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Practical Formal Total Syntheses of the Homocamptothecin Derivative and Anticancer Agent Diflomotecan via Asymmetric Acetate Aldol Additions to Pyridine Ketone Substrates

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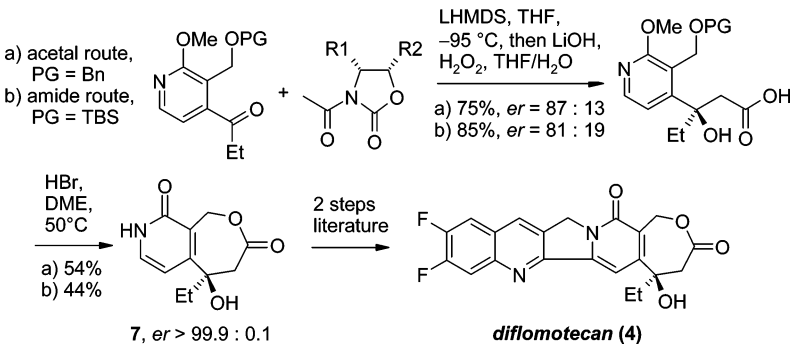

Two practical, efficient, and scalable asymmetric routes to DE ring fragment **7**, a key building block in the synthesis of the homocamptothecin derivative diflomotecan **4**, are described. The "acetal route" starts from 2-chloro-4-cyanopyridine **8** and represents an enantioselective and optimized modification of the original racemic discovery chemistry synthesis. The inefficient optical resolution procedure was replaced by an efficient asymmetric acetate aldol addition (dr 87:13) to a ketone substrate as the key step generating the (*R*)-configured quaternary stereocenter with high stereoselectivity. **7** was finally obtained in 8.9% overall yield (er 99.95:0.05) over nine steps, avoiding chromatographic purifications and comparing favorably with the initial procedure. In the related "amide route" starting from 2-chloroisonicotinic acid **41**, a secondary amide directing group was used to facilitate the ortho lithiation of the pyridine 3-position. The key step of this protocol again consists of a practical asymmetric acetate aldol addition (dr = 87:13). The DE ring building block **7** was thus obtained in 11.1% overall yield (er > 99.95:0.05) over nine steps requiring only one chromatographic purification.

Introduction

The alkaloid camptothecin (CPT, **1**), which was first isolated in 1958 by Wani and Wall[1] from the Chinese tree *Camptotheca accuminata*, shows potent antiproliferative activity and continues to serve as a very attractive and challenging lead structure for the development of new anticancer drugs.[2] The structure of the pentacyclic system, which was determined in 1966,[3] contains a highly electrophilic α-hydroxy-δ-lactone ring (ring E), which rapidly hydrolyzes in basic and neutral media yielding the open-chain carboxylate form **2** (Scheme 1), which is biologically almost inactive.

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(1) Wall, M. E. In *Chronicles of Drug Discovery*; Lednicer D., Ed.; American Chemical Society: Washington D. C., 1993; Vol. 3, p 327.

(2) Selected CPT review articles: (a) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585. (b) Du, W. *Tetrahedron* **2003**, *59*, 8649. (c) Kawato, Y.; Terasawa, H. *Prog. Med. Chem.* **1997**, *34*, 69. (d) Jew, S.-s.; Kim, M. G.; Kim, H.-J.; Roh, E.-Y.; Park, H.-g. *Korean J. Med. Chem.* **1996**, *6*, 263. (e) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047. (f) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385.

(3) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

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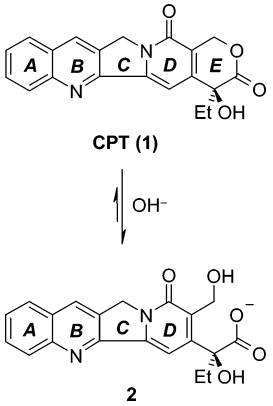
SCHEME 1. Hydrolysis of CPT Leading to Biologically Almost Inactive 2



This equilibrium is shifted toward the carboxylate form **2** in human plasma thus explaining the lower efficacy of most CPT analogues in clinical trials compared to the stunning results obtained with Xenograft models.[4] The development of homocamptothecins (hCPT, Figure 1), which are CPT analogues entailing a seven-membered β-hydroxy-ϵ-lactone ring, addressed this issue: although it was previously generally accepted that an α-hydroxylactone is an indispensable structural feature for anticancer activity of CPT derivatives, Lavergne, Bigg, et al.[5] investigated a modification of the CPT lactone ring, which retains the TOPO I mediated activity and at the same time displays enhanced stability against hydrolysis. hCPT 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**), possessing two fluorine atoms attached to ring A.

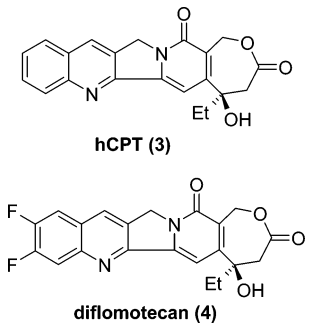
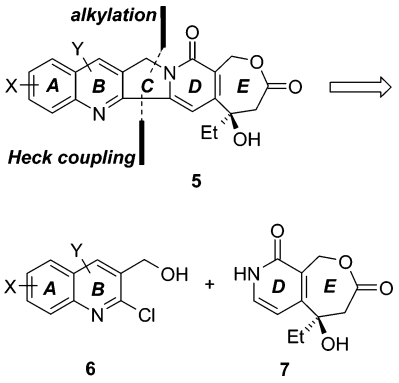


FIGURE 1. hCPT derivative diflomotecan (**4**).

