Enzymatic Resolution of *O*-(Methoxymethyl)-Protected Tropane-diols

by **Olena Affolter**, **Angelika Baro**, **Sabine Laschat***, and **Peter Fischer**

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart (phone: +49-711-68564565; fax: +49-711-68564285; e-mail: sabine.laschat@oc.uni-stuttgart.de)

Dedicated to Professor *Gerhard Simchen* on the occasion of his 75th birthday

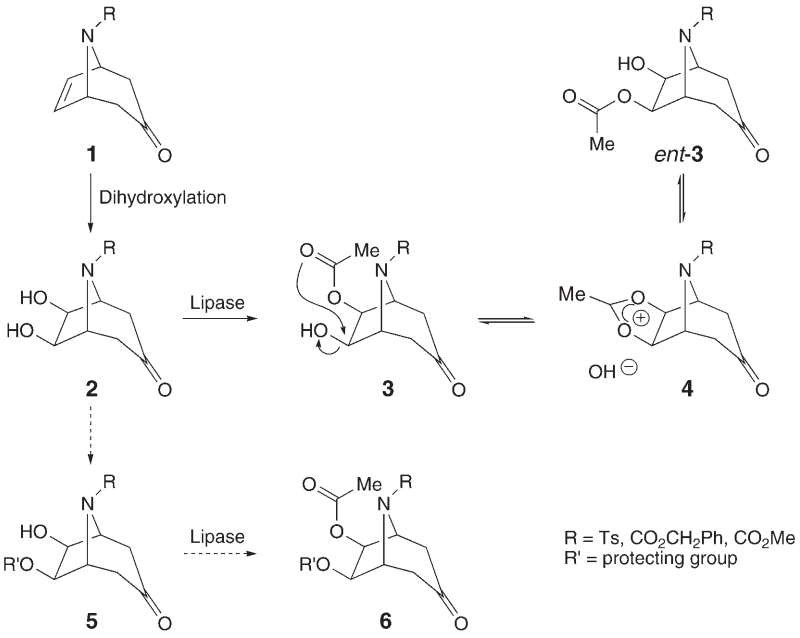
A convenient synthetic route to enantiomerically pure tropane-diol building blocks is described. The reaction sequence started from tropenone derivatives **1**, which were dihydroxylated to give 6,7-dihydroxytropanone derivatives **2**. After introduction of the methoxymethyl (MOM) protecting group in diol **2a**, a lipase-mediated resolution of the resulting racemic mono-MOM ether (±)-**5d** with vinyl acetate and vinyl trifluoroacetate gave the acetates (−)-**6d** and (−)-**6f**, respectively, with 96–99% ee, and MOM ether (+)-**5d** with up to 89% ee. Deacetylation of (−)-**6d** afforded quantitatively MOM ether (−)-**5d** with 99% ee, the absolute configuration of which was assigned *via* the modified *Mosher* method to be (*R*) at C(6). Enzymatic treatment of unprotected diol **2a** with vinyl trifluoroacetate or alkoxycarbonylation resulted in the formation of C_s-symmetrical products **9** and **12** rather than the desired desymmetrized derivatives.

Introduction. – Due to their biological activities, tropane alkaloids and derivatives thereof have been studied extensively over the last decades [1] (for some recent examples, see [2]). Furthermore, tropanes (= 8-methyl-8-azabicyclo[3.2.1]octanes) also provide useful chiral scaffolds for ligands in asymmetric catalysis [2e][3]. While the majority of tropane syntheses relied on either *de novo* routes or scopolamine as starting material [1][2], little work has been devoted to the functionalization *via* enantioselective deprotonation of tropinone [4], hydroboration of tropenone derivatives **1** to the corresponding chiral alcohol [5], or enzymatic resolution of the latter [6]. In a previous paper, we reported the dihydroxylation of tropenone derivatives **1** and subsequent lipase-mediated acetylation of the corresponding diols **2** to give the mono acetates **3**, which might be further functionalized (*Scheme 1*)[1]) [8]. However, it turned out that the direct enzymatic acylation of the diols **2** provided racemic mixtures of mono acetates **3** [9].

We anticipated that, even if the enzyme shows some enantioselectivity, the presence of the free OH group in compounds **3** accelerates the formation of an acetoxonium ion **4**, which may be opened to yield either **3** or *ent*-**3** (*Scheme 1*). Such acyl migration is well-known in carbohydrate chemistry [10], terminal 1,2-diols [11], mono- and diglycerides [7][12], 1,3-diols [13], and amino alcohols [14], resulting in reduced regio- and enantioselectivities. *Bäckvall* and co-workers utilized fast acyl migrations for dynamic kinetic asymmetric transformations, *i.e.*, one-pot lipase-catalyzed acylations of

[1]) For lipase-catalyzed reactions of 1,2-diols, see [7].

Scheme 1

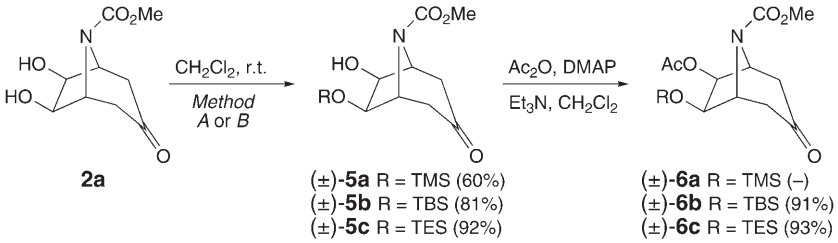


1,2- and 1,3-diols, Ru-catalyzed epimerizations, and intramolecular acyl migration to affect the formation of optically pure *syn*-1,2- and *syn*-1,3-diacetates [15]. With regard to 6,7-dihydroxytropinone derivatives **2**, neither of the above mentioned approaches was successful, and, thus, we decided to introduce a protecting group prior to enzymatic acetylation (*Scheme 1*). The results along this direction are reported below.

Results and Discussion. – To find a suitable protecting group, dihydroxy-tropane-carboxylate **2a**, which was accessible in 75% yield by treatment of **1** (R = CO_2Me) with K_2OsO_4 and *N*-methylmorpholine *N*-oxide monohydrate (NMO) in a mixture of acetone/H_2O/*t*-BuOH 10 : 2 : 1 [9][16], was first reacted with various silylation reagents (*Scheme 2*). While treatment with TMSCl in the presence of *Hünig* base yielded the corresponding racemic mono-silylated carboxylate **5a** in 60% (*Method A*), both silyloxy derivatives **5b** and **5c** were obtained in a similar manner in 81 and 92% yield, respectively (*Method B*). In the case of **5b**, the corresponding disilylated compound was obtained in 3% yield. The chemical acetylation of silyloxy derivatives (±)-**5b** and **5c** with Ac_2O, DMAP, and Et_3N in CH_2Cl_2 gave the corresponding acetates (±)-**6b** and **6c**, respectively in > 90% yield (*Scheme 2*). However, under these conditions the TMS group in (±)-**5a** was removed, finally giving the corresponding mono- and diacetate. It must be noted that desilylation of TMS derivative **5a** was observed even at storage.

