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PRACTICAL RACEMIC AND ASYMMETRIC FORMAL TOTAL SYNTHESES OF THE HOMOCAMPTOTHECIN DERIVATIVE AND ANTICANCER AGENT DIFLOMOTECAN *VIA* TERTIARY HOMOALLYLIC ALCOHOLS AS MASKED ALDOL EQUIVALENTS

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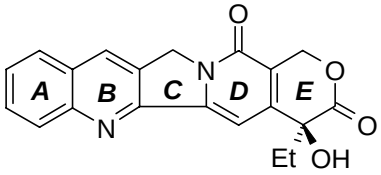
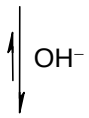
Abstract – An efficient and scalable racemic as well as an asymmetric approach to the key building block for the synthesis of homocamptothecin and derivatives thereof such as the potent anticancer agent diflomotecan (**4**) are described. In the asymmetric route, the pyridone ring was assembled applying straightforward carbonyl chemistry. The selective generation of the quaternary stereocenter was accomplished by self reproduction of chiral information starting from (*S*)-2-hydroxybutyric acid (**22**) utilizing an allyl moiety to act as a masked carbonyl group. The optically pure DE building block (**7**) (*er* > 99.95 : 0.05) was obtained in 9.0% overall yield over 10 steps (two chromatographic purifications). The asymmetric "*de novo pyridone approach*" has the potential to serve as the basis for a technical synthesis of diflomotecan.

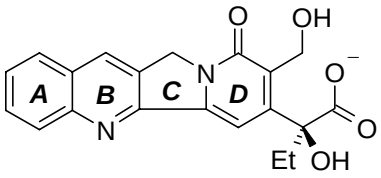
INTRODUCTION

Almost five decades after its first isolation from the Chinese tree *Camptotheca accuminata* by Wani and Wall,[1] the alkaloid camptothecin (CPT, **1**) still serves as a very attractive lead structure for the development of new anticancer drugs due to its potent antiproliferative activity.[2] The structure of the pentacyclic system, which was published in 1966 eight years after the isolation of CPT,[3] contains a highly electrophilic α-hydroxy-δ-lactone ring (ring E), which rapidly hydrolyzes in basic and neutral media leading to the open chain carboxylate form **2** (Scheme 1), which is biologically almost inactive.



CPT (1)





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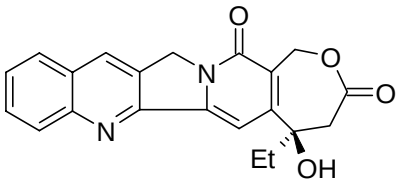
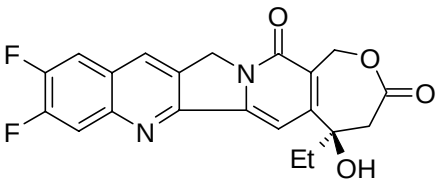
Scheme 1. Hydrolysis of CPT leading to biologically almost inactive **2**.

This equilibrium is shifted toward the carboxylate form in human plasma thus explaining the lower efficacy of most CPT analogues in clinical trials compared to the very promising results measured with Xenograft models.[4] In order to suppress this unwanted hydrolysis, a novel CPT analogue, the so called homocamptothecin (hCPT, **3**, Figure 1), entailing a seven membered β-hydroxy-ε-lactone ring has been developed by the Ipsen scientists Bigg, Lavergne *et al*.[5] Prior to their investigations, it was generally accepted that an α-hydroxy-δ-lactone is an indispensable structural feature for the anticancer activity of CPT derivatives. However, hCPT retains the TOPO I mediated activity and at the same time displays enhanced stability against hydrolysis. hCPT thus provided an excellent template for the preparation of new TOPO I inhibitors with high cytotoxicity toward solid tumor cell lines. The most promising hCPT derivative so far is diflomotecan (**4**) bearing two fluorine atoms at ring A.



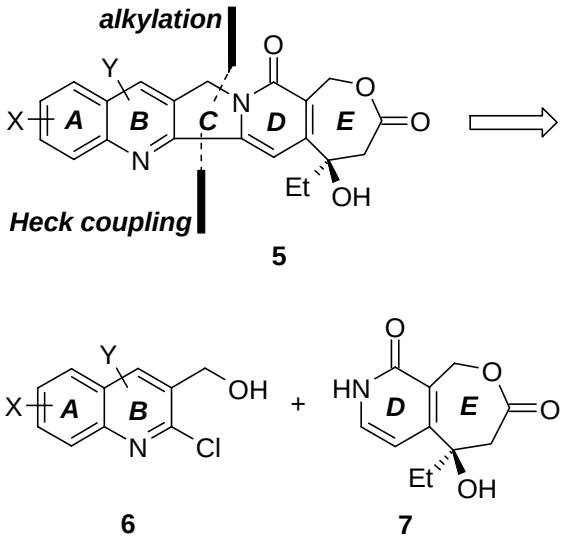
hCPT (3)



diflomotecan (4)

Figure 1. hCPT (**3**) and its currently most active derivative diflomotecan (**4**).

The convergent Ipsen discovery chemistry synthesis utilized a coupling of DE fragment (**7**) with AB quinoline derivatives (**6**) *via* a Mitsunobu alkylation of the pyridone N atom followed by a Heck cyclization to build up ring C of the pentacycle (Scheme 2).[5] This strategy was previously developed by Comins *et al.* for the total synthesis of (*S*)-CPT (**1**).[6] Due to its convergent character and the robustness of the final two steps we decided to maintain this concept for the production of kilogram amounts of **4** for clinical trials.



Scheme 2. Coupling strategy of DE fragment (**7**) with AB quinoline derivatives (**6**).

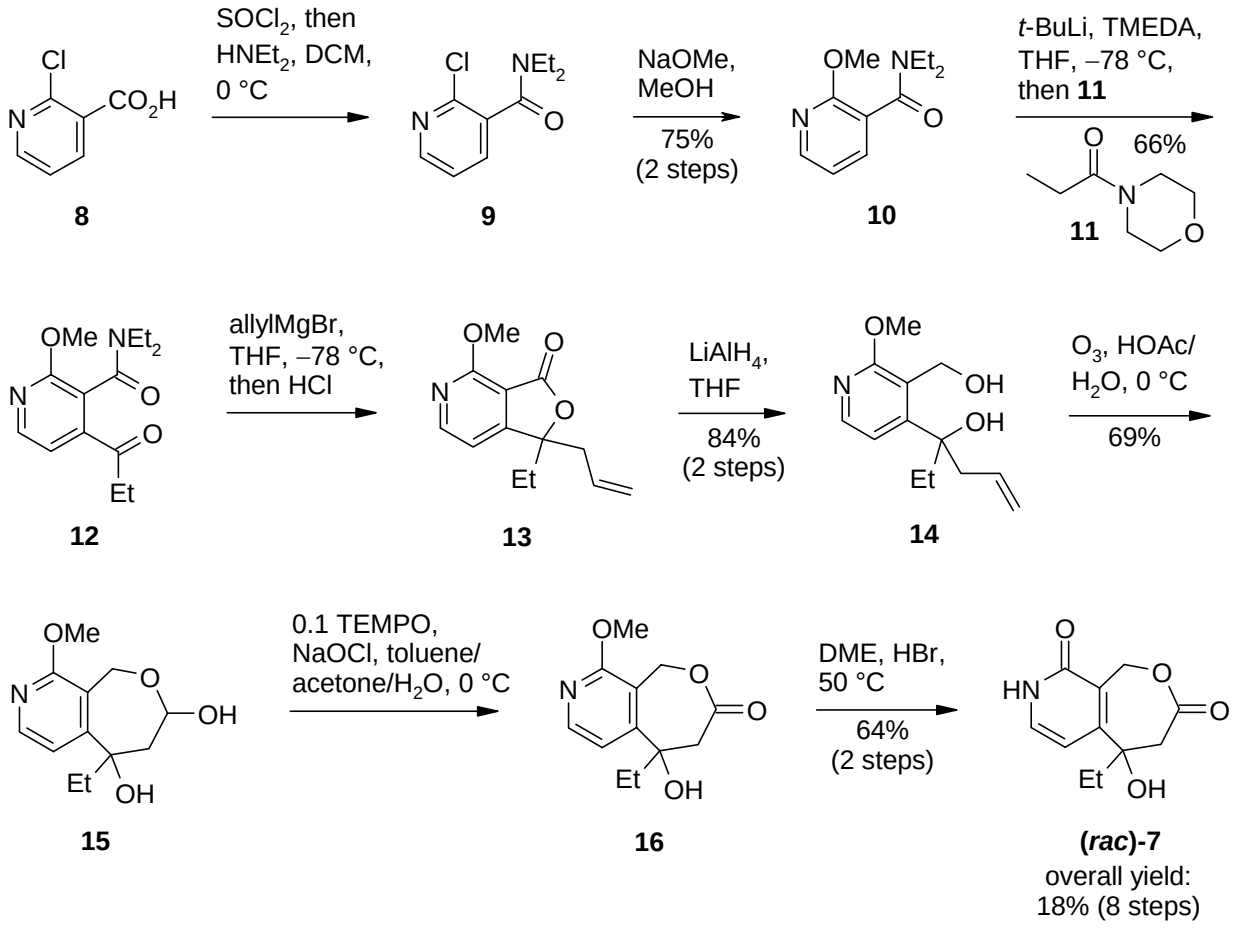
In a previous paper, we have presented two practical approaches to the DE fragment (**7**) highlighting the development of stoichiometric asymmetric acetate aldol additions to pyridinyl ketones.[7] In this paper, we disclose a racemic and an asymmetric route toward **7**, which both rely on the formation of homoallylic