The convergent discovery chemistry synthesis was based on the coupling strategy of DE fragment **7** with AB quinoline derivatives **6** via a Mitsunobu alkylation followed by a Heck cyclization thus forming ring C of the pentacycle (Scheme 2).[5]

SCHEME 2. Coupling Strategy of DE Fragment 7 with AB Quinoline Derivatives 6



This strategy was previously developed by Comins et al. for the total synthesis of (*S*)-CPT (**1**).[6] Because of its convergent character and the robustness of two finishing steps, we decided to maintain this concept for the production of kilogram amounts of **4** for clinical trials.

The discovery chemistry synthesis of the DE ring system **7** is shown in Scheme 3.[5] As a key step, the quaternary stereocenter was generated in racemic form by a Reformatsky addition to ketone **15** as an acceptor component. The subsequent optical resolution of **(*rac*)-17** by crystallization using quinidine as a resolving reagent was not efficient on a large scale because the undesired enantiomer crystallized. The desired enantiomer was isolated from the mother liquid with the consequence of a relatively low enantiomeric ratio (er) of 85:15 and a purity of only 70% as determined by quantitative HPLC. Key intermediate **7** was thus obtained from **8** over 13 linear steps in 1.3% overall yield and requiring four chromatographic purifications.[7,8]

Search for a Scalable Synthesis of DE Ring Fragment 7. (a) Acetal Approach. Herein, we present a practical, efficient, and scalable enantioselective modification of the discovery chemistry synthesis. To circumvent the inefficient optical resolution of β-hydroxycarboxylic acid **(*rac*)-17**, a stoichiometric asymmetric aldol addition protocol was developed. To this end, the steps leading to ketone **15** were modified to obtain **15** in the high purity required for an efficient and selective asymmetric aldol addition reaction. Furthermore, this task should be realized avoiding any chromatographic purification.

Our approach started by methanolysis of 2-chloro-4-cyanopyridine (**8**) with 1.2 equiv of NaOMe in acetonitrile (Scheme 4) providing 2-methoxy pyridine **20**, which was purified by Soxhlet extraction.[9] Grignard addition to the cyano group generated ethyl ketone **21**, which was then protected by 1,3-dioxane formation furnishing **11** isolated in 40% yield over three steps after high vacuum distillation. The subsequent metalation of the pyridine 3-position is ortho directed by the methoxy and the acetal moiety in **11**.[10] The intermediate carbanion, which was generated by using mesityllithium, was trapped by addition

(4) Cao, Z.; Harris, N.; Kozielski, A.; Vardemann, D.; Stehlin, J. S.; Giovanella, B. *J. Med. Chem.* **1998**, *41*, 31.

(5) (a) Lavergne, O.; Demarquay, D.; Bailly, C.; Lanco, C.; Rolland, A.; Huchet, M.; Coulomb, H.; Muller, N.; Baroggi, N.; Camara, J.; Le Breton, C.; Manginot, E.; Cazaux, J.-B.; Bigg, D. C. H. *J. Med. Chem.* **2000**, *43*, 2285. (b) Lavergne, O.; Harnett, J.; Rolland, A.; Lanco, C.; Lesueur-Ginot, L.; Demarquay, D.; Huchet, M.; Coulomb, H.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2599. (c) Lavergne, O.; Lesueur-Ginot, L.; Pla Rodas, F.; Kasprzyk, P. G.; Pommier, J.; Demarquay, D.; Prévost, G.; Ulibarri, G.; Rolland, A.; Schiano-Liberatore, A.-M.; Harnett, J.; Pons, D.; Camara, J.; Bigg, D. C. H. *J. Med. Chem.* **1998**, *41*, 5410. (d) Lavergne, O.; Lesueur-Ginot, L.; Pla Rodas, F.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2235.

