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Asymmetric total synthesis of (20*R*)-homocamptothecin, substituted homocamptothecins and homosilatecans

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Dedicated to Professor Yoshito Kishi in recognition of his receipt of the Tetrahedron Prize

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Abstract—An efficient asymmetric synthesis of a key DE lactone pyridone intermediate in the synthesis of homocamptothecin is reported. The synthesis is scalable and features a Stille coupling and a Sharpless asymmetric epoxidation as the key steps. The key intermediate has been parleyed into homocamptothecin and an assortment of fluorinated homocamptothecins and homosilatecans (7-silylhomocamptothecins), thereby providing the first asymmetric entry to this important new class of antitumor agents. © 2002 Published by Elsevier Science Ltd.

1. Introduction

(20*S*)-Camptothecin **1** is the parent of an important class of anticancer agents that act on the so-called cleavable complex of DNA and the enzyme topoisomerase I.[1] All camptothecins are dynamic drugs and exist in equilibrium with their open carboxylate forms in blood and other biological milieu (Fig. 1).[2] Of late, advances in the total synthesis of camptothecins have driven medicinal chemistry and pharmacology research by providing many new analogs for biological testing. For example, we have prepared a diverse assortment of 7-silylcamptothecins, or silatecans, by a flexible and general total synthesis that features a cascade isonitrile radical annulation.[3] DB-67 **2** has emerged from the pack of silatecans as a potential candidate for cancer chemotherapy by virtue of its high activity, high blood stability and other interesting properties.[4]

In 1997, Lavergne and coworkers described a semi-synthesis of racemic homocamptothecin *rac*-**3** (BN 80245, abbreviated hcpt) from camptothecin **1**,[5] and showed that this E-ring expanded analog was more potent than camptothecin in a number of assays. In contrast to the lactone ring of camptothecin **1**, which opens rapidly and reversibly, the lactone ring of homocamptothecin **3** opens slowly and irreversibly.[6] Resolution of the open hydroxyl carboxylate form of homocamptothecin provided the first sample of the active (20*R*)-enantiomer **3** (Fig. 1).[7] The insertion of a methylene group (C20a) between the stereocenter at C20 and the lactone carbonyl is crucial; insertion of the methylene group on the other side of the lactone carbonyl gives a keto ether analog **4** that is inactive.[8]

To facilitate the synthesis of analogs, Lavergne and co-workers developed a fully synthetic route to racemic homocamptothecin based on the powerful Comins route to camptothecins.[9] Key intermediate **7** (Fig. 2) is alkylated with quinoline **6** to give **8** followed by Pd-catalyzed cyclization to give homocamptothecin **3**. Resolution of a precursor of **7** then opened the door to the corresponding enantioenriched homocamptothecin analogs. Several highly active fluorinated analogs of homocamptothecin were prepared from suitably substituted quinolines **6**.[10]

In 1999, we communicated the adoption of our cascade radical annulation route to camptothecins for the preparation of homocamptothecins.[11] Racemic **9** was prepared and reacted with a number of silyl propargyl halides to provide precursors *rac*-**10a**, which were then reacted with isonitriles **11** to provide a small collection of silatecan/homocamptothecin hybrids *rac*-**12** called homosilatecans (Fig. 3). Several of these compounds exhibited potent anticancer properties coupled with exceptionally high human blood stabilities.[11] Compared to the hybrid Comins/Lavergne route, the radical annulation route allows for a more diverse range of A-ring substituents and incorporates B-ring substituents with equal ease. The generality of the approach has been shown by making a library of over 100 analogs of homosilatecans.[12]

Collectively, the early results suggest that analogs of homocamptothecin and homosilatecans may often possess similar or even better anticancer activities than the parent while at the same time exhibiting very different pharmacodynamic properties due to the reactivity difference of the

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Keywords: homosilatecans; topoisomerase; antitumor.

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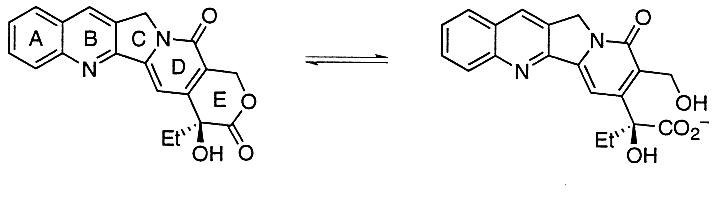
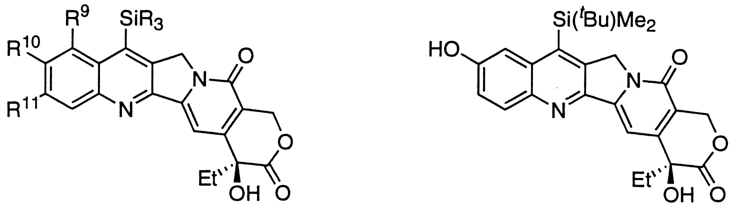


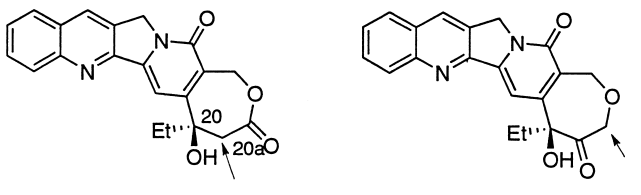
(20*S*)-camptothecin, **1**
active lactone form

carboxylate form
inactive



silatecans
(7-silylcamptothecins)

DB-67, **2**



(20*R*)-homocamptothecin, **3**

inactive keto-ether **4**

arrows show added methylene group

Figure 1. Camptothecin, silatecans and homocamptothecin.

seven-membered lactone ring compared to the parent six-membered ring. To facilitate progress in this exciting area, we undertook the development of an asymmetric synthesis, and we report here the preparation of enantioenriched **9** and its conversion to a number of known and new homocamptothecin and homosilatecan analogs. In addition, we report an asymmetric synthesis of lactone **7** (Fig. 2), the key intermediate in the Comins/Lavergne route.

2. Results and discussion

After briefly evaluating a number of possible asymmetric strategies to lactone pyridone **9**, we set out to explore a classical Sharpless asymmetric expoxidation route, as shown in Scheme 1. As in our previous routes to both camptothecin and homocamptothecin, a trimethylsilyl group was used as a place holder for the radical precursor (iodine).

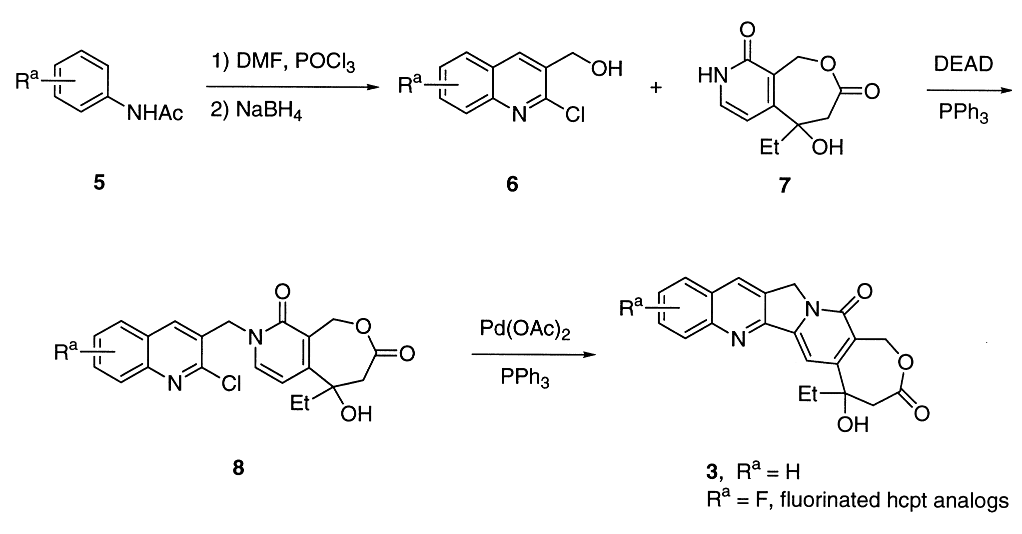


Figure 2. Comins/Lavergne route to hcpt.

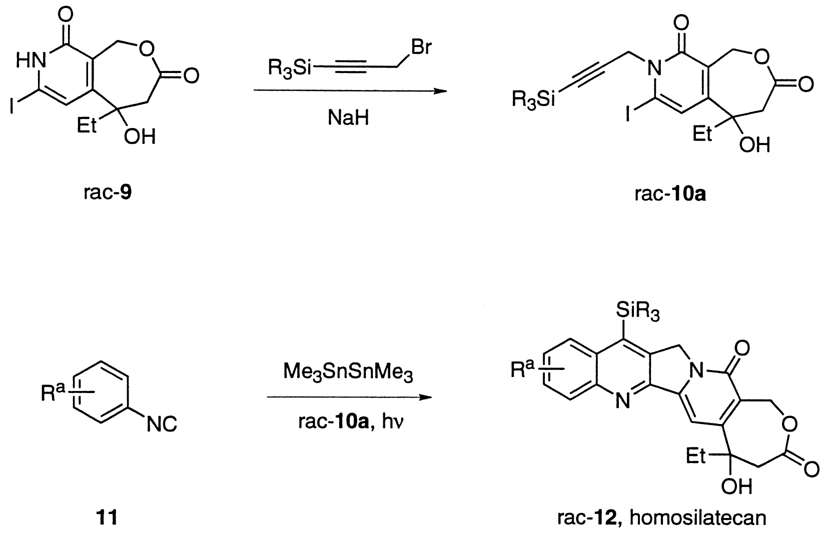
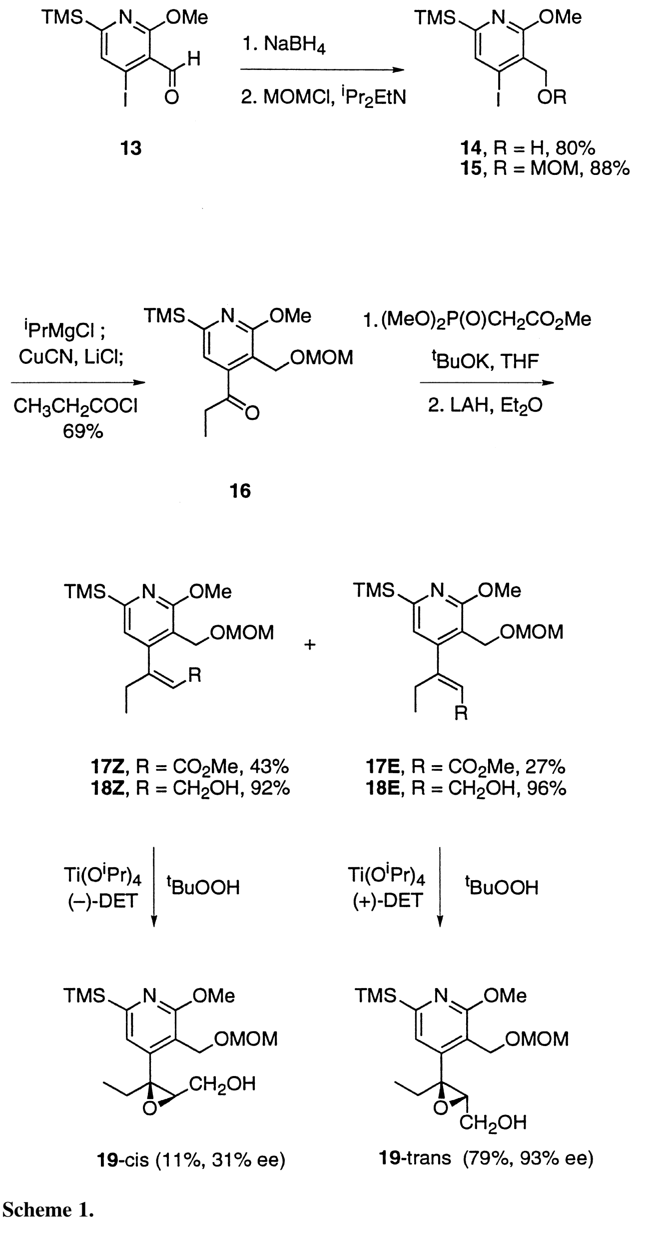