tertiary alcohols acting as masked aldol equivalents, since the oxidative cleavage of the homoallylic C=C double bond furnishes the aldol structural subunit.

RESULTS AND DISCUSSION

Racemic Allyl Addition Approach

The nicotinic amide derivative (**10**) was prepared over two steps starting from 2-chloronicotinic acid (**8**) by acid chloride formation followed by reaction in the same pot with diethylamine yielding **9** (Scheme 3).

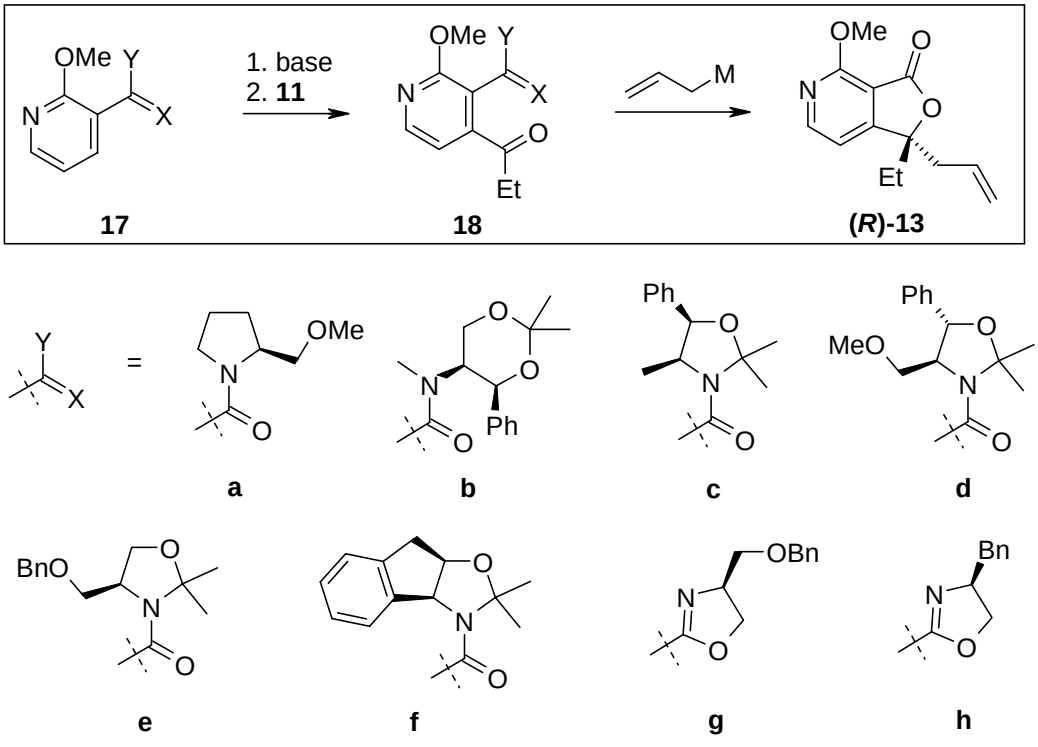


Scheme 3. Racemic allyl addition approach.

Subsequent nucleophilic displacement of the 2-chloro substituent by a methoxy group using NaOMe provided **10**. *Ortho*-Lithiation of the pyridine-4-position of **10** was accomplished by slow addition of a solution of **10** to a THF solution of *tert.*-BuLi / TMEDA at –78 °C. The carbanion thus formed was trapped by morpholine amide (**11**), which was prepared from propionyl chloride using standard conditions.[8] Metalation of **10** was accompanied by intermolecular attack of the generated lithiated species at the amide functionality of **10** resulting in formation of a bispyridinyl ketone as side product, which

became the main product, when the base was added to a solution of **10**. After recrystallization ketone (**12**) was subjected to a nucleophilic allyl Grignard addition, which proceeded smoothly providing the corresponding tertiary alcohol leading to γ-lactone (**13**) during acidic workup with aqueous HCl. The γ-lactone moiety of **13** was then reduced by $LiAlH_4$ providing diol (**14**), which was directly used in an ozonolysis without protection of the free hydroxyl groups. The oxidative cleavage of the C=C double bond proceeded much cleaner in aqueous acetic acid than in dichloromethane and provided 7-membered lactol (**15**) in the form of two diastereomers (*dr* 5 : 1). Lactol (**15**) was subsequently smoothly oxidized by NaOCl and catalytic amounts of TEMPO furnishing lactone (**16**). Methyl ether cleavage with aqueous HBr in DME finally provided **(*rac*)-7** in 18% overall yield (over 8 steps).

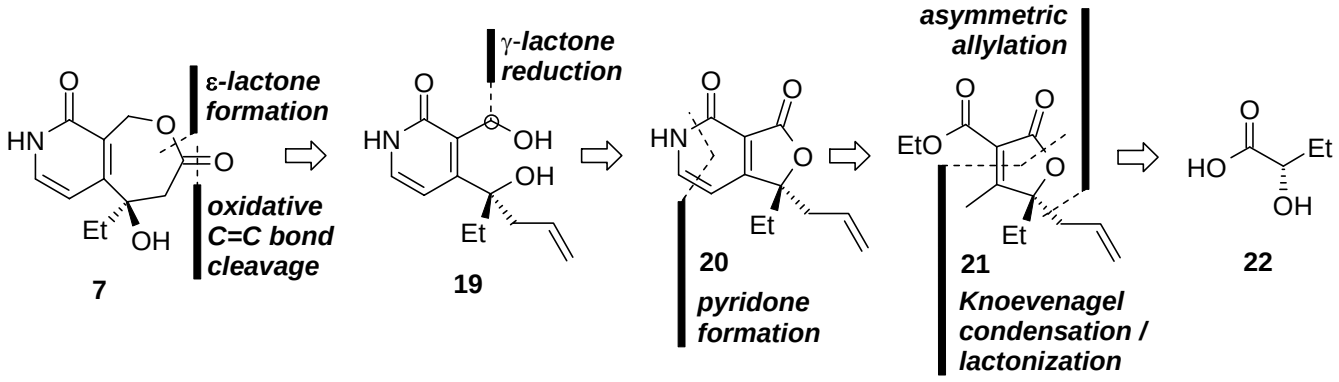
After this racemic proof of concept for the allyl approach, a stereoselective version was sought-after. Several enantiomerically pure analogues of **10** were synthesized bearing either a chiral tertiary amide moiety (**17a-f**) or an oxazoline ring (**17g,h**) at the pyridine 3-position (Scheme 4). However, none of these derivatives allowed for highly efficient acylation of the pyridine 4-position in acceptable yields *via ortho*-metalation due to low conversion and decomposition. The best result was obtained using SMP amide (**17a**), resulting in ca. 40-50% conversion to **18a** (ca. 10% dimerization) with 1.6 equiv. *tert*-BuLi / TMEDA at −78 °C. Since replacement of *tert.*-BuLi by a safer base and variation of the reaction conditions did not lead to higher yields, this approach was abandoned in favor of the '*de novo*' approach described below.



