, 1116s, 1075w, 1060w, 1010w, 995w, 967m, 943w, 891w, 829w, 642w, 675w cm^{-1}. MS (CI, NH_3): *m*/*z* 319 (20), 318 (100, $[M+1]^+$). Anal. Calcd for $C_{17}H_{36}F_3NO$ (317.40): C, 63.33; H, 8.26; N, 4.41. Found: C, 64.23; H, 8.23, N, 4.37. $[\alpha]_D$ = −5.5 (*c* 0.9, $CHCl_3$).

4.3.2.6. (1*R*,2*S*)-3-[(1′*R*)-1′-(Phenylethyl)imino]-2-(trifluoromethyl)bornan-2-ol 9f. Yield: 300 mg (88%). Isolated after chromatography as a pale yellow oil. ^{1}H NMR (200 MHz): δ 0.83, 0.96, 1.11 (3s, 3H each, $3CH_3$), 1.48 (d, 3H, $^2J_{H,H}$ = 6.6 Hz, CH_3CH), 1.53–2.02 (m, 4H, $2CH_2$), 2.83 (d, $^3J_{H,H}$ = 4.9 Hz, 1H, CH), 3.22 (br s, 1H, OH), 4.64 (q, 1H, $^32J_{H,H}$ = 6.6 Hz, CHN), 7.23–7.46 (m, 5H, C_6H_5) ppm. ^{13}C NMR (50 MHz): δ 9.8, 18.5, 21.7 ($3CH_3$), 22.2, 28.9 ($2CH_2$), 24.3 (CH_3CH), 49.5 (CHN), 47.7, 51.1 ($2C_q$), 80.0 (q, $^2J_{C,F}$ = 26.2 Hz, C_q), 125.2 (q, $^1J_{C,F}$ = 287.9 Hz, CF_3), 61.1 (CH_3CH), 126.4, 126.8, 128.3 (5CH arom.), 144.8 (C_q, arom.), 175.2 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.6 (s, CF_3) ppm. IR (film): ν 3543m (br, OH), 3087w, 3063w, 2970vs, 2927vs, 2882s, 1948w, 1875w, 1806w, 1692vs, (C=N), 1604w, 1494s, 1452s, 1395s, 1373s, 353*m*, 1281vs, 1269vs, 1226m, 1197s, 1166vs, 1146vs, 1104vs, 1031w, 1011s, 995s, 968vs, 918w, 831m, 761s, 742s, 700vs cm^{-1}. MS (CI, NH_3): *m*/*z* 341 (21), 340 (100, $[M+1]^+$). Anal. Calcd for $C_{19}H_{24}F_3NO$ (339.40): C, 67.24; H, 7.13. Found: C, 67.25; H, 7.07. $[\alpha]_D$ = +72.6 (*c* 1.0, $CHCl_3$).

4.3.2.7. (1*R*,2*S*)-3-Phenylimino-2-(trifluoromethyl)bornan-2-ol 9g. Yield: 230 mg (74%). Colourless crystals, mp 86–88 °C (hexane). ^{1}H NMR (200 MHz): δ 0.91, 1.07, 1.14 (3s, 3H each, $3CH_3$), 1.53–1.96 (m, 4H, $2CH_2$), 2.52 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 3.41 (br s, 1H, OH), 6.78–7.37 (m, 5H, C_6H_5) ppm. ^{13}C NMR (50 MHz): δ 9.8, 18.3, 21.9 ($3CH_3$), 22.6, 28.8 ($2CH_2$), 51.2 (CH); 47.8, 51.6 ($2C_q$), 79.9 (q, $^2J_{C,F}$ = 26.6 Hz, C_q), 125.2 (q, $^1J_{C,F}$ = 287.9 Hz, CF_3), 119.8, 124.3, 128.8 (5CH arom.), 149.4 (C_q arom.), 178.7 (C=N) ppm. ^{19}F NMR (188 MHz): δ −70.6 (s, CF_3) ppm. IR (KBr): ν 3400s

(br, OH), 3082w, 3061w, 3022w, 2998m, 2988m, 2970s, 2947m, 2884m, 1688s (C=N), 1669s, 1597m, 1490m, 1449w, 1396m, 1385m, 1281s, 1268s, 1172vs, 1268vs, 1150vs, 1104vs, 1011m, 995s, 968s, 908m, 834m, 771m, 741s, 692s cm^{-1}. MS (EI): *m*/*z* 311 (27, $M^{+\cdot}$), 158 (14), 104 (100), 77 (28, $[C_6H_5]^+$), 69 (42, $[CF_3]^+$), 41 (11). Anal. Calcd for $C_{17}H_{20}F_3NO_2$ (311.35): C, 65.58; H, 6.47; N 4.50. Found: C, 65.61; H, 6.29; N, 4.47. $[\alpha]_D$ = +237.9 (*c* 0.8, $CHCl_3$).