Treatment of protected dihydroxy compounds (±)-**5** with vinyl acetate and lipases Chirazyme L-1 and L-6 and Novozyme 435 (*Candida antarctica* lipase B), however, did not give any trace of the desired acylation products **6**. Presumably, the bulky silyl

Scheme 2[a])

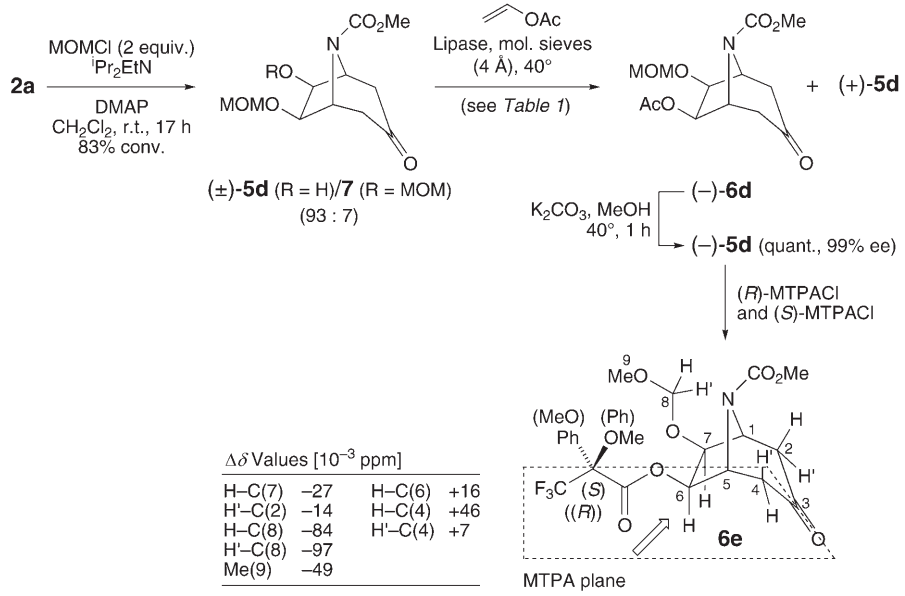


[a]) *Method A*: Me_3SiCl (TMSCl), EtN^iPr_2, 1 h. *Method B*: (*t*-Bu)Me_2SiCl (TBSCl) or Et_3SiCl (TESCl), Et_3N, 4-(dimethylamino)pyridine (DMAP), 5 h.

groups prevent access to the active site of the enzymes. Even Chirazyme L-5 (*Candida antarctica* lipase A), which is known to accept sterically hindered alcohols [17], did not yield **6**.

Therefore, methoxymethyl (MOM) was introduced as an alternative protecting group (*Scheme 3*). The lipophilic binding site of the lipases might favor a MOM acetal over more polar carboxylates, while simultaneously allowing the OH group to be attacked by the enzyme. Treatment of the dihydroxy derivative **2a** with 2 equiv. MOMCl in the presence of *Hünig* base and DMAP gave a mixture of mono- and bis-MOM ether **5d** and **7** in a ratio of 93:7, which was not separable by column chromatography (*Scheme 3*). The chemical acetylation of **5d** to **6d** under the above

Scheme 3. *MOM Protection of Diol* **2a**, *Subsequent Lipase-Catalyzed Resolution of (±)-*__5d__, *and Assignment of the Absolute Configuration of (–)-*__5d__ *According to* Kakisawa *and co-workers* [18]



mentioned conditions proceeded in 74% yield. For enzymatic resolution of (±)-**5d** with vinyl acetate, various lipases and solvents were investigated at 40° (*Table 1*).

Table 1. *Enzymatic Acetylation of MOM Ether (±)-***5d** *with Various Lipases to Acetate* **6d**

Entry	Solvent	Enzyme[a])	Time [h]	Conv. [%]	Yield [%][b])	% ee[c])
1	Toluene	Chirazyme L-1	47	23	–	5
2	Toluene	Chirazyme L-5	48	3	–	–
3	Toluene	Chirazyme L-6	47	38	33	96
4	Toluene	Novozyme 435	48	7	–	–
5	CH_2Cl_2	Chirazyme L-1	26	5	–	–
6	CH_2Cl_2	Chirazyme L-5	24	3	–	–
7	CH_2Cl_2	Chirazyme L-6	24	2	–	–
8	CH_2Cl_2	Novozyme 435	26	3	–	–
9	Et_2O	Chirazyme L-1	4.5	14	–	50[d])
10	Et_2O	Chirazyme L-1	16	38	–	15[d])
11	Et_2O	Chirazyme L-1	18	51	41	8[d])
12	Et_2O	Chirazyme L-5	24	–	–	–
13	Et_2O	Chirazyme L-6	4.0	48	38	96
14	Et_2O	Chirazyme L-6	5.5	40[e])	31	96
15	Et_2O	Novozyme 435	6.0	11	–	> 99
16	Et_2O	Novozyme 435	24	51[e])	45	99

[a]) Chirazyme L-1 from *Pseudomonas* sp., Chirazyme L-5 from *Candida antarctica*, Chirazyme L-6 from *Pseudomonas* cep., and Novozyme 435 from *Candida antarctica*. [b]) Yield of isolated **6d**. [c]) Enantioselectivities were determined by capillary GC on chiral stationary phase *Bondex un-β*. [d]) Opposite enantiomer (+)-**6d** is preferred. [e]) (+)-**5d** was isolated in 59% yield with 65% ee (*Entry 14*) and in 40% yield with 82% ee (*Entry 16*).

Lipase Chirazyme L-6 gave promising results (*Entries 3* and *13*). In toluene and Et_2O, respectively, good conversions and high enantiomeric excesses of 96% ee were obtained. In one case, the hydroxy derivative (+)-**5d** was isolated in 59% yield with 65% ee besides enantiomerically pure (−)-**6d** (96% ee; *Entry 14*). In Et_2O, also Novozyme 435 led to exceptional ee values of 99% but reacted much slower than Chirazyme L-6 (*Entries 15* and *16*). After 24 h reaction time, racemic MOM derivative (±)-**5d** was resolved to give (−)-**6d** with 99% ee, and (+)-**5d** in 40% yield and 82% ee (*Entry 16*). The other lipases Chirazyme L-1 and L-5 are less suitable independent of the solvent, giving low conversion and enantiomeric excess.

Whereas Et_2O was found to be the best solvent, CH_2Cl_2 was not suitable regardless of the enzyme used (*Entries 5–8*). Similar results were obtained for acetone and MeCN (not shown). It should be noted that, in Et_2O, Chirazyme L-1 resulted in the formation of the opposite enantiomer (+)-**6d** (*Entries 9–11*).