Scheme 4. Planned asymmetric allyl additions to ketones (**18**).

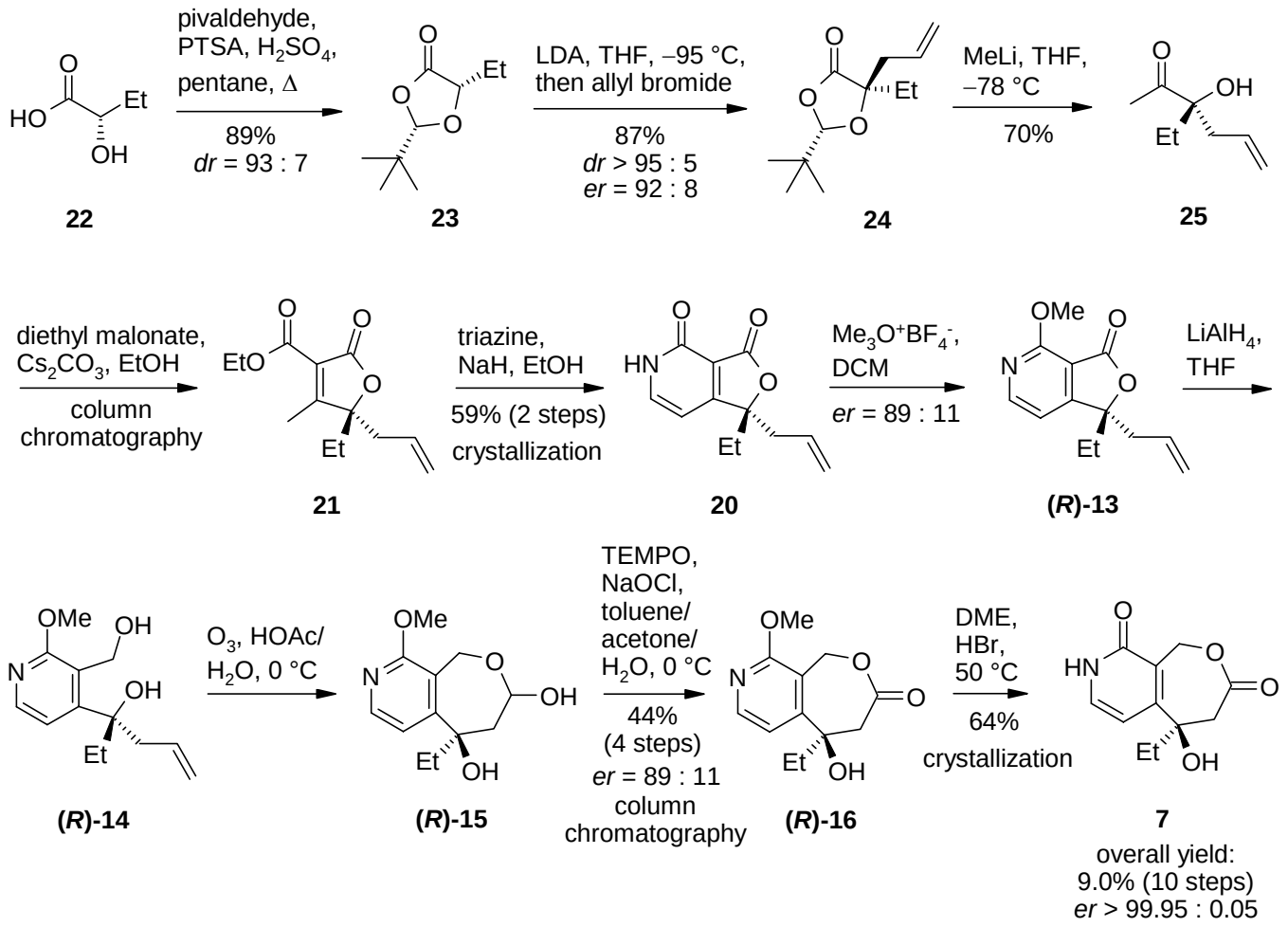
*Asymmetric Synthesis of **7**: de Novo Pyridone Approach*

All existing approaches reported so far for the synthesis of DE-fragment (**7**) started from commercially available pyridine building blocks, which were regioselectively functionalized in the 3- or 4-position by lithiation reactions.[5,7,9] In a conceptually different approach toward **7**, we present herein the construction of the pyridone ring *via* straightforward carbonyl chemistry. The retrosynthetic analysis depicted in Scheme 5 is based on our previously reported practical formal total synthesis of (*S*)-CPT.[10] The quaternary stereocenter was introduced by self reproduction of chiral information[11,12] starting from commercially available optically pure (*S*)-hydroxybutyric acid (**22**) (Scheme 6).[13] This concept finally gave access to lactone intermediate [**(*R*)-13**], the optically active complement of **13** used in the racemic "*allyl addition approach*" described above (Scheme 3).



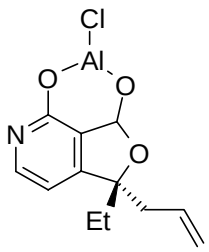
Scheme 5. Retrosynthetic analysis of **7**.

Chiral acetal (**23**) was prepared according to literature in high yield with the kinetically favored *cis* diastereomer (*dr* = 92.7 : 7.3, ^{1}H-NMR) being preferentially formed (Scheme 6).[14,15] Deprotonation of **23** with LDA at low temperature and subsequent trapping of the enolate with allylbromide provided the known acetal (**24**) (*dr* > 95 : 5, *er* = 92.0 : 8.0).[14] MeLi addition to the lactone group and subsequent aqueous HCl workup furnished α-hydroxy ketone (**25**), which was then exposed to a tandem Knoevenagel condensation / lactonization with diethylmalonate. The resulting γ-lactone (**21**) was subsequently purified by column chromatography. The strategy of our *de novo* pyridone formation is based on the pronounced activation of the lactone β-methyl group in **21**. In fact, **21** can be regarded as a vinylogous malonate thus allowing easy dienolate formation with bases like sodium ethoxide. The deprotonated species can be trapped by triazine as HCN equivalent[16] and furnished pyridone (**20**) as crystalline material.



Scheme 6. *De novo* pyridone approach.

All attempts to reduce lactone (**20**) to the corresponding diol were unsuccessful, since the reduction stopped at the lactol stage with Al-based hydride reagents such as $LiAlH_4$, Red-Al or AlH_3 possibly due to the formation of stable Al chelate complexes. Boron derived reducing agents like $NaBH_4$, $Na[HB(OAc)_3]$, superhydride or K-selectride resulted mainly in decomposition of **20**. Complex (**26**) was identified by GC-MS as the main product of $LiAlH_4$ reductions after aqueous workup with HCl (Figure 2).



26

Figure 2. Main product of the $LiAlH_4$ reduction of **20**.