4.3.2.8. (1*R*,2*S*)-3-(4′-Methoxyphenyl)imino-2-(trifluoromethyl)-bornan-2-ol 9h. Yield: 290 mg (85%). Colourless crystals, mp 68–70 °C (hexane). ^{1}H NMR (200 MHz): δ 0.93, 1.05, 1.16 (3s, 3H each, $3CH_3$), 1.55–1.93 (m, 4H, $2CH_2$), 2.61 (d, $^3J_{H,H}$ = 4.6 Hz, 1H, CH), 3.57 (br s, 1H, OH), 3.82 (s, 3H, CH_3O), 6.77–6.92 (m, 4H, C_6H_4) ppm. ^{13}C NMR (50 MHz): δ 9.9, 18.5, 22.0 ($3CH_3$), 22.6, 28.9 ($2CH_2$), 51.3 (CH), 47.9, 51.5 ($2C_q$), 55.4 (CH_3O), 80.1 (q, $^2J_{C,F}$ = 26.5 Hz, C_q), 125.4 (q, $^1J_{C,F}$ = 287.9 Hz, CF_3), 114.2, 121.5 (4CH arom.), 142.5, 156.9 ($2C_q$ arom.), 178.2 (C=N) ppm. ^{19}F NMR (188 MHz): δ −71.6 (s, CF_3) ppm. IR (KBr): *v* 3380s (br, OH), 3019m, 2998m, 2980m, 2971m, 2942m, 2918m, 2879m, 2838m, 2063w, 1874w, 1679s (C=N), 1608m, 1506vs, 1456m, 1442m, 1374m, 1295s, 1283s, 1274s, 1250s, 1158vs, 1145vs, 1108s, 1038s, 1010m, 993m, 972m, 966m, 906m, 844s, 827m, 745m, 674m cm^{-1}. MS (EI): *m*/*z* 342 (10), 341 (61, $M^{+\cdot}$), 188 (20), 134 (100), 77 (5, $[C_6H_5]^+$), 69 (28, $[CF_3]^+$). Anal. Calcd for $C_{18}H_{22}F_3NO_2$ (341.38): C, 63.33; H, 6.50; N, 4.10. Found: C, 63.55; H, 6.38; N, 4.06. $[\alpha]_D$ = +395.4 (*c* 1.0, $CHCl_3$).

4.4. Reduction of imino alcohols 9 with DIBAL-H—a general procedure

To a solution of 1 mmol of the corresponding imino alcohol **9** in 10 ml of anhydrous THF, 2.5 ml of a 1 M solution (2.5 mmol) of DIBAL-H in dichloromethane was added while cooling the reaction flask in an ice-bath. When the addition of DIBAL-H was complete, the mixture was heated at reflux for 40 min. Then, the mixture was cooled in a water-ice bath and carefully treated with a 1% aqueous solution of hydrochloric acid. THF was removed in vacuo, and the residual crude mixture was cooled in a water-ice bath and slowly basified with a saturated aqueous solution of sodium hydroxide. The alkaline solution was thoroughly extracted with diethyl ether, and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. Purification of the crude mixture was performed by column chromatography on alumina using a mixture of petroleum ether and dichloromethane (1:1) containing ca. 0.05% of triethylamine as the eluent.

