Practical formal total synthesis of (*rac*)- and (*S*)-camptothecin

René Peters,*† Martin Althaus and Anne-Laure Nagy

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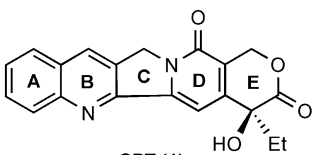
A practical, efficient and scalable formal total synthesis of (*rac*)- and (*S*)-camptothecin is described, which proceeds *via* the known DE ring building blocks **19** and (*S*)-**19**, respectively. The racemic synthesis starts from diethyl oxalate and uses straightforward carbonyl chemistry in order to generate the pyridone ring system. **19** was formed in 8.4% overall yield over 9 linear steps avoiding any chromatographic purification. The asymmetric version of this approach encompassed a diastereoselective Grignard addition to the enantiomerically pure α-ketoester **30** in order to generate the (*S*)-configured quaternary stereocenter. The auxiliary could be recycled in high yield and was successfully reused multiple times. The final steps paralleled the racemic approach. (*S*)-**19** was thus prepared in 9.4% overall yield (*er* = 95 : 5) over 10 steps.

Introduction

The alkaloid camptothecin (CPT, **1**), which was isolated for the first time in 1958 by Wani and Wall from the Chinese tree *Camptotheca accuminata*,[1] shows potent antiproliferative activity and continues to serve as a very attractive and promising lead structure for the development of new anti-cancer drugs.[2]



CPT (1)

Despite exhaustive attempts to develop efficient syntheses of camptothecin and derivatives thereof, there is from a technical point of view still no practical synthesis available.[2] The currently known synthetic approaches suffer either from very low yields (undue waste generation), expensive or commercially not available reagents (cost and time factor), or highly toxic reagents (health hazard and environmental problems) and in most cases the extensive need for column chromatography.

The overall goal of this work was to develop a scalable and practical synthesis of camptothecin due to the importance of CPT derivatives in anti-cancer therapy. We will first briefly describe a route which at the end failed, but which provided important information to develop a racemic and finally an asymmetric approach.

Results and discussion

Initial attempts

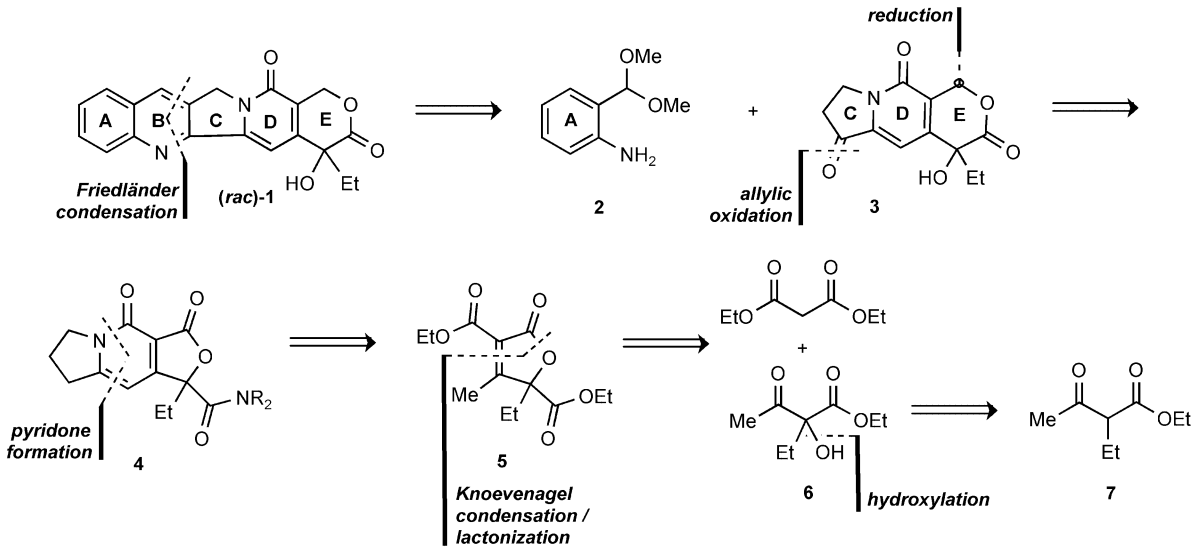
Our initial plan was based on the retrosynthetic analysis shown in Scheme 1. The utility of the Friedländer condensation in the final step using the tricyclic ketone **3** (CDE ring) had been demonstrated before.[3] This concept would have required a chemoselective lactone reduction of the tricyclic key intermediate **4**.

Despite various efforts, all attempts toward this goal remained fruitless mainly due to preferential reduction of the pyridone ring system of **4** (Scheme 2) in preference to the lactone moiety. This unexpected selectivity might be explained by the partial acyliminium character of **4** expressed by the mesomeric formula **4a** shown in Scheme 2.[4] However, due to the novelty of the pyridone formation reaction, this approach will be briefly described: inexpensive β-ketoester **7** was first hydroxylated at the α-position by air furnishing tertiary alcohol **6**,[5] which underwent a tandem Knoevenagel condensation/lactonization reaction with diethyl malonate giving access to α,β-unsaturated γ-lactone **5**. Bromination of the allylic methyl group and subsequent nucleophilic displacement by thioamide **9** yielded the crystalline hydrobromide salt **10** serving as starting material for a tandem vinylogous sulfide contraction reaction/δ-lactam formation providing **11** thus representing a novel reaction for pyridone formation.

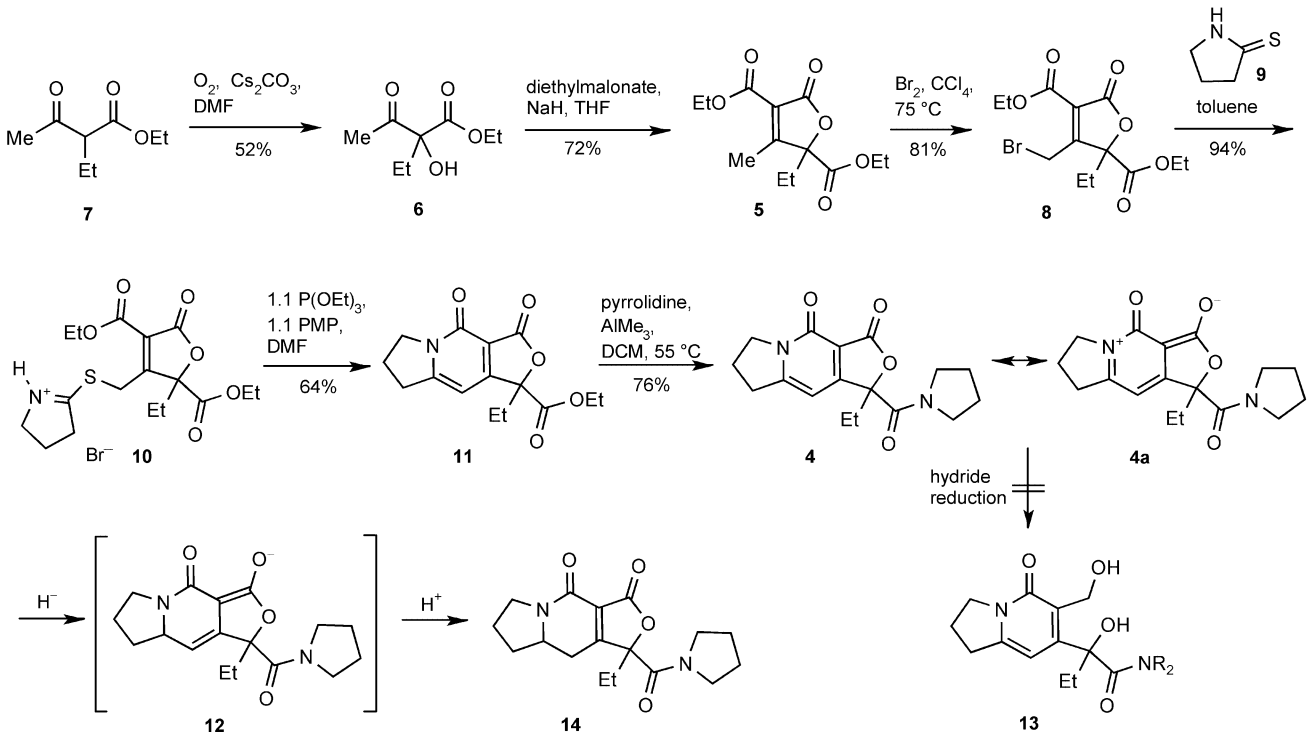
After screening of various bases, phosphines, phosphites, stoichiometries and solvents for this transformation, the combination pentamethylpiperidine (1.1 eq.), triethylphosphite (1.1 eq.) and DMF was found to work very efficiently.[6] This step is practical, since the crude reaction product (ratio of regioisomers: **11**/**15** = 6.7 : 1) can be easily purified by product precipitation from EtOAc/hexane (isolated yield of the desired regioisomer **11**: 64%) thus removing the undesired regioisomer **15**, side products, unreacted starting material **10**, DMF and $S{=}P(OEt)_3$, which is formed during the desulfurization.

The mechanism of this reaction is assumed to be related to the alkylative Eschenmoser sulfide contraction reaction[7] and is initiated by deprotonation of the CH_2S carbon atom in **10**, which is triply activated by the ester, the lactone and the iminothioether moiety (Scheme 3). The carbanion **16** thus formed apparently attacks the imino group resulting in a subsequent δ-lactam formation. The generated tetracyclic episulfide **17** is desulfurized by the phosphite reagent giving rise to pyridone **11**. The undesired regioisomer is formed by intramolecular attack of the carbanion

F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, Safety and Technical Sciences, Synthesis and Process Research, Grenzacherstr. 124, CH-4070 Basel, Switzerland. E-mail: peters@org.chem.ethz.ch
† Current address: ETH Zürich, Laboratory of Organic Chemistry, Wolfgang-Pauli-Str. 10, Hönggerberg HCI E111, CH-8093 Zürich, Switzerland.



Scheme 1



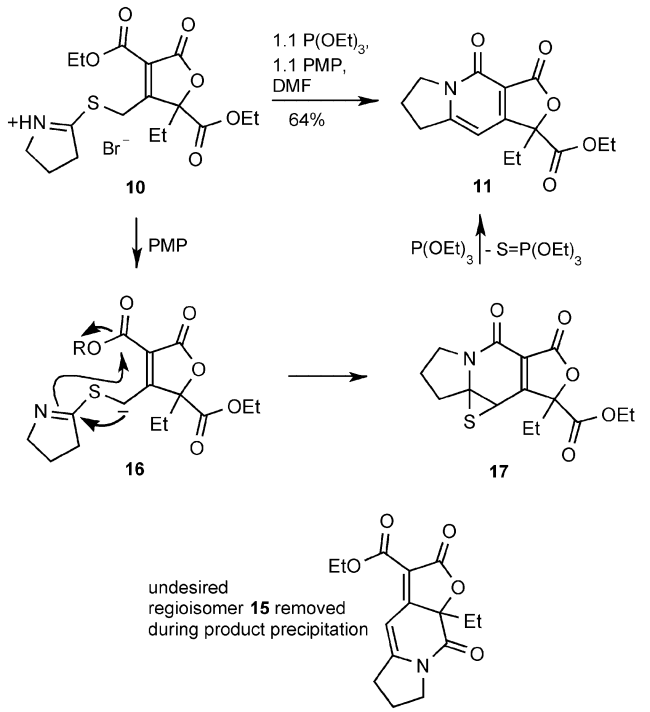
Scheme 2

16 at the imino group and a subsequent nucleophilic attack of the negatively charged N atom at the sterically more hindered ester group.