Attempts to further reduce (**26**) e.g. by Meerwein-Ponndorf reduction failed as well. Consequently, we chose to protect the pyridone oxygen. Silyl protection (TMS, TBS, TIPS) was ineffective, since the silyloxy pyridines were found to be too labile. Therefore, we chose a methyl protecting group which led to the optically active pyridine intermediate [**(*R*)-13**]. The regioselectivity problem for the methylation (*N- versus O*-alkylation) was solved by using Meerwein's salt ($Me_3O^+BF_4^-$). In contrast, methyl iodide in combination with Ag_2CO_3 as base or dimethylsulfate resulted in preferential *N*-alkylation, which was also observed when bases like proton sponge or 2,6-di-*tert.*-butylpyridine were employed in combination with Meerwein's salt. After a solvent screening (dichloromethane, dichloroethane, acetone, THF) dichloromethane was selected as solvent of choice (*er* of **(*R*)-13**: 88.5 : 11.5 as determined by chiral GC). The subsequent reduction, ozonolysis, TEMPO oxidation (*er* of **(*R*)-16**: 88.5 : 11.5 as determined by chiral HPLC) and methyl ether cleavage reactions paralleled the racemic allyl addition approach shown in Scheme 3 (yield: 27% over 5 steps (**20** → **7**), average yield per step: 77%). Gratifyingly, the *er* was significantly increased in the final step due to preferential crystallization of the **(*R*)-7** out of the reaction mixture. The key building block (**7**) was obtained in optically pure form as determined by chiral HPLC. The yield of the final step highly depends on the *er* of [**(*R*)-16**], since the mother liquid contains the almost racemic product. Therefore, starting material **(*R*)-16** with an *er* of 88.5 : 11.5 (*ee* = 77%) could, in principal, lead to a maximum yield of 100 – (2 * 11.5) = 77% for optically pure material. No purification was required for intermediates [**(*R*)-13**], [**(*R*)-14**] and [**(*R*)-15**], while **(*R*)-16** was purified by column chromatography.[17] Enantiomerically pure pyridone (**7**) was thus prepared in 9.0% overall yield over 10 steps.

Summary

In summary, we have described both an efficient racemic and an asymmetric approach to DE ring fragment (**7**), which is the required key building block for the synthesis of homocamptothecin and derivatives thereof such as the potent anticancer agent diflomotecan (**4**). Especially the asymmetric "*de novo pyridone approach*" has the potential to serve as the basis for a technical synthesis of diflomotecan. The pyridone ring was assembled applying straightforward carbonyl chemistry and the selective generation of the quaternary stereocenter was accomplished by self reproduction of chiral information starting from (*S*)-2-hydroxybutyric acid (**22**) by introducing an allyl group serving as a masked carbonyl group. The optically pure DE building block **7** (*er* > 99.95 : 0.05) was obtained in 9.0% overall yield over 10 steps (two chromatographies).

EXPERIMENTAL

General Methods. Unless otherwise noted, solvents and reagents were used as received from commercial suppliers. All reactions were carried out under argon atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, 0.25 mm. Qualitative HPLC was performed with UV detection at a wavelength of 210 nm using Chromolith Performance columns (100 x 4.6 mm) with gradient eluent H_2O/MeCN containing 10% of a phosphate buffer at pH 3.0. ^{1}H NMR are given in ppm (δ) and coupling constants *J* are reported in Hz. Peaks in 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).

Synthesis of 2-chloro-*N*,*N*-diethylnicotinamide (9)

Thionylchloride (99%, 15.0 mL, 204.0 mmol, 1.31 equiv) and DMF (1.0 mL, 13.0 mmol, 0.08 equiv) were added to a stirred solution of 2-chloronicotinic acid (**8**, 98%, 25.0 g, 155.5 mmol) in acetonitrile (250 mL). The mixture was heated to reflux and monitored by HPLC (sample preparation: 5 μL of the reaction mixture were added to 0.2 mL MeOH). After 5.5 h, the reaction mixture was cooled to room temperature and all volatiles were removed in a rotary evaporator (40 °C/10 mbar). The residual oil was dissolved in dichloromethane (250 mL) and the solution was cooled to 0 °C. Diethylamine (48.5 mL, 466.5 mmol, 3.0 equiv) was added and the solution was allowed to slowly warm up to room temperature overnight. Aqueous HCl (65 mL, 1.0 M) was added in order to adjust pH 8 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organic phases were washed with brine (200 mL), dried over sodium sulfate (15 g, 30 min) and filtered. The filter cake was washed with dichloromethane (30 mL). After removal of solvent in a rotary evaporator (40 °C/8 mbar), the crude product (36.78 g, 107% by weight) was obtained as a dark green oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.63 (dd, 1H, *J* = 7.5 Hz, *J* = 1.9 Hz), 7.30 (dd, 1H, *J* = 7.5 Hz, *J* = 4.7 Hz), 3.80 (m, 1H), 3.38 (m, 1H), 3.17 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz) ppm.

Synthesis of *N*,*N*-diethyl-2-methoxynicotinamide (10)

9 (37.10 g, 174.4 mmol) dissolved in methanol (38 mL) was added to a stirred solution of NaOMe (272.5 mL, 3.2 M in MeOH, 872.0 mmol, 5.0 equiv) at room temperature. The solution was heated to 90 °C (oil bath temperature) and the reaction was monitored by HPLC. After 6 h 40 min, the mixture was cooled to room temperature and quenched by addition of saturated aqueous NH_4Cl (250 mL) and water (300 mL). The product was extracted with ethyl acetate (3 x 200 mL) and the combined organic phases were washed with brine (400 mL), dried over sodium sulfate (40 g, 30 min) and filtered. The filter cake was washed with ethyl acetate (80 mL). After removal of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (31.26 g, 86% by weight) was obtained as a brown oil. Purification was achieved by crystallization. The crude product was dissolved in diisopropylether (193 mL) and isopropanol (12.5 mL) at reflux temperature. After hot filtration from undissolved material, heptane (230 mL) was added at room temperature and the

resulting suspension was allowed to stand at 5 °C. After 3 days, the precipitate was collected by filtration and washed with heptane (20 mL) furnishing product (**10**) (25.60 g, 12.29 mmol, 70% by weight (75% over 2 steps from **8**)) as a dark brown solid. mp 88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (dd, 1H, *J* = 4.9 Hz, *J* = 2.0 Hz), 7.52 (dd, 1H, *J* = 7.2 Hz, *J* = 1.9 Hz), 6.92 (dd, 1H, *J* = 7.3 Hz, *J* = 5.0 Hz), 3.96 (s, 3H), 3.56 (q, 2H, *J* = 7.1 Hz), 3.14 (q, 2H, *J* = 7.1 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.06 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 159.5, 147.4, 136.5, 121.1, 116.7, 53.6, 42.9, 39.1, 14.0, 12.8 ppm; IR (Nujol) 2924, 1627, 1579, 1463, 1404, 1304, 1258, 1189, 814 cm^{-1}; MS (ESI) m/z 209.2 (MH^+); HRMS (ESI POS) calcd for $C_{11}H_{17}N_2O_2$ (MH^+) 209.1290, found 209.1290; Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.28; H, 7.57; N, 13.45.

