Enantioselective Synthesis of Hexahydroisobenzofuran and Hexahydroisoindole Derivatives with Quaternary Stereocenters

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Dedicated to Professor Siegfried Blechert on the occasion of his 65th birthday

Abstract: Oxo esters with pyrrolidine and tetrahydrofuran rings were converted into optically active isobenzofuran and isoindole derivatives. The key step of the sequence was a copper-catalyzed asymmetric Michael reaction with methyl vinyl ketone and enamines prepared from the oxo esters and L-valine diethylamide. The chiral auxiliary was cleaved from the products during workup and 1,5-diketones with a quaternary stereocenter are obtained with 97–99% ee. Subsequent annulation reactions were achieved in two steps via the intermediate aldol products.

Key words: tetrahydrofurans, pyrrolidines, isoindoles, isobenzofurans, chirality, Michael addition, quaternary stereocenters

The isoindole moiety is a common structural motif in heterocyclic compounds,[1] and one of the privileged structures in medicinal chemistry.[2] In contrast, isobenzofurans are less frequently reported.[3] Prominent examples of pharmaceutically active isoindoles are the antidepressant tandospirone,[4] the hypoglycemic mitiglinide (diabetes),[5] and the antiviral tecovirimat (ST-246) (Figure 1).[6] Examples for pharmaceutically active isobenzofurans are the topoisomerase II-inhibitor etoposide[7] and the thrombolytic SCH 530348,[8] an analogue of the natural product himbacine.[9]

A couple of years ago we reported on the asymmetric synthesis of optically active octahydroisoquinolone **2** from enamine **1** (Scheme 1).[10] The key step of this reaction was a copper-catalyzed Michael reaction with methyl vinyl ketone (MVK) using L-valine diethylamide as chiral auxiliary.[11] Since then, compound **2** bearing a quaternary stereocenter[12] has continuously been used by us[13] and others[14] as a valuable chiral building block for the synthesis of various heterocyclic compounds, mainly in a medicinal chemistry context. For this reason, we decided to prepare also compound **3a** with a pyrrolidine ring instead of the piperidine moiety as well as its tetrahydrofuran congener **3b**. In order to obtain both products **3a** and **3b** in optically pure form, the enamines **4** derived from L-valine diethylamide were chosen as the starting materials in the copper-catalyzed Michael reaction with MVK.

The starting material **5a** was mentioned before as a by-product,[15] but never isolated and characterized. We prepared it in a one-pot protocol by conjugate addition of *N*-Boc-GlyOMe (**7**)[16] to methyl acrylate followed by Dieckmann condensation (90% yield). Tetrahydrofuran derivative **5b** was reported before and prepared accordingly.[17] In order to develop suitable tools for enantiomeric analyses, racemic products were prepared prior to asymmetric Michael reactions. Therefore, β-oxo esters **5a** and **5b** were converted, with MVK and catalytic amounts of $FeCl_3 \cdot 6H_2O$,[18] into the racemic 1,5-diketones **6a** and **6b** in 84% and 87% yield, respectively (Scheme 2). While the product *rac*-**6b** gave sufficient baseline resolution in GLC on a chiral phase, pyrrolidine derivative *rac*-**6a** did not. For this reason we were seeking for a suitable derivative for GLC analysis and found that the trifluoroacetamide **6c** fulfilled these requirements. The compound *rac*-**6c** was

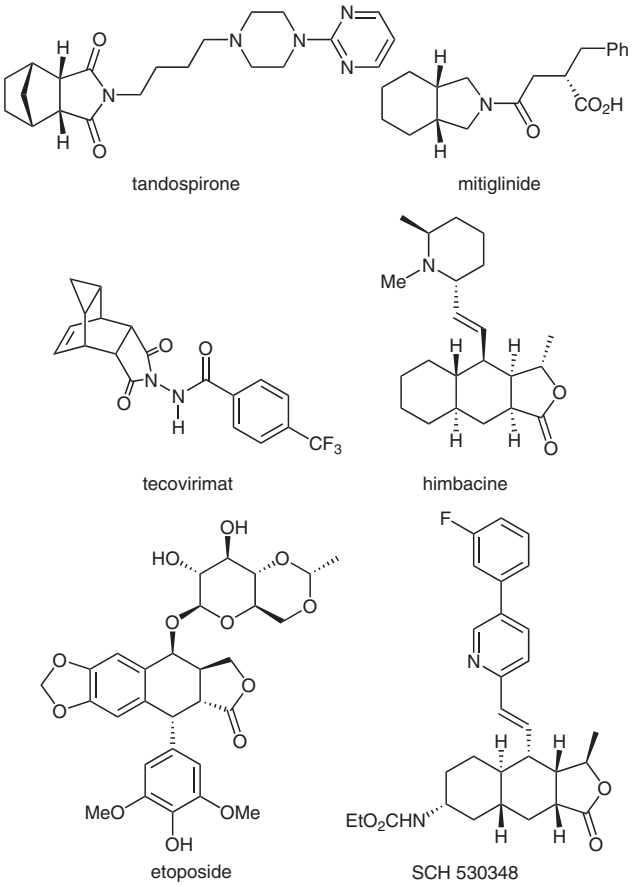

Figure 1 Prominent examples of pharmaceutically active compounds with isoindole and isobenzofuran moieties