Synthesis of the racemic DE ring building block: a formal total synthesis of (*rac*)-CPT

In anticipation to overcome the selectivity problem in the reduction of pyridone **11**, we sought access to pyridone intermediate **20**, in which the pyridone nitrogen is not alkylated thus allowing for deprotonation during the treatment with a hydride reducing agent thereby significantly deactivating the pyridone system toward reduction. The retrosynthetic strategy is depicted in Scheme 4 and is based on the coupling of DE fragment **19** with quinoline derivative **18** *via* a Mitsunobu alkylation and a subsequent Heck cyclization. This coupling strategy was previously established by Comins *et al.* for the total synthesis of (*S*)-CPT.[8]

Our synthetic route started from diethyl oxalate **23** used to prepare α-ketoamide **25** over two steps *via* a known procedure



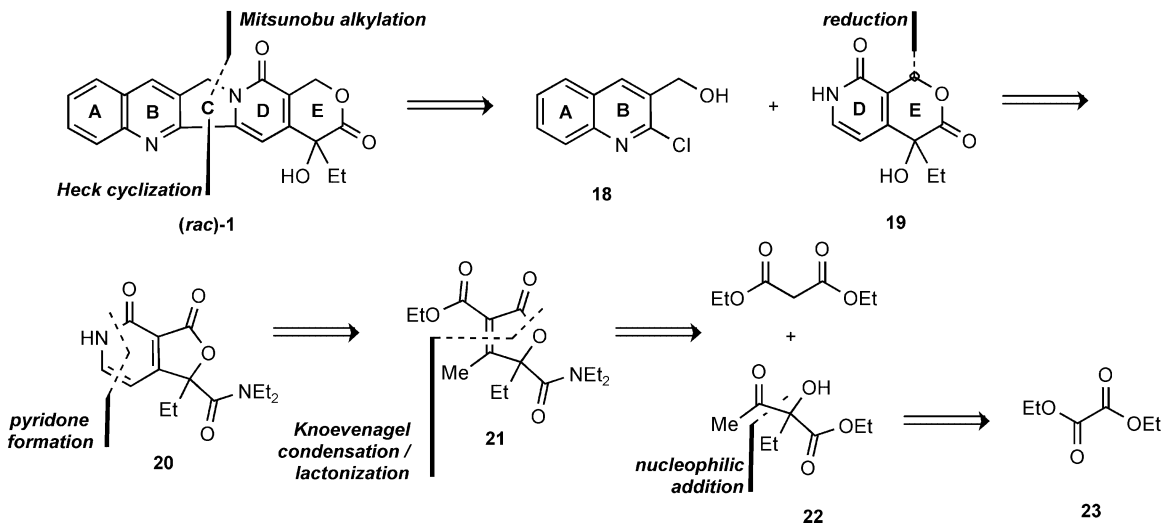
Scheme 3

(Scheme 5).[9] (*E*/*Z*)-1-Methyl-1-propenylmagnesium bromide was subsequently added to **25** at low temperature in THF. This Grignard addition suffers from competing enolate formation thus decreasing the conversion and explaining the low yield of 46% after high vacuum distillation.[10] Oxidative cleavage of the C=C double bond of **26** smoothly furnished α-hydroxy-β-keto amide **22**.[11] Despite steric hindrance, the ketone functionality in **22** is rather reactive toward nucleophiles due to activation by the α-hydroxy moiety. It was thus possible to apply crude **22** to a tandem Knoevenagel condensation/lactonization reaction providing α,β-unsaturated γ-lactone **21**, representing a vinylogous malonate. The reasonably acidic allylic β-methyl group therefore allows for a condensation reaction with tris(dimethylamino)methane or dimethylformamide dimethyl acetal (DMFMDA) in DMF furnishing enamine **27**, which is a push–pull electron system. The amino residue can thus be easily replaced by a nucleophile like ammonia. Treatment of crude **27** with NH_4OAc in DMF at 80 °C gave direct access to pyridone **20**, which was obtained from **22** in 53% yield over four steps after purification by trituration. The chemoselective reduction of the lactone ring to diol **28** was accomplished by a modification of a protocol previously reported by Ciufolini *et al.*[12] The $NaBH_4$ reduction of **20** required Lewis acid activation by $CeCl_3$ and the use of excess $NaBH_4$. Since the reduction did not run to completion even under these forcing conditions, the remaining 2 to 5% of both lactol diastereomers still contained in the crude product, were efficiently removed by trituration with DCM/TBME (2 : 1). Without $CeCl_3$, the reaction proceeded very sluggishly and resulted largely in decomposition of starting material **20**. Other reducing reagents such as $LiBH_4/EuCl_3$, $CaBH_4$ or K-Selectride gave complex product mixtures.

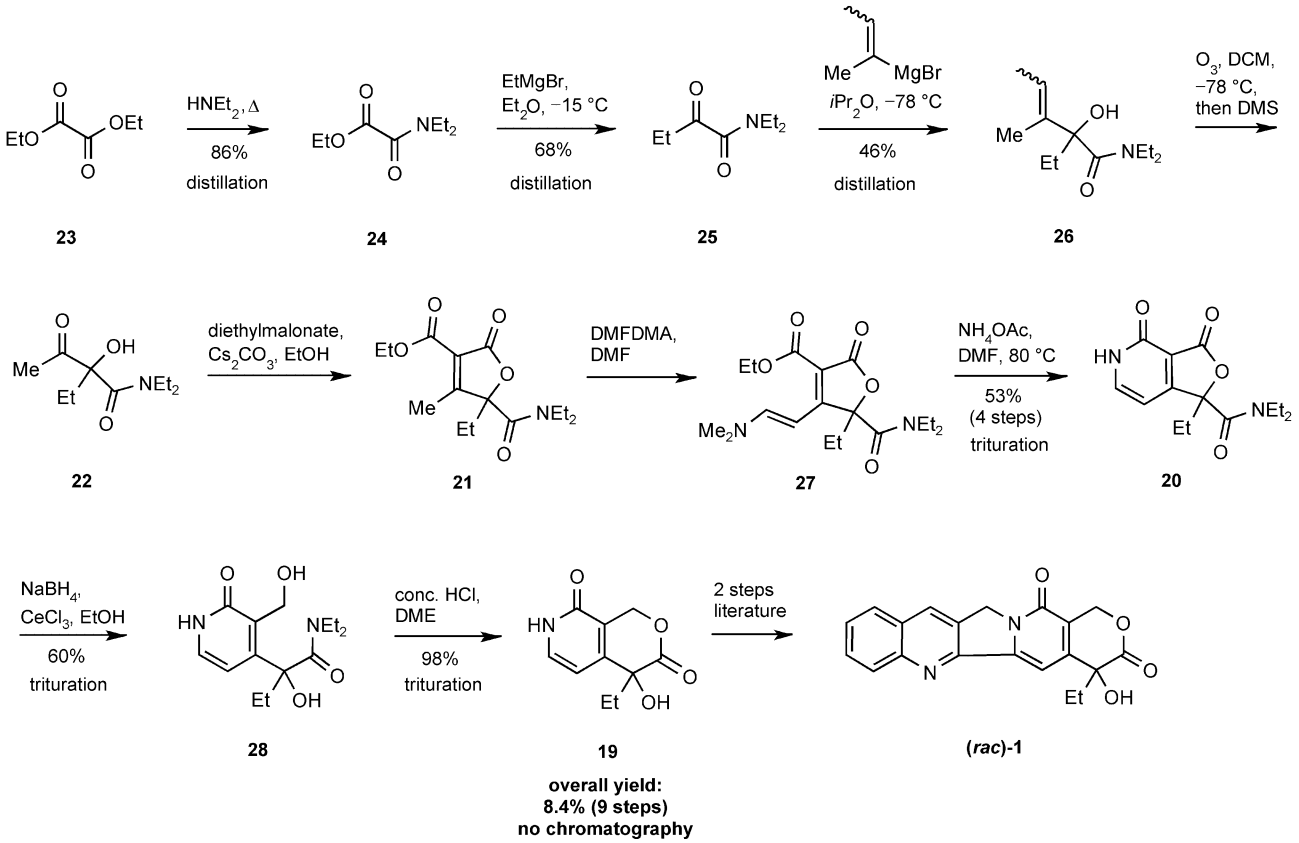
While the subsequent acid promoted cyclization giving rise to the α-hydroxylactone system **19** was remarkably efficient already at room temperature using various mineral acids like conc. HCl, HBr or sulfuric acid, product isolation by aqueous workup (acidic, neutral or basic) was hampered by severe decomposition. Using acidic ion exchange resins such as amberlyst **15** did not efficiently solve this problem, since the product was strongly absorbed on the polymer and large amounts of MeOH were required to elute **19**, which was isolated with low purity (^{1}H-NMR). The best conditions found involved treatment of **28** with 10 eq. concentrated HCl in DME at room temperature. After disappearance of the starting material (HPLC monitoring), the mixture was evaporated to dryness. The diethylammonium chloride salt side product was finally removed by trituration with MeOH furnishing racemic DE fragment **19** in nearly quantitative yield and in 8.4% overall yield from **22** over 9 steps without any chromatographic purification.