Synthesis of *N*,*N*-diethyl-2-methoxy-4-propionylnicotinamide (12)

A solution of TMEDA (99.5%, 11.7 mL, 76.8 mmol, 1.6 equiv) and *tert.*-butyllithium (51.2 mL, 1.5 M in pentane, 76.8 mmol, 1.6 equiv) in THF (150 mL at −78 °C) was treated dropwise over 20 min with a solution of **10** (10.0 g, 48.0 mmol) in THF (50 mL). After 1 h 45 min, a solution of **11** (12.38 g, 86.4 mmol, 1.8 equiv) in THF (25 mL) was added within 20 min and stirring was continued for 2 h at −78 °C. The reaction was then quenched by addition of saturated aqueous NH_4Cl (250 mL). After dilution with toluene (500 mL) and water (250 mL), the phases were separated and the organic phase was washed with brine (300 mL), dried over Na_2SO_4 (20 g, 30 min) and filtered. The filter cake was washed with toluene (40 mL). After evaporation of solvent in a rotary evaporator (50 °C/10 mbar), a yellow solid was obtained (13.38 g, 105% by weight). The crude product was dissolved in TBME (13 mL) and heptane (65 mL) was subsequently added. The resulting suspension was allowed to stand at 5 °C. After 3 days, the precipitate was collected by filtration and washed with heptane (20 mL) furnishing product (**12**) (8.37 g, 31.66 mmol, 66% by weight) as orange crystals. mp 92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, 1H, *J* = 5.2 Hz), 7.09 (d, 1H, *J* = 5.3 Hz), 3.97 (s, 3H), 3.68 (m, 1H), 3.47 (m, 1H), 3.13 (q, 2H, *J* = 7.2 Hz), 2.89 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.3 Hz), 1.08 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 166.0, 160.5, 147.5, 145.4, 119,1, 113.4, 54.1, 42.9, 38.7, 34.4, 13.3, 12.2, 7.6 ppm; IR (Nujol) 2924, 1702, 1629, 1582, 1558, 1453, 1379, 1311, 1286, 1069, 1018, 836 cm^{-1}; MS (ESI) m/z 265.2 (MH^+); HRMS (ESI POS) calcd for $C_{14}H_{21}N_2O_3$ (MH^+) 265.1552, found 265.1553; Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.56; H, 7.53; N, 10.58.

Synthesis of 1-allyl-1-ethyl-4-methoxy-1*H*-furo[3,4-*c*]pyridin-3-one (13)

A solution of **12** (5.0 g, 18.9 mmol) in THF (25 mL) was added at −78 °C to a stirred solution of allyl magnesium bromide (28.4 mL, 1 M in Et_2O, 28.4 mmol, 1.50 equiv) in THF (100 mL). After 2 h at −78 °C, aqueous 1 M HCl (165 mL, 165.0 mmol, 8.7 equiv) was added and stirring was continued for 18 h at room temperature. The pH was then adjusted to 5 by addition of potassium dihydrogen phosphate. The resulting suspension was extracted with ethyl acetate (2 x 150 mL) and the combined organic phases were washed

with brine (300 mL), dried over Na_2SO_4 (20 g, 30 min) and filtered. The solid was washed with ethyl acetate (40 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (4.59 g, 19.7 mmol, 104% by weight) was obtained as a beige solid. mp 89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, 1H, *J* = 5.3 Hz), 6.87 (d, 1H, *J* = 5.3 Hz), 5.53 (m, 1H), 5.08 (br. d, 1H, *J* = 0.9 Hz), 5.03 (dm, 1H, *J* = 5.5 Hz), 4.13 (s, 3H), 2.71 (ddt, 1H, *J* = 14.1 Hz, *J* = 7.5 Hz, *J* = 1.1 Hz), 2.60 (ddt, 1H, *J* = 14.2 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz), 2.10 (dq, 1H, *J* = 14.5 Hz, *J* = 7.3 Hz), 1.89 (dq, 1H, *J* = 14.5 Hz, *J* = 7.5 Hz), 0.76 (t, 3H, *J* = 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 163.9, 160.6, 151.4, 129.2, 119.6, 108.9, 108.4, 87.5, 53.3, 41.4, 29.6, 6.4 ppm; IR (ATR-FTIR) 2969, 1758, 1642, 1607, 1592, 1474, 1409, 1329, 1239, 1134, 1020, 920 cm^{-1}; MS (EI) m/z (rel. intensity) 234 (0.4), 192 (100); HRMS (ESI POS) calcd for $C_{13}H_{16}NO_3$ (MH^+) 234.1130, found 234.1127; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.66; H, 6.58; N, 5.83.

Synthesis of 3-(3-hydroxymethyl-2-methoxy-pyridin-4-yl)-hex-5-en-3-ol (14)

A solution of lithium aluminum hydride (4.46 mL, 1 M in THF, 4.46 mmol, 0.52 equiv) was added at –78 °C to a stirred solution of **13** (2.0 g, 8.57 mmol) in THF (40 mL). After 10 min, the cooling bath was replaced by an ice bath. After 90 min at 0 °C, stirring was continued at room temperature. The reaction was monitored by HPLC. After 2 h 30 min, the reduction was quenched at 0 °C by addition of aqueous 0.5 M HCl (40 mL). Stirring was continued for 15 min and the mixture was extracted with dichloromethane (5 x 80 mL). The combined organic phases were 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 (2.15 g, 105% by weight) was obtained as a yellow oil, which was purified by column chromatography with heptane / ethyl acetate (3 : 2) yielding product (**14**) (1.65 g, 6.94 mmol, 81% by weight (84% over 2 steps from **13**)) as white crystals. mp 88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, *J* = 5.5 Hz), 6.71 (d, 1H, *J* = 5.4 Hz), 5.58 (m, 1H), 5.09 (m, 1H), 5.05 (m, 1H), 4.90 (dd, 1H, *J* = 11.9 Hz, *J* = 6.6 Hz), 4.84 (dd, 1H, *J* = 12.1 Hz, *J* = 6.3 Hz), 3.91 (s, 3H), 2.90 (br. s, 1H), 2.78 (br., 1H), 2.68 (ddt, 1H, *J* = 13.9 Hz, *J* = 7.1 Hz, *J* = 1.1 Hz), 2.48 (ddt, 1H, *J* = 13.9 Hz, *J* = 7.9 Hz, *J* = 1.1 Hz), 1.91 (dq, 1H, *J* = 14.1 Hz, *J* = 7.4 Hz), 1.78 (dq, 1H, *J* = 14.3 Hz, *J* = 7.3 Hz), 0.75 (t, 3H, *J* = 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 154.5, 145.3, 132.8, 121.3, 120.2, 116.0, 78.5, 56.7, 53.8, 47.2, 35.3, 8.0 ppm; IR (ATR-FTIR) 3216, 2972, 1765, 1643, 1592, 1553, 1445, 1380, 1305, 1275, 1058, 978, 826 cm^{-1}; MS (EI) m/z (rel. intensity) 196 (3), 190 (8), 178 (100); HRMS (ESI POS) calcd for $C_{13}H_{20}NO_3$ (MH^+) 238.1443, found 238.1440; Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.80; H, 8.22; N, 5.71.

Synthesis of 5-ethyl-1-methoxy-5,6,7,9-tetrahydro-8-oxa-2-aza-benzocycloheptene-5,7-diol (15)

A stirred solution of **14** (1.23 g, 5.18 mmol) in acetic acid (27 mL) and water (3 mL) was cooled to 0 °C. O_3 was bubbled through the solution (150 L/h) until after 5.5 min a blue color appeared. Subsequently, argon was bubbled through the solution for 10 min and the volume was reduced to ca. 4 mL in a rotary evaporator