Concerning the further functionalization, the MOM acetate (−)-**6d** was deacetylated with K_2CO_3 in MeOH [18]. The reaction proceeded cleanly, and the enantiomerically pure MOM hydroxy derivative (−)-**5d** was obtained quantitatively with 99% ee (*Scheme 3*). The absolute configuration of (−)-**5d** was elucidated by NMR analysis according to the modified *Mosher* method [19] (*Scheme 3*). Compound (−)-**5d** was treated with (+)-(*S*)- and (−)-(*R*)-MTPACl (MTPACl = α-methoxy-α-(trifluoromethyl)phenylacetyl chloride) in the presence of pyridine at room temperature to give the

diastereoisomeric *Mosher* esters (*R*)-**6e** and (*S*)-**6e**. ^{1}H-NMR Spectra in $CDCl_3$ at room temperature, however, revealed a significant broadening of the signals for H–C(2), H–C(4), H–C(1), and H–C(5), rendering an assignment impossible. After considerable experimentation, $C_2D_2Cl_4$ at 393 K turned out to give the best results, thus avoiding any problems with rotamers at lower temperatures [9]. The ^{1}H,^{13}C long-range COSY of ester (*R*)-**6e** at 393 K revealed ^3J correlations between the ^{13}C signal of C(8) at δ 96.4 ppm and the ^{1}H signal of Me(9) at δ 3.30 ppm, as well as the *doublet* for H–C(7) at δ 4.14 ppm. The ^{1}H signal of the ester MeO group at δ 3.70 ppm showed a ^3J coupling with the ^{13}C signal of the ester CO group. The ^{13}C signals of C(2) and C(4) at $\delta = 45.4$ and 44.9 ppm were assigned according to ^3J correlation of C(2) with H–C(7) at δ 4.14 ppm. In the ^{1}H,^{13}C long-range COSY of the diastereoisomeric ester (*S*)-**6e** a ^3J coupling between the C(4) signal at δ 44.9 ppm and the *doublet* of H–C(6) at δ 5.10 ppm, and a ^3J coupling between the signal of C(2) at δ 45.5 ppm and the *doublet* of H–C(7) at δ 4.11 ppm were observed. Further assignments were accomplished by H,H-COSY measurements of both esters **6e** and the $\Delta\delta(\delta_S - \delta_R)$ values were obtained (*Scheme 3*). Applying *Kakisawa*'s rules [19], the configuration at C(6) of (–)-**5d** was assigned as (*R*).

In contrast to the deacetylation, deprotection of (–)-**6d** resulted in all cases in the formation of racemic acetate (±)-**3a** (*Scheme 4* and *Table 2*).

Scheme 4

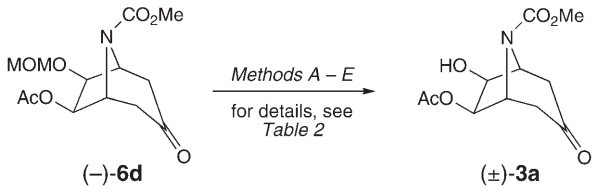


Table 2. *Deprotection of MOM Acetate (–)-***6d** *to Acetate* **3a**

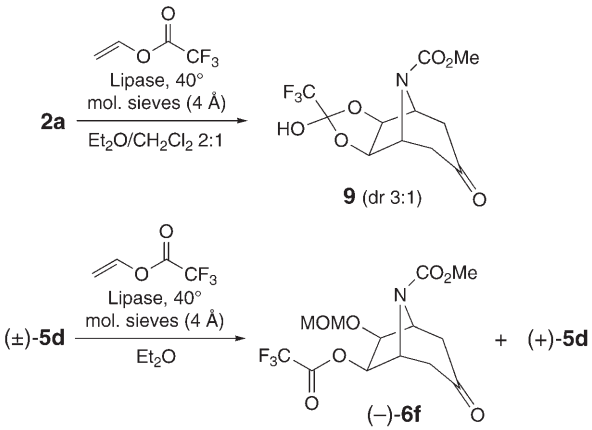
Method	Conditions	Conversion [%]
A	Me_3SiBr, CH_2Cl_2, reflux, 24 h	36
B	$BF_3 \cdot OEt_2$, MeCN/H_2O, 2 h	50
C	TsOH, dioxane/H_2O 6 : 1, reflux, 5 h	48
D	TsOH, dioxane/H_2O 3 : 1, reflux, 6 h	73
E	TFA, CH_2Cl_2, r.t., 5 h	quant.[a])

[a]) Yield of isolated (±)-**3a**: 66%.

As shown in *Table 2*, Me_3SiBr in refluxing CH_2Cl_2 [20], $BF_3 \cdot OEt_2$ in a mixture of MeCN/H_2O [21] and catalytic amounts of TsOH in dioxane/H_2O [22] led to low conversions. Upon increasing the amount of H_2O (*Method D*), the conversion was increased to 73%, but besides the desired acetate **3a**, 10% of dihydroxy derivative **2a** was formed. Complete removal of the MOM group was realized with TFA in CH_2Cl_2 at room temperature [23], and the target acetate **3a** was isolated in 66% yield, albeit being racemic (*Method E*).

Probably, as already observed for the enzymatic acylation of the dihydroxy carboxylate **2a** [9], owing to the free OH group again, the Ac migration dominated under the acidic reaction conditions. We anticipated that the electron-withdrawing CF_3CO group might disfavor the formation of the intermediate acetoxonium cations **4**. Surprisingly, little is known about the enzymatic resolution with lipase employing vinyl trifluoroacetate except one publication by *Miyazawa et al.* who studied the *Achromobacter* sp. lipase [24]. We used Chirazyme L-6 and Novozyme 435 for the enzymatic acylation of **2a** with vinyl trifluoroacetate at 40°. The solvent mixture Et_2O/CH_2Cl_2 2:1 was chosen, because **2a** was not soluble in pure Et_2O (*Scheme 5*).

Scheme 5



Lipase	Compound	*t* [h]	Conv. [%]
Novozyme 435	**2a**	3	57
Novozyme 435	**2a**	24	93
Chirazyme L-6	**2a**	24	45
Novozyme 435	(±)-**5d**	3	55 (–)-**6f** (35%, 98% ee) (+)-**5d** (40%, 89% ee)
Chirazyme L-6	(±)-**5d**	26	11

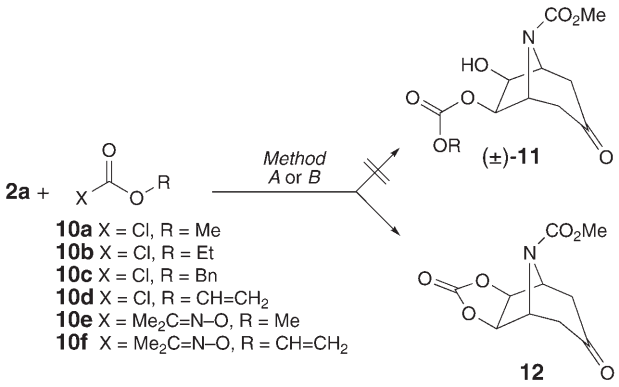
As can be seen, the two lipases differed remarkably in their reactivity. Surprisingly, a closer inspection of the NMR spectra revealed that, independent of the type of lipase, the 2-hydroxy-2-(trifluoromethyl)dioxole derivative **9** was obtained as a 3:1 mixture of diastereoisomers instead of the expected α-hydroxy-trifluoroacetate analogue of **3a**. A spectroscopic evidence for compound **9** is the quaternary-C signal at δ 115.8 and 116.7 ppm in the ^{13}C-NMR spectrum as compared to the signal of the C=O group in **6f** at δ 157.0 ppm. When **2a** was treated with $(CF_3CO)_2O$, again dioxole derivative **9** was formed as a 3:1 diastereoisomeric mixture. That means that the α-hydroxy trifluoroacetate has an even more pronounced tendency to form the acetoxonium ion than the corresponding α-hydroxy-acetate **3a**.

To check whether vinyl trifluoroacetate may lead to enantioselective acylation in cases where no acyl migration is possible, the MOM derivative (±)-**5d** was resolved with vinyl trifluoroacetate, and either Chirazyme L-6 or Novozyme 435 (*Scheme 5*).