Synthesis of the optically active DE ring key building block for the preparation of (*S*)-camptothecin

An asymmetric version relying on the racemic approach described above required the stereoselective access to (*S*)-**22** (Scheme 6) for



Scheme 4



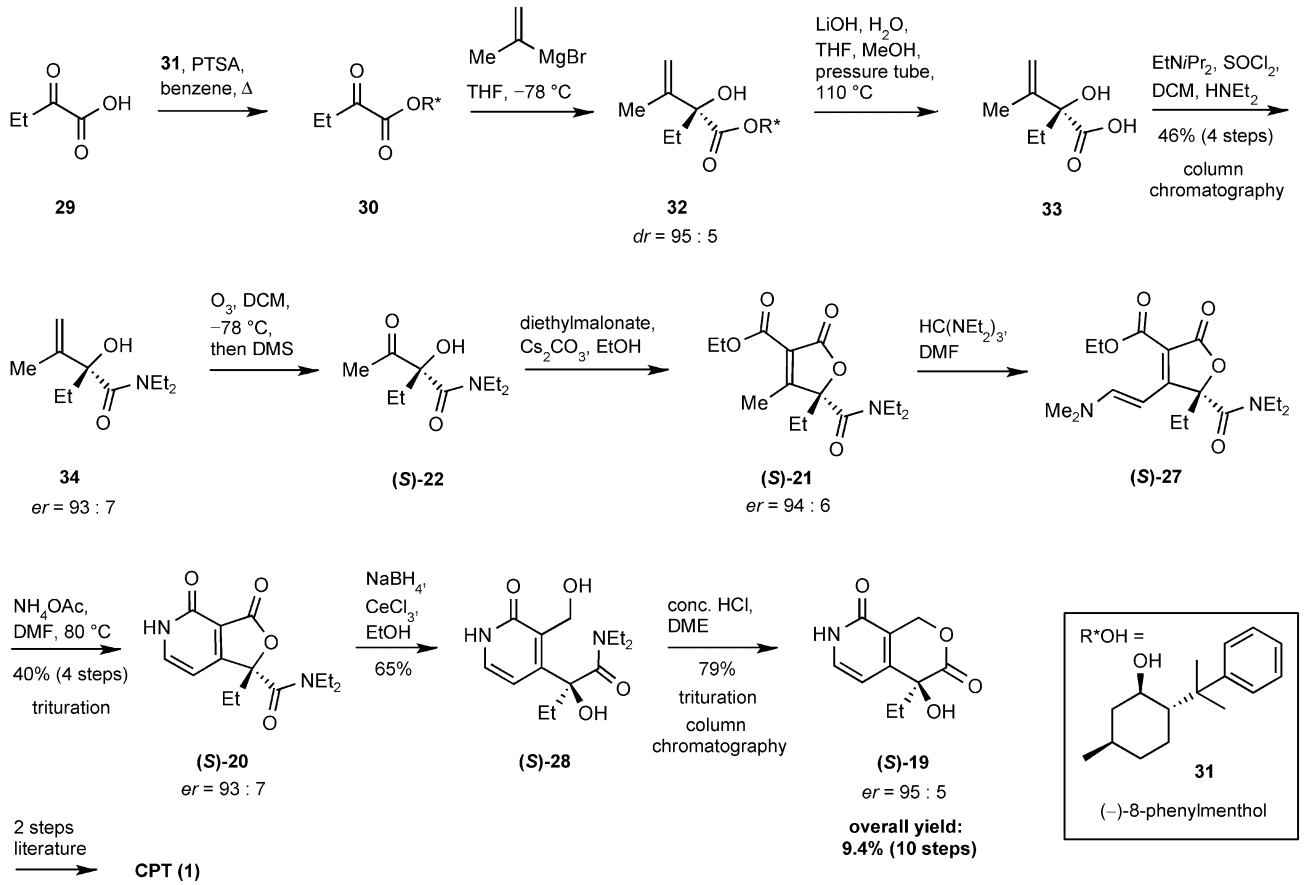
Scheme 5

which an auxiliary based approach was found. According to the literature, enantiomerically pure α-ketoester **30** was prepared from 2-oxobutyric acid **29** and (−)-8-phenylmenthol **31**.[13] The stereo determining step entailed a diastereoselective Grignard addition to **30** using isopropenylmagnesium bromide ($dr = 93:7$, ^{1}H-NMR).[14] Cleavage of the auxiliary using aqueous LiOH in MeOH/THF required heating in an autoclave to 110 °C in order to obtain full conversion after 24 h resulting in a clean hydrolysis. Separation of the resulting carboxylic acid **33** and the auxiliary **31** became feasible by pH-controlled extraction thus allowing a facile recycling of the rather expensive chiral auxiliary, which was successfully reused multiple times. The subsequent diethylamide formation procedure was based on a protocol developed by Merck Process Research for the formation of related α-hydroxy pyrrolidine amides.[15] In contrast to the Merck procedure, the amide formation required in our case a deprotonation of the carboxylic acid moiety by a tertiary amine like ethyldiisopropylamine (Hünig's base) prior to exposure to thionyl chloride (*er* of **34**: 93 : 7). To avoid massive decomposition, the secondary amine had to be added slowly by a syringe pump over 1 h. All attempts to prepare diethylamide **34** directly from **32** were unsuccessful owing to the low reactivity of ester **32** presumably due to steric hindrance, which also prevented transesterification reactions. **34** was purified by column chromatography, since amide formation resulted in formation of various unidentified side products.[16] Ozonolytic C=C double bond cleavage then gave access to optically active α-hydroxy-β-keto amide (*S*)-**22**. The following steps [tandem Knoevenagel condensation/γ-lactone formation (*er* of (*S*)-**21**: 94 : 6], enamine formation and pyridone formation [trituration of crude (*S*)-**20** with TBME, *er*: 93 : 7] paralleled the racemic approach described above. The subsequent reduction furnishing (*S*)-**28** proceeded significantly faster than in the racemic series. The hydrolysis of the initially formed product—boron complex—was, however, significantly slower for the optically active material. Due to the higher purity and also due to the higher solubility of (*S*)-**28** as compared to (*rac*)-**28**, the crude product was not purified by trituration prior to the δ-lactone formation. The trituration procedure, which was used to purify the racemic DE fragment, was not directly applicable to (*S*)-**19**, since the racemate is much less soluble in MeOH than the optically active form.[17] The diethylammonium chloride side product was finally removed by column chromatography ($CHCl_3/MeOH = 10:1$). (*S*)-**19** was thus prepared in 9.4% overall yield over 10 steps (*er* = 95 : 5) requiring only two chromatographic purifications.

Conclusion

A novel, efficient and scalable approach toward (*rac*)-**19**, which is the DE ring key building block for the synthesis of camptothecin derivatives, is described. This synthesis uses straightforward carbonyl chemistry in order to generate the pyridone ring system. DE fragment **19** was formed in 8.4% overall yield over 9 linear steps avoiding any chromatographic purification.

The asymmetric version of this approach leading to (*S*)-**19** encompassed a diastereoselective Grignard addition to the enantiomerically pure α-ketoester **30** in order to generate the



Scheme 6

(*S*)-configured tetrasubstituted carbon. The final steps paralleled the racemic approach. (*S*)-**19** was thus prepared in 9.4% overall yield (*er* = 95 : 5) over 10 steps including two chromatographic purifications. This synthesis should provide a good basis for further process development.

In addition, an unprecedented novel pyridone forming reaction *via* a tandem vinylogous sulfide contraction reaction/δ-lactam formation was established.

Experimental

Unless otherwise noted, solvents and reagents were used as is. All reactions were carried out under an argon atmosphere in oven-dried glassware. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, 0.25 mm (Merck). Qualitative HPLC was performed on a Hewlett-Packard Series 1050 system with UV detection at a wavelength of 210 nm using Chromolith Performance columns (100 × 4.6 mm) with gradient eluent H_2O/MeCN containing 10% of a phosphate buffer at pH 3.0. ^{1}H NMR were recorded using $CDCl_3$ as a reference peak. Spectra are given in ppm (δ) and coupling constants J are reported in Hz. Peaks in the IR spectra are reported in cm^{-1}. Low resolution electron impact mass spectra (EI-MS) were obtained at an ionization voltage of 70 eV. Data are reported in the form of m/z (intensity relative to base = 100).

Syntheses

2-Ethyl-2-hydroxy-3-oxo-butyric acid ethyl ester (6). To a solution of ethyl 2-ethylacetoacetate (**7**, 25.00 g, 142.2 mmol) in DMF (250 mL) was added at room temperature Cs_2CO_3 (4.656 g, 14.22 mmol, 0.1 eq.). Subsequently, O_2 was bubbled through the solution and the reaction was monitored by HPLC. After three days, the reaction was quenched by addition of water (750 mL) and the pH was adjusted to 5 by dropwise addition of conc. aqueous HCl at 0 °C. The mixture was extracted with ethyl acetate (3 × 500 mL). The combined organic phases were washed with water (7 × 250 mL), saturated aqueous $NaHCO_3$ (250 mL), brine (250 mL) and were afterwards dried over sodium sulfate (50 g, 30 min) and filtered. The filter cake was washed with 100 mL ethyl acetate. After evaporation of the solvent in a rotary evaporator (50 °C, 5 mbar), the crude product (22.08 g, 89% by weight) was obtained as an orange liquid, which was purified by column chromatography with hexane/ethyl acetate (9 : 1) furnishing product **6** (12.76 g, 73.25 mmol, 51% by weight) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (2H, m, OCH_2), 4.13 (1H, s, OH), 2.28 (3H, s, MeC=O), 2.35 (1H, dq, J = 14.3, J = 7.4, CC*H*HCH$_3$), 2.00 (1H, dq, J = 14.3, J = 7.4, CCH*H*CH$_3$), 1.30 (3H, t, J = 7.1, OCH_2CH_3), 0.88 (3H, t, J = 7.4, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5 (Me*C*=O), 170.4 (O*C*=O), 84.0 (*C*OH), 62.0 (OCH_2), 27.8 (CCH_2CH_3), 24.1 (H_3CC=O), 13.5 (OCH_2CH_3), 6.8 (CCH_2CH_3) ppm; IR (MIR) 3475, 2983, 1740, 1720, 1249,

1198, 1156, 1097 cm^{-1}; MS (EI) *m/z* (rel. intensity) 175 (8), 157 (5), 132 (100), 104 (32), 89 (16), 57 (66); HRMS (ESI POS) calcd for $C_8H_{14}O_4Na$ (MNa^+) 197.0790, found 197.0788; Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.0; H, 7.8%.

2-Ethyl-3-methyl-5-oxo-2,5-dihydro-furan-2,4-dicarboxylic acid diethyl ester (5). To a solution of **6** (10.50 g, 60.28 mmol) in THF (200 mL) was added diethyl malonate (9.63 mL, 61.49 mmol, 1.02 eq.) and subsequently portionwise NaH (2.46 g, 61.49 mmol, 1.02 eq.). The reaction was monitored by HPLC. After 4 h, the mixture was cooled to 0 °C and saturated aqueous NH_4Cl (200 mL) was added. THF (180 mL) was subsequently removed in a rotary evaporator (50 °C, 5 mbar) and ethyl acetate (200 mL) was added. The organic phase was washed with brine (200 mL) and was thereafter dried over sodium sulfate (15 g, 30 min) and filtered. The filter cake was washed with ethyl acetate (30 mL). After evaporation of solvent in a rotary evaporator (50 °C, 5 mbar), the crude product (17.00 g, 104% by weight) was obtained as a yellow liquid, which was purified by column chromatography with hexane/ethyl acetate (4 : 1) furnishing product **5** (11.67 g, 43.18 mmol, 72% by weight) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (2H, q, J = 7.1, OCH_2), 4.24 (2H, m, OCH_2), 2.37 (3H, s, Me), 2.34 (1H, dq, J = 14.7, J = 7.4, CC*H*HCH$_3$), 1.96 (1H, dq, J = 14.7, J = 7.4, CCH*H*CH$_3$), 1.38 (3H, t, J = 7.1, OCH_2CH_3), 1.28 (3H, t, J = 7.0, OCH_2CH_3), 0.90 (3H, t, J = 7.4, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4 (C=*C*CH$_3$), 167.2 (O*C*=O), 167.1 (O*C*=O), 161.1 (O*C*=O), 120.5 (*C*=CCH$_3$), 89.6 (*C*CH$_2$*C*H$_3$), 63.0 (OCH_2), 61.6 (OCH_2), 27.4 (C*C*H$_2$CH$_3$), 14.2 (OCH_2CH_3), 14.0 (OCH_2CH_3), 13.4 (C=C*C*H$_3$), 7.2 (CCH_2CH_3) ppm; IR (MIR) 2981, 1780, 1733, 1718, 1239, 1037 cm^{-1}; MS (EI) *m/z* (rel. intensity) 271 (6), 214 (18), 197 (15), 168 (18), 152 (100), 151 (57); HRMS (ESI POS) calcd for $C_{13}H_{18}O_6Na$ (MNa^+) 293.1001, found 293.1001; Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.8; H, 6.7. Found: C, 57.5; H, 6.6%.