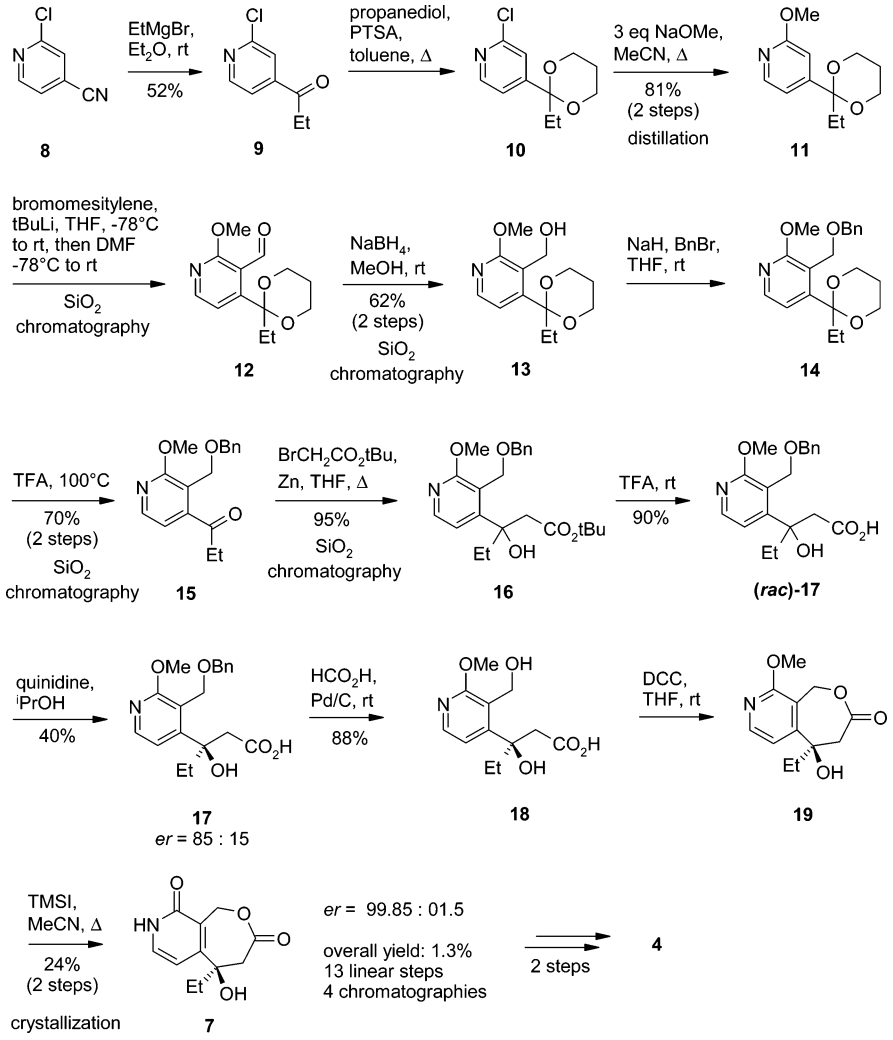
(6) (a) Comins, D. L.; Hong, H.; Saha, J. K.; Jinhua, G. *J. Org. Chem.* **1994**, *59*, 5120. (b) Comins, D. L.; Hong, H.; Jinhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331. (c) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

(7) Application of this chemistry to produce kilogram amounts of **4** resulted in decreased yields: **7** was typically obtained in 0.5% yield starting from **8**.

(8) For an alternative reported total synthesis of hCPT in 1.4% overall yield (longest linear sequence of 15 steps), see: Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329.

(9) All purification attempts of **20** by crystallization or trituration failed.

SCHEME 3. Beaufour−Ipsen Discovery Chemistry Route to DE Ring Fragment 7



of DMF giving rise to aldehyde **12**. All attempts to replace mesityllithium (MesLi) with other bases, which would be commercially available and easier to handle, failed. Whereas alkyllithiums, such as *n*-, *s*-, or *tert*-butyllithium, as well as aryllithiums such as phenyllithium smoothly undergo addition to the pyridine 6-position of **11**, lithium (LHMDS, LDA, LTMP) and potassium amide bases (KHMDS) did not deprotonate the aromatic heterocycle. This forced us to significantly improve the practicality of the mesityllithium preparation procedure. *tert*-BuLi was successfully replaced by *n*-BuLi for halogen−lithium exchange with mesitylbromide, and in this context, we found that it is essential to use a 2.5 M *n*-BuLi solution in hexane (instead of the more common 1.6 M *n*-BuLi in hexane) to reduce the amount of hexane thereby increasing the solubility of MesLi. Aldehyde **12** was purified by silica gel filtration to remove mesityl side products and unreacted starting material as well as several side products. The most prominent side product was identified by LC-MS and NMR as the mesityl addition product to the pyridine 6-position.