4.4.1. (1*R*,2*S*,3*R*)-3-Methylamino-2-(trifluoromethyl)bornan-2-ol 10a

Yield: 190 mg (76%). Colourless crystals, mp 38–40 °C (hexane). ^{1}H NMR (700 MHz): δ 0.82, 1.03, 1.07 (3s, 3H each, $3CH_3$), 1.21–1.24, 1.39–1.43, 1.68–1.73, 1.78–1.83 (4m, 5H, CH and $2CH_2$), 1.57 (br s, 1H, NH), 2.47 (s, 3H, CH_3N), 2.72 (s, 1H, CH) ppm. ^{13}C NMR (175 MHz): δ 10.9 (q, $^4J_{C,F}$ = 1.4 Hz, CH_3), 22.0, 22.2 ($2CH_3$), 27.3 (CH_2), 28.4 (q, $^4J_{C,F}$ = 3.5 Hz, CH_2), 37.4 (CH), 50.5 (q, $^3J_{C,F}$ = 1.9 Hz, C_q), 51.6, 51.7 (CH_3N, C_q), 69.0 (q, $^3J_{C,F}$ = 1.9 Hz, CHN), 80.5 (q, $^2J_{C,F}$ = 25.0 Hz, C_q), 127.3 (q, $^1J_{C,F}$ = 285.2 Hz, CF_3) ppm. ^{19}F NMR (188 MHz): δ −71.6 (s, CF_3) ppm. IR (KBr): *v* 3439s (br, OH), 3375s (NH), 3008m, 2982s, 2968s, 2924s, 2893w, 1636w, 1478w, 1457w, 1432w, 1392w, 1294s, 1285s, 1243s, 1152vs, 1141s, 1123s, 1112m, 1024w, 974s, 960w, 930w 911w, 784w, 730m cm^{-1}. MS (EI): *m*/*z* 251 (13, $M^{+\cdot}$), 154 (13), 112 (37), 98 (100). Anal. Calcd for $C_{12}H_{20}F_3NO$ (251.29): C, 57.36; H, 8.02. Found: C, 57.43; H, 8.04. $[\alpha]_D$ = −5.5 (*c* 0.8, $CHCl_3$).

4.4.2. (1*R*,2*S*,3*R*)-3-Phenylamino-2-(trifluoromethyl)bornan-2-ol 10g

Yield: 230 mg (73%). Isolated after chromatography as a yellowish oil. ^{1}H NMR (700 MHz): δ 0.89, 1.08, 1.27 (3s, 3H each, $3CH_3$), 1.28–1.30, 1.46–1.51, 1.74–1.77, 1.83–1.87 (4m, 5H, CH and $2CH_2$), 1.56 (br s, 1H, NH), 3.62 (br s, 1H, OH), 3.71 (s, 1H, C_6H_5CH), 6.72–6.73, 6.84–6.86, 7.21–7.23 (3m, 5H, C_6H_5) ppm. ^{13}C NMR (175 MHz): δ 10.8 (q, $^4J_{C,F}$ = 1.6 Hz, CH_3), 21.7, 22.1 ($2CH_3$), 26.9 (CH_2), 28.4 (q, $^4J_{C,F}$ = 3.2 Hz, CH_2), 50.5 (q, $^3J_{C,F}$ = 1.8 Hz, C_q), 51.4 (CH), 52.2 (C_q), 65.3 (q, $^3J_{C,F}$ = 1.9 Hz, CHN), 82.2 (q, $^2J_{C,F}$ = 25.2 Hz, C_q), 115.3, 120.1, 129.65 (5CH arom.), 127.1 (q, $^1J_{C,F}$ = 288.7 Hz, CF_3), 147.7 (C_q arom.) ppm. ^{19}F NMR (188 MHz): δ −70.9 (s, CF_3) ppm. IR (KBr): *v* 3394vs (NH), 3370s (br, OH), 3038m, 3004s, 2959vs, 2938vs, 2891s, 2878s, 1717w, 1605vs, 1505vs, 1468s, 1393s, 1371m, 1309s, 1293s, 1292s, 1240vs, 1213vs, 1143vs, 1066s, 1028w, 976s, 917w 820w, 752s, 728s, 695s, cm^{-1}. MS (EI): *m*/*z* 313 (34, $M^{+\cdot}$), 174 (42), 161 (16), 160 (100), 132 (13), 118 (14), 106 (17), 104 (23), 93 (15), 77 (18). Anal. Calcd for $C_{17}H_{22}F_3NO$ (313.37): C, 65.16; H, 7.08; N, 4.47. Found: C, 65.26; H, 7.12; N, 4.42. $[\alpha]_D$ = +12.0 (*c* 1.0, $CHCl_3$).