3-Bromomethyl-2-ethyl-5-oxo-2,5-dihydro-furan-2,4-dicarboxylic acid diethyl ester (8). To a clear yellow solution of **5** (5.000 g, 18.50 mmol) in tetrachlorocarbon (75 mL) was added bromine (975 µL, 18.87 mmol, 1.02 eq.) at room temperature. The solution was heated to reflux and the reaction was monitored by HPLC. After 37 h, additional bromine (300 µL, 5.809 mmol, 0.314 eq.) was added. After refluxing overnight, the reaction mixture was cooled to room temperature and was then evaporated to dryness in a rotary evaporator (40 °C, 10 mbar). The crude product was obtained as an orange oil (7.24 g, 112% by weight), which was purified by column chromatography with hexane/ethyl acetate (4 : 1) furnishing product **8** (5.258 g, 15.06 mmol, 81% by weight as violet crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 (1H, d, J = 10.0, C*H*HBr), 4.51 (1H, d, J = 10.0, CH*H*Br), 4.42 (2H, q, J = 7.1, OCH_2), 4.27 (2H, m, OCH_2), 2.45 (1H, dq, J = 14.6, J = 7.2, CC*H*HCH$_3$), 2.05 (1H, dq, J = 14.6, J = 7.2, CCH*H*CH$_3$), 1.41 (3H, t, J = 7.1, OCH_2CH_3), 1.31 (3H, t, J = 7.1, OCH_2CH_3), 0.98 (3H, t, J = 7.2, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C=*C*CH$_2$Br), 164.7 (O*C*=O), 164.1 (O*C*=O), 158.0 (O*C*=O), 120.7 (*C*=CCH$_3$), 86.8 (*C*CH$_2$*C*H$_3$), 61.4 (OCH_2), 60.3 (OCH_2), 26.5 (C*C*H$_2$CH$_3$), 15.9 (C=C*C*H$_2$Br), 12.1 (OCH_2CH_3), 12.0 (OCH_2CH_3), 5.8 (CCH_2CH_3) ppm; IR (MIR) 2983, 1784, 1730, 1239, 1041 cm^{-1}; MS (EI) *m/z* (rel. intensity) 351 (20), 349 (20), 277 (16), 275 (17), 232 (25), 231 (25), 230 (21), 229 (21), 197 (30), 151 (100); HRMS (ESI POS) calcd for $C_{13}H_{17}BrO_6Na$ (MNa^+) 371.0106, found 371.0107; Anal. Calcd for $C_{13}H_{18}BrO_6$: C, 44.7; H, 4.9. Found: C, 44.7; H, 4.8%.

3-(4,5-Dihydro-3*H*-pyrrol-2-ylsulfanylmethyl)-2-ethyl-5-oxo-2,5-dihydro-furan-2,4-dicarboxylic acid diethyl ester hydrogen bromide salt (10). To a clear yellow solution of **8** (39.85 g, 114.1 mmol) in toluene (390 mL) was added **9** (11.54 g, 114.1 mmol) at room temperature. After 5 min, the product started to precipitate. The suspension was stirred overnight and the solid was finally collected by filtration. The filter cake was washed with toluene (50 mL) furnishing product **10** as white crystals (48.29 g, 94% by weight). Mp: 127 °C (decomp., gas evolution); ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.31 (1H, br. s, NH), 5.24 (1H, d, J = 12.8, C*H*HS), 5.03 (1H, d, J = 12.8, CH*H*S), 4.39 (2H, q, J = 7.2, OCH_2), 4.24 (4H, m, OCH_2 & NCH_2), 3.15 (2H, m, N=CCH_2), 2.52 (1H, dq, J = 14.9, J = 7.4, CC*H*HCH$_3$), 2.37 (3H, m, CC*H*HCH$_3$ & $CH_2CH_2CH_2$), 1.39 (3H, t, J = 7.2, OCH_2CH_3), 1.31 (3H, t, J = 7.2, OCH_2CH_3), 0.92 (3H, t, J = 7.4, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5 (N=C), 167.4 (C=*C*CH$_2$S), 166.8 (O*C*=O), 165.0 (O*C*=O), 160.3 (O*C*=O), 124.5 (*C*=CCH$_3$), 89.3 (*C*CH$_2$*C*H$_3$), 63.6 (OCH_2), 62.7 (OCH_2), 54.3 (NCH_2), 38.8 (N=C*C*H$_2$), 30.6 (C=C*C*H$_2$S), 27.8 (C*C*H$_2$CH$_3$), 21.3 (NCH_2CH_2), 14.1 (OCH_2CH_3), 14.1 (OCH_2CH_3), 7.4 (CCH_2CH_3) ppm; IR (Nujol) 2923, 2712, 1783, 1757, 1736, 1712, 1606, 1231 cm^{-1}; MS (ESI) *m/z* 392.2 (MNa^+ − HBr); Anal. Calcd for $C_{17}H_{24}BrNO_6S$: C, 45.3; H, 5.4; N, 3.1. Found: C, 45.1; H, 5.25; N, 3.4%.

1-Ethyl-3,4-dioxo-4,6,7,8-tetrahydro-1*H*,3*H*-furo[3,4-*f*]indolizine-1-carboxylic acid ethyl ester (11). To a solution of **10** (12.00 g, 26.65 mmol) in DMF (240 mL) was rapidly added triethylphosphite (5.26 mL, 29.32 mmol, 1.10 eq.) at room temperature. Subsequently, 1,2,2,6,6-pentamethylpiperidine (5.35 mL, 29.32 mmol, 1.10 eq.) was added dropwise (addition time 5 min). After the addition of 4 mL, the color of the solution changed from yellow to orange. The reaction was allowed to stir overnight. After 18 h, the dark greenish-brown solution was poured onto dichloromethane (1.5 L) and was washed with aqueous HCl (750 mL, 0.5 M) and with water (5 × 1 L). The organic phase was dried over sodium sulfate (50 g, 30 min) and filtered. The filter cake was washed with dichloromethane (100 mL). The organic phase was evaporated to dryness in a rotary evaporator (50 °C, 1 mbar). The crude product was obtained as a brown oil (14.02 g, 181% by weight, regioselectivity: 6.7 : 1). The residue was dissolved in ethyl acetate (280 mL) at reflux temperature (oil bath temperature 100 °C). Hexane (433 mL) was added to the heated solution resulting in the formation of a few crystals. The mixture was allowed to slowly cool to room temperature overnight and was then kept in a freezer at −22 °C for 3 days. The crystals were collected by filtration and washed with 30 mL hexane furnishing product **11** (4.99 g, 17.13 mmol, 64% by weight, regioselectivity >50 : 1) as slightly yellow crystals. Mp: 146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (1H, s, C=CH), 4.22 (4H, m, OCH_2 & CH_2N), 3.21 (2H, t, J = 7.8, C=CCH_2), 2.32 (3H, m, CC*H*HCH$_3$ & $CH_2CH_2CH_2$), 2.00 (1H, dq, J = 14.5, J = 7.3, CCH*H*CH$_3$), 1.28 (3H, t, J = 7.2, OCH_2CH_3), 0.92 (3H, t, J = 7.4, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (O*C*=O), 166.4 (O*C*=O), 165.6 (O=CC=*C*), 159.9 (N*C*=CH), 156.3 (N*C*=O), 110.3 (O=C*C*=C), 95.2 (NC=*C*H), 85.9 (*C*CH$_2$*C*H$_3$), 62.8 (OCH_2), 49.0 (NCH_2), 32.9 (NC*C*H$_2$), 29.8 (C*C*H$_2$CH$_3$), 21.3 (NCH_2CH_2),

14.0 (OCH_2CH_3), 7.6 (CCH_2CH_3) ppm; IR (Nujol) 2923, 1776, 1750, 1667, 1586, 1554, 1230 cm^{-1}; MS (EI) *m/z* (rel. intensity) 291 (6), 218 (100); HRMS (ESI POS) calcd for $C_{15}H_{17}NO_5Na$ (MNa^+) 314.1004, found 314.1004; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.9; N, 4.8. Found: C, 61.6; H, 6.0; N, 4.8%.

11-Ethyl-1-(pyrrolidine-1-carbonyl)-7,8-dihydro-1*H*,6*H*-furo[3,4-*f*]indolizine-3,4-dione (4). To a solution of pyrrolidine (1.22 mL, 13.90 mmol, 4.05 eq.) in dichloromethane (4.8 mL) trimethylaluminium (6.95 mL, 14.75 mmol, 4.30 eq.) was added dropwise at 0 °C. The cooling bath was then removed and stirring was continued for 2.5 h at room temperature. Subsequently, a solution of **11** (1.000 g, 3.433 mmol) in dichloromethane (6.4 mL) was added dropwise (addition time 5 min) and the clear solution was heated for 1.5 h to 50 °C and then for 24 h to 55 °C (reaction control by HPLC). The reaction mixture was allowed to cool to room temperature and was poured on aqueous HCl (80 mL, 1.0 M). The biphasic system was vigorously stirred for 4 h at room temperature. The aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over sodium sulfate (15 g, 30 min) and filtered. The filter cake was washed with dichloromethane (30 mL). The organic phase was evaporated to dryness in a rotary evaporator (40 °C, 10 mbar). The crude product was obtained as a yellow foam (1.058 g, 97% by weight), which was dissolved in ethyl acetate (20 mL) at reflux temperature (oil bath temperature 100 °C). Hexane (5 mL) was added to the heated solution. The mixture was allowed to slowly cool to room temperature overnight. Additional hexane (16 mL) was added at room temperature and stirring was continued for 15 min. The crystals were collected by filtration and washed with hexane (2 mL). The filtrate was afterward filtered again. Product **4** (823.0 mg, 2.601 mmol, 76% by weight) was obtained as dark green crystals. Mp: 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (1H, s, C=CH), 4.22 (2H, m, CH_2NC=CH), 3.90 (1H, m, O=CNC*H*H), 3.48 (3H, m, O=CNC*HH*), 3.20 (2H, t, J = 7.8, C=CCH_2), 2.40 (1H, dq, J = 14.2, J = 7.0, CC*H*HCH_3), 2.28 (2H, pent, J = 7.5, $NCH_2CH_2CH_2C$), 2.01 (1H, dq, J = 14.2, J = 7.0, $CCHHCH_3$), 1.91 (2H, m, $NCH_2CH_2CH_2CH_2$), 1.78 (2H, m, $NCH_2CH_2CH_2CH_2$), 0.89 (3H, t, J = 7.0, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (O=CC=*C*), 165.3 (O*C*=O), 164.6 (C_4H_8NC=O), 158.0 (N*C*=CH), 155.1 (N*C*=OC=C), 108.7 (O=C*C*=C), 96.0 (NC=*C*H), 86.7 (CCH_2CH_3), 47.5 (NCH_2), 47.2 (NCH_2), 46.6 (NCH_2), 31.5 ($NCCH_2$), 30.1 (CCH_2CH_3), 25.5 (NCH_2CH_2), 21.7 (NCH_2CH_2), 20.0 (NCH_2CH_2), 6.3 (CCH_2CH_3) ppm; IR (Nujol) 2925, 2854, 1775, 1662, 1623, 1586, 1557, 1458, 1436, 1404, 1052, 804 cm^{-1}; MS (EI) *m/z* (rel. intensity) 316 (68), 218 (88), 98 (100); HRMS (ESI POS) calcd for $C_{17}H_{21}N_2O_4$ (MH^+) 317.1501, found 317.1501; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 64.5; H, 6.4; N, 8.9. Found: C, 64.3; H, 6.1; N, 8.9%.