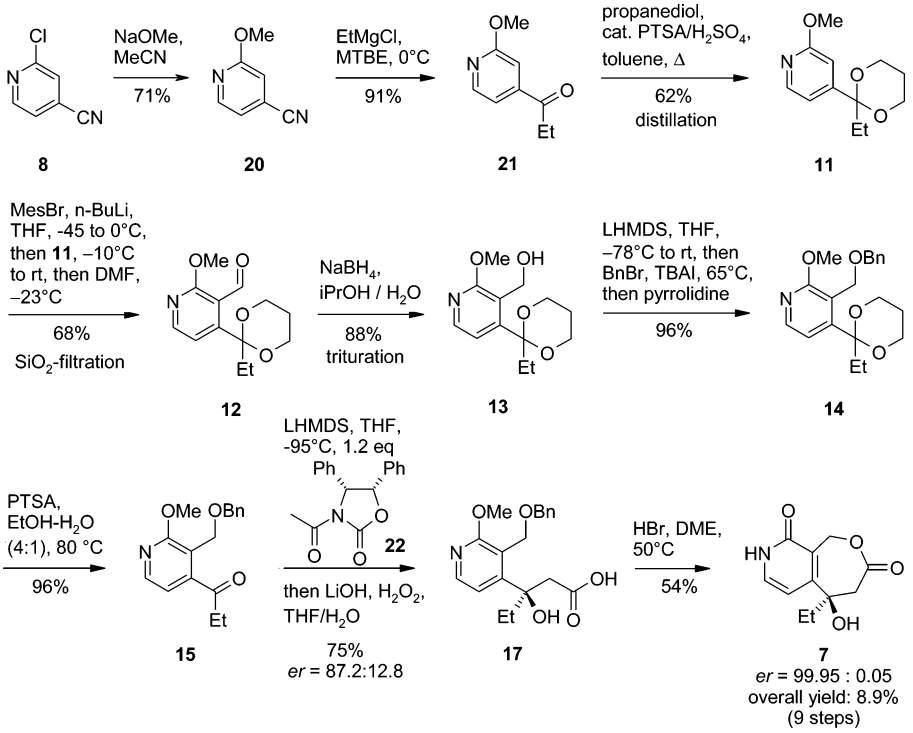
Reduction of the aldehyde group in **12** with $NaBH_4$ provided **13** in high yield and purity after trituration with heptane. In the subsequent benzylation step, it was desirable to replace NaH by an alternative base. In addition to the safety issue related to NaH, we encountered formation of considerable amounts of high-boiling dibenzyl ether as a side product depending on the NaH quality. Furthermore, even under activation by addition of catalytic amounts of tetrabutylammonium iodide, conversion was incomplete. Interestingly, even only marginally nucleophilic bases such as potassium or sodium *tert*-butoxide led to not yet fully rationalized degradation reactions of primary alcohol **13** to form aldehyde **12** and acetal **11** in equal amounts (Scheme 5). In the absence of oxygen, 50% of starting material **13** was already decomposed after 2 h at room temperature (9% decomposition after 5 min, 35% decomposition after 1 h).

Using lithium *tert*-butoxide, the degradation was negligible, but benzylation was extremely slow. However, the nonnucleophilic base LHMDS was successfully employed for clean preformation of the corresponding lithium alkoxide. By addition of 10 mol % of dry tetrabutylammonium iodide (dried to constant weight in high vacuum prior to use to avoid formation of dibenzyl ether as the side product), the alkylation proceeded without decomposition at 65 °C furnishing benzyl ether **14** in high purity. To remove excess benzyl bromide, pyrrolidine was added after almost complete conversion and the resulting tertiary benzylamine was removed by extraction with aqueous HCl.

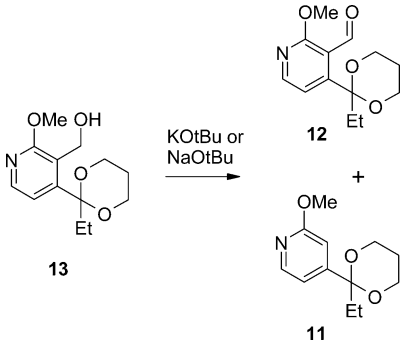
The acetal cleavage of **14** in TFA/water (1:1 or 2:1) was completed within 24 h at room temperature. However, product **15**

(10) Review about the directed metalation of π-deficient azaaromatics: Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

SCHEME 4. Practical Asymmetric Synthesis of DE Ring Fragment 7 (Acetal Route)



SCHEME 5. Unexpected Decomposition of Benzylic Alcohol 13 with *tert*-Butoxide Bases



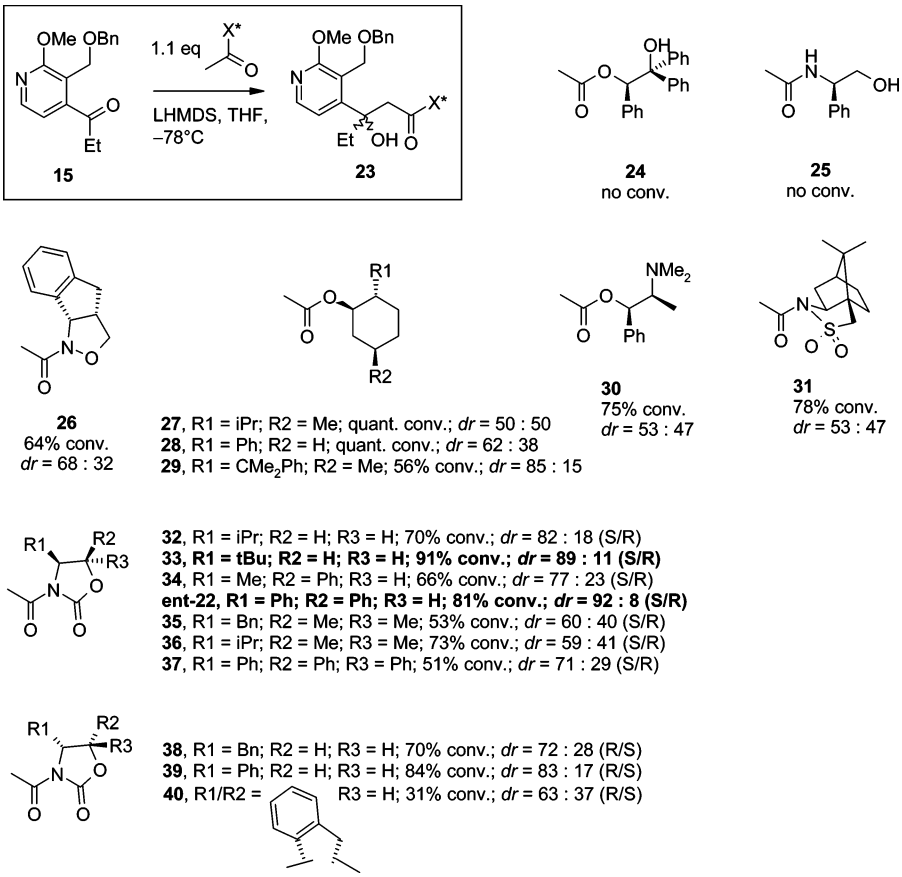
was not pure enough to achieve high conversion in the subsequent asymmetric aldol addition reaction. A highly pure product **15** was however directly obtained by utilizing a catalytic amount of *para*-toluenesulfonic acid (0.2 equiv) in EtOH/water (4:1) for the acetal cleavage.