Chirazyme L-6 gave only low conversion. In contrast, Novozyme 435 yielded (−)-**6f** in 35% with 98% ee, and MOM derivative (+)-**5d** in 40% with 89% ee.

In a final attempt, the enzymatic alkoxycarbonylation[2]) of unprotected dihydroxy compound **2a** was investigated because the corresponding carbonate is proposed to be less prone to acyl migration. First, as shown in *Scheme 6*, unprotected **2a** was reacted with various carbonic acid derivatives **10a** – **10d** in the presence of Et_3N and DMAP, but surprisingly, instead of derivative (±)-**11**, only *meso*-carbonate **12** was formed (*Method A*). In the case of **10a** and **10b**, compound **12** was isolated in 91 and 51% yield, respectively.

Scheme 6[a])



[a]) *Method A*: **10a** – **10b**, Et_3N, DMAP, CH_2Cl_2. *Method B*: **10e** and **10f**, Novozyme 435 or Chirazyme L-6, THF, 40°.

Upon treatment of **2a** with carbonic acid derivatives **10e** and **10f** in the presence of lipases Novozyme 435 or Chirazyme L-6 (*Method B*), again only compound **12** and no trace of the desired carbonate **11** was observed. Carbonate **12** was independently obtained in 58% yield by reaction of **2a** with *N*,*N*-carbonyldiimidazole in CH_2Cl_2 at room temperature.

Conclusions. – To overcome the racemization by acyl migration, dihydroxy derivative **2a** was protected with MOMCl prior to the lipase-mediated acetylation. Indeed, this synthetic strategy allowed resolution of the MOM derivative (±)-**5d** with vinyl acetate and lipases Chirazyme L-6 and Novozyme 435 to give enantiomerically pure acetate (−)-**6d** (96 – 99% ee) and (+)-**5d** (up to 82% ee). Deacetylation of (−)-**6d** with K_2CO_3 in MeOH yielded quantitatively (−)-**5d** with 99% ee, being (*R*)-configured at C(6), as assigned by the *Mosher* method. Novozyme 435 also worked well in the resolution of (±)-**5d** with vinyl trifluoroacetate to afford the corresponding acetate (−)-**6f** (98% ee) and (+)-**5d** (89% ee). Thus, in this manner, enantiomerically pure dihydroxytropane building blocks are conveniently accessible, which can be used for

[2]) For previous work on regio- and/or enantioselective lipase-catalyzed alkoxycarbonylation of diols, see [25].

further manipulations. In contrast, when a free OH group adjacent to the acyl function is present, as in removal of MOM in **6d** or enzymatic acylation of **2a** with vinyl trifluoroacetate, acyl migration was favored, leading either to racemic products, or the intermediate acetoxonium ions were trapped as dioxole **9**. Even the use of alkoxycarbonylation reagents **10** did not overcome the strong neighboring-group effect of the second OH group in diol **2a**.

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Experimental Part

1. *General*. Commercial reagents were used without further purification unless otherwise indicated. All solvents were distilled prior to use. Reactions were performed in oven-dried glassware. Flash chromatography (FC): was performed on silica gel *60* (230–400 mesh; *Fluka*). GC: *Hewlett-Packard HP 6890* instrument; column *HP 5TA* (30 m × 0.32 mm); temp. program: 16° min^{-1} gradient from 80° to 300°; *Finnigan Trace GC 2000 Ultra*, column trifluoroacetyl-γ-cyclodextrine (30 m × 0.25 mm), *Lipodex E*, *Bondex un-β, Bondex un-α*, *Bondex un-α + β*, *Amidex P2210*. M.p.: *Büchi SMP-20*; uncorrected. IR Spectra: *Bruker Vector-22* FT-IR spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance-500* instrument; at 500/125 MHz; δ in ppm, J in Hz; signal assignments are based on DEPT and COSY experiments; * denotes signals of the minor rotamer, and # denotes the minor diastereoisomer. MS and ESI-MS: *Finnigan MAT-95*, *Varian MAT-711*, and *Bruker Daltonics micrOTOF_Q*; in *m/z* (rel. %).

2. *Methyl 6-Hydroxy-3-oxo-7-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate* ((±)-**5a**). A soln. of TMSCl (92 µl, 0.716 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a soln. of **2a** (140 mg, 0.651 mmol) and ^{i}Pr$_2$EtN (215 µl, 1.30 mmol) in CH_2Cl_2 (6 ml) under N_2, and the mixture was stirred for 16 h. After removal of the solvent and all volatile materials *in vacuo*, the residue was chromatographed (SiO_2; AcOEt/hexane 4:1; R_f (AcOEt/hexane 2:1) 0.51) to give (±)-**5a** (110 mg, 0.383 mmol, 60%). Colorless oil. FT-IR (ATR): 3472*m*, 1702v*s*, 1451*s*, 1394*s*, 1253*s*, 1094*s*, 1009*m*, 886*s*, 632*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.19 (*s*, Me_3Si, Me_3Si*); 2.40 (*s*, 1 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 2.44 (*s*, 2 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 2.47 (*s*, 1 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 2.53–2.63, 2.65–2.75 (2*m*, 2 × 2 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 3.45 (br. *s*, OH*); 3.54–3.60 (br. *m*, OH); 3.77 (*s*, MeO, MeO*); 3.91–3.96 (*m*, 2 H, H–C(6), H–C(6)*); 4.02 (*s*, 1 H, H–C(7)); 4.03 (*s*, 1 H, H–C(7)*); 4.20–4.27 (*m*, 1 H, H–C(1)* or H–C(5)*); 4.31–4.40 (br. *m*, 2 H, H–C(1), H–C(5)); 4.43–4.48 (*m*, 1 H, H–C(1)* or H–C(5)*). ^{13}C-NMR (125 MHz, $CDCl_3$): 0.0 (Me_3Si, Me_3Si*); 45.7, 46.0, 46.3 (C(2), C(4), C(2)*, C(4)*); 53.2 (MeO, MeO*); 61.4, 61.5, 61.7 (C(1), C(5), C(1)*, C(5)*); 74.1, 74.7, 75.5 (C(6), C(7), C(6)*, C(7)*); 155.3 (COO, COO*); 171.4 (OCO, OCO*); 206.0 (C(3), C(3)*). CI-MS: 288 (40, $[M+H]^+$), 256 (100), 240 (20), 213 (20), 197 (10), 155 (15), 123 (30), 103 (15). Anal. calc. for $C_{12}H_{21}NO_5Si$ (287.39): C 50.15, H 7.37, N 4.87; found: C 50.05, H 7.32, N 4.54.