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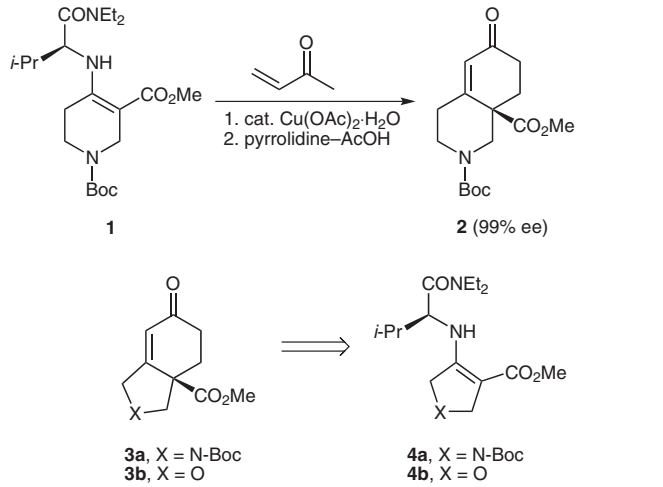
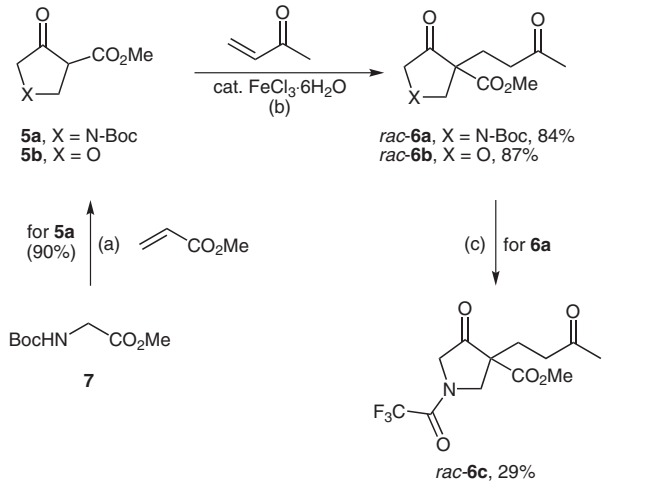


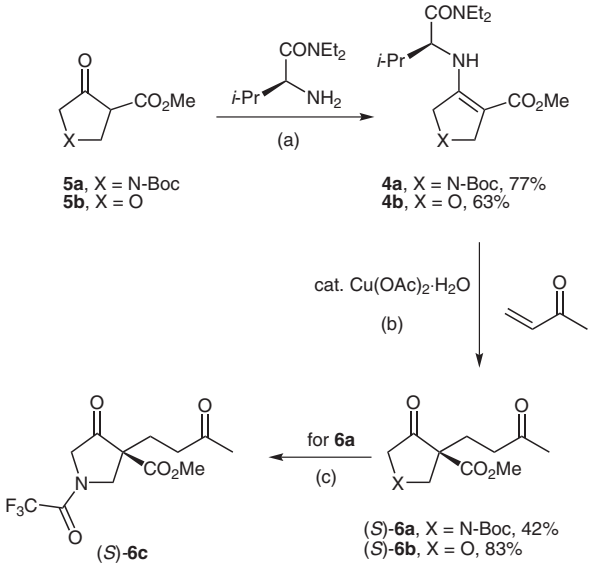
Scheme 1 Synthesis of optically active octahydroisoquinolone **2** from enamine **1** and the synthetic plan for isoindole **3a** and isobenzofuran **3b** from enamines **4**

obtained on a preparative as well as on an analytical scale. Treatment of carbamate **6a** with TFA led to cleavage of the Boc-group. The N-unprotected pyrrolidine turned out to be an unstable compound and was therefore not isolated. Subsequent conversion with TFAA formed the amide **6c**. The resulting crude reaction mixture could directly be submitted to GLC analysis.



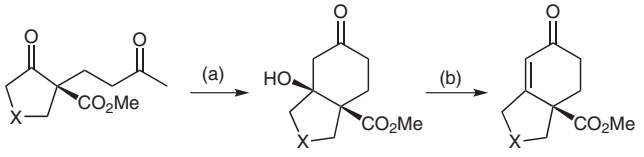
Scheme 2 Synthesis of starting material **5a**, racemic Michael reactions, and derivatization of product **6a**. *Reagents and conditions*: (a) *t*-BuOK (1.1 equiv), methyl acrylate (1 equiv), THF, 23 °C, 16 h, 90% (for **5a**); (b) $FeCl_3·6H_2O$ (10 mol%), MVK (3 equiv), CH_2Cl_2, 23 °C, 3 d, 84% (for *rac*-**6a**), 16 h, 87% (for *rac*-**6b**); (c) 1. TFA, CH_2Cl_2, 23 °C, 1 h, 2. TFAA, Et_3N, CH_2Cl_2, –10 → 23 °C, 1.5 h, 29%.

The reaction of the oxo esters **5a** and **5b** with the chiral auxiliary[19] gave the enamines **4a** and **4b** in 77% and 63% yield, respectively (Scheme 3). Their conversion with MVK in the presence of 5 mol% copper catalyst proceeded smoothly to furnish imines as intermediate products, which were subsequently hydrolyzed with hydrochloric acid or aqueous citric acid to give the diketones **6a** and **6b** in 42% and 83% yield, respectively. The product **6b** was directly submitted to enantiomeric analysis by GLC on a chiral phase. Only one isomer was detectable (>99% ee) and based on our experience with product **2** (Scheme 1)[20] and other cyclopentanone carboxylates[19] we presume it to be the *S*-enantiomer. Analysis of carbamate **6a** was performed after conversion of a small sample into trifluoroacetamide **6c**; GLC on a chiral phase gave 97% ee for this derivative. Again, compounds **6a** and **6c** should have the *S*-configuration.