4.5. Cyclization of amino alcohol 10a with phosgene

To a solution of 250 mg (1 mmol) of **10a** and 230 mg (2.3 mmol) of triethylamine in 2 ml of abs. toluene, 0.8 ml (1.5 mmol) of a 20% solution of phosgene in toluene was added while cooling the reaction flask in a water-ice bath. The solution was magnetically stirred for 12 h, then the mixture was diluted with water (10 ml) and extracted three times with dichloromethane (3 × ca. 10 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the solvents were evaporated. The residue obtained was purified by fast filtration through an alumina layer using a mixture of petroleum ether and dichloromethane (1:1) as the eluent. The isolated product **11a** was additionally purified by crystallization.

4.5.1. (1*R*,2*S*,6*R*)-1,5,10,10-Tetramethyl-2-(trifluoromethyl)-3-oxa-5-aza-tricyclo[5.2.1.0^{2,6}]-decan-4-one 11a

Yield: 250 mg (90%). Colourless crystals, mp 66–68 °C (petroleum ether). ^{1}H NMR (700 MHz): δ 0.96, 1.06, 1.11 (3s, 3H each, $3CH_3$), 1.09–1.14, 1.54–1.57, 1.73–1.76, 1.85–1.90 (4m, 4H, $2CH_2$), 2.06 (d, $^3J_{H,H}$ = 5.6 Hz, 1H, CH), 2.88 (s, 3H, CH_3N), 3.68 (s, 1H, CHN) ppm. ^{13}C NMR (175 MHz): δ 10.1 (q, $^4J_{C,F}$ = 1.6 Hz, CH_3), 19.4 (CH_2), 23.5, 24.7 ($2CH_3$), 27.7 (q, $^4J_{C,F}$ = 3.2 Hz, CH_2), 29.6 (CH), 44.9 (CH_3N), 50.1 (q, $^3J_{C,F}$ = 1.8 Hz, C_q), 51.3 (C_q), 67.1 (q, $^3J_{C,F}$ = 1.8 Hz, CHN), 87.6 (q, $^2J_{C,F}$ = 28.3 Hz, C_q), 124.9 (q, $^1J_{C,F}$ = 285.2 Hz, CF_3), 156.9 (C=O) ppm. ^{19}F NMR (188 MHz): δ −73.2 (s, CF_3) ppm. IR (KBr): *v* 3016w, 2979w, 2952w, 2900w, 2886w, 1765s (C=O), 1636w, 1502w, 1483w, 1432w, 1405w, 1321w, 1308w, 1284w, 1231w, 1178m, 1170m, 1150m, 1117w, 1077m, 1038m, 1024w, 983m, 754w cm^{-1}. MS (CI, isobutane): *m*/*z* 278 (100, $[M+1]^+$). Anal. Calcd for $C_{13}H_{18}F_3NO_2$ (277.29): C, 56.31; H, 6.54. Found: C, 56.33; H, 6.52. $[\alpha]_D$ = −16.5 (*c* 1.0, $CHCl_3$).

4.6. Reduction of hydroxy ketone 8

4.6.1. Method A

To a magnetically stirred and cooled (water-ice bath) solution of 240 mg (1 mmol) of **8** in 2 ml of methanol, 150 mg (4 mmol) of sodium borohydride was added in small portions. The mixture was stirred for 6 h, and then the solvent was evaporated to dryness. The solid residue was treated with water and extracted with dichloromethane (5 × ca. 10 ml). The organic solutions were combined, dried over anhydrous $MgSO_4$, filtered, and the solvents were evaporated. Based on the ^{19}F NMR spectrum, the ratio of the diaste-

reoisomers 2-*exo*,3-*exo*-**12** and 2-*exo*,3-*endo*-**12** was determined to be 9:1.

4.6.2. Method B

To a magnetically stirred and cooled (water-ice bath) solution of 240 mg (1 mmol) of **8** in 2 ml of abs. THF, 2.5 ml of a 1 M solution (2.5 mmol) of DIBAL-H in dichloromethane was added drop-wise while cooling in an ice-bath. The mixture was stirred for 2 h and then treated with water and a 1% aqueous solution of hydrochloric acid. Subsequently, the reaction mixture was extracted with dichloromethane (5 × ca. 10 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvents were evaporated. Based on the ^{19}F NMR spectrum, the ratio 2-*exo*,3-*exo*-**12**/2-*exo*,3-*endo*-**12** was determined to be 10:1.