3. *Methyl 7-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* ((±)-**5b**). A soln. of TBSCl (14.5 mg, 0.095 mmol) in CH_2Cl_2 (1 ml), was added dropwise to a soln. of **2a** (17 mg, 0.079 mmol), Et_3N (0.1 ml), and DMAP (5 mg) in CH_2Cl_2 (1 ml) at 0°, and the mixture was stirred at r.t. for 5 h. Then CH_2Cl_2 (30 ml) was added, and the mixture washed with 1N aq. HCl (2 × 10 ml). The org. layer was successively washed with a sat. soln. of $NaHCO_3$ and H_2O (10 ml each), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; AcOEt/hexane 1:1; R_f 0.44) to give (±)-**5b** (21 mg, 0.064 mmol, 81%). Colorless solid. M.p. 90°. FT-IR (ATR): 3486*m*, 2958*m*, 2857*m*, 1703v*s*, 1446*s*, 1386v*s*, 1251*s*, 1198*s*, 1080v*s*, 1008*s*, 772v*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.12 (*s*, Me_2Si); 0.14 (*s*, Me_2Si*); 0.91 (*s*, Me_3C, Me_3C*); 2.40, 2.44, 2.47, 2.49 (4*s*, 4 × 1 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 2.53–2.64, 2.65–2.75 (2*m*, 2 × 2 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 3.45 (*d*, J = 5.4, OH*); 3.58 (*d*, J = 5.2, OH); 3.77 (*s*, COOMe, COOMe*); 3.92–3.98 (*m*, 2 H, H–C(6), H–C(6)*); 4.05 (br. *s*, 1 H, H–C(7)*); 4.06 (*s*, 1 H, H–C(7)); 4.23–4.29 (*m*, 1 H, H–C(1)* or

H–C(5)*); 4.31–4.41 (*m*, 2 H, H–C(1), H–C(5)); 4.44–4.51 (*m*, 1 H, H–C(1)* or H–C(5)*). ^{13}C-NMR (125 MHz, $CDCl_3$): −5.2, −4.8 (Me_2Si, Me_2Si*); 18.1 (Me_3C, Me_3C*); 25.6 (Me_3C, Me_3C*); 45.4, 45.7, 45.9 (C(2), C(4), C(2)*, C(4)*); 52.9 (MeO, MeO*); 61.2, 61.5 (C(1), C(5), C(1)*, C(5)*); 74.1, 74.6 (C(6), C(6)*); 75.0, 75.7 (C(7), C(7)*); 155.0 (COO, COO*); 205.6 (C(3), C(3)*). CI-MS: 330.2 (100, $[M+H]^+$), 298 (10), 272 (75), 257 (20), 240 (20), 212 (15), 197 (10), 127 (10), 75 (10). Anal. calc. for $C_{15}H_{27}NO_5Si$ (329.47): C 54.68, H 8.26, N 4.25; found: C 54.71, H 8.26, N 4.13.

3.1. *Methyl 6-Hydroxy-3-oxo-7-[(triethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate* ((±)-**5c**). As described above for **5b**, from **2a** (81 mg, 0.38 mmol), Et_3N (140 µl), DMAP (12 mg) in CH_2Cl_2 (3 ml), and TESCl (82 µl, 0.49 mmol); FC with AcOEt/hexane 1:2. Yield: 92% (114 mg, 0.35 mmol). Colorless oil. TLC: R_f 0.34. FT-IR (ATR): 3475*m*, 2955*m*, 2912*m*, 2878*m*, 1703v*s*, 1449*s*, 1390*s*, 1189*m*, 1091v*s*, 1005*s*, 729v*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.65 (*q*, *J* = 8.0, 12 H, $SiCH_2Me$, $SiCH_2Me$*); 0.96 (*t*, *J* = 8.0, 18 H, $SiCH_2Me$, $SiCH_2Me$*); 2.40 (*s*, 1 H, H–C(2)* or H–C(4)*); 2.43 (*s*, 2 H, H–C(2), H–C(4)); 2.52–2.62, 2.64–2.75 (2*m*, 2 × 2 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 3.51–3.57 (br. *m*, OH*); 3.61–3.69 (br. *m*, OH); 3.76 (*s*, COO*Me*, COO*Me*); 3.92–3.96 (*m*, 2 H, H–C(6), H–C(6)*); 4.02–4.07 (*m*, 2 H, H–C(7), H–C(7)*); 4.20–4.28 (br. *m*, 1 H, H–C(1)* or H–C(5)*); 4.30–4.40 (br. *m*, 2 H, H–C(1), H–C(5)); 4.42–4.50 (br. *m*, 1 H–C(1)* or H–C(5)*). ^{13}C-NMR (125 MHz, $CDCl_3$): 4.5 ($SiCH_2Me$, $SiCH_2Me$*); 6.5 ($SiCH_2Me$, $SiCH_2Me$*); 45.4, 45.7, 45.8, 46.1 (C(2), C(4), C(2)*, C(4)*); 52.9 (MeO, MeO*); 61.3, 61.5 (C(1), C(5), C(1)*, C(5)*); 74.1, 74.6, 75.3 (C(6), C(7), C(6)*, C(7)*); 155.0 (COO, COO*); 205.7 (C(3), C(3)*). CI-MS: 330.1 (100, $[M+H]^+$), 300 (90), 268 (65), 255 (15), 240 (20), 225 (15), 196 (10), 155 (20), 127 (10), 103 (10), 87 (10). Anal. calc. for $C_{15}H_{27}NO_5Si$ (329.47): C 54.68, H 8.26, N 4.25; found: C 54.82, H 8.29, N 4.16.

4. *Methyl 6-Hydroxy-7-(methoxymethoxy)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* ((±)-**5d**). MOMCl (140 µl, 1.86 mmol) was added dropwise to a soln. of **2a** (200 mg, 0.93 mmol), ^{i}Pr$_2$EtN (790 µl, 4.65 mmol), and DMAP (12 mg, 0.09 mmol) in anh. CH_2Cl_2 (3 ml) at 0°, and the mixture was stirred at 0° for 0.5 h and for a further 16.5 h at r.t. Then, CH_2Cl_2 (30 ml) was added, and the mixture was washed with a sat. soln. of NH_4Cl (20 ml). The org. layer was dried (Na_2SO_4) and concentrated. The residue was purified by FC (SiO_2; AcOEt/hexane 3:1; R_f 0.23) to give (±)-**5d** (116 mg, 0.45 mmol, 48%). Yellowish oil. FT-IR (ATR): 3438*m*, 2954*m*, 2903*m*, 2828*m*, 1698v*s*, 1451*s*, 1398*s*, 1192*m*, 1102*s*, 1040*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.44 (*s*, 2 H, H–C(2)*, H–C(4)*); 2.47 (*s*, 2 H, H–C(2), H–C(4)); 2.53–2.75 (*m*, 4 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 3.23 (br. *s*, OH*); 3.33 (br. *s*, OH); 3.40 (*s*, CH_2OMe, CH_2OMe*); 3.76 (*s*, COOMe, COOMe*); 3.97 (*s*, 1 H, H–C(6)*); 3.99 (*s*, 1 H, H–C(6)); 4.07–4.10 (*m*, 2 H, H–C(7), H–C(7)*); 4.34–4.59 (br. *m*, 4 H, H–C(1), H–C(5), H–C(1)*, H–C(5)*); 4.70 (*d*, *J* = 6.7, CH_2); 4.73 (*d*, *J* = 6.8, CH_2*). ^{13}C-NMR (125 MHz, $CDCl_3$): 45.2, 45.6, 45.7, 46.0 (C(2), C(4), C(2)*, C(4)*); 52.9 (MeO, MeO*); 56.2 (CH_2OMe, CH_2OMe*); 59.0, 61.3 (C(1), C(5), C(1)*, C(5)*); 74.3 (C(6)*); 74.9 (C(6)); 78.9 (C(7)); 79.7 (C(7)*); 96.9 (CH_2, CH_2*); 154.9 (COO, COO*); 205.3 (C(3), C(3)*). EI-MS: 259.1 (10, $M^{+\bullet}$), 214 (20), 197 (25), 155 (85), 127 (30), 87 (15), 59 (20), 45 (100), 28 (20). HR-EI-MS: 259.1056 ($M^{+\bullet}$, $C_{11}H_{17}NO_6^{+\bullet}$; calc. 259.1056).