Figure 3. Cascade radical annulation route to racemic homosilatecans.

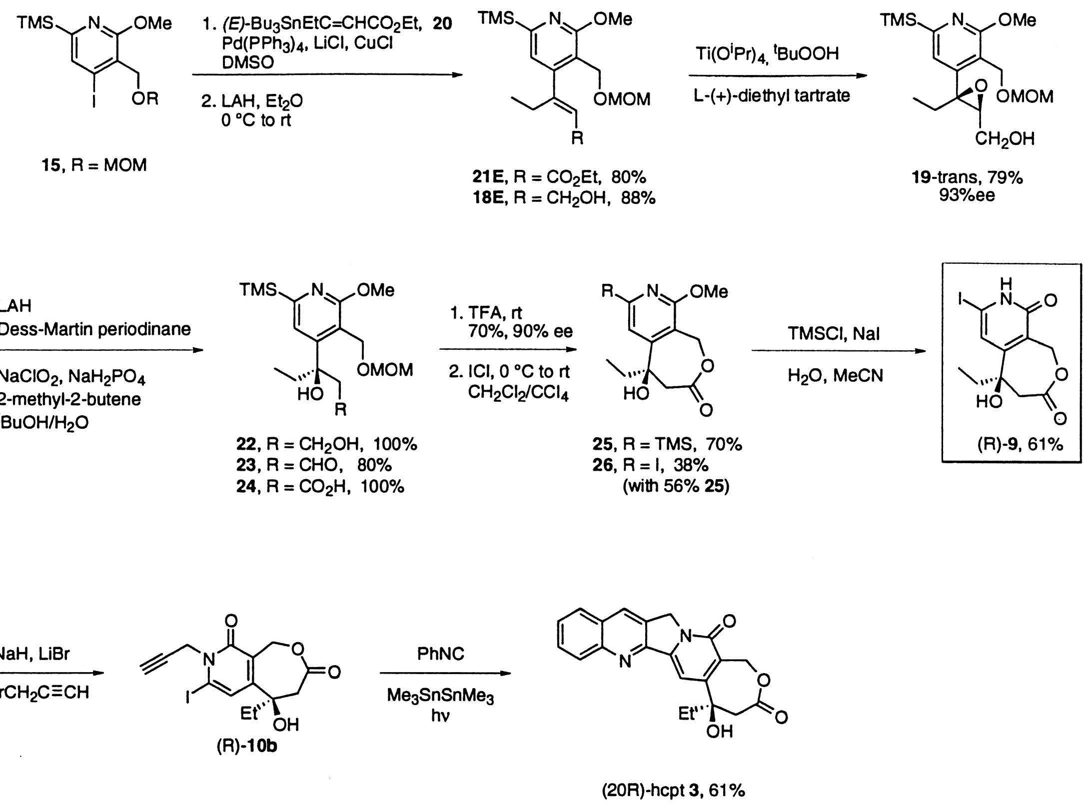


Scheme 1.

The synthesis of allylic alcohols **18*E*** and **18*Z*** began with iodoformyl pyridine **13**, which is an early intermediate in the total synthesis of camptothecin.[3] Treatment of **13** with $NaBH_4$ in EtOH at −40°C afforded hydroxymethyl pyridine **14** in 80% yield. Exposure of this alcohol to MOMCl and ^{i}Pr$_2$EtN in CH_2Cl_2 at 0°C provided MOM ether **15** in 88% yield. The cuprate reagent derived from pyridine **15** was prepared by iodine–magnesium exchange reaction[13] with ^{i}PrMgCl at −40°C, followed by addition of CuCN and LiCl.[14] Quenching with propionyl chloride provided the ketone **16**[15] in 69% isolated yield. The Horner–Wadsworth–Emmons[16] olefination of this ketone with trimethyl phosphonoacetate (^{t}BuOK, THF, 55°C) provided esters **17*E*** (27%) and **17*Z*** (43%) after separation on silica gel. LAH reduction gave the corresponding alcohols **18*Z*** (92%) and **18*E*** (96%).

The Sharpless asymmetric epoxidation of allylic alcohols **18*E*** and **18*Z*** to install the key C20 stereocenter was attempted under standard conditions.[17] Epoxidation of **18*Z*** with 1 equiv. of D-(−)-diethyl tartrate, ^{t}BuOOH and 80 mol% of Ti(O^{i}Pr)$_4$ in CH_2Cl_2 at −20°C was sluggish. Warming the reaction mixture to 0°C led to epoxide **19**-*cis* in 12% yield and 31% ee, based on chiral HPLC analysis. The starting allylic alcohol **18Z** was also recovered in 38% yield. In contrast, treatment of alcohol **18*E*** with ^{t}BuOOH/Ti(O^{i}Pr)$_4$ and a stoichiometric amount of L-(+)-diethyl tartrate in CH_2Cl_2 at −20°C for 2 h followed by workup and flash chromatography provided epoxide **19**-*trans* in 79% yield and 93% ee.

The highly selective Sharpless epoxidation makes ester **18*E*** and alcohol **19**-*trans* key intermediates, thus their selective preparation was necessary. Attempts to increase the *E*-selectivity of the Horner–Emmons olefination were unsuccessful, and the isomerization of **17*Z*** into the desired isomer **17*E*** was inefficient at best.[12a] Accordingly, focus shifted towards the preparation of **18*E*** by means of a palladium-catalyzed cross-coupling reaction starting from iodopyridine **15** and ethyl (*E*)-3-(tributylstannyl)-2-pentenoate **20**[18] (Scheme 2). This was achieved by using Corey's protocol[19] (LiCl, CuCl, Pd(Ph$_3$P)$_4$, DMSO, 60°C, 17 h) to provide **21*E***

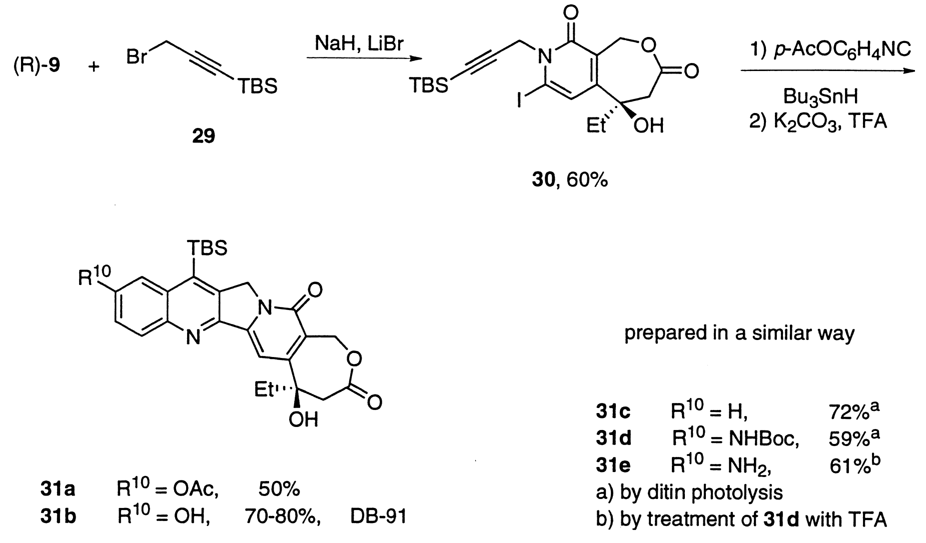


Scheme 2.

(the ethyl ester analog of **19***E*) in 80% isolated yield. Treatment of ethyl ester **21***E* with LAH provided alcohol **18***E*, which was subjected to Sharpless epoxidation as above to give **19**-*trans*.

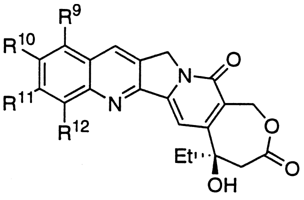
With a satisfactory route to epoxide **19**-*trans* in hand, we next identified a straightforward route to parlay this intermediate into the needed iodopryridone (*R*)-**10b** (Scheme 2). Regioselective opening[20] was accomplished quantitatively by treatment of **19**-*trans* with LAH. Oxidation of the resulting alcohol **22** with Dess–Martin periodinane[21] in CH_2Cl_2 at room temperature for 3 h afforded **23**. Immediate oxidation of aldehyde **23** with $NaClO_2$ in ${}^tBuOH$, buffered with an aqueous solution of sodium dihydrogen phosphate and in the presence of 2-methyl-2-butene, provided acid **24**. Finally, MOM ether deprotection and in situ lactonization to **25** were accomplished by treatment of acid **24** with TFA at room temperature for 16 h. The overall isolated yield for the five-step process to convert the allylic alcohol **18***E* into the TMS-lactone **25** was 44%. The enantiomeric excess of **25** was estimated to be 90% by chiral HPLC analysis.

Completion of the preparation of the central iodopyridone (*R*)-**9** followed the established racemic route.[11]



Scheme 3.