Scheme 3 Synthesis of enamines **4** and asymmetric Michael reactions. *Reagents and conditions*: (a) cat. HCl–H_2O, mol. sieves, toluene, 60 °C, 16 h, 77% (**4a**), 63% (**4b**); (b) for (*S*)-**6a**: 1. $Cu(OAc)_2·H_2O$ (5 mol%), MVK (2 equiv), acetone, 23 °C, 18 h, 2. HCl–H_2O–acetone, 23 °C, 2 h, 42%; for (*S*)-**6b**: 1. $Cu(OAc)_2·H_2O$ (5 mol%), MVK (3 equiv), acetone, 23 °C, 1 h; 2. citric acid–acetone–H_2O, 23 °C, 1 h, 83%, >99% ee; (c) 1. TFA, CH_2Cl_2, 23 °C, 1 h, 2. TFAA, Et_3N, CH_2Cl_2, –10 → 23 °C, 1.5 h, 97% ee (analytical scale, 32% conversion).

Annulation reactions were performed with a mixture of pyrrolidine and AcOH for racemic as well as optically active 1,5-diketones **6a** and **6b**. In contrast to our previous observations[21] regarding this reaction, it stopped at the stage of the tertiary alcohols **8a** and **8b**, which were isolated in 91% and 67% yield, respectively (Scheme 4). The relative configuration was established to be *cis* in the case of isobenzofuran derivative **8b** by X-ray analysis (Figure 2).[22] Elimination reaction of carbamate **8a** was achieved with TFAA and Et_3N (93% yield of product **3a**). The more robust tetrahydrofuran derivative **8b** was converted to the hexahydroisobenzofuranone **3b** with concentrated sulfuric acid (73% yield).



6a, X = N-Boc
6b, X = O

8a, X = N-Boc, 91%
8b, X = O, 67%

3a, X = N-Boc, 93%
3b, X = O, 73%

Scheme 4 Annulation reaction. *Reagents and conditions*: (a) pyrrolidine (0.3 equiv), AcOH (0.3 equiv), DMSO, 23 °C, 2 h, 91% (for **8a**), 67% (for **8b**); (b) for **3a**: TFAA (1.5 equiv), Et_3N (1 equiv), DMAP (0.05 equiv), CH_2Cl_2, 23 °C, 16 h, 93%; for **3b**: concd H_2SO_4 (4 equiv), CH_2Cl_2, 23 °C, 1 h, 73%.

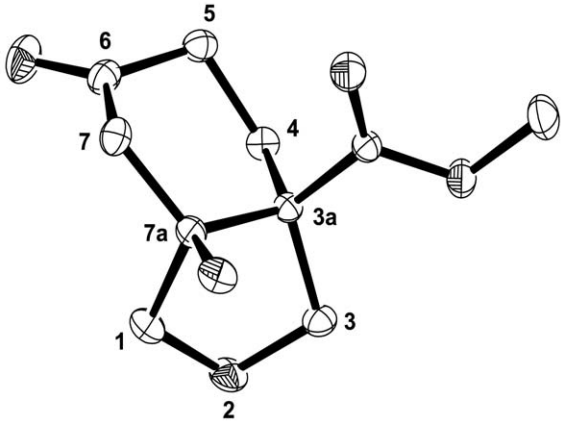


Figure 2 ORTEP-representation of the structure of compound **8b** in the solid state

Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane, EtOAc, or *tert*-butyl methyl ether (MTBE) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminum sheets. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer. Multiplicities of carbon signals were determined with DEPT experiments. Spectra of all Boc-protected compounds showed broad, partly doubled signal sets due to hindered rotation along the carbamate C–N bond (*E*,*Z*-isomers). MS and HRMS spectra were obtained with a Finnigan MAT 95 (CI with isobutane and EI) and a Waters Q-TOF Premier (ESI, positive mode) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a 'GoldenGate' diamond-ATR unit. Elemental analyses were measured with a Euro EA-CHNS from HEKAtech. GLC analysis on a chiral phase was performed with a Focus/Triplus (Thermo Electron) with FID on a column Lipodex E (25 m × 0.25 mm) with H_2 as carrier gas (+0.4 bar). *N*-Boc-GlyOMe (**7**)[16] and oxo ester **5b**[17] were prepared according to literature procedures. L-Valine diethylamide was prepared as reported previously.[19] All other starting materials were commercially available.

1-*tert*-Butyl 3-Methyl 4-Oxopyrrolidine-1,3-dicarboxylate (5a)

Methyl acrylate (11.4 g, 133 mmol, 1 equiv) and powdered *t*-BuOK (17.9 g, 146 mmol, 1.1 equiv) were subsequently added to a cooled (ice-water bath) solution of carbamate **7** (25.1 g, 133 mmol) in anhyd THF (250 mL). The reaction mixture was stirred under an inert atmosphere for 16 h at 23 °C and then evaporated. The residue was redissolved in CH_2Cl_2 (250 mL) and acidified with HCl (ca. 150 mL, $c = 2$ mol L^{-1}). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), and after filtration, the solvent was evaporated. The residue was chromatographed (SiO_2, hexane–MTBE, 1:2, $R_f = 0.35$) to yield the title compound **5a** (29.0 g, 119 mmol, 90%) as a red oil.