5. *Methyl 6-Acetoxy-7-(methoxymethoxy)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* (*rac*-**6d**). *Typical Procedure.* Ac_2O (20 µl, 0.20 mmol) was added to a soln. of **5d** (30 mg, 116 µmol), DMAP (5 mg, 41.0 µmol), and Et_3N (55 µl, 0.31 mmol) in anh. CH_2Cl_2 (1.5 ml), and the mixture was stirred at r.t. for 0.5 h. Then, CH_2Cl_2 (20 ml) was added, and the mixture was washed successively with 0.1N aq. NaOH and brine (10 ml each). The org. layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by FC (SiO_2; AcOEt/hexane 2:1; R_f (AcOEt/hexane 3:1) 0.32) to give **6d** (26 mg, 86.3 µmol, 74%). Colorless oil. FT-IR (ATR): 2956*m*, 2900*m*, 1739*s*, 1702v*s*, 1450*s*, 1396*s*, 1234*s*, 1196*m*, 1104*s*, 1042*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.09 (*s*, MeCO, MeCO*); 2.48–2.50 (*m*, 2 H, H–C(2)* or H–C(4)*); 2.50–2.52 (*m*, 1 H, H–C(2) or H–C(4)); 2.53 (*s*, 1 H, H–C(2) or H–C(4)); 2.57–2.67, 2.76–2.78 (2*m*, 2 × 2 H, H–C(2), H–C(4), H–C(2)*, H–C(4)*); 3.37 (*s*, CH_2OMe, CH_2OMe*); 3.77 (*s*, COOMe, COOMe*); 4.07, 4.08 (2*s*, 2 × 1 H, H–C(7), H–C(7)*); 4.42–4.61 (br. *m*, 4 H, H–C(1), H–C(5), H–C(1)*, H–C(5)*); 4.57 (*d*, *J* = 11.8, CH_2); 4.59 (*d*, *J* = 11.8, CH_2*); 4.93 (*s*, 1 H, H–C(6)); 4.94 (*s*, 1 H, H–C(6)*). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.6 (*Me*CO, *Me*CO*); 45.1, 45.6, 45.8, 46.2 (C(2), C(4), C(2)*, C(4)*); 53.0 (COO*Me*, COO*Me*); 56.1 (CH_2OMe, CH_2OMe*); 58.0, 59.4 (C(1), C(5), C(1)*, C(5)*); 76.2 (C(6), C(6)*); 78.9, 79.8 (C(7), C(7)*); 97.3 (CH_2, CH_2*); 154.5 (COO, COO*); 170.3

(OCO, OCO*); 204.6 (C(3), C(3)*). EI-MS: 301.1 (5, $M^{+\bullet}$), 256 (20), 241 (25), 214 (20), 196 (60), 154 (100), 127 (20), 59 (15), 45 (100), 28 (15). HR-EI-MS: 301.1161 ($M^{+\bullet}$, $C_{13}H_{19}NO_7^{+\bullet}$; calc. 301.1162).

5.1. *Methyl 6-Acetoxy-7-{[(*tert*-butyl)dimethy)silyl]oxy}-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* (*rac*-**6b**). R_f (AcOEt/hexane 1:3) 0.25. Yield: 91%. Colorless oil. FT-IR (ATR): 2955*m*, 2930*m*, 2857*m*, 1740*s*, 1703v*s*, 1449*s*, 1388*s*, 1237v*s*, 1194*s*, 1101*s*, 1007*s*, 775*s*, 679*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.03 (*s*, Me_2Si); 0.08 (*s*, Me_2Si*); 0.87 (*s*, Me_3C, Me_3C*); 2.08 (*s*, MeCO); 2.09 (*s*, MeCO*); 2.43, 2.46 (2*s*, 2 × 1 H, H−C(2), H−C(2)*, H−C(4), H−C(4)*); 2.49, 2.53 (2*d*, *J* = 10.5, 2 × 1 H, H−C(2), H−C(2)*, H−C(4), H−C(4)*); 2.59 (*t*, *J* = 5.0, 2 H, H−C(2), H−C(2)*, H−C(4), H−C(4)*); 2.68–2.78 (*m*, 2 H, H−C(2), H−C(2)*, H−C(4), H−C(4)*); 3.77 (*s*, COOMe); 3.78 (*s*, COOMe*); 4.17 (*d*, *J* = 6.2, 1 H, H−C(7)*); 4.19 (*d*, *J* = 6.0, 1 H, H−C(7)); 4.27–4.31, 4.33–4.37, 4.44–4.48, 4.56–4.60 (4*m*, 4 × 1 H, H−C(1), H−C(1)*, H−C(5), H−C(5)*); 4.86 (*d*, *J* = 5.8, 1 H, H−C(6)); 4.89 (*d*, *J* = 5.8, 1 H, H−C(6)*). ^{13}C-NMR (125 MHz, $CDCl_3$): −5.3, −5.1 (Me_2Si, Me_2Si*); 18.1 (Me_3C, Me_3C*); 20.7 (*Me*CO, *Me*CO*); 25.6 (Me_3C, Me_3C*); 45.3, 45.6, 45.9, 46.1 (C(2), C(4), C(2)*, C(4)*); 52.9 (MeO, MeO*); 58.3, 58.4, 61.8 (C(1), C(5), C(1)*, C(5)*); 75.2, 75.9 (C(7), C(7)*); 76.5, 77.1 (C(6), C(6)*); 154.5, 154.7 (COO, COO*); 170.1 (OCO, OCO*); 205.0 (C(3), C(3)*). CI-MS: 372.2 (100, $[M+H]^+$), 340 (10), 314 (50), 272 (15), 240 (10), 212 (10), 155 (5), 127 (5), 43 (5). HR-ESI-MS: 394.1661 ($[M + Na]^+$, $C_{17}H_{29}NNaO_6Si^+$; calc. 394.1662).

5.2. *Methyl 6-Acetoxy-3-oxo-7-[(triethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate* (*rac*-**6c**). R_f (AcOEt/hexane 1:3) 0.21. Yield: 78%. Colorless oil. FT-IR (ATR): 2955*m*, 2912*m*, 2878*m*, 1740*s*, 1703v*s*, 1449*s*, 1386*s*, 1229v*s*, 1102*s*, 1005*s*, 727*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.59 (*q*, *J* = 8.0, 12 H, SiCH_2Me, SiCH_2Me*); 0.94 (*t*, *J* = 8.0, 18 H, $SiCH_2Me$, $SiCH_2Me$*); 2.08 (*s*, MeCO); 2.09 (*s*, MeCO*); 2.43, 2.46 (2*s*, 2 × 1 H, H−C(2), H−C(2)*); 2.47–2.51, 2.51–2.55 (2*m*, 2 × 1 H, H−C(4), H−C(4)*); 2.56–2.65, 2.68–2.78 (2*m*, 2 × 2 H, H−C(2), H−C(4), H−C(2)*, H−C(4)*); 3.77 (*s*, MeO, MeO*); 4.16–4.22 (*m*, 2 H, H−C(7), H−C(7)*); 4.23–4.29, 4.31–4.36, 4.42–4.48, 4.53–4.59 (4*m*, 4 × 1 H, H−C(1), H−C(5), H−C(1)*, H−C(5)*); 4.84–4.90 (*m*, 2 H, H−C(6), H−C(6)*). ^{13}C-NMR (125 MHz, $CDCl_3$): 4.3 (SiCH_2Me, SiCH_2Me*); 6.6 ($SiCH_2Me$, $SiCH_2Me$*); 20.7 (*Me*CO, *Me*CO*); 45.3, 45.7, 45.8, 46.1 (C(2), C(4), C(2)*, C(4)*); 52.9 (MeO, MeO*); 58.3, 61.8 (C(1), C(5), C(1)*, C(5)*); 74.8 (C(7)*); 75.6 (C(7)); 76.5 (C(6)); 77.1 (C(6)*); 154.7 (COO, COO*); 170.2 (OCO, OCO*); 205.0 (C(3), C(3)*). CI-MS: 372.1 (100, $[M+H]^+$), 342 (75), 330 (30), 300 (60), 268 (25), 237 (15), 196 (5), 145 (10), 49 (10). HR-ESI-MS: 394.1658 ($[M + Na]^+$, $C_{17}H_{29}NNaO_6Si^+$; calc. 394.1662).