Table 1. Fluorinated homocamptothecins prepared from iodopyridone (*R*)-**10b**



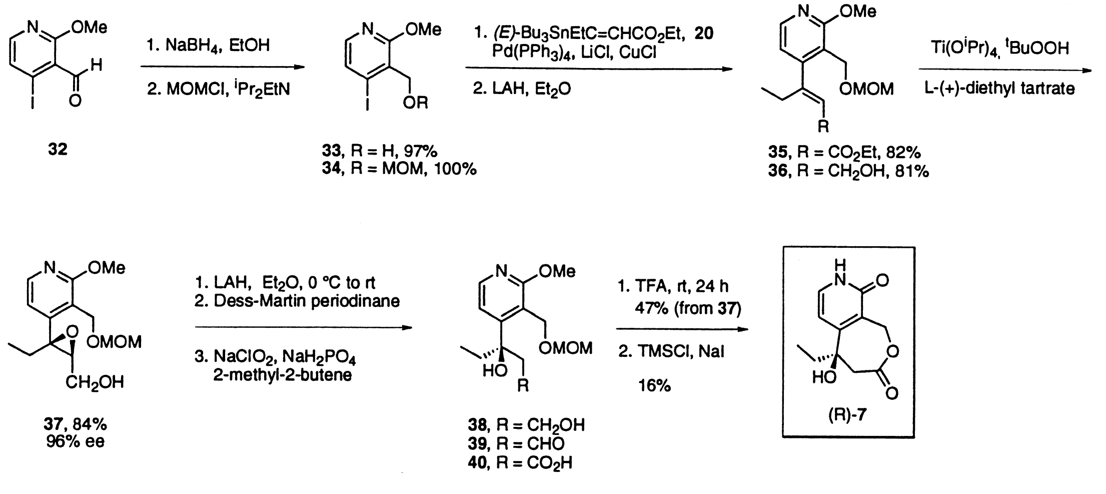
Cmpd	R^9	R^{10}	R^{11}	R^{12}	Yield (%)	Isonitrile	Comments
27a	H	H	H	F	49	2-FC_6H_4NC	Single siomer
27b	H	F	H	H	38	4-FC_6H_4NC	Single isomer
27c	F	H	H	H	16	3-FC_6H_4NC	1/1 Mix with **27d**
27d	H	H	F	H	16	3-FC_6H_4NC	1/1 Mix with **27c**
28a	F	F	H	H	33	3,4-diFC_6H_3NC	1/1 Mix with **28b**
28b	H	F	F	H	35	3,4-diFC_6H_3NC	1/1 Mix with **28a**

TMS-lactone **25** was subjected to ICl mediated iododesilylation in CH_2Cl_2/CCl_4 at room temperature. Iodolactone **26** was isolated by column chromatography in 38% yield and the starting TMS-lactone **25** was recovered (56%) for recycling. Demethylation was achieved in 61% yield by adding TMSCl to a mixture of iodolactone **26** and NaI in CH_3CN at 65°C for 5 h. The route in Scheme 3 is an efficient means for the stereocontrolled preparation of the key iodopyridone (*R*)-**9** in 7% overall yield from the iodoaldehyde **13**.

The final steps to assemble the homocamptothecin ring system also followed the established route (Scheme 2). *N*-Alkylation of (*R*)-**9** with propargyl bromide gave (*R*)-**10b**, which in turn provided (20*R*)-homocamptothecin **3** in 61% yield on irradiation in the presence of phenyl isonitrile and hexamethylditin. Likewise, all possible A-ring mono fluorinated isomers of homocamptothecin were made by a series of reactions with fluorinated isonitriles. The structures of these known analogs[7,10] are shown in Table 1. 2-Fluoroisonitrile provided 12-fluorohomocamptothecin **27a**, 4-fluoroisonitrile provided the 10-fluoroisomer **27b**, and 3-fluoroisonitrile provided a separable 1/1 mixture of 9-fluoro- and 11-fluoroisomers **27c**,**d**.[22] Reaction of 3,4-difluoroisonitrile provided a separable 1/1 mixture of 9,10-difluorohcpt and 10,11-difluorohcpt **28a**,**b** (BN80915).[7,10]

Several homosilatecans were also prepared from (*R*)-**9**, and the synthesis DB-91 **31b** shown in Scheme 3 is representative. This compound is the homocamptothecin version of DB-67 **2** and is an important touchstone between the two series since the behavior of DB-67 is now relatively well understood. For detailed chemical and pharmacological studies, we prepared 805 mg of DB-91 **31b** by total synthesis. *N*-Propargylation of (*R*)-**9** with **29** provided **30** in reproducible 60% yields on gram scale. The ditin photolysis was deemed inconvenient for larger scales and a standard tin hydride syringe pump procedure (see Section 4) was used instead. This provided acetate **31a** in reliable 50% yields on 200–500 mg scale. Finally, deacylation provided DB-91 **31b** in 70–80% yields on 50–500 mg scale. The ee of DB-91 was measured by chiral hplc and was the same as the ee of precursor **9**. 7-TBS-hcpt **31c**, 10-Boc-amino-7-TBS-hcpt **31d** and 10-amino-7-TBS-hcpt **31c** were prepared by analogous strategies (see Section 4). All these compounds were identical to the corresponding racemic samples,[3] except for optical rotation.

Recognizing that the Comins/Lavergne route[7,10] to homocamptothecins also provides powerful synthetic options, we decided to apply the chemistry in Scheme 2 towards the preparation of (*R*)-**7**, which is currently made by classical resolution of a racemic intermediate (Fig. 2). This synthesis is outlined in Scheme 4. Pyridine **34** is the requisite



Scheme 4.

substrate for the key Stille coupling, and this was prepared from readily available iodoaldehyde[23] **32** by $NaBH_4$ reduction and protection of the resulting alcohol **33** as its MOM ether. Stille coupling of ethyl (*E*)-3-(tributylstannyl)-2-pentenoate[18] with iodopyridine **34**, under Corey's conditions,[19] followed by reduction with LAH, gave allylic alcohol **36**. Stoichiometric Sharpless asymmetric epoxidation of **36** with L-(+)-diethyl tartrate led to **37** in 96% ee.[24] This epoxide was then converted to pyridone (*R*)-**7** via a five-step sequence: (1) regioselective opening of the epoxide **37** with LAH; (2) Dess–Martin oxidation of the resulting alcohol **38**; (3) further oxidation of aldehyde **39** with $NaClO_2$; (4) MOM ether deprotection and in situ cyclization of **40** with TFA; and finally, (5) demethylation. Overall, the route provided easy access to pyridone (*R*)-**7** in 4% overall yield from the aldehyde **32** and with 96% ee.[25] Many of the later steps of the sequence were only conducted once or twice, so prospects for yield improvement are still open.

3. Conclusions

The first asymmetric synthesis of (20*R*)-homocamptothecins and homosilatecans has been developed. A convenient and enantioselective synthetic route to the DE-fragment (*R*)-**9** has been achieved. The synthetic strategy relies on the application of a Stille reaction and a Sharpless asymmetric epoxidation to establish the *R* configuration at C20. A similar route is used to make the key intermediate (*R*)-**7** in the Comins/Lavergne homocamptothecin total synthesis.

The asymmetric process to the DE-fragment has the scope to produce homocamptothecin and many derivatives in an enantioenriched form. Looking ahead towards the development of a homocamptothecin analog as a promising anticancer drug, this process can be of significant importance.

4. Experimental

4.1. General

4.1.1. 4-Iodo-2-methoxy-6-(trimethylsilanyl)pyridin-3-yl]-methanol (14). To a solution of $NaBH_4$ (1.1 g, 26.4 mmol) in EtOH (100 mL) at −40°C was slowly added a solution of 4-iodo-2-methoxy-6-trimethylsilanyl-3-pyridinecarboxaldehyde[3a] **13** (31.8 g, 94.9 mmol) in EtOH (50 mL). After stirring for 1 h, the reaction mixture was carefully quenched with brine and then extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography (gradient hexanes to hexanes/EtOAc 91:9) to afford **14** (25.1 g, 78% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 2.5 (bs, 1H), 4.01 (s, 3H), 4.8 (s, 2H), 7.5 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 53.8, 65.3, 11.6, 125.3, 133.2, 160.9, 165.8; IR (film, NaCl, cm^{-1}) 3485, 2960, 1580, 1450, 1039, 839; LRMS (70 eV, EI) *m/z* (rel int %) 337 (M^+), 322 (100), 306, 194, 180, 73; HRMS *m/z* calcd for $C_{10}H_{16}NO_2SiI$ (M^+) 336.9996, found 337.000.

4.1.2. 4-Iodo-2-methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridine (15). MOMCl (2.0 mL, 26.7 mmol) was added dropwise to a 0°C solution of **14** (3 g, 8.9 mmol) and $^{i}Pr_2EtN$ (4.6 mL, 26.7 mmol) in dry CH_2Cl_2 (35 mL). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 5% aqueous $NaHCO_3$ solution and the product was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 3.0 g (88% yield) of the crude product **15** as an orange oil. The crude product was sufficiently pure for the subsequent reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 3.46 (s, 3H), 3.98 (s, 3H), 4.71 (s, 2H), 4.75 (s, 2H), 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.1, 53.8, 55.5, 67.9, 96.4, 113.8, 122.6, 133.0, 161.4, 166.4; IR (film, NaCl, cm^{-1}) 2946, 1528, 1340, 1042, 840; LRMS (70 eV, EI) *m/z* (rel int %) 381 (M^+), 366, 336, 320, 306, 169, 128, 84 (100), 73; HRMS *m/z* calcd for $C_{12}H_{20}NO_3SiI$ (M^+) 381.0257, found 381.0241.

4.1.3. 1-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]propan-1-one (16). To a solution of **15** (4.0 g, 10.5 mmol) in THF (25 mL) at −40°C was added dropwise ^{i}PrMgCl (7.0 mL, 2.0 M in THF). The mixture was stirred at −40°C for 1 h, and then CuCN·2LiCl (prepared from CuCN (1.2 g, 13.4 mmol) and LiCl (1.2 g, 27.4 mmol)) in THF (30 mL) was added. After 15 min propionyl chloride (2.7 mL, 31.5 mmol) was added, then the reaction mixture was stirred 1 h at −40°C and 15 min at room temperature. The reaction was quenched with brine and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexanes to hexanes/Et_2O 95:5) to afford **16** (2.2 g, 69%) as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 1.98 (t, J=7.1 Hz, 3H), 2.82 (q, J=7.1 Hz, 2H), 3.37 (s, 3H), 3.99 (s, 3H), 4.62 (s, 2H), 4.64 (s, 2H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −2.0, 7.7, 36.4, 53.5, 61.1, 96.4, 115.2, 118.4, 148.5, 161.1, 165.5, 206.8; IR (film, NaCl, cm^{-1}) 2951, 1708, 1451, 1342, 1046, 839; LRMS (70 eV, EI) *m/z* (rel int %) 296 (M^+-15), 266 (100), 248, 234, 100, 89, 73, 591; HRMS *m/z* calcd for $C_{14}H_{22}NO_4Si$ (M^+-CH_3) 296.1318, found 296.1313.