The crude product obtained either by method A or by method B was purified by column chromatography on silica gel, and a mixture of petroleum ether with increasing amounts of dichloromethane (0–90%) was used as the eluent. The isolated material was additionally purified by crystallization to give an analytically pure sample of the major product 2-*exo*,3-*exo*-**12**.

4.6.2.1. (1*R*,2*S*,3*R*)-2-(Trifluoromethyl)bornane-2,3-diol 2-*exo*, 3-*exo*-12. Yield: 200 mg (83%) for method A and 220 mg (90%) for method B. Colourless crystals, mp 99–101 °C (hexane). ^1H NMR (200 MHz): δ 0.85, 1.04, 1.19 (3s, 3H each, $3CH_3$), 1.07–1.83 (m, 5H, CH, $2CH_2$), 2.46 (br. d, $^2J_{H,H}$ = 6.2 Hz, 1H, CHO*H*), 3.49 (br s, 1H, OH), 3.99–4.02 (d, $^2J_{H,H}$ = 6.1 Hz, 1H, C*H*OH) ppm. ^{13}C NMR (50 MHz): δ 10.3, 21.6 ($3CH_3$), 24.2; 28.0 ($2CH_2$), 50.2, 51.7 ($2C_q$), 51.1 (CH), 76.1 (CHOH), 81.9 (q, $^2J_{C,F}$ = 25.2 Hz, C_q), 126.6 (q, $^1J_{C,F}$ = 286.6 Hz, CF_3) ppm. ^{19}F NMR (188 MHz): δ −73.7 (s, CF_3) ppm. IR (KBr): 3408s (br, OH), 3008w, 2959m, 2941m, 2881w, 1636w, 1497w, 1483w, 1464w, 1448w, 1397m, 1373w, 1316m, 1291m, 1254m, 1162vs, 1146vs, 1132vs, 1060s, 989w, 977m, 961m, 941w, 816w, 768w, 737m, 726w cm^{-1}. MS (CI, isobutane): *m*/*z* 239 ([M+1]$^+$, 3), 221 ([M+1−H_2O]$^+$, 100), 203 (13), 109 (11), 95 (17). Anal. Calcd for $C_{11}H_{17}F_3O_2$ (238.25): C, 55.45; H, 7.19. Found: C, 55.63; H, 7.13. $[\alpha]_D$ = −28.9 (*c* 1.1, $CHCl_3$).

4.7. Cyclization of the diol 2-*exo*,3-*exo*-12 with 1,1′-carbonyldiimidazole

To a solution of 240 mg (1 mmol) of 2-*exo*,3-*exo*-**12** and 230 mg (2.3 mmol) of triethylamine in 2 ml of abs. dichloromethane, 200 mg (1.2 mmol) of 1,1′-carbonyldiimidazole was added. The mixture was magnetically stirred for 48 h at room temperature, then diluted with dichloromethane and subsequently washed with a 5% solution of hydrochloric acid and water. The organic layer was separated and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated, and the crude product was purified by column chromatography on silica gel using hexane with increasing amounts of dichloromethane (0–50%) as the eluent. Additional crystallization afforded an analytically pure sample.

4.7.1. (1*R*,2*S*,6*R*)-1,10,10-Trimethyl-2-(trifluoromethyl)-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decan-4-one 13