5.3. *Methyl 7-(Methoxymethoxy)-3-oxo-6-(trifluoroacetoxy)-8-azabicyclo[3.2.1]octane-8-carboxylate* (*rac*-**6f**). $(CF_3CO)_2O$ instead of Ac_2O. R_f (AcOEt/hexane 1:2) 0.15. Yield: 53%. Colorless oil. FT-IR (ATR): 3392*w*, 2958*w*, 1784*w*, 1696v*s*, 1457*s*, 1402*s*, 1193*s*, 1107*m*, 632*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.51, 2.52, 2.54, 2.55 (4*s*, 4 × 1 H, H−C(2), H−C(4), H−C(2)*, H−C(4)*); 2.68, 2.79 (2*dt*, *J* = 17.0, 4.5, 2 × 2 H, H−C(2), H−C(4), H−C(2)*, H−C(4)*); 3.36 (*s*, CH_2OMe, CH_2OMe*); 3.80 (*s*, COOMe, COOMe*); 4.14, 4.15 (2*s*, 2 × 1 H, H−C(7), H−C(7)*); 4.47–4.52 (br. *m*, 1 H, H−C(1) or H−C(5)); 4.54 (*d*, *J* = 7.0, CH_2*); 4.58 (*d*, *J* = 7.0, CH_2); 4.57–4.62, 4.64–4.69, 4.73–4.78 (3*m*, 3 × 1 H, H−C(1) or H−C(5), H−C(1)*, H−C(5)*); 5.06–5.12 (*m*, 2 H, H−C(6), H−C(6)*). ^{13}C-NMR (125 MHz, $CDCl_3$): 45.2, 45.4, 45.7, 45.9 (C(2), C(4), C(2)*, C(4)*); 53.2 (COO*Me*, COO*Me*); 56.4 (CH_2OMe, CH_2OMe*); 57.5, 59.0, 59.1 (C(1), C(5), C(1)*, C(5)*); 78.5, 79.3 (C(7), C(7)*); 79.1, 79.9 (C(6), C(6)*); 97.2, 97.3 (CH_2, CH_2*); 114.4 (*q*, *J* = 285.2, CF_3, CF_3*); 154.4 (COO, COO*); 157.0 (*q*, *J* = 36.9, O*C*OCF_3, O*C*OCF_3*); 204.0 (C(3), C(3)*). CI-MS: 356.1 (20, $[M+H]^+$), 324 (100), 294 (50), 260 (15), 228 (45), 196 (35), 154 (20), 115 (60), 45 (35). Anal. calc. for $C_{13}H_{16}F_3NO_7$ (355.27): C 43.95, H 4.54, N 3.94; found: C 43.98, H 4.69, N 3.85.

5.4. *Methyl 4,5,6,7,8,8a-Hexahydro-2-hydroxy-6-oxo-2-(trifluoromethyl)-4,8-epimino-3a*H*-cyclohepta[*d*][1,3]dioxole-9-carboxylate* (**9**). $(CF_3CO)_2O$ instead of Ac_2O. R_f (AcOEt) 0.61. Yield: 73% (82% GC purity). Colorless solid. M.p. 183°. FT-IR (ATR): 3301*m*, 1694v*s*, 1674v*s*, 1448*s*, 1402v*s*, 1228*s*, 1173v*s*, 1056v*s*, 984v*s*, 644*s*. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$): 2.43–2.49 (*m*, 4 H, H−C(2), H−C(4), H−C(2)$^{\#}$, H−C(4)$^{\#}$); 2.70–2.76 (*m*, 4 H, H−C(2), H−C(4), H−C(2)$^{\#}$, H−C(4)$^{\#}$); 3.70 (*s*, Me$^{\#}$); 3.72 (*s*, Me); 4.48 (br. *d*, *J* = 5.3, 2 H, H−C(1), H−C(5)); 4.53, 4.57 (2*d*, *J* = 5.2, 2 × 1 H, H−C(1)$^{\#}$, H−C(5)$^{\#}$); 4.77 (*d*, *J* = 3.8, 2 H, H−C(6), H−C(7)); 4.93 (*d*, *J* = 1.6, 2 H, H−C(6)$^{\#}$, H−C(7)$^{\#}$); 7.57 (br. *s*, OH$^{\#}$); 8.24 (br. *s*, OH). ^{13}C-NMR (500 MHz, $(CD_3)_2CO$): 43.7, 44.2 (C(2), C(4)); 44.2, 44.7 (C(2)$^{\#}$, C(4)$^{\#}$); 52.4 (MeO$^{\#}$); 52.6 (MeO); 58.7, 58.8 (C(1)$^{\#}$, C(5)$^{\#}$); 59.3 (C(1), C(5)); 84.2, 85.1 (C(6), C(7)); 84.3, 85.0 (C(6)$^{\#}$, C(7)$^{\#}$);

115.8 (q, J = 25.4, $F_3CCOH^{\#}$); 116.7 (q, J = 25.3, F_3CCOH); 120.5 (q, J = 285.1, $F_3C^{\#}$); 121.5 (q, J = 288.3, F_3C), 154.5 ($CO^{\#}$); 155.1 (CO); 203.9 (C(3)); 204.3 (C(3)$^{\#}$). EI-MS: 311.1 (35, $M^{+\cdot}$), 242 (10), 197 (10), 154 (100), 127 (30), 97 (10), 82 (10), 59 (15), 42 (10). Anal. calc. for $C_{11}H_{12}F_3NO_6$ (311.21): C 42.45, H 3.89, N 4.50; found: C 42.49, H 4.06, N 4.31.

6. *General Procedure for Enzymatic Acylations.* To a soln. of **2a** or *rac*-**5d** (0.07 mmol) in the given solvent (1 ml) was added vinyl acetate or vinyl trifluoroacetate (13 µl), molecular sieves (4 Å; 4 pellets), and the respective enzyme (20–27 mg). The mixture was stirred at 40°. At time intervals from 1 to 3 h and sedimentation of the enzyme, aliquots of 30 µl were taken from the supernatant, filtered, diluted with CH_2Cl_2 (300 µl), and directly analyzed by cap. GC on chiral phase *Bondex un-β*. The reaction was terminated after 48 h.