4.1.4. 3-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pent-2-enoic acid methyl ester (17*E*/*Z*). To a mixture of trimethyl phosphonoacetate (2.5 mL, 15.3 mmol) and ^{t}BuOK (1.7 g, 15.3 mmol) in THF (20 mL) at 0°C (1 h) was added a THF (10 mL) solution of **16** (1.2 g, 3.7 mmol). The mixture was stirred at reflux for 36 h. Purification of the crude residue by flash chromatography (hexanes/EtOAc 92:8) followed by preparative HPLC (hexanes/EtOAc 92:8, Novapak normal phase cartridge column, 10 mL/min), afforded in order of elution; **16** (123.3 mg, 10%), **17*E*** (387.0 mg, 27%) and **17*Z*** (609.3 mg, 43%) as clear oils: **17*E***; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 0.99 (t, J=7.6 Hz, 3H), 2.99 (q, J=7.6 Hz, 2H), 3.42 (s, 3H), 3.75 (s, 3H), 4.02 (s, 3H), 4.47 (s, 2H), 4.72 (s, 2H), 5.8 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 12.3, 26.6, 51.2, 53.4, 55.3, 61.9, 96.7, 115.4, 118.9, 121.1, 150.9, 160.3, 162.2, 164.9, 166.2; IR (film, NaCl, cm^{-1}) 2949, 1723, 1341, 1042, 840; LRMS (70 eV, EI) *m/z* (rel int %) 367 (M^+), 352, 322, 308 (100), 290, 276, 246, 232, 99, 57; HRMS *m/z* calcd for $C_{18}H_{29}NO_5Si$ (M^+) 367.1815, found 367.1802. **17Z**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.11 (t, J=7.2 Hz, 3H), 2.38–2.48 (m, 2H), 3.4 (s, 3H), 3.53 (s, 3H), 3.99 (s, 3H), 4.35 (d, J=10.2 Hz, 1H), 4.51 (d, J=10.2 Hz, 1H), 4.66 (dd, J=6.3, 14.2 Hz, 2H), 5.94 (s, 1H), 6.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ δ −1.9, 11.4, 33.1, 51.1, 53.2, 55.2, 61.9, 96.5, 114.5, 116.3, 120.6, 150.0, 159.0, 161.7, 164.3, 165.6; IR (film, NaCl, cm^{-1}) 2941, 1732, 1559, 1457, 1342, 1054, 836; LRMS (70 eV, EI) *m/z* (rel int %) 367 (M^+), 322, 290, 278, 262, 139 (100), 89, 73; HRMS *m/z* calcd for $C_{18}H_{29}NO_5Si$ (M^+) 367.1815, found 367.1820.

4.1.5. (*Z*)-3-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pent-2-en-1-ol (18*Z*). LAH (0.25 mL, 1 M solution in Et_2O) was slowly added to a −78°C solution of **17Z** (100 mg, 0.3 mmol) in Et_2O (3 mL). The resulting mixture was allowed to warm to 0°C. Then, the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate. The aqueous layer was extracted three times with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product **18Z** (86.0 mg, 93% yield) as colorless oil. The crude product was sufficiently pure for the subsequent reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 1.05 (t, J=7.4 Hz, 3H), 2.25 (q, J=7.4 Hz, 2H), 3.43 (s, 3H), 3.63–3.81 (m, 2H), 4.01 (s, 3H), 4.31 (d, J=10.3 Hz, 1H), 4.64–4.81 (m, 3H), 5.76–5.92 (m, 1H), 6.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 11.9, 31.6, 53.3, 55.6, 59.2, 61.5, 96.5, 115.8, 122.7, 126.2, 142.8, 150.1, 162.1, 164.9; IR (film, NaCl, cm^{-1}) 3393, 2962, 1552, 1340, 1042, 839; LRMS (70 eV, EI) *m/z* (rel int %) 339 (M^+), 324, 308, 292, 277, 262, 248 (100), 234, 73; HRMS *m/z* calcd for $C_{17}H_{29}NO_4Si$ (M^+) 339.1865, found 339.1864.

4.1.6. (+)-{3-Ethyl-3-[2-methoxy-6-(trimethylsilanyl)-pyridin-4-yl]oxiranyl} methanol (19-*cis*). To a solution of **18Z** (50.0 mg, 0.1 mmol) and activated 4 Å molecular sieves (25.0 mg) in CH_2Cl_2 (1.5 mL) at −20°C was added D-(−)-diethyl tartrate (30.0 mg, 0.1 mmol) and Ti(O^{i}Pr)$_4$ (33.5 mg, 0.1 mmol). After stirring for 1 h, ^{t}BuOOH (60.0 mL, 5.0–6.0 M in decane, predried over 4 Å molecular sieves for 1 h) was added with a syringe. The reaction mixture was kept in the freezer at −20°C for 12 h and next warmed to 0°C. After stirring for 1 week at 0°C, the solution was diluted with Et_2O (0.2 mL) and quenched with a saturated Na_2SO_4 solution (0.1 mL). The resulting heterogeneous mixture was allowed to warm to room temperature and stirred for 2 h. Then it was filtered through a celite pad (washing with hot EtOAc several times). The combined filtrates were concentrated under vacuum. The residue was dissolved in Et_2O (0.7 mL) at 0°C and a 1N NaOH solution saturated with NaCl was added (0.5 mL). The two-phase mixture was vigorously stirred at 0°C for 1 h and then transferred to a separatory funnel. The aqueous layer was separated and extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/EtOAc, 70:30) to give, in order of elution, starting alcohol **18Z** (19.0 mg, 34%), and **19**-*cis* (6.0 mg, 11%) as a clear oil. Epoxide **19**-*cis* was analyzed for enantiomeric purity by using a Regis (*S*,*S*) Whelk-O1 column with 99.5:0.5 hexanes/^{i}PrOH as the eluent (2 mL/min), and the racemate as the standard. The enantiomeric excess was shown to be 30% ((2*S*, 3*R*) major, Rt 9.3 min, (2*R*, 3*S*) minor Rt 10.5 min): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 0.88 (t, J=7.3 Hz, 3H), 1.62–1.73 (m, 1H), 2.02–2.13 (m, 1H), 2.94–3.03 (m, 1H), 3.36–3.45 (m, 2H), 3.47 (s, 3H), 4.01 (s, 3H), 4.61 (d, J=10.9 Hz, 1H), 4.74 (d, J=10.9 Hz, 1H), 4.73 (d, J=6.5 Hz, 1H), 4.85 (d, J=6.5 Hz, 1H), 7.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 8.4, 30.4, 53.4, 55.9, 60.5, 61.3, 62.7, 65.4, 97.1, 114.8, 122.1, 145.9, 161.8, 165.7; IR (film, NaCl, cm^{-1}) 3502, 2953, 1562, 1451, 1343, 1042, 839; LRMS (70 eV, EI) *m/z* (rel int %) 355 (M^+), 340, 323, 310, 278, 262 (100), 250, 220, 73; HRMS *m/z* calcd for $C_{17}H_{29}NO_5Si$ (M^+) 355.1815, found 355.1827; $[\alpha]_D^{23}$=+8.2 (c=0.5, MeOH).

4.1.7. (*E*)-3-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pent-2-enoic acid ethyl ester (21*E*). A round bottom flask was charged with LiCl (66.6 mg, 1.6 mmol) and flamed dried under vacuum. Pd(PPh$_3$)$_4$ (32.6 mg, 0.03 mmol), CuCl (129.6 mg, 1.3 mmol) and DMSO (2.0 mL) were added and the mixture was degassed. Ketone **15** (100 mg, 0.26 mmol) was added, followed by ethyl (*E*)-3-(tri-*n*-butylstannyl)-2-pentenoate[15] **20** (131.4 mg, 0.31 mmol) and the resulting mixture was degassed. The reaction mixture was then heated at 60°C for 17 h. After cooling, the reaction was diluted with Et_2O (30 mL) and washed with a mixture of brine (40 mL) and 5% aqueous NH_4OH (8 mL). The aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient hexanes to hexanes/EtOAc 95:5) to yield **21*E*** (80 mg, 80%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 0.99 (t, J=7.5 Hz, 3H), 1.3 (t, J=7.1 Hz, 3H), 2.98 (q, J=7.5 Hz, 2H), 3.42 (s, 3H), 4.02 (s, 3H), 4.2 (q, J=7.1 Hz, 2H), 4.47 (s, 2H), 4.72 (s, 2H), 5.79 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 12.3, 14.3, 26.6, 53.6, 55.4, 60.0, 62.0, 96.7, 115.5, 119.5, 121.2, 151.2, 159.9, 162.2, 164.8, 165.8; IR (film, NaCl, cm^{-1}) 2; LRMS (70 eV, EI) *m/z* (rel int %) 381 (M^+), 366, 336, 320, 308 (100), 290, 262, 246, 89, 73; HRMS *m/z* calcd for $C_{19}H_{31}NO_5Si$ (M^+) 381.1976, found 381.19667.

4.1.8. 3-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pent-2-en-1-ol (18*E*). To a −78°C mixture of **21*E*** (100 mg, 0.26 mmol) in Et_2O (3 mL) was slowly added LAH (0.26 mL, 0.26 mmol, 1.0 M solution in Et_2O). The resulting mixture was allowed to warm to 0°C and then quenched by addition of a chilled saturated aqueous solution of potassium sodium tartrate. The aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc 75:25) to yield **18*E*** (80 mg, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.91 (t, J=7.5 Hz, 3H), 2.43 (q, J=7.5 Hz, 2H), 3.43 (s, 3H), 4.01 (s, 3H), 4.33 (d, J=6.9 Hz, 2H), 4.53 (s, 2H), 4.69 (s, 2H), 5.61

(t, J=6.9 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 13.0, 25.3, 53.4, 55.3, 58.8, 61.6, 95.9, 115.9, 122.3, 128.7, 142.4, 152.2, 162.3, 164.3; IR (film, NaCl, cm^{-1}) 3388, 2949, 1576, 1450, 1340, 1042, 854; LRMS (70 eV, EI) *m/z* (rel int %) 339 (M^+), 324, 308, 294, 277, 262 (100), 248, 232, 218, 188, 174, 117, 89, 73, 59; HRMS *m/z* calcd for $C_{17}H_{29}NO_2Si$ (M^+) 339.1866, found 339.1861.