The key step of this synthesis is the asymmetric acetate aldol addition reaction **15** → **17**. Eighteen chiral acetate derivatives were screened (Scheme 6). The best results were obtained with 3-acetyl-(4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**(*ent*)-22**). The screening was performed on a 100 mg scale adding a solution of ketone **15** to the corresponding chiral lithium enolates at −78 °C. Monitoring of the reactions proved problematic due to the thermal instability of the intermediate lithium alkoxides undergoing rapid retro-aldol reactions during sampling with a syringe. However, the additions generally took place very rapidly and no significant difference in conversion was observed when reactions were quenched either after 10 min or after 1 h.

In contrast to propionate aldol additions, which often provide excellent stereoselectivities, stoichiometric asymmetric acetate aldol addition reactions usually suffer from low diastereoselectivities.[11] Furthermore, stereoselective acetate aldol additions to ketones as acceptor substrates are a largely unexplored field. Only two auxiliaries, namely, **24**[12] (dr = 65:35 to 79:21) and **25**[13] (dr = 82:18), have been reported in the literature to provide reasonable stereoselectivities in the addition reaction to acetophenone or similar phenylalkyl ketones. With **15** as the substrate, no addition reaction took place using either **24** or **25**, presumably because the di- or trianions formed from **24** or **25** are too basic and preferentially deprotonate ketone **15**. Monolithiated acetates **26**−**31** suffer from either low conversion or low diastereoselectivity.[14] The relatively high dr of 85:15 obtained for acetate **29** derived from 8-phenylmenthol is exceptional in this series. The most promising auxiliaries were the chiral oxazolidinones **(*ent*)-22** and **32**−**40** (acylated Evans-type auxiliaries). The highest selectivities were obtained with auxiliaries bearing bulky R1 groups. An R2 substituent cis to R1 seems to be advantageous in terms of both conversion and selectivity, whereas an R3 group trans to R1 appears to exhibit a negative influence. Two auxiliaries proved synthetically exceptionally useful: (4*S*)-4-*tert*-butyloxazolidin-2-one providing acetate **33** and (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (***ent*-22**). Auxiliary cleavage revealed that the (*S*)-isomer of **17** was preferentially formed using (4*S*)-configured oxazolidinones **32**−**37**.[15] (4*R*)-Configured oxazolidinones are therefore required to obtain **17** with (*R*)-configuration. This configurational outcome is in agreement with the results obtained by Evans et al. for aldehyde electrophiles.[16] Whereas the commercial availability of kilogram amounts of (4*R*)-4-*tert*-butyloxazolidin-2-one is uncertain (annual produc-

(11) Review: Palomo, C.; Oiarbide, M.; García, J. M. *Chem.−Eur. J.* **2002**, *8*, 36.
(12) Dongala, E. B.; Dull, D. L.; Mioskowski, C.; Solladié, G. *Tetrahedron Lett.* **1973**, 4983.
(13) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, 5031.
(14) The configuration of the generated stereocenter has not been assigned using **26**−**31**.
(15) Conversion of **(*ent*)-17** to **(*ent*)-7** and comparison with a sample of **(*R*)-7** by chiral HPLC.

SCHEME 6. Screening of the Asymmetric Acetate Aldol Addition to Ketone 15



tion of only ca. 1 kg, Degussa: 23 000 €/kg), (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one is produced in ton amounts each year (ChemPacific: 2000 USD/kg). On this basis, (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one was selected as the auxiliary of choice.

The efficiency of Evans-type auxiliaries for the acetate aldol reaction described is rather surprising because it has been reported in the literature that even with aldehyde acceptors the chiral acetyl oxazolidinone **32** led to moderate or almost no diastereoselectivity. Thus, the corresponding boron enolate provided disappointing results with acetaldehyde (dr = 72:28) or with isobutyraldehyde (dr = 52:48).[16]

Scale-up experiments at −78 °C (acetone/dry ice cooling bath) revealed that the stereoselectivity of the initial aldol product dropped with increasing reaction scale presumably due to less-efficient cooling of the reaction mixture upon addition of the ketone substrate. For that reason, the addition was performed under optimized conditions at −95 °C (MeOH, liquid N_2 cooling) and the ketone solution was slowly added using a syringe pump.