(40 °C/10 mbar). Dichloromethane (50 mL) was added and the mixture was cooled to 0 °C before addition of dimethylsulfide (99%, 3.84 mL, 51.8 mmol, 10.0 equiv). Stirring was continued overnight and the mixture was allowed to slowly warm up to room temperature. pH-7 buffer (20 mL) was added and pH 5 was adjusted by addition of potassium dihydrogen phosphate. After phase separation, the aqueous phase was extracted with dichloromethane (3 x 30 mL) and subsequently with dichloromethane / ethanol (4 : 1, 3 x 30 mL). The combined organic phases were dried over Na_2SO_4 (10 g, 30 min) and filtered. The solid was washed with chloroform / ethanol (4 : 1, 20 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (0.85 g, 69% by weight, *dr* = 5 : 1) was obtained as a yellow semisolid. An analytical sample (white semisolid) was obtained by column chromatography with heptane / ethyl acetate (1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: δ 8.03 (d, 1H, *J* = 5.4 Hz), 7.15 (d, 1H, *J* = 5.5 Hz), 5.41 (dd, 1H, *J* = 7.3 Hz, *J* = 6.0 Hz), 5.05 (d, 1H, *J* = 16.4 Hz), 4.86 (d, 1H, *J* = 16.4 Hz), 3.94 (s, 3H), 3.4 (br. s, 1H), 2.71 (br. s, 1H), 2.41 (m, 1H), 2.39 (m, 1H), 1.91 (m, 2H), 1.03 (t, 3H, *J* = 7.5 Hz) ppm; minor diastereomer: δ 8.06 (d, 1H, *J* = 5.5 Hz), 7.02 (d, 1H, *J* = 5.6 Hz), 5.55 (m, 1H), 5.05 (d, 1H, *J* = 16.4 Hz), 4.94 (d, 1H, *J* = 16.6 Hz), 3.95 (s, 3H), 3.4 (br. s, 1H), 2.76 (br. s, 1H), 2.41 (m, 1H), 2.39 (m, 1H), 1.91 (m, 2H), 0.82 (t, 3H, *J* = 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ 161.0, 157.5, 145.2, 120.0, 116.5, 93.0, 74.8, 57.3, 54.2, 43.9, 33.9, 8.5 ppm; minor diastereomer: δ 161.9, 153.5, 145.8, 122.6, 115.8, 94.0, 74.7, 57.4, 54.3, 43.0, 35.4, 9.2 ppm; IR (ATR-FTIR) 3367, 2948, 1595, 1561, 1359, 1263, 1122, 1027, 986, 838 cm^{-1}; MS (EI) m/z (rel. intensity) 239 (20), 221 (76), 192 (100), 177 (89), 164 (91); HRMS (ESI POS) calcd for $C_{12}H_{18}NO_4$ (MH^+) 240.1236, found 240.1237; Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.42; H, 7.32; N, 5.77.

Synthesis of 5-ethyl-5-hydroxy-1-methoxy-5,9-dihydro-6*H*-8-oxa-2-aza-benzocyclohepten-7-one (16)

2,2,6,6-Tetramethylpiperidin-1-oxy radical (TEMPO, 96%, 17.6 mg, 0.11 mmol, 0.1 equiv) was added to a stirred solution of **15** (258.7 mg, 1.08 mmol) in acetone (2.6 mL) and toluene (7.8 mL). After cooling to 0 °C, a mixture of saturated aqueous $NaHCO_3$ / aqueous 10% NaOCl (10 : 7, 3.0 mL) was added while vigorously stirring the biphasic system. After 1 h, additional saturated aqueous $NaHCO_3$ / aqueous 10% NaOCl (10 : 7, 3.0 mL) was added. After 90 min, water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 (10 g, 30 min) and filtered. The solid was washed with dichloromethane (20 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (268.6 mg, 105% by weight) was obtained as an orange oil. An analytical sample (white solid) was obtained by column chromatography with heptane / ethyl acetate (1 : 1). mp 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, 1H, *J* = 5.4 Hz), 7.13 (d, 1H, *J* = 5.7 Hz), 5.52 (d, 1H, *J* = 15.0 Hz), 5.25 (d, 1H, *J* = 15.1 Hz), 3.97 (s, 3H), 3.44 (d, 1H, *J* = 13.6 Hz), 3.07 (d, 1H, *J* = 13.5 Hz), 2.43 (br. s, 1H), 1.92 (q, 2H, *J* = 7.4 Hz), 0.90 (t, 3H, *J* = 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 160.7, 153.8, 147.1, 116.0, 115.7, 73.7, 61.9, 54.1, 42.9, 37.3, 8.3 ppm; IR (film) 3336, 2972, 1729,

1599, 1566, 1456, 1371, 1285, 1266, 1141, 1047, 1024, 837 cm^{-1}; MS (ESI) m/z 238.1 (MH^+); HRMS (ESI POS) calcd for $C_{12}H_{16}NO_4$ (MH^+) 238.1079, found 238.1078; Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.56; H, 6.49; N, 5.78.

Synthesis of (*rac*)-5-ethyl-5-hydroxy-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene ((*rac*)-7)

Aqueous HBr (48%) (77 μL, 0.69 mmol, 1.05 equiv) was added to a stirred solution of **16** (155 mg, 0.65 mmol) in 1,2-dimethoxyethane (1.55 mL). After 6 h at room temperature, the solution was heated to 50 °C. The reaction was monitored by HPLC. After 17 h 30 min at 50 °C, the reaction mixture was allowed to stand at 5 °C for 48 h. The precipitate was then filtered and subsequently washed with heptane (0.2 mL). After evaporation of residual solvent in a rotary evaporator (40 °C/10 mbar), the product (88.7 mg, 61% by weight (64% over 2 steps)) was obtained as a white powder. mp > 210 °C (decomp.); ^{1}H NMR (300 MHz, DMSO): δ 11.67 (br. s, 1H), 7.34 (d, 1H, 7.2 Hz), 6.33 (d, 1H, 7.2 Hz), 5.72 (br. S, 1H), 5.34 (d, 1H, *J* = 15.1 Hz), 5.21 (d, 1H, *J* = 15.1 Hz), 3.32 (d, 1H, *J* = 13.5 Hz), 2.98 (d, 1H, *J* = 13.7 Hz), 1.68 (m, 2H), 0.80 (t, 3H, *J* = 7.5 Hz) ppm. The other analytical data are in accordance with those for **7** described in Ref [7].

Synthesis of 1-morpholin-4-yl-propan-1-one (11)

Propionyl chloride (98%, 18.9 mL, 200.2 mmol) was rapidly added at 0 °C to a solution of morpholine (99%, 18.3 mL, 208.2 mmol, 1.04 equiv) in dichloromethane (200 mL) containing 32.3 mL triethylamine (232.2 mmol, 1.16 equiv). After complete addition, the mixture was stirred for 1 h at 0 °C and 2.5 h at room temperature. The solution was subsequently washed with saturated aqueous NH_4Cl (200 mL), saturated aqueous $NaHCO_3$ (200 mL) and brine (200 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), product (**11**) was obtained as a yellow liquid (23.70 g, 165.5 mmol, 83% by weight). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (m, 4H), 3.64 (m, 2H), 3.46 (m, 2H), 2.33 (q, 2H, *J* = 7.4 Hz), 1.16 (t, 3H, *J* = 7.3 Hz) ppm.

Synthesis of (*2S,5S*)-2-*tert.*-butyl-5-ethyl-[1,3]dioxolan-4-one (23)

p-Toluenesulfonic acid monohydrate (99%, 309.8 mg, 1.61 mmol, 0.018 equiv) and sulfuric acid (9.8 μL, 0.19 mmol, 0.002 equiv) were added to a suspension of 9.80 g (*S*)-2-hydroxybutyric acid (**22**, 97%, 91.3 mmol) and 20.6 mL pivaldehyde (97%, 1.98 equiv, 180.8 mmol) in 400 mL pentane. The mixture was heated vigorously to reflux overnight (oil bath temperature 55 °C). After cooling down to room temperature, the mixture was washed with water (2 x 300 mL). The organic phase was dried over sodium sulfate (20 g, 30 min) and filtered. The filter cake was washed with pentane (40 mL). After evaporation of solvent in a rotary evaporator (50 °C/5 mbar), product (**23**) was obtained as a colorless liquid (13.96 g, 81.1 mmol, 89% by weight, *dr* (*cis*/*trans*) = 92.7 : 7.3 (^{1}H-NMR)). ^{1}H NMR (300 MHz, $CDCl_3$): *cis*-isomer: δ 5.12 (d, 1H, *J* = 1.1 Hz), 4.22 (m, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.03 (t, 3H, *J* = 7.4 Hz), 0.97 (s, 9H) ppm.

trans-isomer: δ 5.27 (d, 1H, *J* = 1.5 Hz), 4.32 (m, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.03 (t, 1H, *J* = 7.4 Hz), 0.95 (s, 9H) ppm. Analytical data are in accordance with literature data.[14]