2-Pyrrolidinethione (9). Thioamide **9** was produced according to a modified literature procedure:[18] to a suspension of P_2S_5 (213.2 g, 959.2 mmol, 1.63 eq.) in THF (3.0 L) Na_2CO_3 (59.77 g, 563.9 mmol, 0.96 eq.) was added at room temperature. The mixture was stirred for 40 min at 60 °C. 2-Pyrrolidinone (50.00 g, 587.0 mmol) was then added and stirring was continued at 60 °C for 19 h. The solid was removed by filtration and the filter cake was washed with THF (200 mL) and dichloromethane (200 mL). The filtrate was evaporated to dryness in a rotary evaporator (40 °C, 10 mbar). The crude product was obtained as a slightly brown solid (122.5 g, 206% by weight), which was stirred with dichloromethane (400 mL) at room temperature. The mixture was filtered and the filter cake was washed with dichloromethane (2 × 60 mL). The filtrate was evaporated to dryness in a rotary evaporator (40 °C, 10 mbar) providing a beige solid (95.0 g, 160% by weight), which was stirred with toluene (150 mL) under reflux conditions. The hot mixture was filtered and the filtrate was evaporated to *ca.* 75 mL in a rotary evaporator (50 °C, 10 mbar) and was then allowed to stand overnight at 0 °C. The mixture was filtered and the crystals were washed with toluene (2 × 20 mL) furnishing product **9** as white crystals (28.1 g, 47% by weight). ^{1}H NMR (300 MHz, $CHCl_3$): δ 8.43 (1H, br. s, NH), 3.67 (2H, t, J = 10.0, CH_2N), 2.92 (2H, t, J = 10.0, S=CCH_2), 2.23 (2H, pent, J = 10.0, $CH_2CH_2CH_2$) ppm.

***N*,*N*-Diethyl-oxalamic acid ethyl ester (24)[9].** To diethyl oxalate (**23**, 30.00 g, 203.2 mmol) diethylamine (42.2 mL, 406.4 mmol, 2.0 eq.) was added at room temperature. The colorless clear solution was heated to reflux (oil bath temperature: 90 °C) and the reaction was monitored by HPLC. After 2.5 h, the resulting yellow-orange liquid was cooled to room temperature and all volatile compounds (ethanol, diethylamine) were removed in a rotary evaporator (50 °C, 10 mbar) furnishing the crude product (35.073 g, 100% by weight) as a yellow liquid. Purification was achieved using a high vacuum distillation (bp 85 °C at 0.08 mbar, oil bath temperature 111 °C, 40 cm Vigreux column) furnishing product **24** (30.216 g, 174.4 mmol, 86% by weight) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34 (2H, q, J = 7.1, OCH_2), 3.43 (2H, q, J = 7.2, NCH_2), 3.29 (2H, q, J = 7.2, NCH_2), 1.37 (3H, t, J = 7.1, OCH_2CH_3), 1.23 (3H, t, J = 7.2, NCH_2CH_3), 1.19 (3H, t, J = 7.2, NCH_2CH_3) ppm.

***N*,*N*-Diethyl-2-oxo butyramide (25)[9].** A solution of ethyl magnesium bromide in diethyl ether (3.0 M, 63.95 mL 191.8 mmol, 1.10 eq.) was diluted with diethyl ether (183 mL). The solution was cooled to −15 °C and a solution of **24** (30.20 g, 174.4 mmol) in diethyl ether (60 mL) was added dropwise (addition time: 30 min). The resulting viscous suspension was stirred for an additional 75 min at −15 °C. Subsequently, the reaction was quenched by addition of acetic acid (14.96 mL, 261.6 mmol, 1.5 eq.). 5 min later, water (35 mL) was added to dissolve all salts and the cooling bath was removed. After 15 min, the mixture was washed with pH-7-buffer (2 × 200 mL) and the organic phase was dried over Na_2SO_4 (20 g, 30 min) and filtered. The filter cake was washed with diethyl ether (40 mL). After evaporation of solvent in a rotary evaporator (40 °C, 10 mbar), the crude product (26.33 g, 96% by weight) was obtained as a yellow liquid. Purification was achieved using a high vacuum distillation (bp 86 °C at 2.5 mbar, oil bath temperature 110 °C, 40 cm Vigreux column) furnishing product **25** (18.66 g, 118.7 mmol, 68% by weight) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (2H, q, J = 7.1, NCH_2), 3.25 (2H, q, J = 7.2, NCH_2), 2.78 (2H, q, J = 7.3, O=CCH_2), 1.18 (3H, t, J = 7.2, Me), 1.16 (3H, t, J = 7.1, Me), 1.18 (3H, t, J = 7.3, Me) ppm.

2-Ethyl-2-hydroxy-3-methyl-pent-3-enoic acid diethylamide (26). A solution of 1-methyl-1-propenyl magnesium bromide (500 mL, 250.0 mmol, 3.0 eq.) in THF was cooled to −78 °C prior to slow addition of a precooled solution (−78 °C) of **25** (13.10 g, 83.2 mmol) in diisopropyl ether (260 mL) *via* canula (addition

time: 10 min). After 60 min, saturated aqueous ammonium chloride (250 mL) was added and the mixture was extracted with dichloromethane (3 × 250 mL). The combined organic phases were dried over sodium sulfate (25 g, 30 min) and filtered. The filter cake was washed with dichloromethane (50 mL). After removal of solvent in a rotary evaporator (40 °C, 10 mbar), the crude product (18.05 g, 102% by weight) was obtained as a yellow liquid (E/Z = 5.3 : 1), which was purified by high vacuum distillation (bp 65 °C at 0.28 mbar, oil bath temperature 110 °C, 40 cm Vigreux column) furnishing product **26** (8.145 g, 38.18 mmol, 46%) as a light yellow liquid in the form of E/Z isomers (E/Z = 5.1 : 1). An analytical sample of the (*E*)-isomer was obtained by column chromatography with hexane/ethyl acetate (4 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (1H, q, J = 6.8, C=CH), 5.28 (1H, s, OH), 3.40 (4H, m, NCH_2), 1.96 (1H, dq, J = 13.8, J = 7.3, CC*H*HCH$_3$), 1.87 (1H, dq, J = 13.8, J = 7.3, CCH*H*CH$_3$), 1.67 (3H, d, J = 6.8, CHC*H*$_3$), 1.57 (3H, br. s, HC=CC*H*$_3$), 1.15 (3H, t, J = 6.8, NCH_2CH_3), 1.08 (3H, t, J = 6.9, NCH_2CH_3), 0.86 (3H, t, J = 7.3, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) of the (*E*)-isomer: δ 173.0 (N*C*=O), 137.7 (*C*=CH), 120.1 (C=*C*H), 78.5 (COH), 41.4 (NCH_2), 41.2 (NCH_2), 28.1 (C*C*H$_2$CH$_3$), 13.5 (C=CH*C*H$_3$), 13.3 (NCH_2CH_3), 12.8 (HC=C*C*H$_3$), 12.4 (NCH_2CH_3), 8.0 (CCH_2CH_3) ppm; IR (MIR) 3353, 2974, 1616, 1380, 1362, 1019 cm^{-1}; MS (EI) m/z (rel. intensity) 214 (5), 196 (23), 113 (100); HRMS (ESI POS) calcd for $C_{12}H_{23}NO_2Na$ (MNa^+) 236.1626, found 236.1629; Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.6; H, 10.9; N, 6.6. Found: C, 67.3; H, 10.9; N, 6.55%.

2-*N*,*N*-Triethyl-2-hydroxy-3-oxo-butyramide (22). O_3 (150 L h^{-1}) was bubbled through a stirred solution of **26** (8.000 g, 37.50 mmol) in dichloromethane (400 mL) at −78 °C until a blue colour appeared (after 18 min). Subsequently, argon was bubbled through the solution for 10 min. Dimethyl sulfide (28 mL, 375 mmol, 10.0 eq.) was subsequently added and the solution was allowed to slowly warm to room temperature overnight. The mixture was washed with 750 mL water (3 × 250 mL). The organic phase was dried over Na_2SO_4 (20 g, 30 min) and filtered. The solid was washed with dichloromethane (40 mL). After evaporation of solvent in a rotary evaporator (40 °C, 10 mbar), the crude product (7.85 g, 104% by weight) was obtained as a yellow oil. An analytical sample was obtained by column chromatography (pentane/diethyl ether 10 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (1H, s, OH), 3.41 (2H, m, NCH_2), 3.29 (2H, q, J = 7.0, NCH_2), 2.19 (3H, s, O=CMe), 2.01 (1H, dq, J = 15.0, J = 7.4, CC*H*HCH$_3$), 1.96 (1H, dq, J = 15.0, J = 7.4, CCH*H*CH$_3$), 1.15 (3H, t, J = 7.0, NCH_2CH_3), 1.12 (3H, t, J = 7.0, NCH_2CH_3), 0.83 (3H, t, J = 7.4, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2 (Me*C*=O), 170.2 (NC=O), 84.8 (COH), 43.1 (NCH_2), 42.9 (NCH_2), 28.9 (C*C*H$_2$CH$_3$), 26.1 (H$_3$*C*C=O), 15.0 (NCH_2CH_3), 13.6 (NCH_2CH_3), 8.6 (CCH_2CH_3) ppm; IR (film) 3314, 2978, 1719, 1632, 1466, 1384, 1211, 1136, 1084 cm^{-1}; MS (EI) m/z (rel. intensity) 202 (2), 158 (50), 100 (100); HRMS (ESI POS) calcd for $C_{10}H_{20}NO_3$ (MH^+) 202.1443, found 202.1445%; Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0. Found: C, 59.4; H, 9.3; N, 7.0%.