NMR spectra showed doubled signal sets due to the presence of keto and enol tautomers (ratio 2:1). Because of *E*- and *Z*-isomers of the carbamate moieties, these two signals sets are further doubled in part (ratio 1:1).

IR (ATR): 2973 (w), 2900 (w), 2871 (w), 1682 (s), 1629 (s), 1404 (s), 1366 (s), 1325 (s), 1226 (s), 1167 (s), 1113 (s), 1044 (s), 875 (m), 855 (m), 770 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 18 H), 1.49 (s, 18 H), 3.57–3.65 (m, 2 H), 3.79 (s, 12 H), 3.81–3.96 (m, 6 H), 3.98–4.04 (m, 2 H), 4.04–4.13 (m, 2 H), 4.16–4.25 (m, 6 H), 10.00 (s, 1 H), 10.04 (s, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (enol tautomer) = 28.7 (3 CH_3), 28.8 (3 CH_3), 48.7 (CH_2), 49.1 (CH_2), 51.4 (CH_2), 51.7 (CH_2), 53.36 (2 CH_3), 80.5 (C), 81.2 (C), 97.49 (C), 97.54 (C), 154.4 (C), 154.5 (C), 168.1 (C), 168.4 (C), 168.5 (C), 168.7 (C); δ (keto tautomer) = 28.7 (3 CH_3), 28.8 (3 CH_3), 45.9 (CH_2), 46.4 (CH_2), 52.1 (CH), 52.5 (CH), 52.7 (CH_2), 53.0 (CH_2), 53.39 (2 CH_3), 80.5 (C), 81.2 (C), 154.3 (C), 154.4 (C), 167.5 (2 C), 204.0 (C), 204.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}NO_5$ + MeOH + Li: 282.1529; found: 282.1537 [M + MeOH + Li^+].

***N*-(1-*tert*-Butyloxycarbonyl-3-methoxycarbonyl-2,5-dihydropyrrol-4-yl)-L-valine Diethylamide (4a)**

Anhyd molecular sieves (4 Å, ca. 5 g), L-valine diethylamide (793 mg, 4.60 mmol), and a catalytic amount of concd HCl (ca. 30 mg) were subsequently added under an inert atmosphere to a solution of oxo ester **5a** (1.12 g, 4.60 mmol) in anhyd toluene (8 mL). The mixture was heated to 60 °C under an inert atmosphere for 16 h and subsequently filtered through a glass frit. The residue was washed with CH_2Cl_2 (20 mL), the filtrates were evaporated and submitted to chromatography [neutral Al_2O_3, hexane–EtOAc, 2:1, $R_f = 0.30$ (SiO_2, hexane–EtOAc, 1:1)] to yield the title compound **4a** (1.41 g, 3.55 mmol, 77%) as a colorless resin; $[\alpha]_D^{20}$ +24 (c = 10 g/L in CH_2Cl_2).

IR (ATR): 3334 (w, br), 2975 (m), 2938 (m), 2877 (w), 1780 (m), 1739 (m), 1684 (s), 1623 (s), 1368 (s), 1281 (s), 1153 (s), 985 (m), 889 (m), 853 (m), 774 cm^{-1} (s).

^1H NMR (500 MHz $CDCl_3$): δ = 0.97 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.12 (t, J = 7.0 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.47 (s, 9 H), 2.01 (oct, J = 6.1 Hz, 1 H), 3.09–3.18 (m, 1 H), 3.19–3.28 (m, 1 H), 3.33–3.41 (m, 1 H), 3.60–3.68 (m, 1 H), 3.72 (s, 3 H), 3.78 (dd, J = 10.3, 5.6 Hz, 1 H), 4.17–4.23 (m, 3 H), 4.29–4.35 (m, 1 H), 7.58 (br s, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 13.3 (CH_3), 15.2 (CH_3), 17.5 (CH_3), 20.2 (CH_3), 28.8 (3 CH_3), 33.1 (CH), 40.6 (CH_2), 42.1 (CH_2), 50.86 (CH_2), 50.92 (CH_3), 51.8 (CH_2), 60.0 (CH), 80.3 (C), 90.3 (C), 154.0 (C), 154.8 (C), 166.5 (C), 170.3 (C).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{20}H_{35}N_3O_5$: 397.2577; found: 397.2569 [M^+].

***N*-(3-Methoxycarbonyl-2,5-dihydro-4-furyl)-L-valine Diethylamide (4b)**

According to the procedure given above for product **4a**, anhyd molecular sieves (4 Å, ca. 5 g), L-valine diethylamide (979 mg, 5.68 mmol), a catalytic amount of concd HCl (ca. 50 mg), and oxo ester **5b** (910 mg, 5.68 mmol) were converted in anhyd toluene (10 mL) to give the title compound **4b** (1.13 g, 3.60 mmol, 63%) as a colorless solid after chromatography [neutral Al_2O_3, hexane–EtOAc, 2:1, $R_f = 0.21$ (SiO_2, hexane–EtOAc, 1:1)]; mp 70 °C. De-

composition occurred during storage even at –20 °C, but the material could be repurified by recrystallization from hexane–MTBE (10:1); $[\alpha]_D^{20}$ –3.3 (*c* = 10 g/L in CH_2Cl_2).