Cleavage of the auxiliary was found to proceed in the same pot by addition of aqueous LiOH and H_2O_2. The (*R*)-configured product **17** was isolated in 75% yield starting from **15** with an er of 87.2:12.8. This aldol addition step is practical because of (i) the ease of auxiliary recycling by simple filtration from the reaction mixture after treatment with LiOH and H_2O_2 followed by recrystallization from toluene (yield of recovered auxiliary was 90%; the auxiliary was reused successfully multiple times without significant changes in selectivity and yield) and (ii) the ease of product isolation/purification by pH-dependent extraction.[17]

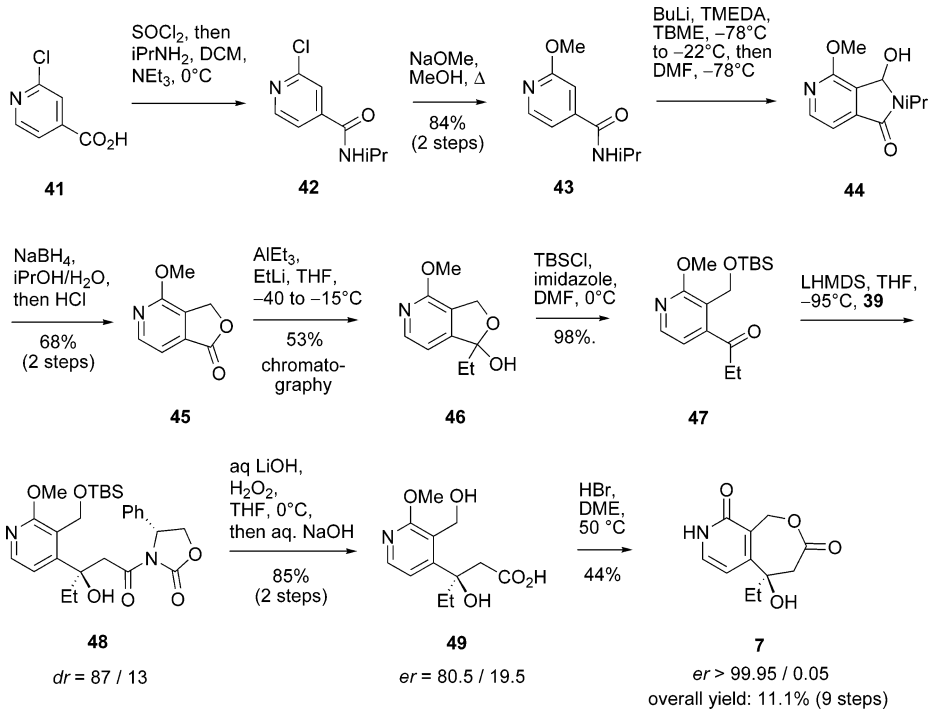
For the formation of the Li enolate, it is important to add the LHMDS solution to a solution of chiral auxiliary **22** because the opposite order of addition can result in crystallization of **22** in the syringe during the addition.

β-Hydroxy carboxylic acid **17** was then treated with aqueous HBr in DME resulting in both methyl and benzyl ether cleavage as well as in lactone formation. Gratifyingly, the er was significantly increased due to preferential crystallization of the **(*R*)-7** out of the reaction mixture. The key building block **7** was thus obtained with an er of 99.95:0.05 (chiral HPLC). The yield of the final step highly depends on the er of **17** because the mother liquid contains the almost racemic product. Therefore, a starting material **17** with an er of 87.2:12.8 could in principle lead to a maximum yield of 100 − (2 × 12.8) = 74.4% (= ee value of **17**). In conclusion, the optically active key intermediate **7** was thus synthesized over nine linear steps avoiding any chromatographic purification (and requiring only one chromatographic filtration) in 8.9% overall yield, which compares favorably with the discovery chemistry route. The experiments described in the experimental part have been performed on either a 40 g scale (**8** → **11**) or a 5 g scale (**11** → **7**).

(16) (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. See also: (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3788. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (d) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (e) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (f) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(17) The result described here for the formation of **17** was achieved with **22**, which had been prepared from an auxiliary having been recycled already five times.

SCHEME 7. Practical Asymmetric Synthesis of DE Ring Fragment 7 (Amide Route)

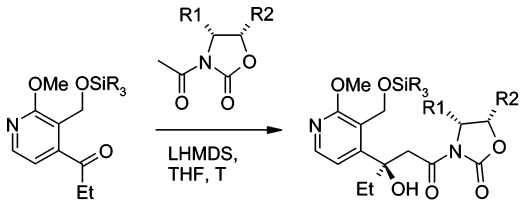


(b) Amide Approach. Because the asymmetric acetate aldol addition reaction to ketone substrate **15** worked unexpectedly well regarding stereoselectivity and conversion, an alternative route toward a suitable ketone substrate was sought to avoid the use of MesLi generating the problem of the formation of high-boiling mesityl side products only removable by silica gel filtration. For this purpose, a more efficient ortho-directing group in the pyridine 4-position other than the 1,3-dioxane moiety was required.