(*S*)-2-*N*,*N*-Triethyl-2-hydroxy-3-oxo-butyramide ((*S*)-22). O_3 (150 L h^{-1}) was bubbled through a stirred solution of **34** (595.0 mg, 2.985 mmol) in dichloromethane (30 mL) at −78 °C until a blue colour appeared (after 6 min). Subsequently, argon was bubbled through the solution for 20 min. Dimethyl sulfide (2.21 mL, 200.7 mmol, 10.0 eq.) was subsequently added and the solution was allowed to slowly warm to room temperature overnight (16 h 40 min). The mixture was washed with water (3 × 20 mL) and the organic phase was dried over Na_2SO_4 (5 g, 30 min) and filtered. The solid was washed with dichloromethane (10 mL). After evaporation of solvent in a rotary evaporator (24 °C, 10 mbar), the product (*S*)-**22** (587.3 mg, 98% by weight) was obtained as a yellow oil. An analytical sample was obtained by column chromatography (pentane/diethyl ether 3 : 1). $[a]_D^{20}$ (c = g dL^{-1}, $CHCl_3$) = +77.1. The other analytical data are in accordance with (*rac*)-**22**.

5-Diethylcarbamoyl-5-ethyl-4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (21). To a solution of **22** (2.500 g, 12.42 mmol) and diethyl malonate (9.73 mL, 62.10 mmol, 5.0 eq.) in ethanol (100 mL), Cs_2CO_3 (16.27 g, 49.68 mmol, 4.0 eq.) was added at room temperature. The reaction was monitored by HPLC. After 26 h, the yellow suspension was cooled to 0 °C and aqueous HCl (0.5 M, 200 mL, 65.25 mmol, 5.0 eq.) was added dropwise over 60 min. Ethanol (95 mL) was subsequently removed in a rotary evaporator (50 °C, 5 mbar) and, ethyl acetate (200 mL) was added. The organic phase was washed with brine (2 × 150 mL), and was afterwards dried over sodium sulfate (20 g, 30 min) and then filtered. The filter cake was washed with ethyl acetate (40 mL). After evaporation of the solvent in a rotary evaporator (50 °C, 5 mbar), volatile components were removed in a Kugelrohr apparatus (55 °C, 0.08 mbar). The crude product (6.758 g, 183% by weight) was obtained as a yellow liquid. An analytical sample was obtained by column chromatography (hexane/ethyl acetate 9 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (2H, q, J = 7.1, OC*H*$_2$), 3.58 (1H, m, NC*H*H), 3.12–3.48 (3H, m, NC*HH*), 2.50 (3H, s, CCH_3), 2.35 (1H, dq, J = 14.4, J = 7.3, CC*H*HCH$_3$), 2.00 (1H, dq, J = 14.4, J = 7.3, CCH*H*CH$_3$), 1.38 (3H, t, J = 7.1, OCH_2CH_3), 1.21 (3H, m, NCH_2CH_3), 1.15 (3H, m, NCH_2CH_3), 0.86 (3H, t, J = 7.3, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0 (C=*C*CH$_3$), 166.5 (OC=O), 164.8 (NC=O), 160.5 (OC=O), 119.0 (*C*=CCH$_3$), 90.9 (*C*CH$_2$CH$_3$), 60.8 (OCH_2), 42.2 (NCH_2), 42.1 (NCH_2), 29.1 (C*C*H$_2$CH$_3$), 14.5 (C=C*C*H$_3$), 13.8 (NCH_2CH_3), 13.4 (OCH_2CH_3), 11.8 (NCH_2CH_3), 6.5 (CCH_2CH_3) ppm; IR (MIR) 2977, 1777, 1718, 1632, 1320, 1241, 1212, 1035 cm^{-1}; MS (EI) m/z (rel. intensity) 297 (1), 282 (2), 100 (100), 72 (21); HRMS (ESI POS) calcd for $C_{15}H_{23}NO_5Na$ (MNa^+) 320.1474, found 320.1472; Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.7; H, 7.7; N, 4.6%.

(*S*)-5-Diethylcarbamoyl-5-ethyl-4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester ((*S*)-21). According to the preparation of **21**, a solution of (*S*)-**22** (587.3 mg, 2.918 mmol) and diethyl malonate (2.29 mL, 14.59 mmol, 5.0 eq.) in ethanol (23 mL) was treated with Cs_2CO_3 (3.822 g, 11.67 mmol, 4.0 eq.) yielding the crude product (1.224 g, 141% by weight) as a yellow liquid (*er* = 94.15 : 5.85, chiral GC Method [carrier gas: H_2, 110 kPa (split ratio 1/20), equipment: HP5890_1A, column: BGB-175, 30 m × 0.25 mm, temperature: 155 °C (isotherm), injector temperature: 200 °C, detector temperature: 220 °C, retention time: 58.16 min (*S*)-**21**, 57.02 min (*R*)-**21**]). An analytical sample was obtained by column chromatography (heptane/ethyl acetate

7 : 3). $[\alpha]_D^{20}$ (c = 1.025 g dL^{-1}, $CHCl_3$) = −134.8. The other analytical data are in accordance with (*rac*)-**21**.

5-Diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (27). To a solution of **21** (500.0 mg, 22.73 mmol) in DMF (3.0 mL), tris(dimethylamino)methane (3.0 mL, 17.3 mmol, 10.3 eq.) was added at room temperature. The color of the reaction mixture changed from orange to brown to green. The reaction was monitored by HPLC. After 17 h, the mixture was diluted with dichloromethane (50 mL) and washed with aqueous HCl (25 mL, 1.0 M) and subsequently with brine (3 × 50 mL). The organic phase was dried over sodium sulfate (2 g, 30 min) and filtered. The filter cake was washed with dichloromethane (4 mL). After evaporation of solvent in a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as an orange oil (627.0 mg, 106% by weight), which was liberated from residual DMF in a high vacuum rotary evaporator (50 °C, 0.5 mbar) yielding product **27** (536.0 mg, 1.517 mmol, 90% by weight) as orange crystals. Mp: 105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (1H, br., NC*H*=CH), 6.47 (1H, br., NCH=C*H*), 4.32 (2H, m, OCH_2), 3.52 (1H, dq, J = 13.2, J = 7.0, NC*H*H), 3.18 (3H, s, NCH_3), 3.17 (2H, m, NCH_2), 3.00 (3H, s, NCH_3), 2.99 (1H, m, NC*H*H), 2.41 (1H, dq, J = 14.3, J = 7.2, CC*H*HCH$_3$), 2.03 (1H, dq, J = 14.3, J = 7.2, CCH*H*CH$_3$), 1.39 (3H, t, J = 7.1, OCH_2CH_3), 1.20 (3H, t, J = 7.0, NCH_2CH_3), 1.08 (3H, t, J = 7.0, NCH_2CH_3), 0.84 (3H, t, J = 7.2, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (O=CC=*C*), 169.6 (OC=O), 168.0 (NC=O), 164.4 (OC=O), 154.3 (N*C*H=CH), 99.3 (O=C*C*=C), 91.9 (NCH=*C*H), 87.7 (*C*CH_2CH_3), 60.1 (OCH_2), 45.7 (NMe), 43.0 (N*C*H_2CH_3), 42.4 (N*C*H_2CH_3), 36.8 (NMe), 34.6 (C*C*H_2CH_3), 14.4 (OCH_2CH_3), 14.0 (NCH_2CH_3), 12.3 (NCH_2CH_3), 7.3 (CCH_2CH_3) ppm; IR (MIR) 2973, 1745, 1677, 1630, 1613, 1541, 1393, 1177, 1024, 976 cm^{-1}; MS (ESI) m/z 353.3 (MH$^+$); HRMS (ESI POS) calcd for $C_{18}H_{28}N_2O_5$ (M$^+$) 352.1998, found 352.2003; Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.3; H, 8.0; N, 7.95. Found: C, 61.0; H, 8.1; N, 8.0%.

(*S*)-5-Diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester ((*S*)-27). According to the preparation of **27**, a solution of (*S*)-**21** (1.220 g, 4.103 mmol) in DMF (7.3 mL) was treated with tris(dimethylamino)methane (7.55 mL, 42.26 mmol, 10.3 eq.) yielding the crude product as an orange oil (1.463 mg, 101% by weight). An analytical sample (yellow oil) was prepared starting from (*S*)-**21**, which had been purified by column chromatography prior to use. The sample was liberated from residual DMF in a high vacuum rotary evaporator (50 °C, 0.5 mbar). $[\alpha]_D^{20}$ (c = 1.020 g dL^{-1}, $CHCl_3$) = −238.9. The other analytical data are in accordance with (*rac*)-**27**.

Synthesis of 5-diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (27) using DMFDMA. To a solution of **21** (6.758 g, 22.73 mmol) in DMF (40 mL), dimethylformamide dimethyl acetal (DMFDMA, 40.0 mL, 285.1 mmol, 12.5 eq.) was added at room temperature. The color of the reaction mixture changed from orange to brown to green. The reaction was monitored by HPLC. After 2.5 h, the mixture was diluted with dichloromethane (150 mL) and washed with aqueous HCl (150 mL, 1.0 M) and subsequently with brine (3 × 150 mL). The organic phase was dried over sodium sulfate (20 g, 30 min) and filtered. The filter cake was washed with dichloromethane (40 mL). After evaporation of the solvent in a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a red-brown liquid (10.632 g, 144% by weight), which still contains DMF and which was directly used for the preparation of **20** without further purification.