Synthesis of (*2S,5R*)-5-allyl-2-butyl-5-ethyl-[1,3]dioxolan-4-one (24)

n-Butyllithium (56.8 mL, 85.1 mmol, 1.05 equiv) was added at 0 °C to a solution of diisopropylamine (12.6 mL, 89.2 mmol, 1.1 equiv) in THF (420 mL). After 30 min at 0 °C, the solution was cooled to –95 °C. A solution of **23** (13.96 g, 81.1 mmol) in THF (42 mL) was added dropwise over 30 min. The resulting yellow solution was kept for additional 2 h at –95 °C. Subsequently, a solution of allylbromide (99%, 10.4 mL, 121.6 mmol, 1.5 equiv) in THF (35 mL) was added dropwise over 10 min. The reaction mixture was allowed to slowly warm to room temperature overnight and was then poured into saturated aqueous NH_4Cl (750 mL). The mixture was extracted with TBME (3 x 500 mL). The combined organic phases were dried over sodium sulfate (30 g, 30 min) and then filtered. The filter cake was washed with TBME (60 mL). After evaporation of solvent in a rotary evaporator (50 °C/5 mbar), product (**24**) was obtained as a yellow oil (14.98 g, 70.6 mmol, 87% by weight, *dr* > 95 : 5 (^{1}H-NMR), *er* = 92.0 : 8.0 (chiral GC: carrier gas: H_2, 90 kPa (split ratio 1/20), column: BGB-172, 30 m * 0.25 mm, temperature: 70 – 3 – 200 °C, injector temperature: 200 °C, detector temperature: 210 °C, retention time: 21.74 min **(*S*)-24**, 22.31 min **(*R*)-24**)).^{1}H NMR (300 MHz, $CDCl_3$): *cis*-isomer: δ 5.82 (m, 1H), 5.20 (br. s, 1H), 5.19 (m, 2H), 2.48 (m, 2H), 1.81 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz), 0.96 (s, 9H) ppm. The analytical data are in accordance with literature data.[14]

Synthesis of (*R*)-3-ethyl-3-hydroxy-hex-5-en-2-one (25)

Methyllithium (15.6 mL, 1.6 M in Et_2O, 99%, 24.7 mmol, 1.05 equiv) was added dropwise over 7.5 min to a solution of **24** (5.0 g, 23.6 mmol) in THF (135 mL) at –78 °C. The reaction was monitored by TLC. After 2 h 40 min at –78 °C, additional methyllithium (15.0 mL, 23.8 mmol, 1.01 equiv) was added dropwise over 7.5 min. After additional 2 h at –78 °C, aqueous HCl (1.0 M, 135 mL) was added and the cooling bath was subsequently removed. The resulting mixture was allowed to stir at room temperature overnight and was then extracted with dichloromethane (3 x 200 mL). The combined organic phases were dried over 20 g sodium sulfate (30 min) and then filtered. The filter cake was washed with dichloromethane (40 mL). After evaporation of the solvent in a rotary evaporator (50 °C/5 mbar), crude product was obtained as a light yellow liquid (3.58 g, 107% by weight), which was purified by high vacuum Kugelrohr distillation (bp 80 °C at 0.030 mbar) furnishing product (**25**) (2.36 g, 16.6 mmol, 70% by weight) as colorless liquid. An analytical sample (colorless liquid) was obtained by column chromatography with pentane / diethyl ether (1 : 1). $[\alpha]_D^{20}$ (c = 0.9939 g/dL, MeOH) = –23.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (m, 1H), 5.12 (dd, 1H, *J* = 7.2 Hz, *J* = 1.3 Hz), 5.07 (br. s, 1H), 3.83 (s, 1H), 2.47 (m, 2H, *J* = 12.3 Hz, *J* = 6.4 Hz), 2.17 (s, 3H), 1.77 (q, 2H, *J* = 7.5 Hz), 0.82 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5, 132.3, 118.5, 81.9, 43.0, 31.2, 24.2, 7.4 ppm; IR (ATR-FTIR) 3478, 2967, 1707, 1641, 1357, 1153, 1000, 918 cm^{-1}; MS

(EI) m/z (rel. intensity) 99 (15), 57 (100), 43 (62); Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.61; H, 10.22.

Synthesis of (*R*)-5-allyl-5-ethyl-4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (21)

Cs_2CO_3 (99.5%, 10.68 g, 32.63 mmol, 2.5 equiv) was added at room temperature to a solution of **25** (1.86 g, 13.05 mmol) and diethylmalonate (97%, 6.13 mL, 39.15 mmol, 3.0 equiv) in ethanol (62 mL). The reaction was monitored by HPLC. After 26 h 20 min, the brown suspension was cooled to 0 °C and aqueous HCl (130 mL, 0.5 M, 65.5 mmol, 5.0 equiv) was added dropwise over 30 min. Ethanol (45 mL) was subsequently removed in a rotary evaporator (50 °C/5 mbar) and subsequently, ethyl acetate (50 mL) was added. The organic phase was washed with brine (50 mL), and was after that dried over sodium sulfate (5 g, 30 min) and next filtered. The filter cake was washed with ethyl acetate (10 mL). After evaporation of solvent in a rotary evaporator (50 °C/5 mbar), crude product was obtained as a yellow liquid (4.40 g, 142% by weight), which was purified by column chromatography with heptane / ethyl acetate (7 : 3) yielding product (**21**) (3.30 g, 13.84 mmol, 106% by weight) as yellow oil. $[\alpha]_D^{20}$ (c = 0.6496 g/dL, MeOH) = –21.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.55 (m, 1H), 5.14 (m, 1H, *J* = 7.2 Hz, *J* = 1.3 Hz), 5.09 (m, 1H), 4.33 (q, 2H, *J* = 7.1 Hz), 2.66 (ddt, 1H, *J* = 14.5 Hz, *J* = 6.8 Hz, *J* = 1.3 Hz), 2.40 (ddt, 1H, *J* = 14.5 Hz, *J* = 7.5 Hz, *J* = 1.0 Hz), 2.25 (s, 3H), 1.98 (dq, 1H, *J* = 14.6 Hz, *J* = 7.4 Hz), 1.72 (dq, 1H, *J* = 14.5 Hz, *J* = 7.3 Hz), 1.36 (t, 3H, *J* = 7.1 Hz), 0.77 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 167.7, 161.4, 129.8, 120.7, 120.2, 89.7, 61.3, 40.5, 28.9, 14.2, 13.4, 7.0 ppm; IR (ATR-FTIR) 2978, 1765, 1714, 1651, 1316, 1238, 1044, 967 cm^{-1}; MS (EI) m/z (rel. intensity) 239 (20), 197 (89), 151 (100); HRMS (ESI POS) calcd for $C_{13}H_{18}O_4Na$ (MNa^+) 261.1103, found 261.1104; Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.84; H, 7.88.