2-Methoxy-4-isopropylamide **43** was identified to be a suitable intermediate for a more practical metalation procedure of the 3-pyridine position (Scheme 7). **43** was prepared over two steps starting from 2-chloroisonicotinic acid **41**, which was obtained via reaction of the corresponding acid chloride with isopropylamine. The 2-chloro substituent in **42** was subsequently substituted by a methoxy group using NaOMe. Metalation of the 3-position of **43** was already achieved with *n*-BuLi in the presence of TMEDA or LiCl. Gratifyingly, no butyl addition to the pyridine 6-position was observed for this substrate, presumably due to electronic deactivation of the pyridine nucleus toward an addition reaction caused by deprotonation of the secondary isopropylamide functionality. Although the regioselectivity is low in THF (3-Li/5-Li = ca. 3:1) regardless of the metalation temperature, metalation of the 3-position is significantly favored in TBME. This might be rationalized by the weaker donor ability of TBME, thus enhancing the effect of the coordinating and directing methoxy group. No reaction occurred with *n*-BuLi in the absence of the activating additives TMEDA or LiCl. The use of *s*-BuLi does not require these additives, but the regioselectivity is lower than with *n*-BuLi. The lithiated species was trapped by DMF yielding *N*,*O*-hemiacetal **44**. The crude product, which still contained large amounts of DMF, was reduced by $NaBH_4$ in 2-propanol/water to the corresponding hydroxyamide, which was then cyclized in the same pot by addition of aqueous HCl furnishing lactone **45** which was purified by trituration. The choice of 2-propanol/water for the reduction step is important to reduce the amount of $NaBH_4$ because the reducing agent is more stable in this solvent mixture than in EtOH (in EtOH, the reduction was not complete even with 4 equiv of $NaBH_4$, which was added in four portions).

Ethyllithium addition to lactone **45** provided lactol **46**, which is in equilibrium with the open hydroxyketone form (lactol/hydroxyketone ca. 6:1 in $CDCl_3$). With EtMgCl, Et_3ZnLi, Et_4ZnLi_2, and Et_3ZnMgX, lactol **46** was not accessible because the ethyl addition occurred faster to **46** than to **45**. EtMgBr provided complex mixtures, whereas EtMgBr in combination with $CeCl_3$ gave almost no conversion. Ethyllithium was therefore the reagent of choice. Although the addition works almost quantitatively on a 100 mg scale, it was difficult to obtain high conversion on a multigram scale. The reasons are manifold: the ethyllithium reagent is purchased as a 0.5 M solution in benzene/cyclohexane, which rapidly freezes in the syringe upon dropwise addition to the cooled solution of lactone **45**. For that reason, a solution of **45** was added to an EtLi suspension. On the other hand, **45** also rapidly crystallizes from concentrated THF solutions. For that reason, the dilution factor should be at least 25. During the addition of **45**, there is initially a large excess of reagent causing some double addition. An improved version involves a combination of triethylaluminum (1.1 equiv) and ethyllithium (2 × 1.1 equiv). Equimolar amounts of $AlEt_3$ (1.1 equiv) and EtLi are precoordinated at 0 °C followed by the rapid addition of the solution of the starting material **45** at −40 °C. To reach high conversion, a second equivalent of EtLi is required, which is slowly added at −40 °C. The reaction mixture is then allowed to slowly warm to −15 °C and is stirrable at any time (in contrast to the version without $AlEt_3$). Surprisingly, there was no conversion when $AlEt_3$ was precoordinated with the 2 equiv of EtLi (potential formation of Et_5AlLi_2). For that reason, we suggest that EtLi is still the reactive species and that Et_4AlLi might help to activate the lactone toward the nucleophilic addition acting as a Lewis acid. Although the yield of **46** could thus be increased to 53%, product purification still requires column chromatography.

TABLE 1. Screening of Asymmetric Acetate Aldol Additions to Ketones 47, 50, and 51



(1)

47: SiR_3 = TBS; **50**: SiR_3 = TES; **51**: SiR_3 = TBDPS

ketone	oxazolidinone	equiv (auxiliary)	*T*/°C	conversion/%[c]	dr[c]
47	**22** (R1 = Ph, R2 = Ph)	1.1	−78	25	66:34
47	**39** (R1 = Ph, R2 = H)	1.1	−78	40	78:22
47	**39** (R1 = Ph, R2 = H)	1.1	−78	40	50:50[a]
47	**39** (R1 = Ph, R2 = H)	1.1	−95	41	78:22
47	**39** (R1 = Ph, R2 = H)	2.0	−95	57	80:20
47	**39** (R1 = Ph, R2 = H)	2.0	−95	51	85:25[b]
47	**39** (R1 = Ph, R2 = H)	3.0	−95	72	82:18
47	**39 (R1 = Ph, R2 = H)**	**3.0**	**−95**	**88**	**87:13[b]**
47	**38** (R1 = Bn, R2 = H)	1.1	−78	45	73:27
47	**(*ent*)-32** (R1 = *i*Pr, R2 = H)	3.0	−78	23	77:23
47	**40** (R1/2 = $C_6H_4CH_2$)	3.0	−78	64	62:38
47	**(*ent*)-33** (R1 = *t*Bu, R2 = H)	1.1	−95	60	90:10
47	**(*ent*)-33** (R1 = *t*Bu, R2 = H)	1.5	−95	78	93:7
47	**(*ent*)-33 (R1 = *t*Bu, R2 = H)**	**2.0**	**−95**	**87**	**91:9**
47	[e]	2.5	−78	81	52:48
51	**39** (R1 = Ph, R2 = H)	3.0	−78	63	82:18
51	**39** (R1 = Ph, R2 = H)	3.0	−95	75	85:15
51	**22** (R1 = Ph, R2 = Ph)	3.0	−95	54	57:43
51	**38** (R1 = Bn, R2 = H)	4.0	−78	90	80:20
51	**(*ent*)-32** (R1 = *i*Pr, R2 = H)	3.0	−78	58	82:18
51	[e]	2.5	−78	76	67:33
50	**39** (R1 = Ph, R2 = H)	1.1	−95	62	62:38
50	**39** (R1 = Ph, R2 = H)	2.0	−95	84	62:38
50	**22** (R1 = Ph, R2 = Ph)	1.1	−95	48	68:32
50	**38** (R1 = Bn, R2 = H)	1.1	−95	59	61:39[d]
50	**(*ent*)-32** (R1 = *i*Pr, R2 = H)	1.1	−95	54	72:28