IR (ATR): 3342 (w, br), 2968 (m), 2935 (m), 2875 (m), 1670 (s), 1630 (s), 1596 (vs), 1460 (s), 1430 (s), 1273 (vs), 1196 (s), 1122 (s), 1062 (s), 912 (m), 771 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.9 Hz, 6 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.97–2.07 (m, 1 H), 3.10–3.17 (m, 1 H), 3.18–3.28 (m, 1 H), 3.35–3.44 (m, 1 H), 3.60–3.68 (m, 2 H), 3.71 (s, 3 H), 4.59–4.66 (m, 1 H), 4.69–4.80 (m, 3 H), 7.31 (br s, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 12.8 (CH_3), 14.6 (CH_3), 17.2 (CH_3), 19.7 (CH_3), 32.6 (CH), 40.2 (CH_2), 41.5 (CH_2), 50.4 (CH_3), 60.1 (CH), 72.1 (CH_2), 73.9 (CH_2), 90.8 (C), 156.5 (C), 165.5 (C), 169.8 (C).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{15}H_{26}N_2O_4$: 298.1893; found: 298.1895 [M^+].

1-*tert*-Butyl 3-Methyl 4-Oxo-3-(3-oxobutyl)pyrrolidine-1,3-dicarboxylate (6a)

Racemic: $FeCl_3 \cdot 6H_2O$ (3.2 g, 12 mmol, 10 mol%) was added to a solution of oxo ester **5a** (29.0 g, 119 mmol) in CH_2Cl_2 (60 mL). After stirring for 5 min at 23 °C, MVK (25.1 g, 358 mmol, 3 equiv) was added and the resulting mixture stirred for further 3 d at 23 °C. Subsequently, all volatile materials were removed under vacuum and the residue was chromatographed (SiO_2, hexane–MTBE, 1:2, R_f = 0.23) to yield *rac*-**6a** (31.3 g, 100 mmol, 84%) as a light yellow oil.

Enantiopure: $Cu(OAc)_2 \cdot H_2O$ (27 mg, 0.13 mmol, 5 mol%) was added to a solution of enamine **4a** (1.06 g, 2.68 mmol) in acetone (10 mL). After stirring for 45 min at 23 °C, MVK (0.45 mL, 5.35 mmol, 2 equiv) was added and the resulting mixture stirred for further 18 h. Subsequently, all volatile materials were removed under vacuum and the residue was redissolved in a mixture of acetone (1 mL) and HCl (5 mL, *c* = 1 mol L^{-1}). After stirring for 2 h at 0 °C, the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (50 mL) and dried ($MgSO_4$). After filtration, all volatile materials were removed under vacuum and the residue was chromatographed (SiO_2, hexane–MTBE, 1:2, R_f = 0.23) to yield the optically active (*S*)-**6a** (353 mg, 1.13 mmol, 42%) as a light yellow oil; $[\alpha]_D^{20}$ –12.4 (*c* = 7.3 g/L in $CHCl_3$).

IR (ATR): 2977 (w), 2933 (w), 1768 (m), 1696 (s), 1400 (s), 1367 (s), 1256 (m), 1163 (s), 1125 (s), 884 (m), 770 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 1.99–2.06 (m, 1 H), 2.11 (s, 3 H), 2.14–2.22 (m, 1 H), 2.41–2.49 (m, 1 H), 2.60–2.71 (m, 1 H), 3.49–3.61 (m, 1 H), 3.71 (s, 3 H), 3.82 (d, *J* = 19.6 Hz, 1 H), 3.86–3.99 (m, 1 H), 4.15 (d, *J* = 11.9 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 26.2 (CH_2), 28.3 (3 CH_3), 29.8 (CH_3), 38.3 (CH_2), 52.0 (CH_2), 52.8 (CH_2), 53.0 (CH_3), 58.9 (C), 80.8 (C), 154.1 (C), 169.5 (2 C), 206.7 (C).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}NO_6$ + Na: 336.1423; found: 336.1425 [M + Na^+].

Methyl 4-Oxo-3-(3-oxobutyl)tetrahydrofuran-3-carboxylate (6b)

Racemic: $FeCl_3 \cdot 6H_2O$ (608 mg, 2.25 mmol, 10 mol%) was added to a solution of oxo ester **5b** (3.25 g, 22.5 mmol) in CH_2Cl_2 (4 mL). After stirring for 5 min at 23 °C, MVK (3.16 g, 45.1 mmol, 3 equiv) was added and the resulting mixture stirred for further 16 h. Subsequently, all volatile materials were removed under vacuum and the residue distilled through a Vigreux column (bp 91–93 °C/0.2 mbar) to yield the title compound *rac*-**6b** (4.20 g, 19.6 mmol, 87%) as a colorless oil.

Enantiopure: $Cu(OAc)_2 \cdot H_2O$ (16 mg, 0.082 mmol, 5 mol%) was added to a solution of enamine **4b** (490 mg, 1.64 mmol) in acetone (3 mL). After stirring for 0.5 h at 23 °C, MVK (346 mg, 4.93 mmol, 3 equiv) was added and the resulting mixture stirred for further 1 h. Subsequently, all volatile materials were removed under vacuum and the residue redissolved in a mixture of acetone (2 mL), H_2O (2 mL), and citric acid (345 mg, 1.64 mmol, 1 equiv). After stirring for 1 h at 23 °C, the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). After filtration, all volatile materials were removed under vacuum and the residue was chromatographed (SiO_2, hexane–EtOAc, 1:1, R_f = 0.34) to give the optically active (*S*)-**6b** (292 mg, 1.36 mmol, 83%) as a colorless oil; $[\alpha]_D^{20}$ +81 (*c* = 13 g/L in CH_2Cl_2).