Yield: 250 mg (94%). Colourless crystals, mp 128–130 °C (CH_2Cl_2/hexane). ^1H NMR (700 MHz): δ 1.00, 1.14, 1.15 (3s, 3H each, $3CH_3$), 1.11–1.13, 1.54–1.60, 1.69–1.73, 1.89–1.94 (4m, 4H, $2CH_2$), 2.24 (d, $^3J_{H,H}$ = 5.6 Hz, 1H, CH), 4.66 (s, 1H, CH(O)) ppm. ^{13}C NMR (175 MHz): δ 10.0 (q, $^4J_{C,F}$ = 1.6 Hz, CH_3), 19.9 (CH_2), 23.0, 23.1 ($2CH_3$), 27.3 (q, $^4J_{C,F}$ = 3.5 Hz, CH_2), 47.4 (CH), 49.8 (q, $^3J_{C,F}$ = 1.8 Hz, C_q), 51.4 (C_q), 84.2 (q, $^3J_{C,F}$ = 1.6 Hz, CH(O)), 90.7 (q, $^2J_{C-F}$ = 29.0 Hz, C_q), 124.3 (q, $^1J_{C,F}$ = 283.4 Hz, CF_3), 153.7 (C=O) ppm. ^{19}F NMR (188 MHz): δ −72.3 (s, CF_3) ppm. IR (KBr): *v* 3024w, 3002w, 2979w, 2940m, 2884w, 1813s (C=O), 1629w, 1505w, 1457w, 1401w, 1366w, 1310m, 1270w, 1205s, 1190s, 1173s, 1159s, 1128m, 1080s, 1065s, 1052m, 984m, 812w, 767m, 728w, 673w cm^{-1}. MS (EI): *m*/*z* 264 (6, M$^{+\cdot}$), 205 (11), 202 (26), 189 (11), 177 (22), 163 (15), 162 (33), 160 (25), 110 (31), 109 (28), 95 (100), 93 (16), 70 (10), 69 (19, $[CF_3]^+$), 55 (12), 43 (11), 41 (19). Anal. Calcd for $C_{12}H_{15}F_3O_3$ (264.25): C, 54.55; H, 5.72. Found: C, 54.40; H, 5.59. $[\alpha]_D$ = −8.6 (*c* 1.0, $CHCl_3$).

4.8. X-ray crystal-structure determination of 8 and *rac*-9a

All measurements were performed on a Nonius KappaCCD area-detector diffractometer[27] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below,[28] and views of the molecules are shown in Figure 1. Data reduction was performed with HKL DENZO and SCALEPACK.[29] The intensities were corrected for Lorentz and polarization effects but not for absorption. Equivalent reflections were merged. The structures were solved by direct methods using SIR92,[30] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydroxy H-atoms were placed in the positions indicated by difference electron density maps, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinements of the structures were carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the case of **8**. Two and three reflections, respectively, whose intensities were considered to be extreme outliers, were omitted from the final refinement of **8** and *rac*-**9a**. Neutral atom scattering factors for non-H-atoms were taken from Ref. 31, and the scattering factors for H-atoms were taken from Ref. 32. Anomalous dispersion effects were included in F_c;[33] the values for f' and f'' were those of Ref. 34. The values of the mass attenuation coefficients are those of Ref. 35. All calculations were performed using the SHELXL97[36] program.

4.8.1. Crystal data for 8

$C_{11}H_{15}F_3O_2$, M = 236.23, colourless, prism, crystal dimensions 0.10 × 0.15 × 0.25 mm, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.1321(4) Å, b = 7.4872(3) Å, c = 21.007(1) Å, V = 1121.8(1) Å^3, T = 160 K, D_x = 1.399 g cm^{-3}, μ(MoK_α) = 0.127 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}$ = 50°, total reflections measured 14,503, symmetry independent reflections 1171, reflections with $I > 2\sigma(I)$ 1002, reflections used in refinement 1169, parameters refined 153, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0486, $wR(F^2)$ [all data] = 0.1228 ($w = [\sigma^2(F_o^2) + (0.0585P)^2 + 0.4099P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.147, secondary extinction coefficient 0.11(1), final Δ_{max}/σ 0.001, $\Delta\rho$(max; min) = 0.27; −0.24 e Å^{-3}.

4.8.2. Crystal data for *rac*-9a

$C_{12}H_{18}F_3NO$, M = 249.28, colourless, prism, crystal dimensions 0.20 × 0.20 × 0.20 mm, monoclinic, space group $P2_1/n$, Z = 4, a = 9.2167(3) Å, b = 13.6986(5) Å, c = 9.6071(3) Å, β = 92.446(2); V = 1211.85(7) Å^3, T = 160 K, D_x = 1.366 g cm^{-3}, μ(MoK_α) = 0.117 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}$ = 55°, total reflections measured 26,775, symmetry independent reflections 2782, reflections with $I > 2\sigma(I)$ 2239, reflections used in refinement 2779, parameters refined 162, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0437, $wR(F^2)$ [all data] = 0.1186 ($w = [\sigma^2(F_o^2) + (0.0593P)^2 + 0.3486P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.043, final Δ_{max}/σ 0.001, $\Delta\rho$(max; min) = 0.27; −0.27 e Å^{-3}.

The crystallographic data for the ethylimino analogue of *rac*-**9a** have also been deposited.[28]

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