For separation and isolation of (−)-**6d** or (−)-**6f**, and (+)-**5d**, the mixture was filtered through *Celite*, and the filtrate was concentrated. Chromatography of the residue on SiO_2 with AcOEt/hexane 2:1 gave in a first fraction **6d** (R_f (AcOEt/hexane 3:1) 0.32) and in a second fraction **5d** (R_f (AcOEt/hexane 3:1) 0.23). Second chromatography on SiO_2 with AcOEt/hexane 1:2.5 → 1:2 gave in a first fraction **6f** (R_f (AcOEt/hexane 3:1) 0.63) and in a second fraction **5d** (R_f (AcOEt/hexane 3:1) 0.23).

7.1. *Methyl (6*R,7S*)-7-(Methoxymethoxy)-6-[(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* ((6*R*,7*S*)-(R)-**6e**). To a soln. of (−)-**5d** (17 mg, 65.6 µmol) in anh. pyridine (0.5 ml) was added (+)-(*S*)-MTPACl (24 µl), and the mixture was stirred at r.t. for 18 h. After addition of toluene (1 ml), the mixture was concentrated three times *in vacuo*. The residue was purified by FC (SiO_2; AcOEt/hexane 1:1; R_f 0.34) to give (6*R*,7*S*)-(*R*)-**6e** (24 mg, 50.5 µmol, 77 %). Colorless solid. M.p. 105°. FT-IR (ATR): 2963*w*, 2860*w*, 1742v*s*, 1703v*s*, 1451*s*, 1393*s*, 1337*s*, 1260v*s*, 1158v*s*, 1105*s*, 1045v*s*, 996v*s*, 921*s*, 803*m*, 771*s*, 715v*s*, 696v*s*, 640*s*. ^{1}H-NMR (500 MHz, $C_2D_2Cl_4$, 393 K): 2.46 (dt, J = 16.8, 1.7, H_{eq}−C(4)); 2.47 (dt, J = 16.8, 1.7, H_{eq}−C(2)); 2.65 (dd, J = 16.8, 5.3, H_{ax}−C(2)); 2.67 (dd, J = 16.8, 5.3, H_{ax}−C(4)); 3.30 (*s*, CH_2OMe); 3.54 (*s*, MeO); 3.70 (*s*, COOMe); 4.14 (d, J = 6.2, H−C(7)); 4.50 (*s*, CH_2O); 4.52–4.57 (*m*, H−C(1), H−C(5)); 5.08 (d, J = 6.2, 1 H, H−C(6)); 7.33–7.37 (*m*, 3 arom. H); 7.56–7.58 (*m*, 2 arom. H). ^{13}C-NMR (125 MHz, $C_2D_2Cl_4$, 393 K): 44.9 (C(4)); 45.4 (C(2)); 52.1 (COO*Me*); 54.7 (MeO); 55.3 (CH_2OMe); 57.9, 58.6 (C(1), C(5)); 78.3 (C(6)); 79.3 (C(7)); 96.4 (CH_2O); 127.1, 127.6, 128.9, 131.7 (Ph); 153.8 (NCO); 165.4 (CO); 202.9 (C(3)). EI-MS: 475.1 (10, $M^{+\cdot}$), 430 (30), 370 (5), 241 (25), 210 (10), 197 (35), 189 (100), 154 (50), 127 (10), 114 (15), 105 (10), 45 (50). HR-ESI-MS: 498.1330 ([M + Na]$^+$, $C_{21}H_{24}F_3NNaO_8^+$; calc. 498.1352).

7.2. *Methyl (6*R,7S*)-7-(Methoxymethoxy)-6-[(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* ((6*R*,7*S*)-(*S*)-**6e**). As described above, from (−)-**5d** and (−)-(*R*)-MTPACl. R_f (AcOEt/hexane 1:1) 0.34. Yield: 40%. Colorless solid. ^{1}H-NMR (500 MHz, $C_2D_2Cl_4$, 393 K): 2.46 (dt, J = 16.8, 1.7, H_{eq}−C(2)); 2.51 (dt, J = 16.8, 1.7, H_{eq}−(4)); 2.66 (dd, J = 16.8, 5.3, H_{ax}−C(2)); 2.67 (dd, J = 16.8, 5.3, H_{ax}−C(4)); 3.25 (*s*, CH_2OMe); 3.50 (*s*, MeO); 3.71 (*s*, COOMe); 4.11 (d, J = 6.2, H−C(7)); 4.40 (d, J = 12.1, CH_2O); 4.42 (d, J = 12.1, CH_2O); 4.52–4.55 (*m*, H−C(1)); 4.58–4.61 (*m*, H−C(5)); 5.10 (d, J = 6.2, H−C(6)); 7.33–7.39 (*m*, 3 arom. H); 7.54–7.57 (*m*, 2 arom. H). ^{13}C-NMR (125 MHz, $C_2D_2Cl_4$, 393 K): 44.9 (C(4)); 45.5 (C(2)); 52.1 (COO*Me*); 54.6 (MeO); 55.2 (CH_2OMe); 58.0 (C(5)); 58.6 (C(1)); 78.0 (C(6)); 79.1 (C(7)); 84.4 (q, J = 28.4, CCF_3); 96.2 (CH_2O); 122.7 (q, J = 289.3, CF_3); 127.2, 127.6, 128.9, 131.6 (Ph); 153.8 (NCO); 165.4 (CO); 202.9 (C(3)).

8. *Methyl 4,5,6,7,8,8a-Hexahydro-2,6-dioxo-4,8-epimino-3a*H*-cyclohepta[*d*][1,3]dioxole-9-carboxylate* (**12**). To a soln. of **2a** (50 mg, 0.233 mmol), DMAP (2 mg, 16.4 µmol), and Et_3N (90 µl, 0.652 mmol) in anh. CH_2Cl_2 (1.5 ml) was added at 0° methyl chloroformate (18 µl, 0.233 mmol), and the mixture was stirred at r.t. for 3 h. Then, CH_2Cl_2 (10 ml) was added, and the mixture was successively washed with a soln. of $NaHCO_3$ and brine (10 ml each). The org. layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by FC (SiO_2; AcOEt/hexane 2:1; R_f (AcOEt/hexane 3:1) 0.40) to give **12** (51 mg, 0.212 mmol, 91%). Colorless solid. M.p. 159°. FT-IR (ATR): 3011*w*, 2962*w*, 2908*w*, 1779v*s*, 1713v*s*, 1697v*s*, 1453*s*, 1379v*s*, 1166v*s*, 1078v*s*, 1053v*s*, 979*s*, 766v*s*, 687*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.52 (br. d, J = 16.8, 2 H, H−C(2), H−C(4)); 2.68–2.94 (br. *m*, 2 H, H−C(2), H−C(4)); 3.83 (*s*, Me); 4.61–4.82 (br. *m*, H−C(1), H−C(5)); 4.90 (*s*, H−C(6), H−C(7)). ^{13}C-NMR (125 MHz, $CDCl_3$): 44.0, 44.5 (C(2), C(4)); 53.6 (Me); 58.6 (C(1), C(5)); 81.0, 81.6 (C(6), C(7)); 153.1 (OCO); 154.4 (COO); 202.7 (C(3)). EI-MS: 241.1 (30, $M^{+\cdot}$), 154 (100), 127 (55), 82 (20), 59 (30), 42 (30). HR-ESI-MS: 264.0474 ([M + Na]$^+$, $C_{10}H_{11}NNaO_6^+$; calc. 264.0484).

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