4.1.9. (+)-{3-Ethyl-3-[2-methoxy-6-(trimethylsilanyl)-pyridin-4-yl]-oxiranyl}methanol (19-*trans*). To a solution of **18*E*** (937 mg, 2.76 mmol) and activated 4 Å molecular sieves (280 mg) in CH_2Cl_2 (26 mL) at −20°C was added diethyl-L-(+)-tartrate (568 mg, 2.75 mmol), and Ti(O^{i}Pr)$_4$ (629 mg, 2.2 mmol). After stirring for 1 h, ^{t}BuOOH (1.1 mL, 5.0–6.0 M in decane, predried over 4 Å molecular sieves for 1 h) was added with a syringe. The reaction mixture was kept in the freezer at −20°C for 2 h. The solution was removed from the freezer, diluted with Et_2O (5.2 mL) and quenched with a saturated Na_2SO_4 solution (2.6 mL). The resulting heterogeneous mixture was stirred and allowed to warm to room temperature for 2 h. Then it was filtered through a celite pad (washing with hot EtOAc several times). The combined filtrates were concentrated under vacuum. The residue was dissolved in Et_2O (13 mL) at 0°C and a 1N NaOH solution saturated with NaCl was added (8 mL). The two-phase mixture was vigorously stirred at 0°C for 1 h and then transferred to a separatory funnel. The aqueous layer was separated and extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 651 mg (66% yield) of the crude product **19**-*trans* as a clear oil with 92% ee and sufficiently pure for the subsequent reaction. Epoxide **19**-*trans* was analyzed for enantiopurity using a Chiralcel OD-H column with 98.5:1.5 hexanes/^{i}PrOH as the eluent, using the racemate as the standard: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.9 (t, J=7.5 Hz, 3H), 1.79 (m, 1H), 1.97 (m, 1H), 3.23 (t, J=5.8 Hz, 1H), 3.45 (s, 3H), 3.9 (m, 2H), 3.99 (s, 3H), 4.67 (d, J=10.6 Hz, 2H), 4.72 (d, J=10.6 Hz, 2H) 7.09 (s, 1H) (–OH proton resonance not detected); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 9.2, 25.6, 53.4, 55.6, 60.6, 61.2, 63.5, 64.6, 96.4, 115.5, 121.3, 148.4, 161.9, 165.2; IR (film, NaCl, cm^{-1}) 3463, 2945, 1562, 1451, 1345, 1041, 840; LRMS (70 eV, EI) *m/z* (rel int %) 355 (M^+), 340, 324, 310, 294, 280, 262, 250, 89, 73, 57; HRMS *m/z* calcd for $C_{17}H_{29}NO_5Si$ (M^+) 355.1815, found 355.1812, $[\alpha]_D^{23}$=+28 (c=0.25, CH_2Cl_2).

4.1.10. (−)-3-[2-Methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pent-2-en-1-ol (22). LAH (0.3 mL, 0.3 mmol) was slowly added to a 0°C mixture of **19**-*trans* (144 mg, 0.4 mmol) in Et_2O (9 mL). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate. The aqueous layer was extracted three times with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give (144 mg, 99% yield) of the crude product **22** as colorless oil. The crude product was sufficiently pure for the subsequent reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 0.78 (t, J=7.4 Hz, 3H), 1.9 (m, 2H), 2.13 (m, 2H), 3.43 (s, 3H), 3.59 (m, 1H), 3.7 (m, 1H), 4.0 (s, 3H), 4.71 (s, 2H), 4.89 (d, J=10.6 Hz, 1H), 5.09 (d, J=10.6 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 7.6, 36.4, 43.7, 53.6, 55.7, 60.1, 70.0, 80.9, 96.2, 116.7, 121.2, 153.7, 162.6, 164.1; IR (film, NaCl, cm^{-1}) 3383, 2962, 1545, 1342, 1038, 839; LRMS (70 eV, EI) *m/z* (rel int %) 339 (M^+-H_2O), 324, 308, 294, 266, 250, 85, 73 (100), 57; HRMS *m/z* calcd for $C_{17}H_{29}NO_4Si$ (M^+-H_2O) 339.1866, found 339.1876; $[\alpha]_D^{23}$=−1.9 (c=1.05, CH_2Cl_2).

4.1.11. (−)-3-Hydroxy-3-[2-methoxy-3-methoxymethoxymethyl-6-(trimethylsilanyl)pyridin-4-yl]pentanoic acid (24). To a mixture of **22** (0.75 g, 2.1 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (1.4 g, 3.3 mmol). The mixture was stirred at room temperature for 3 h and then poured into a well-stirred mixture of sat. $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (15 mL). The layers were separated after 30 min. The aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude aldehyde **23** (750 mg, 2.1 mmol), which was used immediately after workup.

To a solution of the aldehyde **23** (750 mg, 2.11 mmol) in *tert*-butyl alcohol (40 mL) was added 2-methyl-2-butene (12 mL). To this mixture was added dropwise a solution containing sodium chlorite (1.7 g, 18.8 mmol) and sodium dihydrogen phosphate (2.0 g, 14.5 mmol) in H_2O (20 mL). The resulting mixture was stirred at room temperature for 16 h, concentrated under vacuum, diluted with water and extracted with EtOAc. The aqueous layer was acidified (pH 3.5) with 5% HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to give the crude acid **24** (740 mg, 94%) as a clear oil and sufficiently pure for the subsequent reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.84 (t, J=7.3 Hz, 3H), 1.91 (q, J=7.3 Hz, 2H), 2.89 (d, J=15.8 Hz, 1H), 3.1 (d, J=15.8 Hz, 1H), 3.43 (s, 3H), 3.97 (s, 3H), 4.73 (s, 2H), 4.9 (d, J=10.6 Hz, 1H), 5.0 (d, J=10.6 Hz, 1H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 8.0, 35.6, 45.7, 53.6, 55.6, 61.1, 77.3, 96.3, 116.1, 120.4, 152.5, 162.9, 164.7, 175.2; IR (film, NaCl, cm^{-1}) 3474, 1712, 1345, 1036, 840; LRMS (70 eV, EI) *m/z* (rel int %) 353 (M^+-H_2O), 326, 308 (100), 294, 280, 262, 250, 236, 190, 89, 73, 571; HRMS *m/z* calcd for $C_{17}H_{27}O_5Si$ (M^+-H_2O) 353.1659, found 353.1655; $[\alpha]_D^{23}$=−6.8 (c=0.54, CH_2Cl_2).

4.1.12. (+)-5-Ethyl-5-hydroxy-1-methoxy-3-(trimethylsilanyl)-5,9-dihydro-6*H*-8-oxa-2-aza-benzocyclohepten-7-one (25). To a round bottom flask was added **24** (0.74 g, 1.99 mmol) followed by TFA (50 mL). The mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in Et_2O and neutralized with sat. $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc 75:25) to yield **25** (0.43 g, 70%) with 90% ee as a white foam. Spectroscopic data agreed well with the reported values;[4] $[\alpha]_D^{23}$=+45.1 (c=0.86, CH_2Cl_2). Lactone **25** was analyzed for enantiomeric purity using a Chiralcel OD-H column with 92:8 hexanes/^{i}PrOH as the eluent, using the racemate as the standard.

4.1.13. (+)-5-Ethyl-5-hydroxy-3-iodo-1-methoxy-5,9-dihydro-6*H*-8-oxa-2-aza-benzocyclohepten-7-one (26). A sonicated solution of ICl (160 mg, 0.98 mmol) in CCl_4 (0.7 mL) at 0°C was added to a solution of **25** (77.5 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) at 0°C. The resulting mixture was stirred and allowed to warm to room temperature in the dark for 24 h. The solution was diluted with CH_2Cl_2 and washed with aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 75:25) to yield recovered **25** (44 mg, 56%) and **26** (35 mg, 38%) as a white foam. Spectroscopic data agreed well with the reported values;[4] $[\alpha]_D^{23}=+34.1$ (c=0.6, CH_2Cl_2).

4.1.14. (+)-5-Ethyl-5-hydroxy-3-iodo-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene-1,7-dione ((*R*)-9). Chlorotrimethylsilane (112 μL, 0.88 mmol) and H_2O (5 μL, 0.27 mmol) were added to a solution of **26** (200 mg, 0.55 mmol) and NaI (132 mg, 0.88 mmol) in CH_3CN (1.8 mL). The mixture was heated in the dark at 65°C for 5 h. After cooling, the reaction was diluted with CH_2Cl_2 and washed with a 1:1 mixture of brine and 5% aqueous $Na_2S_2O_3$. The aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) affording (*R*)-**9** (97 mg, 50%) as a white foam. Spectroscopic data agreed well with the reported values;[4] $[\alpha]_D^{23}=+43.7$ (c=0.54, MeOH).

4.1.15. (+)-5-Ethyl-hydroxy-3-iodo-2-prop-2-ynyl-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene-1,7-dione ((*R*)-10b). This was prepared with (*R*)-**9** and propargyl bromide following the procedure for **30** listed below: ^1H NMR (300 MHz, CD_3OD) δ 0.93 (t, J=7.4 Hz, 3H), 1.71–1.86 (m, 2H), 3.09 (d, J=13.8 Hz, 1H), 3.31 (s, 1H), 3.36 (d, J=13.8 Hz, 1H), 5.88 (s, 2H), 5.28 (d, J=15.3 Hz, 1H), 5.41 (d, J=15.3 Hz, 1H), 7.18 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 6.9, 35.4, 41.8, 44.0, 61.9, 72.4, 73.2, 76.9, 100.2, 119.7, 122.1, 155.4, 160.5, 172.8; LRMS (70 eV, EI) m/z (rel int %) 387 (M+), 327, 316, 288, 167, 149, 128 (100), 57; HRMS m/z calcd for $C_{14}H_{14}NO_4I$ (M+) 386.9967, found 386.9961; $[\alpha]_D^{23}=+58.3$ (c=0.18, 3/1 CH_2Cl_2/MeOH).

4.1.16. (+)-5-Ethyl-1,4,5-trihydro-5-hydroxy-7-iodo-8-(*tert*-butyldimethylsilyl-2-propynol)-oxepino[3,4,*c*]pyridine-3,9-dione (30). In a 25 mL round bottom flask, equipped with a stirbar, were successively introduced the iodopyridone (*R*)-**9** (1.05 g, 3 mmol), DME (9 mL) and DMF (3 mL). The reaction flask was put under argon and allowed to cool at 0°C (ice bath) before sodium hydride 60% in mineral oil (150 mg, 3.3 mmol) was added in one portion. After 10 min at 0°C, flame-dried LiBr (521 mg, 6 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 15 min the propargyl bromide **29** (2.1 g, 9 mmol) was added next (weighed in the syringe) and the reaction mixture was immediately warmed to 70°C. The reaction was run in the dark to avoid any possible decomposition of the starting material (flask covered with aluminum foil). After 20 h, the reaction mixture was quenched with brine and ethyl acetate. After separation of the two phases, the aqueous phase was extracted with ethyl acetate. The organic phases were dried over magnesium sulfate. Filtration and evaporation of the solvents gave a thick yellow oil. The crude product was purified by chromatography on silica gel (chloroform/ethyl acetate 75/25) to yield iodopyridone **30** as a yellow solid (905 mg, 60%): Spectroscopic data agreed well with reported values.[4] $[\alpha]_D^{23}=+65$ (c=0.74 CH_2Cl_2) ee=97% (NMR shift experiment with Eu(hfc)$_3$).