1-Ethyl-3,4-dioxo-1,3,4,5-tetrahydro-furo[3,4-*c*]pyridine-1-carboxylic acid diethylamide (20). To a solution of crude **27** (10.63 g, 30.17 mmol) in DMF (85 mL), ammonium acetate (23.7 g, 301.7 mmol, 10.0 eq.) was added at room temperature resulting in the formation of a shiny red solution, which was heated to 80 °C. The reaction was monitored by HPLC. After 19 h, the mixture was diluted with dichloromethane (150 mL) and successively washed with water (130 mL), aqueous HCl (130 mL, 0.5 M) and subsequently with brine (3 × 130 mL). The organic phase was dried over sodium sulfate (20 g, 30 min) and filtered. The filter cake was washed with dichloromethane (40 mL). After evaporation of solvent in a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a red liquid (6.611 g, 79% by weight). All volatile components were removed in a Kugelrohr distillation apparatus. The residue was purified by trituration for 18 h at room temperature with heptane/TBME (1 : 1, 12 mL), then with heptane/TBME (1 : 1, 8 mL) and finally with TBME (10 mL) furnishing product **20** (1.797 g, 6.46 mmol, 21% by weight (yield over 4 steps (**26** → **20**): 53%) as violet crystals. Mp: 177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.03 (1H, br. s, NH), 7.78 (1H, d, J = 6.6, HNC*H*=CH), 6.93 (1H, d, J = 6.6, HNCH=C*H*), 3.94 (1H, dq, J = 13.8, J = 6.9, NCH_2), 3.50 (1H, dq, J = 13.8, J = 6.9, NCH_2), 3.28 (1H, dq, J = 13.8, J = 6.9, NCH_2), 3.17 (1H, dq, J = 13.8, J = 6.9, NCH_2), 2.39 (1H, dq, J = 14.5, J = 7.3, CC*H*HCH$_3$), 2.09 (1H, dq, J = 14.5, J = 7.3, CCH*H*CH$_3$), 1.24 (3H, t, J = 6.9, NCH_2CH_3), 1.14 (3H, t, J = 6.9, NCH_2CH_3), 0.89 (3H, t, J = 7.3, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2 (O=CC=*C*), 166.6 (OC=O), 166.2 (Et_2NC=O), 160.3 (HNC=O), 141.9 (HN*C*H=CH), 112.7 (O=C*C*=C), 104.5 (HNCH=*C*H), 89.0 (*C*CH_2CH_3), 42.7 (NCH_2), 31.7 (C*C*H_2CH_3), 14.7 (NCH_2CH_3), 12.4 (NCH_2CH_3), 7.6 (CCH_2CH_3) ppm; IR (Nujol) 3123, 2924, 1776, 1662, 1637, 1609, 1560, 1459, 1247 cm^{-1}; MS (ESI) m/z 279.1 (MH$^+$); HRMS (ESI POS) calcd for $C_{14}H_{18}N_2O_4Na$ (MNa$^+$) 301.1164, found 301.1164; Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.4; H, 6.5; N, 10.1. Found: C, 60.4; H, 6.7; N, 9.7%.

(*S*)-1-Ethyl-3,4-dioxo-1,3,4,5-tetrahydro-furo[3,4-*c*]pyridine-1-carboxylic acid diethylamide ((*S*)-20). According to the preparation of **20**, a solution of (*S*)-**27** (1.462 g, 4.148 mmol) in DMF (11.7 mL) was treated with ammonium acetate (3.263 g, 41.48 mmol, 10.0 eq.) yielding the crude product as a red liquid (3.175 g, 275% by weight). All volatile components were removed in a Kugelrohr distillation apparatus (50 °C, 0.05 mbar). The residue (402.8 mg, 35% by weight) was purified by trituration for 18 h at room temperature with 4.8 mL TBME furnishing product (*S*)-**20** (329.2 mg, 1.18 mmol, 29% by weight (yield over 4 steps (**34** → (*S*)-**20**): 41%), *er* = 93.3 : 6.7 (chiral HPLC, sample preparation: ethanol, equipment: Agilent 1100, column: Chiralpak-ADH, 250 × 4.6 mm, temperature: 25 °C, mobile phase: 90% heptane, 10% ethanol/trifluoroacetic acid (99 : 1), flow: 0.8 mL min^{-1}, injection volume: 5 μL, detection: UV 326 nm, retention time: 29.78 min (*S*)-**20**, 26.01 min (*R*)-**41**) as

yellow crystals. Mp: 199 °C; $[\alpha]_D^{20}$ ($c = 0.364$ g dL^{-1}, $CHCl_3$) = −67.9. The other analytical data are in accordance with (*rac*)-**20**.

***N*,*N*-Diethyl-2-hydroxy-2-(3-hydroxymethyl-2-oxo-1,2-dihydro-pyridin-4-yl)-butyramide (28).** To a solution of **20** (1.000 g, 3.595 mmol) in ethanol (40 mL), ground cerium(III) chloride (2.215 g, 8.99 mmol, 2.5 eq.) was added at room temperature. The suspension was placed in an ultrasonic bath for 10 min and was then cooled to 15 °C by a water bath. Sodium borohydride (2.40 g, 61.1 mmol, 17 eq.) was added in 6 portions over 3 h. After each addition, the water bath was removed immediately. After an additional 2 h at room temperature, the suspension was poured onto saturated aqueous $NaHCO_3$/brine (1 : 1, 800 mL) and the mixture was vigorously stirred for 13 h prior to extraction with dichloromethane/ethanol (4 : 1, 5 × 400 mL). The combined organic extracts were evaporated in a rotary evaporator (50 °C, 5 mbar). The crude product was obtained as a purple-red solid (879.6 mg, 87% by weight), which was purified by trituration with dichloromethane/TBME (2 : 1, 5.25 mL) yielding product **28** (623.2 mg, 2.21 mmol, 61% by weight) as a white solid. Mp: 193 °C; ^{1}H NMR (300 MHz, DMSO): δ 11.68 (1H, br. s, NH), 7.32 (1H, d, $J = 7.1$, HNC*H*=CH), 6.41 (1H, d, $J = 7.1$, HNCH=C*H*), 6.06 (1H, s, COH), 4.68 (1H, br. s, CH_2OH), 4.37 (2H, s, CH_2OH), 3.05–3.40 (4H, m, NCH_2), 2.07 (1H, dq, $J = 14.3$, $J = 7.3$, CC*H*HCH_3), 1.86 (1H, dq, $J = 14.3$, $J = 7.3$, CCH*H*CH_3), 1.01 (3H, t, $J = 7.0$, NCH_2CH_3), 0.74 (3H, t, $J = 7.0$, NCH_2CH_3), 0.68 (3H, t, $J = 7.3$, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, DMSO): δ 171.5 (Et_2NC=O), 163.3 (HNC=O), 152.5 (O=CC=*C*), 132.3 (N*C*H=CH), 126.8 (O=C*C*=C), 103.8 (HNCH=*C*H), 77.9 (COH), 55.6 (OCH_2), 40.9 (NCH_2), 32.8 (NCH_2), 12.6 (NCH_2CH_3), 12.2 (NCH_2CH_3), 7.5 (CCH_2CH_3) ppm; IR (Nujol) 3315, 3104, 2922, 2725, 1639, 1596, 1526, 1466, 1376, 1145, 1070, 1021 cm^{-1}; MS (ESI) *m*/*z* 283.0 (MH^+), 305.3 (MNa^+); HRMS (ESI POS) calcd for $C_{14}H_{22}N_2O_4Na$ (MNa^+) 305.1477, found 305.1476; Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.5; H, 7.85; N, 9.9. Found: C, 59.2; H, 8.0; N, 9.6%.

(*S*)-*N*,*N*-Diethyl-2-hydroxy-2-(3-hydroxymethyl-2-oxo-1,2-dihydro-pyridin-4-yl)-butyramide ((*S*)-28). According to the preparation of **28**, a solution of (*S*)-**20** (694.0 mg, 2.494 mmol) in ethanol (28 mL) was treated with ground cerium(III) chloride (1.537 g, 6.235 mmol, 2.5 eq.) and sodium borohydride (1.081 g, 27.4 mmol, 11 eq., added in 4 portions over 1 h, reaction time: 4 h 50 min) yielding the crude product as a beige solid (576.0 mg, 82% by weight), which was redissolved in methanol (10 mL) at 60 °C. The solution was poured on saturated aqueous $NaHCO_3$/brine (1 : 1, 88 mL) and the resulting suspension was stirred for an additional 24 h prior to extraction with dichloromethane/ethanol (4 : 1, 5 × 88 mL). The combined organic extracts were evaporated in a rotary evaporator (50 °C, 5 mbar) yielding product (*S*)-**28** (461.5 mg, 1.63 mmol, 66% by weight) as an off-white solid. Mp: 174 °C (decomp.); $[\alpha]_D^{20}$ ($c = 0.253$ g dL^{-1}, $CHCl_3$) = −81.8. The other analytical data are in accordance with (*rac*)-**28**.

4-Ethyl-4-hydroxy-1,7-dihydro-4*H*-pyrano[3,4-*c*]pyridine-3,8-dione (19). To a suspension of **28** (560.0 mg, 1.983 mmol) in DME (11.2 mL), conc. aqueous HCl (36.5%, 1.68 mL 19.83 mmol, 10.0 eq.) was added dropwise at 0 °C. The ice bath was removed after 15 min and the triphasic mixture was vigorously stirred. The reaction was monitored by HPLC. After 4 h, the mixture was evaporated to dryness in a rotary evaporator (27 °C, 1 mbar). The crude product was obtained as an off-white semisolid (805.4 mg, 194% by weight). 333.3 mg of the crude product were purified by trituration with 0.7 mL methanol at room temperature for 18 h furnishing product **19** (168.7 mg, 0.425 mmol, 98% by weight) as white crystals. Mp: 227 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$/MeOH (1 : 1)): δ 7.18 (1H, d, $J = 6.9$, HNC*H*=CH), 6.44 (1H, d, $J = 6.9$, HNCH=C*H*), 5.31 (1H, d, $J = 16.2$, OC*H*H), 4.97 (1H, d, $J = 16.2$, OCH*H*), 1.65 (2H, m, CH_2CH_3), 0.76 (3H, t, $J = 7.3$, CH_2CH_3) ppm; ^{1}H NMR (400 MHz, DMSO): δ 11.80 (1H, s, NH), 7.43 (1H, d, $J = 6.8$, HNC*H*=CH), 6.36 (1H, d, $J = 6.8$, HNCH=C*H*), 6.22 (1H, s, OH), 5.24 (1H, d, $J = 16.2$, OC*H*H), 5.19 (1H, d, $J = 16.2$, OCH*H*), 1.75 (2H, m, CH_2CH_3), 0.80 (3H, t, $J = 7.4$, CH_2CH_3) ppm; ^{13}C NMR (100 MHz, DMSO): δ 171.9 (OC=O), 158.2 (NC=O), 149.2 (O=CC=*C*), 134.0 (N*C*H=CH), 118.4 (O=C*C*=C), 101.4 (HNCH=*C*H), 71.3 (COH), 64.5 (OCH_2), 29.8 (CH_2CH_3), 7.0 (CH_2CH_3) ppm; IR (Nujol) 3308, 3122, 2923, 1751, 1641, 1620, 1556, 1460, 1156, 1031, 842 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 209 (68), 180 (34), 165 (55), 136 (100); HRMS (ESI POS) calcd for $C_{10}H_{12}NO_4$ (MH^+) 210.0766, found 210.0765. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 57.5; H, 5.4; N, 6.7%.

(*S*)-4-Ethyl-4-hydroxy-1,7-dihydro-4*H*-pyrano[3,4-*c*]pyridine-3,8-dione ((*S*)-19). According to the preparation of **19**, a suspension of (*S*)-**28** (461.0 mg 1.633 mmol) in DME (9.2 mL) was treated with conc. aqueous HCl (36.5%, 1.38 mL, 16.33 mmol, 10.0 eq.) yielding the crude product as an off-white solid (722.8 mg, 212% by weight, *er* = 94.1 : 5.9 [chiral HPLC, sample preparation: ethanol/ethyl acetate solution, equipment: Agilent 1100, column: Chiralcel-ODH, 250 × 4.6 mm, temperature: 25 °C, mobile phase: 90% heptane, 10% ethanol/trifluoroacetic acid (99 : 1), flow: 0.8 mL min^{-1}, injection volume: 5 μL, detection: UV 305 nm, retention time: 30.00 min (*S*)-**19**, 24.52 min (*R*)-**19**], which was stirred with 2.2 mL methanol at room temperature overnight. The mixture was filtered and product (*S*)-**19** was washed with additional methanol (2.2 mL) furnishing white crystals (117.4 mg, 34% by weight), *er* = 95.0 : 5.0 (chiral HPLC). The filtrate was evaporated to dryness furnishing an off-white solid (564.0 mg, 165% by weight), which was purified by column chromatography with chloroform/methanol (10 : 1) giving rise to product (*S*)-**19** (153.7 mg, 0.735 mmol, 45% by weight), *er* = 95.5 : 4.5 (chiral HPLC) as white crystals. Mp: 230 °C (decomp.); $[\alpha]_D^{20}$ ($c = 0.168$ g dL^{-1}, MeOH) = +102.6 (for a sample with *er* = 98.1 : 1.9). The other analytical data are in accordance with (*rac*)-**19**.