GLC (Lipodex E, 5 min at 50 °C, then 1.5 K min^{-1} to 180 °C): t_R (*S*) = 64.37 min, t_R (*R*) = 65.07 min, >99% ee.

IR (ATR): 2657 (w), 2886 (w), 1770 (s), 1714 (vs), 1433 (m), 1359 (m), 1237 (s), 1165 (s), 1066 (s), 925 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.02 (ddd, *J* = 14.7, 9.2, 5.7 Hz, 1 H), 2.09 (s, 3 H), 2.16 (ddd, *J* = 14.6, 9.2, 5.9 Hz, 1 H), 2.45 (ddd, *J* = 14.9, 9.2, 5.7 Hz, 1 H), 2.67 (ddd, *J* = 15.1, 9.2, 5.9 Hz, 1 H), 3.70 (s, 3 H), 3.97 (d, *J* = 9.8 Hz, 1 H), 3.97 (B-part of an AB-system, *J* = 17.1 Hz, 1 H), 4.03 (A-part of an AB-system, *J* = 17.1 Hz, 1 H), 4.49 (d, *J* = 9.7 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 25.3 (CH_2), 29.8 (CH_3), 38.2 (CH_2), 52.9 (CH_3), 58.1 (C), 71.0 (CH_2), 75.3 (CH_2), 169.4 (C), 206.8 (C), 210.2 (C).

HRMS (CI): *m*/*z* calcd for $C_{10}H_{15}O_5$: 215.0919; found: 215.0916 [M + H^+].

Anal. Calcd for $C_{10}H_{14}O_5$ (214.22): C, 56.07; H, 6.59. Found: C, 55.90; H, 6.91.

Methyl 4-Oxo-3-(3-oxobutyl)-1-trifluoroacetylpyrrolidine-3-carboxylate (6c)

TFA (1.2 mL, 16 mmol, 10 equiv) was added to a solution of 1,5-diketone **6a** (500 mg, 1.60 mmol) in CH_2Cl_2 (2 mL). After stirring for 1 h at 23 °C, all volatile materials were removed under vacuum. The residue was redissolved in CH_2Cl_2 (4 mL) and cooled to –10 °C (NaCl/ice bath). TFAA (2.2 mL, 16 mmol, 10 equiv) and Et_3N (3.3 mL, 24 mmol, 15 equiv) were added and the resulting mixture was stirred for 1.5 h at 23 °C. Subsequently, the solution was washed with H_2O (20 mL) and sat. aq $NaHCO_3$ (20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), and after filtration, the solvent was evaporated. The residue was chromatographed (SiO_2, hexane–EtOAc, 1:1, R_f = 0.30) to yield the title compound **6c** (144 mg, 0.466 mmol, 29%) as a light yellow oil; $[\alpha]_D^{20}$ –35.9 (*c* = 1.7 g/L in EtOAc).

GLC (Lipodex E, 5 min at 70 °C, then 0.3 K min^{-1} to 120 °C, 1 min at 120 °C, then 0.6 K min^{-1} to 180 °C): t_R (*R*) = 232.78 min, t_R (*S*) = 234.61 min, 97% ee.

The NMR spectra showed doubled signal sets due to *E*- and *Z*-isomers of the amide moiety (ratio A/B = 1.3:1).

IR (ATR): 2960 (w), 2922 (m), 2852 (w), 1773 (w), 1694 (s), 1461 (w), 1375 (w), 1141 (s), 1021 (w), 966 (w), 799 (w), 757 (w), 719 cm^{-1} (w).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.05–2.13 (m, 2 × 1 H, A and B), 2.14 (s, 3 H, A), 2.15 (s, 3 H, B), 2.24–2.31 (m, 2 × 1 H, A and B), 2.45–2.54 (m, 2 × 1 H, A and B), 2.66–2.80 (m, 2 × 1 H, A and B), 3.76 (s, 3 H, A), 3.77 (s, 3 H, B), 3.79–3.85 (m, 2 × 1 H, A and B), 4.01 (d, *J* = 20.2 Hz, 1 H, A), 4.19–4.26 (m, 1 H + 2 H, A and 2 B), 4.44 (d, *J* = 13.1 Hz, 1 H, A), 4.55 (d, *J* = 12.0 Hz, 1 H, B).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (isomer A) = 26.1 (CH_2), 29.9 (CH_3), 38.18 (CH_2), 52.4 (CH_2), 52.9 (CH_2), 53.5 (CH_3), 57.5 (C), 115.8 (q, J = 287.1 Hz, C), 155.9 (q, J = 37.1 Hz, C), 168.7 (C), 202.6 (C), 206.8 (C): δ (isomer B) = 25.8 (CH_2), 29.9 (CH_3), 38.15 (CH_2), 52.3 (CH_2), 53.0 (CH_2), 53.6 (CH_3), 59.6 (C), 115.9 (q, J = 286.9 Hz, C), 155.9 (q, J = 37.1 Hz, C), 168.3 (C), 203.6 (C), 206.5 (C).

HRMS (CI): m/z calcd for $C_{12}H_{15}F_3NO_5$: 310.0902; found: 310.0906 [M + H$^+$].