4.2. General procedure for synthesis of homocamptothecins by tandem radical cyclization

A solution of the iodopyridone **10b** or **30** (0.03 mmol) in benzene (0.5 mL) was added to an NMR tube under argon. Then, a 1 M solution of the isonitrile in benzene (0.1 mL, 0.1 mmol) and hexamethylditin (15 μL) were added successively. The NMR tube was sealed with a cap and irradiated with 275 W GE sunlamp for 1.5 h. The reaction turned to dark brown. Then, the reaction mixture was applied directly on silica gel column. The column was first washed with dichloromethane to remove less polar impurities. Elution with 5–20% acetone in dichloromethane gave the desired homocamptothecins in 30–60% yield.

4.2.1. (20*R*)-Homocamptothecin (3). Using the general procedure, the title compound (5.7 mg, 61% yield) was prepared as yellow solid: $[\alpha]_D^{23}=+54$ (c=0.1, $CHCl_3$/MeOH 4:1); ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 0.95 (t, J=8.7 Hz, 3H), 1.99 (m, 2H), 3.18 (d, J=13.7 Hz, 1H), 3.39 (d, J=13.7 Hz, 1H), 5.25 (s, 2H), 5.40 (d, J=15.4 Hz, 1H), 5.48 (d, J=15.4 Hz, 1H), 7.63–7.64 (m, 2H), 7.79 (t, J=7.6 Hz, 1H), 7.95 (d, J=7.7 Hz, 1H), 8.13 (d, J=7.7 Hz, 1H), 8.46 (s, 1H); HRMS m/z calcd for $C_{21}H_{18}N_2O_4$ 362.1267, found 362.1268.

4.2.2. (*R*)-12-Fluorohomocamptothecin (27a). Using the general procedure, the title compound was prepared in 49% yield. ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 0.95 (t, J=7.4 Hz, 3H), 1.98 (q, J=7.4 Hz, 2H), 3.18 (d, J=13.7 Hz, 1H), 3.38 (d, J=13.7 Hz, 1H), 5.20 (d, J=19.7 Hz, 1H), 5.30 (d, J=19.7 Hz, 1H), 5.35 (d, J=15.5 Hz, 1H), 5.61 (d, J=15.5 Hz, 1H), 7.42 (m, 1H), 7.54 (m, 1H), 7.66 (s, 1H), 7.69 (d, J=8.3 Hz, 1H), 8.40 (s, 1H); HRMS m/z calcd for $C_{21}H_{17}N_2O_4F$ 380.1172, found 380.1187.

4.2.3. (*R*)-10-Fluorohomocamptothecin (27b). Using the general procedure, the title compound was prepared in 38% yield. ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 0.97 (t, J=7.4 Hz, 3H), 1.98 (m, 2H), 3.22 (d, J=13.7 Hz, 1H), 3.42 (d, J=13.7 Hz, 1H), 5.15 (d, J=19.5 Hz, 1H), 5.31 (d, J=19.5 Hz, 1H), 5.33 (d, J=15.5 Hz, 1H), 5.66 (d, J=15.5 Hz, 1H), 7.45 (m, 2H), 7.49 (s, 1H), 7.92 (m, 1H), 8.28 (s, 1H); HRMS m/z calcd for $C_{21}H_{17}N_2O_4F$ 380.1172, found 380.1165.

4.2.4. Compounds 27c,d. Using the general procedure, the two title compounds were prepared in 32% combined yield and in 1:1 ratio. The two compounds were separated by careful chromatography on a silica gel column.

(R)-9-Fluorohomocamptothecin ***27c***. ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 0.96 (t, J=7.5 Hz, 3H), 2.02 (m, 2H),

3.18 (d, J=13.7 Hz, 1H), 3.41 (d, J=13.7 Hz, 1H), 5.23 (dd, J=19.1, 1.2 Hz, 1H), 5.31 (dd, J=19.1, 1.2 Hz, 1H), 5.36 (d, J=15.4 Hz, 1H), 5.64 (d, J=15.4 Hz, 1H), 7.28 (m, 1H), 7.58 (s, 1H), 7.70 (td, J=8.6, 6.0 Hz, 1H), 7.90 (d, J=8.6 Hz, 1H), 8.63 (d, J=1 Hz, 1H); HRMS *m/z* calcd for $C_{21}H_{17}N_2O_4F$ 380.1172, found 380.1177.

*(R)-11-Fluorohomocamptothecin **27d***. ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 0.96 (t, J=7.4 Hz, 3H), 2.02 (m, 2H), 3.20 (d, J=13.7 Hz, 1H), 3.40 (d, J=13.7 Hz, 1H), 5.19 (d, J=19.0 Hz, 1H), 5.29 (d, J=19.1 Hz, 1H), 5.35 (d, J=15.5 Hz, 1H), 5.63 (d, J=15.4 Hz, 1H), 7.41 (td, J=9.3, 2.5 Hz, 1H), 7.54 (s, 1H), 7.65 (dd, J=9.9, 2.4 Hz, 1H), 7.90 (dd, J=9.1, 5.8 Hz, 1H), 8.38 (s, 1H); HRMS *m/z* calcd for $C_{21}H_{17}N_2O_4F$ 380.1172, found 380.1176.

4.2.5. Compounds 28a,b. Using the general procedure, the two title compounds were prepared in 68% yield as a 1:1 mixture. Separation by flash chromatography on silica gel column (20% acetone in dichloromethane), in the order of elution, gave pure **28a** (3.4 mg, 33% yield) and **28b** (3.6 mg, 35%).

(R)-9,10-Difluorohomocamptothecin (28a). $[\alpha]_D^{23}$=+41.3 (c=1.03, CH_2Cl_2/MeOH 4:1); IR 3355, 2923, 1746, 1646, 1590, 1507, 1253, 1061, 826: ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.95 (m, 1H), 2.06 (m, 1H), 3.32 (d, J=13.6 Hz, 1H), 3.43 (d, J=13.6 Hz, 1H), 5.11 (d, J=19.0 Hz, 1H), 5.32 (d, J=15.6 Hz, 1H), 5.42 (d, J=19.0 Hz, 1H), 5.64 (d, J=15.6 Hz, 1H), 7.44 (s, 1H), 7.49 (m, 1H), 7.60 (m, 1H), 8.46 (s, 1H); The aromatic region (7–9 ppm) in ^{19}F-decoupled ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.49 (d, J=9.0 Hz, 1H), 7.61 (d, J=9.0 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 7.9, 36.1, 42.1, 50.4, 62.0, 73.3, 101.7, 119.8 (d, J=12.5 Hz), 121.0 (d, J=21.1 Hz), 123.2, 124.4, 125.8, 129.4, 143.9 (dd, J=254, 13.8 Hz), 143.9, 144.9, 147.1 (dd, J=250, 12.5 Hz), 152.5, 156.6, 159.8, 172.6; HRMS *m/z* calcd for $C_{21}H_{16}N_2O_4F_2$ 398.1078, found 398.1070.

(R)-10,11-Difluorohomocamptothecin (28b). $[\alpha]_D^{23}$=+44.3 (c=0.58, CH_2Cl_2/MeOH 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J=7.4 Hz, 3H), 2.0 (m, 2H), 3.10 (d, J=13.8 Hz, 1H), 3.30 (d, J=13.8 Hz, 1H), 5.14 (d, J=19.3 Hz, 1H), 5.19 (d, J=19.3 Hz, 1H), 5.31 (d, J=15.4 Hz, 1H), 5.52 (d, J=15.4 Hz, 1H), 7.50 (s, 1H), 7.63 (m, 1H), 7.80 (m, 1H), 8.32 (s, 1H); the aromatic region (7–9 ppm) in ^{19}F-decoupled ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.64 (s, 1H), 7.81 (s, 1H), 8.32 (s, 1H); HRMS *m/z* calcd for $C_{21}H_{16}N_2O_4F_2$ 398.1078, found 398.1083.

4.2.6. (*R*)-10-Acetoxy-12-*tert*-butyldimethylsilylhomocamptothecin (31a). In a 25 mL round bottom flask equipped with a stirbar were successively introduced the TBDMS propargylated iodopyridone **30** (502 mg, 1 mmol), 4-acetoxyphenylisonitrile (805 mg, 5 mmol) and benzotrifluoride (BTF, 8 mL). The reaction flask was sealed with a septum and put under argon, warmed to 80°C, and a solution of AIBN (246 mg, 1.5 mmol) and tributyltin hydride (0.4 mL, 1.5 mmol) in BTF (4 mL) was slowly added over a period of 4 h by the means of a syringe pump.

The solvent was then removed under vacuum and the brown residue was purified by chromatography on silica gel (CH_2Cl_2/acetone 95/5–75/25) to yield **31a** as a brown solid (280 mg, 52%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.74 (s, 3H) 0.97 (t, J=7 Hz, 3H), 1.07 (s, 9H), 1.94–2.08 (m, 2H), 2.42 (s, 3H) 3.29 (d, J=14 Hz, 1H), 3.44 (d, J=14 Hz, 1H), 3.78 (br s, 1H), 5.16 (d, J=18 Hz, 1H), 5.37 (d, J=15 Hz, 1H), 5.48 (d, J=18 Hz, 1H), 5.65 (d, J=15 Hz, 1H), 7.33 (dd, J=9 Hz, 2 Hz, 1H), 7.36 (s, 1H), 7.70 (d, J=9 Hz, 1H), 7.97 (d, J=2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, −0.5, 8.4, 19.3, 21.5, 27.2, 35.8, 42.8, 52.9, 62.2, 73.9, 100.5, 120.0, 122.8, 124.7, 131.1, 133.1, 133.1, 136.5, 143.0, 145.0, 145.4, 148.9, 149.9, 156.3, 159.9, 169.0, 171.5; HRMS (EI) *m/z* calcd for $C_{29}H_{34}N_2O_6Si$ (M+) 534.2186, found 534.2187; LRMS (EI) *m/z* 534 (M+), 516, 488, 477, 459, 435, 417, 393, 375, 335, 320, 291, 275, 234, 164, 137, 125, 111, 97, 83, 69 57; $[\alpha]_D^{23}$=+98 (c=0.5, CH_2Cl_2).