2-Oxo-butyric acid (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester (30)[13]. According to the literature,[13] a solution of 2-oxobutyric acid (2.28 g, **29**, 22.11 mmol, 1.3 eq.), (−)-8-phenylmenthol (**31**, 4.04 g, 17.02 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (169.9 mg, 0.884 mmol, 0.52 eq.) in benzene (48 mL) was heated to reflux for 20.5 h (HPLC control). After cooling down to room temperature, the solution was washed twice with saturated aqueous $NaHCO_3$ (2 × 100 mL), and subsequently with water (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (5 g, 30 min) and filtered. The filter cake was washed with benzene (10 mL). The organic phase was evaporated to dryness in a rotary evaporator

(40 °C, 20 mbar) yielding product **30** as colorless solid (4.98 g, 92% by weight). An analytical sample was obtained by column chromatography (hexane/TBME 96 : 4). $[\alpha]_D^{20}$ ($c = 0.827$ g dL^{-1}, $CHCl_3$) = +1.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.27 (4H, m, Ar), 7.09 (1H, m, Ar), 4.95 (1H, td, $J = 10.7$, $J = 4.5$, OCH), 2.36 (1H, dq, $J = 19.4$, $J = 7.1$, C*H*HCH$_3$), 2.19 (1H, dq, $J = 19.4$, $J = 7.1$, CH*H*CH$_3$), 2.14 (1H, m, aliphatic), 1.84 (2H, m, aliphatic), 1.69 (1H, m, aliphatic), 1.50 (1H, m, aliphatic), 1.31 (3H, s, CCH$_3$), 1.22 (3H, s, CCH$_3$), 1.10–1.40 (3H, m, aliphatic), 0.94 (3H, t, $J = 7.1$, CH$_2$C*H*$_3$), 0.89 (3H, d, $J = 6.4$, CHC*H*$_3$) ppm. The other analytical data are in accordance with the data reported in the literature.[13]

(2*S*)-2-Ethyl-2-hydroxy-3-methyl-but-3-enoic acid (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester (32). To a solution of **30** (4.200 g, 13.27 mmol) in THF (168 mL), isopropenylmagnesium bromide (39.8 mL, 19.91 mmol, 1.5 eq.) was added dropwise at −78 °C (addition time: 30 min). After an additional 50 min (HPLC control), the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (110 mL) and was extracted with ethyl acetate (2 × 110 mL). The combined organic phases were washed with brine (110 mL). The organic phase was dried over sodium sulfate (15 g, 30 min) and filtered. The filter cake was washed with ethyl acetate (30 mL). The organic phase was evaporated to dryness in a rotary evaporator (40 °C, 8 mbar) yielding product **32** as a yellow oil (4.790 g, 101% by weight, $dr = 93 : 7$). An analytical sample was obtained by column chromatography (heptane/ethyl acetate 95 : 1, $dr = 94 : 6$). $[\alpha]_D^{20}$ ($c = 0.615$ g dL^{-1}, $CHCl_3$) = −44.0; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.29 (5H, m, Ar), 5.11 (1H, br., C=C*H*H), 4.97 (1H, m, C=CH*H*), 4.84 (1H, td, $J = 10.8$, $J = 4.2$, OCH), 2.83 (1H, br. s, OH), 2.09 (1H, m, Me$_2$CC*H*), 1.97 (1H, m, OCHC*H*H), 1.74 (3H, s, H$_2$C=CC*H*$_3$), 1.31 (3H, s, PhCC*H*$_3$), 1.21 (3H, s, PhCC*H*$_3$), 0.90–1.80 (8H, m, aliphatic), 0.87 (3H, d, $J = 6.4$, CHC*H*$_3$), 0.80 (3H, t, $J = 7.4$, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 (C=O), 151.0 (*ipso*-C$_6$H$_5$), 144.5 (*C*=CH$_2$), 128.2 (*meta*-C$_6$H$_5$), 125.4 (*ortho*-C$_6$H$_5$), 125.4 (*para*-C$_6$H$_5$), 113.1 (C=*C*H$_2$), 79.7 (COH), 77.8 (OCH), 49.9 (PhC*C*H), 41.0 (OCH*C*H$_2$), 39.9 (PhC), 34.5 (MeCH*C*H$_2$CH$_2$), 31.4 (Me*C*H), 28.8 (*C*H$_2$CH$_3$), 27.3 (H$_3$*C*CCH$_3$), 27.1 (MeCHCH$_2$*C*H$_2$), 26.4 (H$_3$CC*C*H$_3$), 21.7 (CH*C*H$_3$), 19.3 (H$_3$*C*C=CH$_2$), 7.8 (CH$_2$*C*H$_3$) ppm; IR (MIR) 3516, 2961, 1717, 1653, 1457, 1228, 1149, 907, 764, 702 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 359 (1), 215 (7), 119 (100), 105 (92); Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.6. Found: C, 76.8; H, 9.2%.

(*S*)-2-Ethyl-2-hydroxy-3-methyl-but-3-enoic acid (33). A solution of **32** (3.025 g, 8.435 mmol) in MeOH/THF (1 : 1, 40 mL) was treated with aqueous LiOH (1.0 M, 16.9 mL, 16.9 mmol, 2.0 eq). The resulting colorless suspension was heated to 110 °C for 18.5 h providing a slightly brown solution (HPLC control). After cooling to room temperature, the reaction mixture was diluted with TBME (150 mL) and aqueous LiOH (150 mL). The aqueous phase was extracted with TBME (150 mL) to remove the auxiliary (the combined TBME phases were evaporated to dryness furnishing **31** in >95% yield). Subsequently, the pH was adjusted to 2 by addition of 10% aqueous $KHSO_4$. The aqueous phase was extracted with 400 mL $CHCl_3$/EtOH (4 : 1, 4 × 100 mL). The combined organic phases were evaporated to dryness in a rotary evaporator (40 °C, 10 mbar). The product was obtained as a yellow solid (931.4 mg, 77% by weight). An analytical sample was obtained by semipreparative HPLC (Zorbax Extend C18, 21.2 × 150 mm). Despite these efforts, a satisfactory microanalysis could not be not obtained. $[\alpha]_D^{20}$ ($c = 0.251$ g dL^{-1}, $CHCl_3$) = −11.9; mp: 77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (1H, s, C=C*H*H), 5.06 (1H, br. s, C=C*H*H), 2.04 (1H, dq, $J = 14.3$, $J = 7.4$, C*H*HCH$_3$), 2.04 (1H, dq, $J = 14.3$, $J = 7.4$, CH*H*CH$_3$), 1.85 (3H, s, H$_2$C=CC*H*$_3$), 0.94 (3H, t, $J = 7.4$, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO): δ 179.4 (C=O), 144.3 (*C*=CH$_2$), 113.5 (C=*C*H$_2$), 79.9 (COH), 29.1 (*C*H$_2$CH$_3$), 19.1 (H$_3$*C*C=CH$_2$), 7.7 (CH$_2$*C*H$_3$) ppm; IR (film) 3439, 2924, 2627, 1722, 1643, 1295, 1230, 1140 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 126 (4), 119 (9), 99 (100), 43 (26), 41 (9); HRMS (ESI NEG) calcd for $C_7H_{11}O_3$ (M − H)$^-$ 143.0708, found 143.0707.

(*S*)-2-Ethyl-2-hydroxy-3-methyl-but-3-enoic acid diethylamide (34). o a solution of **33** (1.000 g, 6.95 mmol) in dichloromethane (30 mL), *N*-ethyldiisopropylamine (2.50 mL, 14.6 mmol, 2.1 eq.) and after an additional 8 min thionyl chloride (1.53 mL, 20.85 mmol, 3.0 eq.) were added dropwise at −15 °C. After 50 min, a solution of diethylamine (7.22 mL, 69.5 mmol, 10.0 eq.) in dichloromethane (20 mL) was added dropwise using a syringe pump (addition time: 60 min). The reaction mixture was allowed to slowly warm to room temperature overnight. After dilution with dichloromethane (50 mL), the solution was washed with aqueous HCl (50 mL, 1.0 M). The organic phase was dried over Na_2SO_4 (5 g, 30 min) and filtered. The solid was washed with dichloromethane (10 mL). After evaporation of solvent in a rotary evaporator (40 °C, 10 mbar), the crude product (1.36 g, 98% by weight) was obtained as a yellow oil, which was purified by column chromatography with heptane/ethyl acetate (9 : 1) yielding product **34** (0.900 g, 4.515 mmol, 65% by weight, *er* = 93.4 : 6.6, chiral GC [carrier gas: H_2, 90 kPa (split ratio 1/20), equipment: HP6890_2A, column: BGB-176, 30 m × 0.25 mm, injector temperature: 200 °C, detector temperature: 220 °C, retention time: 15.50 min (*S*)-**34**, 15.72 min (*R*)-**34**]) as yellow oil. $[\alpha]_D^{20}$ ($c = 0.990$ g dL^{-1}, $CHCl_3$) = +63.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (1H, s,), 5.12 (1H, br. s,), 5.03 (1H, m,), 3.42 (4H, m,), 2.00 (1H, dq, $J = 13.9$, $J = 7.4$), 1.91 (1H, dq, $J = 14.0$, $J = 6.9$), 1.71 (3H, s,), 1.16 (3H, t, $J = 6.9$), 1.12 (3H, t, $J = 6.9$), 0.88 (3H, t, $J = 7.4$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (N*C*=O), 146.9 (*C*=CH$_2$), 111.5 (C=*C*H$_2$), 77.5 (COH), 41.4 (NCH$_2$), 41.1 (NCH$_2$), 28.2 (C*C*H$_2$CH$_3$), 18.9 (H$_2$C=C*C*H$_3$), 13.1 (NCH$_2$*C*H$_3$), 12.2 (NCH$_2$*C*H$_3$), 7.8 (CCH$_2$*C*H$_3$) ppm; IR (MIR) 3365, 2973, 1615, 1381, 1363, 1124, 1081, 903 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 200 (21), 182 (31), 170 (9), 142 (26), 100 (100), 72 (60); Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.6; N, 7.0. Found: C, 66.0; H, 10.75; N, 7.0%.

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