2-*tert*-Butyl 3a-Methyl *cis*-7a-Hydroxy-6-oxooctahydro-1*H*-isoindole-2,3a-dicarboxylate (8a)

Pyrrolidine (2.05 g, 28.9 mmol, 30 mol%) and AcOH (1.73 g, 28.9 mmol, 30 mol%) were added subsequently to a cooled (ice-water bath) solution of diketone **6a** (30.2 g, 96.3 mmol) in DMSO (70 mL). After warming to r.t., the mixture was stirred for 16 h, subsequently diluted with EtOAc (150 mL), and washed with brine (250 mL). The layers were separated and the aqueous phase was extracted twice with EtOAc (2 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated after filtration. The residue was chromatographed (SiO_2, hexane–EtOAc, 1:2, R_f = 0.35) to yield the title compound **8a** (27.6 g, 87.9 mmol, 91%) as a colorless solid; mp 126 °C (racemic) or oil (enantiopure); $[\alpha]_D^{20}$ –15 (c = 11.2 g/L in CH_2Cl_2).

The NMR spectra show doubled signal sets due to *E*- and *Z*-isomers of the carbamate moiety (ratio 1:1).

IR (ATR): 3355 (m, br), 2977 (w), 1722 (s), 1656 (s), 1421 (s), 1403 (s), 1363 (m), 1290 (s), 1141 (s), 1087 (s), 1016 (s), 880 (m), 771 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.45 (s, 9 H), 1.75–1.87 (m, 2 H), 2.29–2.39 (m, 4 H), 2.41–2.51 (m, 2 H), 2.67–2.79 (m, 2 H), 2.95 (s, 1 H), 2.98 (s, 1 H), 3.21–3.34 (m, 2 H), 3.41–3.54 (m, 4 H), 3.59–3.69 (m, 2 H), 3.80–3.83 (m, 2 H), 3.84 (s, 6 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 28.25 (3 CH_3), 28.29 (3 CH_3), 29.7 (2 CH_2), 37.1 (CH_2), 37.2 (CH_2), 48.1 (CH_2), 48.3 (CH_2), 51.7 (CH_2), 52.3 (CH_2), 52.5 (CH_3), 52.6 (CH_3), 53.3 (C), 53.9 (C), 55.4 (CH_2), 55.7 (CH_2), 79.4 (C), 80.0 (2 C), 80.3 (C), 154.3 (2 C), 172.9 (C), 173.2 (C), 206.4 (C), 206.8 (C).

HRMS (ESI): m/z calcd for $C_{15}H_{23}NO_6$ + Na: 336.1423; found: 336.1422 [M + Na$^+$].

Anal. Calcd for $C_{15}H_{23}NO_6$ (313.35): C, 57.50; H, 7.40; N 4.47. Found: C, 57.68; H, 7.76; N, 4.47.

Methyl *cis*-7a-Hydroxy-6-oxooctahydroisobenzofuran-3a-carboxylate (8b)

Pyrrolidine (26 mg, 0.36 mmol, 30 mol%) and AcOH (22 mg, 0.36 mmol, 30 mol%) were subsequently added to a cooled (ice-water bath) solution of diketone **6b** (260 mg, 1.21 mmol) in DMSO (1 mL). After warming to r.t., the mixture was stirred for 2 h, diluted with EtOAc (5 mL), and washed with brine (10 mL). The layers were separated and the aqueous phase was extracted twice with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated after filtration. The residue was chromatographed (SiO_2, hexane–EtOAc, 1:1, R_f = 0.15) to yield the title compound **8b** (174 mg, 0.813 mmol, 67%) as a colorless solid; mp 104 °C (racemic); mp 88 °C (*S*,*S*-isomer); $[\alpha]_D^{20}$ –17 (c = 8 g/L in $CHCl_3$).

GLC (Lipodex E, 5 min at 50 °C, then 1.5 K min^{-1} to 180 °C): t_R (*S*,*S*) = 84.55 min, t_R (*R*,*R*) = 85.22 min, >99% ee.

IR (ATR): 3465 (m, br), 2988 (w), 2955 (m), 2897 (w), 2878 (w), 1724 (s), 1435 (m), 1325 (m), 1287 (s), 1210 (s), 1090 (m), 1043 (s), 1017 (s), 915 (s), 743 (m), 709 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.93–2.00 (m, 1 H), 2.34–2.42 (m, 2 H), 2.48–2.57 (m, 1 H), 2.75 (d, J = 15.0 Hz, 1 H), 2.92 (d, J = 15.0 Hz, 1 H), 3.31 (s, 1 H), 3.74 (d, J = 10.0 Hz, 1 H), 3.83 (s, 3 H), 3.85 (d, J = 10.0 Hz, 1 H), 3.85 (d, J = 8.5 Hz, 1 H), 4.35 (d, J = 8.5 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 29.3 (CH_2), 36.8 (CH_2), 47.5 (CH_2), 52.6 (CH_3), 55.4 (CH_2), 74.2 (C), 77.2 (CH_2), 81.4 (C), 173.0 (C), 207.1 (C).

HRMS (EI, 70 eV): m/z calcd for $C_{10}H_{14}O_5$: 214.0841; found: 214.0839 [M$^+$].

Anal. Calcd for $C_{10}H_{14}O_5$ (214.22): C, 56.07; H, 6.59. Found: C, 55.65; H, 6.80.

Methyl 6-Oxo-2,3,3a,4,5,6-hexahydro-1*H*-isoindole-3a-carboxylate (3a)

DMAP (47.4 mg, 0.388 mmol, 0.05 equiv), Et_3N (785 mg, 7.76 mmol, 1 equiv), and TFAA (2.44 mg, 11.6 mmol, 1.5 equiv) were subsequently added to a cooled (ice-water bath) solution of alcohol **8a** (2.43 mg, 7.76 mmol, 1 equiv) in CH_2Cl_2 (7 mL). After warming to r.t., the mixture was stirred for 16 h, then diluted with EtOAc (7 mL), and chromatographed (SiO_2, hexane–EtOAc, 1:1, R_f = 0.29) to yield the title compound **3a** (2.12 g, 7.19 mmol, 93%) as a colorless oil; $[\alpha]_D^{20}$ +34 (c = 8.5 g/L in $CHCl_3$).