4.2.7. (*R*)-10-Hydroxy-12-*tert*-butyldimethylsilylhomocamptothecin (31b, DB-91). To a solution of **31a** (272 mg, 0.5 mmol) in methanol (10 mL) and distilled water (10 mL) was added K_2CO_3 (700 mg, 5 mmol). The solution became dark and stirring was maintained for 3 h. The solvents were removed under vacuum. The final removal of water was effected by adding toluene and evaporating under vacuum twice. The solid brown residue was taken up in CH_2CL_2 (10 mL) and trifluoroacetic acid (5 mL, 65 mmol) was carefully added dropwise with stirring. After stirring at room temperature for 4 h, the solvent and excess trifluoroacetic acid were removed under vacuum and the resulting brown residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 80/20) to yield **31b** as a brown solid (203 mg, 82%): ^1H NMR (300 MHz, $CD_3OD/CDCl_3$ 1:1) δ 0.65 (s, 6H), 0.90–0.99 (m, 12H), 1.89–2.06 (m, 2H), 3.14 (d, J=14 Hz, 1H), 3.33 (d, J=14 Hz, 1H), 5.25 (s, 2H), 5.37 (d, J=15 Hz, 1H), 5.56 (d, J=15 Hz, 1H), 7.42 (dd, J=9 Hz, 2 Hz, 1H), 7.58 (d, J=2 Hz, 1H), 7.70 (s, 1H), 8.15 (d, J=9 Hz 1H); ^{13}C NMR (75 MHz, $CD_3OD/CDCl_3$ 1:1) δ −1.0, 8.1, 19.3, 26.9, 36.2, 42.2, 52.9, 62.1, 73.5, 101.9, 111.5, 122.7, 123.6, 127.5, 129.0, 135.0, 136.5, 139.8, 143.0, 145.4, 156.7, 157.0, 159.7, 172.7; LRMS (EI) *m/z* 588, 548, 491 (M−1), 474, 448, 434, 391, 377, 363, 333, 320, 306, 291, 277, 264, 249, 235, 221, 205, 227, 91, 73, 57; $[\alpha]_D^{23}$=+48 (c=0.47 $CHCl_3$/MeOH 1:1).

4.2.8. (*R*)-7-*tert*-Butyldimethylsilyl homocamptothecin (31c). To a solution of **30** (7.0 mg, 0.014 mmol) in benzene (0.5 mL) was added phenyl isonitrile[3a] (4.3 mg, 0.042 mmol, 1 M in benzene) and hexamethylditin (9.1 mg, 5.7 μL, 0.15 mmol). The mixture was irradiated with a 275 W GE sunlamp for 1 h. The solvent was evaporated and the residue purified by flash chromatography (gradient CH_2Cl_2 to CH_2Cl_2/acetone 85:15) to yield **31a** (2.8 mg, 42%) as a pale yellow solid. Spectroscopic data agreed well with the reported values;[4] $[\alpha]_D^{23}$=+53 (c=0.1, $CDCl_3$).

4.2.9. (*R*)-12-*tert*-Butyldimethylsilyl-10-(*tert*-butyloxycarbonylamino)homocamptothecin (31d). To a solution of **30** (15.0 mg, 0.03 mmol) in benzene (0.5 mL) was added 4-*tert*-butyloxycarbonylaminophenyl isonitrile[3a] (19.5 mg, 0.09 mmol) and hexamethylditin (19.5 mg, 12.4 μL, 0.06 mmol). The mixture was irradiated with a 275 W GE sunlamp for 1 h. The solvent was evaporated and the residue purified by flash chromatography (gradient CH_2Cl_2 to CH_2Cl_2/acetone 85:15) to yield **31c** (10.4 mg, 59%) as a pale brown solid. Spectroscopic data agreed well with the reported values;[4] $[\alpha]_D{}^{23}=+123$ (c=0.2, CH_2Cl_2).

4.2.10. (+)-10-Amino-12-*tert*-butyldimethylsilylhomocamptothecin (31e). To a solution of **31d** (7.5 mg, 0.013 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.3 mL). The mixture was stirred at room temperature for 6 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (gradient CH_2Cl_2 to CH_2Cl_2/acetone 4:1) to yield **31e** (3.8 mg, 61%) as a yellow solid. Spectroscopic data agreed well with the reported values;[11] $[\alpha]_D{}^{23}=+36.2$ (c=0.23, CD_3OD).

4.2.11. 4-Iodo-2-methoxypyridine-3-carboxaldehyde (32). Methyllithium in diethyl ether (1.4 M, 23.5 mL, 33 mmol) was added to a solution of 2-methoxypyridine (1.93 mL, 18.3 mmol) in THF (120 mL) at −40°C. To this mixture was added diisopropylamine (0.13 mL, 0.9 mmol) upon which the mixture turned yellowish orange. After warming to 0°C and stirring for 3 h, the mixture was cooled to −78°C and N,N,N'-trimethyl-N'-formylethylenediamine (2.62 g, 20 mmol) was added slowly. The mixture was allowed to warm to −40°C. *n*BuLi in hexanes (1.6 M, 22.9 mL, 36.6 mmol) was injected and the mixture was stirred for 3 h at −30°C. A solution of I_2 (11.2 g, 44 mmol) in THF (70 mL) was then added dropwise through a dropping funnel at −78°C with vigorous stirring. After 30 min, the resulting mixture was allowed to warm slowly to 0°C (1 h), poured into 5% Na_2SO_3 (250 mL) and extracted with Et_2O (3×150 mL) and the residue obtained after removal of the solvents was subjected to flash chromatography (hexanes/ethyl acetate 95:5) to provide **32** as a yellow oil (1.9 g, 40%); ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3H), 7.54 (d, J=5.3 Hz, 1H), 7.86 (d, J=5.3 Hz, 1H), 10.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.6, 108.8, 119.4, 130.5, 151.0, 164.4, 190.4; IR (CH_2Cl_2, NaCl, cm^{-1}) 1703, 1551, 1462, 1368, 1298, 1265, 1017, 847, 736; LRMS (70 eV, EI) m/z (rel int %) 263 (M^+, 100), 234 (80), 205 (30), 127 (30), 93 (28), 78 (72); HRMS m/z calcd for $C_7H_6INO_2$ (M^+) 262.9443, found 262.9431.

4.2.12. (4-Iodo-2-methoxy-pyridin-3-yl)methanol (33). Following the procedure in **14**, the reaction was carried out with **32** (1.88 g, 7.1 mmol) and $NaBH_4$ (0.135 g, 3.56 mmol) in EtOH (40 mL) to afford **33** as a pale yellow oil (1.83 g, 97%). The crude product was sufficiently pure for the subsequent reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (t, J=7 Hz, 1H), 3.99 (s, 3H), 4.82 (d, J=7 Hz, 2H), 7.35 (d, J=5.4 Hz, 1H), 7.7 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3, 64.9 112.1, 126.5, 128.2, 146.6, 161.7; IR (CH_2Cl_2, NaCl, cm^{-1}) 3391, 2946, 1561, 1459, 1380, 1019, 805; LRMS (70 eV, EI) m/z (rel int %) 265 (M^+, 53), 250 (84), 138 (30), 84 (100), 78 (30); HRMS m/z calcd for $C_7H_8NO_2I$ (M^+) 264.9600, found 264.9598.

4.2.13. 4-Iodo-2-methoxy-3-methoxymethoxymethylpyridine (34). Following the procedure in **15**, the reaction was carried out with **33** (1.77 g, 6.68 mmol), MOMCl (1.52 mL, 20 mmol) and ^{i}Pr$_2$EtN (3.49 mL, 20 mmol) in dry CH_2Cl_2 (40 mL) to afford **34** as an orange-yellow oil (2.06 g, 100%). The crude product was sufficiently pure for the subsequent reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.96 (s, 3H), 4.72 (s, 2H), 4.75 (s, 2H), 7.35 (d, J=5.4 Hz, 1H), 7.71 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.4, 55.8, 67.89, 96.7, 114.2, 124.0, 128.1, 147.1, 162.4; IR (CH_2Cl_2, NaCl, cm^{-1}) 2949, 1561, 1459, 1380, 1265, 1039, 741; LRMS (70 eV, EI) m/z (rel int %) 309 (M^+, 19), 277 (20), 264 (45), 248 (100), 218 (68), 152 (39), 92 (50), 79 (35); HRMS m/z calcd for $C_9H_{12}NO_3I$ (M^+) 308.9862, found 308.9860.

4.2.14. 3-(2-Methoxy-3-methoxymethoxymethylpyridin-4-yl)pent-2-enoic acid ethyl ester (35). Following the procedure in **21*E***, the reaction was carried out with **34** (1.0 g, 3.23 mmol), LiCl (0.82 g, 19.4 mmol), predried under vacuum at 120°C for a period of 24 h CuCl (1.60 g, 16.2 mmol), $Pd(PPh_3)_4$ (0.19 g, 0.16 mmol) and ethyl (E)-3-(tributylstannyl)-2-pentenoate (1.62 g, 3.88 mmol) in dry DMSO (35 mL). The crude product was subjected to flash chromatography (hexanes/ethyl acetate 95:5) to afford **35** as a yellow oil (0.82 g, 82%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J=7.6 Hz, 3H), 1.30 (t, J=7.1 Hz, 3H), 2.99 (q, J=7.6 Hz, 2H), 3.43 (s, 3H), 4.01 (s, 3H), 4.21 (q, J=7 Hz, 2H), 4.49 (s, 2H), 4.73 (s, 2H), 5.81 (s, 1H), 6.69 (d, J=5 Hz, 1H), 8.11 (d, J=5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 14.4, 26.6, 54.1, 55.6, 60.3, 62.1, 97.0, 116.3, 116.9, 120.0, 146.4, 153.3, 159.4, 163.4, 165.9; IR (CH_2Cl_2, NaCl, cm^{-1}) 2982, 1713, 1640, 1593, 1560, 1453, 1392, 1266, 1186, 1040, 743; LRMS (70 eV, EI) m/z (rel int %) 309 (M^+, 32), 277 (42), 236 (100), 190 (84), 174 (73), 160 (22), 77 (10); HRMS (EI) m/z calcd for $C_{16}H_{23}NO_5$ (M^+) 309.1576, found 309.1587.