Synthesis of (*R*)-1-allyl-1-ethyl-1*H*,5*H*-furo[3,4-*c*]pyridine-3,4-dione (20)

Sodium ethoxide (1.10 g, 15.31 mmol, 1.1 equiv) was added at 0 °C to a solution of **21** (3.32 g, 13.92 mmol) in ethanol (33 mL). 11 min later, a solution of s-1,3,5-triazine (1.28 g, 15.31 mmol, 1.1 equiv) in ethanol (25 mL) was added and the ice bath was removed. The reaction was monitored by HPLC. After 22 h 20 min, additional sodium ethoxide (199.4 mg, 2.78 mmol, 0.2 equiv) was added. After 3 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL). The mixture was extracted with dichloromethane (3 x 75 mL). The combined organic phases were dried over sodium sulfate (15 g, 30 min) and next filtered. The filter cake was washed with dichloromethane (30 mL). After evaporation of solvent in a rotary evaporator (40 °C/29 mbar), the crude product was obtained as red oil (2.05 g, 67% by weight), which was dissolved in ethyl acetate (12 mL) under reflux (oil bath temperature 100 °C). Heptane (5 mL) was subsequently added and the resulting mixture was allowed to slowly cool down to room temperature overnight. The precipitate was collected by filtration and washed with heptane (1 mL) furnishing product (**20**) (1.70 g, 7.73 mmol, 56% by weight (59% over 2 steps)) as red solid. $[\alpha]_D^{20}$ (c = 0.6496 g/dL, MeOH) =

–25.0; mp 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.0 (br. s, 1H), 7.93 (d, 1H, *J* = 6.6 Hz), 6.33 (d, 1H, *J* = 6.4 Hz), 5.57 (m, 1H), 5.12 (s, 1H), 5.08 (dm, 1H, *J* = 6.6 Hz), 2.72 (dd, 1H, *J* = 14.3 Hz, *J* = 7.6 Hz), 2.57 (dd, 1H, *J* = 14.3 Hz, *J* = 7.1 Hz), 2.10 (dq, 1H, *J* = 14.5 Hz, *J* = 7.3 Hz), 1.87 (dq, 1H, *J* = 14.5 Hz, *J* = 7.2 Hz), 0.81 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 167.7, 160.1, 143.2, 129.8, 120.9, 114.1, 100.3, 88.0, 41.9, 30.2, 7.3 ppm; IR (ATR-FTIR) 3360 (br), 2921, 1758, 1715, 1660, 1614, 1563, 1189, 1157, 968, 826, 814, 724 cm^{-1}; MS (EI) m/z (rel. intensity) 219 (2), 178 (100); HRMS (ESI POS) calcd for $C_{12}H_{13}NO_3Na$ (MNa^+) 242.0793, found 242.0793; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.65; H, 5.97; N, 6.44.

Synthesis of (*R*)-1-allyl-1-ethyl-4-methoxy-1*H*-furo[3,4-*c*]pyridin-3-one ((*R*)-13))

Trimethyloxonium tetrafluoroborate (95%, 1.06 g, 6.77 mmol, 1.1 equiv) was added to a solution of **20** (1.35 g, 6.16 mmol) in dichloromethane (40 mL). The reaction was monitored by HPLC. After 6 h 25 min, additional trimethyloxonium tetrafluoroborate (958.8 mg, 6.16 mmol, 0.9 equiv) was added portion wise over the next 19 h. After 28 h, the reaction was quenched by addition of brine (20 mL). The mixture was extracted with dichloromethane (20 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 the solvent in a rotary evaporator (40 °C/10 mbar), the crude product was obtained as a brown solid (1.35 g, 94% by weight, *er* = 88.5 : 11.5 (chiral GC: carrier gas: H_2, 120 kPa (split ratio 1/20), column: BGB-172, 30 m * 0.25 mm, temperature: 100 – 2 – 200 °C, injector temperature: 200 °C, detector temperature: 220 °C, retention time: 45.71 min **(*S*)-13**, 46.36 min **(*R*)-13**)). An analytical sample (white crystals) was obtained by column chromatography with heptane / ethyl acetate (7 : 3). $[\alpha]_D^{20}$ (c = 0.9885 g/dL, $CHCl_3$) = –8.1 (corrected for *ee* = 100%); mp: 87 °C. The other analytical data are in accordance with the racemate (**13**).

Synthesis of (*R*)-3-(3-hydroxymethyl-2-methoxy-pyridin-4-yl)-hex-5-en-3-ol ((*R*)-14)

According to the preparation of **(*rac*)-14** described above, **(*R*)-13** (660.0 mg, 2.83 mmol) was treated with lithium aluminum hydride (1.75 mL, 1.75 mmol, 0.62 equiv) yielding the crude product (622.6 mg, 93% by weight) as a brown oil, which was used without further purification in the next step. An analytical sample (white crystals) was obtained by column chromatography with heptane / ethyl acetate (3 : 2). $[\alpha]_D^{20}$ (c = 0.9957 g/dL, $CHCl_3$) = 13.4; mp: 83 °C. The other analytical data are in accordance with the racemate (**14**).

Synthesis of (*R*)-5-ethyl-1-methoxy-5,6,7,9-tetrahydro-8-oxa-2-aza-benzocycloheptene-5,7-diol ((*R*)-15)

According to the preparation of **(*rac*)-15** described above, **(*R*)-14** (618.3 mg, 2.61 mmol) was treated with O_3 furnishing the crude product (673.0 mg, 108% by weight, *dr* = 5 : 1) as a yellow waxy solid. An analytical sample (white semisolid) was obtained by column chromatography with heptane / ethyl acetate (2 : 1). $[\alpha]_D^{20}$ (c = 0.5879 g/dL, $CHCl_3$) = –69.1. The other analytical data are in accordance with the racemate (**15**).

Synthesis of (*R*)-5-ethyl-5-hydroxy-1-methoxy-5,9-dihydro-6*H*-8-oxa-2-aza-benzocyclohepten-7-one ((*R*)-16)

According to the preparation of **(*rac*)-16** described above, **(*R*)-15** (657.3 mg, 2.75 mmol) was treated with 2,2,6,6-tetramethylpiperidin-1-oxy radical (TEMPO, 44.7 mg, 0.32 mmol, 0.1 equiv) and saturated aqueous $NaHCO_3$ / aqueous 10% NaOCl (10 : 7, 7.9 mL) furnishing the crude product (535.8 mg, 82% by weight) as a yellow-brown oil (*er* = 88.5 : 11.5 (chiral HPLC sample preparation: ethanol solution, column: chiralpak-ADH, 250 x 4.6, temperature: 25 °C, mobile phase: 90% heptane, 10% ethanol / trifluoroacetic acid (99 : 1), flow: 0.8 mL/min, injection volume: 5 μL, detection: UV 275 nm, retention time: 35.49 min **(*R*)-16**, 45.43 min **(*S*)-16**)), which was purified by column chromatography with heptane / ethyl acetate (1 : 1). Product **(*R*)-16** (285.5 mg, 1.21 mmol, 44% by weight, 42% over 4 steps) was obtained as a white powder. An analytical sample (white crystals) was obtained by column chromatography with heptane / ethyl acetate (1 : 1). $[\alpha]_D^{20}$ (c = 0.9884 g/dL, $CHCl_3$) = +23.2; mp 103 °C. The other analytical data are in accordance with the racemate (**16**).

Synthesis of (*R*)-5-ethyl-5-hydroxy-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene (7)

According to the preparation of **(*rac*)-7** described above, **(*R*)-16** (286.0 mg, 1.21 mmol) was treated with aqueous HBr (48%, 284 μL, 2.53 mmol, 2.1 equiv) yielding product **7** (171.9 mg, 64% by weight, 0.77 mmol, *er* > 99.95 : 0.05 (chiral HPLC: sample preparation: ethanol solution, column: chiralcel-ODH, 250 x 4.6, temperature: 25 °C, mobile phase: 75% heptane, 25% ethanol / trifluoroacetic acid (99 : 1), flow: 0.8 mL/min, injection volume: 5 μL, detection: UV 308 nm, retention time: 9.68 min **(*S*)-7**, 13.28 min **(*R*)-7**)) as a white powder. $[\alpha]_D^{20}$ (c = 0.178 g/dL, DMSO-*d6*) = +137.7; mp > 270 °C (decomp.); ^{1}H NMR (300 MHz, DMSO): δ 11.67 (br. s, 1H), 7.34 (d, 1H, 7.2 Hz), 6.33 (d, 1H, 7.2 Hz), 5.72 (br. S, 1H), 5.34 (d, 1H, *J* = 15.1 Hz), 5.21 (d, 1H, *J* = 15.1 Hz), 3.32 (d, 1H, *J* = 13.5 Hz), 2.98 (d, 1H, *J* = 13.7 Hz), 1.68 (m, 2H), 0.80 (t, 3H, *J* = 7.5Hz) ppm. The other analytical data are in accordance with those for **7** described in Ref [7].

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