GLC (Lipodex E, 5 min at 50 °C, then 1.5 K min^{-1} to 180 °C): t_R (*R*) = 96.68 min, t_R (*S*) = 97.86 min, 96% ee.

The NMR spectra showed a partly doubled signal set due to *E*,*Z*-isomers of the carbamate moiety.

IR (ATR): 2976 (w), 2932 (w), 2873 (m), 1783 (w), 1732 (s), 1678 (vs), 1476 (w), 1396 (s), 1366 (m), 1344 (w), 1305 (w), 1271 (w), 1256 (m), 1226 (w), 1203 (s), 1163 (vs), 1115 (s), 1081 (w), 985 (w), 967 (w), 903 (w), 991 (w), 949 (w), 772 (m), 731 (s), 698 (w), 647 cm^{-1} (w).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.91 (td, J = 12.8, 6.6 Hz, 1 H), 2.35–2.45 (m, 2 H), 2.54–2.62 (m, 1 H), 3.15 (d, J = 11.5 Hz, 1 H), 3.71 (s, 3 H), 4.07 (br d, J = ca. 16 Hz, 1 H), 4.12 (d, J = 11.5 Hz, $^1/_2$ H), 4.19 (d, J = 11.5 Hz, $^1/_2$ H), 4.36 (d, J = 15.9 Hz, $^1/_2$ H), 4.38 (d, J = 15.9 Hz, $^1/_2$ H), 5.96 (s, $^1/_2$ H), 5.99 (s, $^1/_2$ H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 28.1 (3 CH_3), 30.5 (CH_2), 33.95 ($^1/_2$ CH_2), 34.04 ($^1/_2$ CH_2), 49.9 ($^1/_2$ CH_2), 50.3 ($^1/_2$ CH_2), 51.7 ($^1/_2$ C), 52.5 ($^1/_2$ C), 52.97 ($^1/_2$ CH_3), 53.00 ($^1/_2$ CH_3), 55.4 ($^1/_2$ CH_2), 56.1 ($^1/_2$ CH_2), 80.4 (C), 123.0 ($^1/_2$ CH), 123.2 ($^1/_2$ CH), 153.9 (C), 160.5 ($^1/_2$ C), 161.3 ($^1/_2$ C), 171.7 ($^1/_2$ C), 171.9 ($^1/_2$ C), 197.3 ($^1/_2$ C), 197.4 ($^1/_2$ C).

HRMS (EI, 70 eV): m/z calcd for $C_{15}H_{22}NO_5$: 296.1498; found: 296.1504 [M + H$^+$].

Methyl 6-Oxo-1,3,3a,4,5,6-hexahydroisobenzofuran-3a-carboxylate (3b)

Concd H_2SO_4 (251 mg, 2.56 mmol, 4 equiv) was added to a cooled (ice-water bath) solution of alcohol **8b** (137 mg, 0.640 mmol) in CH_2Cl_2 (2 mL). After warming to r.t., the mixture was stirred for 1 h. Then sat. aq $NaHCO_3$ (15 mL) was added and the stirring continued for 10 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed (SiO_2, hexane–EtOAc, 1:1, R_f = 0.22) to yield the title compound **3b** (92 mg, 0.47 mmol, 73%) as a colorless oil, if optically active. The racemate was a colorless solid; mp 87 °C; $[\alpha]_D^{20}$ +158 (c = 10 g/L in $CHCl_3$).

GLC (Lipodex E, 5 min at 50 °C, then 1.5 K min^{-1} to 180 °C): t_R (*R*) = 72.08 min, t_R (*S*) = 75.57 min, >99% ee.

IR (ATR): 3048 (w), 2951 (m), 2868 (m), 1723 (s), 1665 (s), 1450 (m), 1372 (m), 1257 (s), 1229 (s), 1195 (s), 1104 (m), 1043 (s), 911 (s), 723 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.93 (ddd, *J* = 13.9, 13.2, 5.1 Hz, 1 H), 2.39 (ddd, *J* = 17.7, 13.9, 5.0 Hz, 1 H), 2.48 (dddd, *J* = 17.9, 5.1, 1.8, 0.7 Hz, 1 H), 2.57 (ddd, *J* = 13.1, 4.9, 2.2 Hz, 1 H), 3.55 (d, *J* = 9.1 Hz, 1 H), 3.77 (s, 3 H), 4.48 (ddd, *J* = 16.0, 2.7, *J* = 1.7 Hz, 1 H), 4.49 (d, *J* = 9.1 Hz, 1 H), 4.75 (dd, *J* = 15.9, 2.2 Hz, 1 H), 5.98 (t, *J* = 2.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 29.3 (CH_2), 34.1 (CH_2), 53.0 (CH_3), 54.3 (C), 69.7 (CH_2), 77.2 (CH_2), 121.5 (CH), 163.7 (C), 172.2 (C), 197.3 (C).

HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_{12}O_4$: 196.0736; found: 196.0739 [M^+].

Anal. Calcd for $C_{10}H_{12}O_4$ (196.20): C, 61.22; H, 6.16. Found: C, 60.85; H, 6.35.

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(22) CCDC 785562 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.