4.2.15. 3-(2-Methoxy-3-methoxymethoxymethylpyridin-4-yl)pent-2-en-1-ol (36). Following the procedure in **18*E***, the reaction was carried out with **35** (1.2 g, 3.88 mmol) and a 1 M solution of LAH in diethyl ether (9.7 mL, 9.7 mmol) to afford **36** as a very pale yellow oil (0.84 g, 81%). The crude product was sufficiently pure for the subsequent reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.6 Hz, 3H), 2.44 (q, J=7.6 Hz, 2H), 3.44 (s, 3H), 4.00 (s, 3H), 4.33 (dd, J=5.6, 6.7 Hz, 2H), 4.55 (s, 2H), 4.70 (s, 2H), 5.63 (t, J=6.8 Hz, 1H), 6.68 (d, J=5.2 Hz, 1H), 8.07 (d, J=5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 15.5, 25.4, 54.0, 55.6, 59.0, 61.8, 96.3, 117.3, 129.4, 142.1, 146.1, 154.6, 163.6; IR (CH_2Cl_2, NaCl, cm^{-1}) 3383, 2945, 1594, 1555, 1452, 1391, 1320, 1268, 1148, 1038, 739, 541; LRMS (70 eV, EI) m/z (rel int %) 268 (M^++H, 38), 249 (31), 236 (62), 190 (48), 176 (100), 160 (35), 91 (16), 77 (15); HRMS m/z calcd for $C_{13}H_{18}NO_3$ (M^+-CH_3O) 236.1287, found 236.1292.

4.2.16. (+)-[3-Ethyl-3-(2-methoxy-3-methoxymethoxymethylpyridin-4-yl)oxiranyl]methanol (37). Following the procedure in **19-*trans***, the reaction was carried out with **36** (161 mg, 0.6 mmol), Ti(O^{i}Pr)$_4$ (0.14 mL, 0.48 mmol), diethyl-L-(+)-tartrate (0.1 mL, 0.6 mmol), ^{t}BuOOH (0.19 mL, 5.0–6.0 M in decane) and 4 Å molecular sieves (48 mg) in dry CH_2Cl_2 for 24 h to afford **37** as a yellow oil (144 mg, 84%) with 96% ee. The crude product was sufficiently pure for the subsequent reaction. Epoxide **37** was analyzed for enantiomeric purity using a Chiralcel OD-H column with 98:2 hexanes/^{i}PrOH as the eluent with the racemate as the standard. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.6 Hz, 3H), 1.81 (dq, J=7.4 Hz, 14.8 Hz, 1H), 2.01 (dq, J=7.6 Hz, 15.0 Hz, 1H), 3.24 (t, J=5.8 Hz, 1H), 3.46 (s, 3H), 3.90 (m, 2H), 3.99 (s, 3H), 4.71 (s, 2H), 4.73 (s, 2H), 6.93 (d, J=5.2 Hz, 1H), 8.12 (d, J=5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 25.7, 54.1, 55.8, 60.8, 61.3, 63.7, 64.7, 96.7, 116.5, 116.8, 146.6, 151.0, 163.1; IR (CH_2Cl_2, NaCl, cm^{-1}) 3408, 2980, 1765, 1607, 1457, 1410, 1393, 1266, 1040, 742, 546; LRMS (70 eV, EI) *m/z* (rel int %) 284 (M$^+$+H, 58), 190 (100), 178 (73), 162 (27), 148 (27), 77 (13); HRMS *m/z* calcd for $C_{14}H_{22}NO_5$ (M$^+$+H) 284.1498, found 284.1507; $[\alpha]_D^{23}$=+65.6 (c=0.25, CH_2Cl_2).

4.2.17. (+)-3-(2-Methoxy-3-methoxymethoxymethylpyridin-4-yl)pentane-1,3-diol (38). Following the procedure in **22**, the reaction was carried out with **37** (0.71 g, 2.5 mmol) and LAH in dry ether (50 mL) for 24 h to afford **38** as colorless oil (0.54 g, 76%). The crude product was sufficiently pure for the subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J=7.3 Hz, 3H), 1.91 (q, J=7.3 Hz, 2H), 2.15 (m, 2H), 3.42 (s, 3H), 3.60 (m, 1H), 3.74 (m, 1H), 3.98 (s, 3H), 4.71 (s, 2H), 4.89 (d, J=10.7 Hz, 1H), 5.10 (d, J=10.7 Hz, 1H), 6.77 (d, J=5.5 Hz, 1H), 8.05 (d, J=5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 36.7, 43.8, 54.1, 55.9, 60.2, 61.1, 80.9, 96.5, 116.3, 117.9, 146.2, 156.5, 163.8; IR (CH_2Cl_2, NaCl, cm^{-1}) 3391, 3056, 2984, 1593, 1446, 1382, 1265, 1037, 743, 546; LRMS (70 eV, EI) *m/z* (rel int %) 286 (M$^+$+H, 39), 235 (23), 222 (86), 205 (52), 194 (74), 178 (100), 150 (49), 92 (30), 77 (15); HRMS *m/z* calcd for $C_{14}H_{24}NO_5$ (M$^+$+H) 286.1654, found 286.1658; $[\alpha]_D^{23}$=+0.185 (c=1.08, CH_2Cl_2).

4.2.18. (−)-3-Hydroxy-3-(2-Methoxy-3-methoxymethoxymethylpyridin-4-yl)pentanal (39). To a mixture of **38** (0.5 g, 1.78 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (1.2 g, 2.85 mmol). The mixture was stirred at room temperature for 3 h and then poured into a well-stirred mixture of sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (10 mL). The layers were separated after 30 min. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude aldehyde **39** (0.47 g, 89%) as pale yellow oil. The crude product was sufficiently pure for the subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7.4 Hz, 3H), 1.91 (m, 2H), 2.85 (dd, J=2.1, 16.4 Hz, 1H), 3.10 (dd, J=2.2, 16.3 Hz, 1H), 3.41 (s, 3H), 3.96 (s, 3H), 4.74 (s, 2H), 4.98 (q, J=10.9 Hz, 2H), 6.74 (d, J=5.5 Hz, 1H), 8.06 (d, J=5.5 Hz, 1H), 9.73 (t, J=2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 36.4, 54.2, 55.3, 56.0, 60.9, 77.90, 96.5, 115.8, 117.4, 146.6, 155.6, 163.9, 202.2; IR (CH_2Cl_2, NaCl, cm^{-1}) 3380, 3057, 2982, 1763, 1655, 1596, 1422, 1264, 895, 735, 547; LRMS (70 eV, EI) *m/z* (rel int %) 284 (M$^+$+H, 15), 265 (25), 192 (20), 178 (72), 148 (24), 84 (100), 57 (26); HRMS *m/z* calcd for $C_{14}H_{22}NO_5$ (M$^+$+H) 284.1498, found 284.1498; $[\alpha]_D^{23}$=−11.5 (c=0.125, CH_2Cl_2).

4.2.19. (+)-5-Ethyl-5-hydroxy-1-methoxy-5,6-dihydro-9*H*-8-oxa-2-aza-benzocyclohepten-7-one (40). To a solution of the aldehyde **39** (0.13 g, 0.46 mmol) in *tert*-butyl alcohol (7.1 mL) was added 2-methyl-2-butene (2.13 mL). To this mixture was added dropwise a solution of sodium chlorite (0.37 g, 4.13 mmol) and sodium dihydrogen phosphate (0.44 g, 3.2 mmol) in H_2O (3.8 mL). The resulting mixture was stirred at room temperature for 36 h. The crude mixture was extracted with ethyl acetate. The aqueous layer was then acidified (pH≈3.5) with dropwise addition of 5% HCl and subsequently extracted with ethyl acetate (in cases where a yellow coloration was observed, the mixture was washed with 5% sodium sulfite solution). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under vacuum to give the crude product **40** (0.12 g, 84%) as a light green oil which was used immediately after the workup.

4.2.20. (+)-5-Ethyl-5-hydroxy-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene-1,7-dione ((*R*)-7)). To a round-bottom flask was added **40** (0.11 g, 0.38 mmol) followed by TFA (8 mL). The mixture was stirred for 24 h at room temperature. The mixture was then neutralized with sat. $NaHCO_3$ (pH≈8) and extracted with diethyl ether (3×6 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude lactone as a yellowish brown oil (72 mg, 80%) and sufficiently pure for the subsequent reaction. ^{1}H NMR (300 MHz, CD_3OD) δ 0.84 (t, J=7.4 Hz, 3H), 1.85 (q, J=7.4 Hz, 2H), 3.01 (d, J=13.9 Hz, 1H), 3.41 (d, J=13.9 Hz, 1H), 3.94 (s, 3H), 5.29 (d, J=15.2 Hz, 1H), 5.44 (d, J=15.2 Hz, 1H), 7.15 (d, J=5.5 Hz, 1H), 8.13 (d, J=5.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 9.01, 38.48, 43.81, 54.97, 61.36, 62.66, 74.68, 117.12, 147.84, 155.98, 161.91, 173.06; IR (MeOH, NaCl, cm^{-1}) 3390, 2958, 1725, 1683, 1596, 1377, 1204, 1140, 1041; LRMS (70 eV, EI) *m/z* (rel int %) 237 (M$^+$, 75), 208 (22), 166 (100), 136 (25), 106 (7), 77 (7); HRMS *m/z* calcd for $C_{12}H_{15}NO_4$ (M$^+$) 237.1001, found 237.0996; $[\alpha]_D^{23}$=+3.0 (c=0.1, MeOH).

To a dry round-bottom flask was added the crude lactone (70 mg, 0.3 mmol) followed by dry acetonitrile (1 mL). Sodium iodide (0.07 g, 0.49 mmol) was added followed by chlorotrimethylsilane (0.06 mL, 0.49 mmol). The resulting mixture was stirred at room temperature for 15 min at which point H_2O was added (2.7 μL, 0.15 mmol) and the reaction mixture was heated to 60°C for 7 h. The mixture was then poured into a 1:1 solution of 5% sodium sulfite/brine (7 mL) and then quickly extracted with ethyl acetate (4×5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was subjected to flash chromatography ($MeOH/CH_2Cl_2$ 5:95) to afford pure **33** as pale yellow oil (10.4 mg, 16%). ^{1}H NMR (300 MHz, CD_3OD) δ 0.91 (t, J=7.5 Hz, 3H), 1.82 (m, 2H), 3.10 (d, J=13.8 Hz, 1H), 3.40 (d, J=13.8 Hz, 1H), 5.30 (d, J=15.2 Hz, 1H), 5.46 (d, J=15.2 Hz, 1H), 6.57 (d, J=7 Hz, 1H), 7.35 (d, J=7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$) δ 6.76, 35.22, 41.46, 60.98, 72.43, 105.93, 122.42, 132.76, 156.35, 161.60, 172.57; IR (MeOH, NaCl, cm^{-1}) 3370 (br), 1655, 1049, 1025, 823, 768; LRMS (70 eV, EI) *m/z* (rel int %) 224 (M$^+$+H, 32), 195 (21), 163 (43), 153 (100), 91 (40), 77 (19), 55 (24); HRMS *m/z* calcd for $C_{11}H_{13}NO_4$ (M$^+$) 223.0845, found 223.0851; $[\alpha]_D^{23}$=+35.0 (c=0.08, MeOH).

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