[a] In the presence of 1.1 equiv of LiCl. [b] Slow ketone addition by syringe pump. [c] Determined from crude ^{1}H NMR. [d] Determined by HPLC. [e] 8-Ph-menthol was used as the chiral auxiliary.

To obtain a suitable ketone substrate for the asymmetric aldol addition reaction, **46** had to be opened by an appropriate electrophile. Attempts failed to synthesize **15** using, e.g., BnO-(HN═)$CCCl_3$ (DCM, cat. TfOH, or TMSOTf, 0 °C) due to decomposition, incomplete conversion, and formation of only trace amounts of **15**. Similar results were obtained for tritylation with trityl chloride (NEt_3, DMAP, DCM, rt to 50 °C), methoxymethylation with formaldehyde dimethyl acetal (TFA, DCM, 0 °C), ethoxyethylation with ethyl vinyl ether (PTSA, DCM), acetylation with acetic anhydride (pyridine, 0 °C), or 2-bromoacetylation with bromo acetyl bromide (2,6-lutidine, DCM, −78 °C) as electrophilic components. However, the intended strategy was finally realized using silyl chlorides and worked especially well with TBSCl (*tert*-butyldimethylsilyl chloride) and TBDPSCl (*tert*-butyldiphenylsilyl chloride); TMSCl (trimethylsilyl chloride) failed to give the desired product, and TESCl (triethylsilyl chloride) resulted in formation of significant amounts of a side product formed by silylation of the tertiary lactol hydroxy group. The workup of the TBS and TBDPS ether formation benefits from the solubility of the lipophilic silyl ethers in heptane. As a result, the polar components DMF and imidazole were completely removed by aqueous workup and the crude ketone product **47** was isolated with excellent purity.

Unfortunately, the protecting group on the primary benzylic oxygen, although rather remote from the reacting carbonyl carbon, exerts a major influence on conversion and selectivity of the asymmetric aldol addition reaction. To obtain high conversions, an enolate excess of ca. 2−3 equiv was necessary.[18] The chiral enolate formed from (4*R*,5*S*)-3-acetyl-4,5-diphenyl-oxazolidin-2-one (**22**) led to disappointingly low diastereoselectivities for all silyl ethers, thus necessitating an additional auxiliary screening for each derivative (Table 1). As a general trend, it may be concluded that the conversion decreases with increasing steric bulk of the silyl protecting group while the diastereoselectivity increases. Thus, TBS evolved as the best compromise. Slow addition of the ketone solution to the chiral Li enolate generally increased conversion and the diastereomeric ratio. Under optimized conditions, lithiated (*R*)-4-phenyloxazolidinone (**39**) (3.0 equiv) was reacted with TBS ketone **47** at −95 °C resulting in 88% conversion and a dr of 87:13. The auxiliary was recycled in 87% yield. Less auxiliary (2.0 equiv) is required when (*R*)-3-acetyl-4-*tert*-butyl-oxazolidinone (**33**) is used (conversion 87%). Moreover, the diastereoselectivity increased to 91:9. However, because of the low annual produc-

(18) We assume that the lower reactivity of **47** as compared to **15** might be best rationalized by steric and not by electronic reasons. In accordance with this hypothesis, conversions (as determined by ^{1}H NMR) using chiral lithium enolates were generally higher for TES derivative **50** than for TBS ether **47** and the TBDPS ether **51** (eq 1, Table 1). This illustrates that the lower conversion as compared to **15** cannot be mainly attributed to a weak Si···O═C interaction and a resulting enhanced acidity of the α-CH_2 group because in this case lower conversions with smaller silyl protecting groups such as, e.g., TES would be expected.

tion of (*R*)-3-acetyl-4-*tert*-butyl-oxazolidinone, we selected **39** as the chiral reagent of choice.

Treatment of **48** with aqueous $LiOH/H_2O_2$ in THF resulted in rapid cleavage of the chiral oxazolidinone furnishing the corresponding carboxylic acid. Because purification of the free acid by pH-dependent extraction was hampered by the insolubility of the corresponding lipophilic silyl ether in aqueous media, we chose to simultaneously cleave the silyl ether protecting group in the same pot using aqueous NaOH at room temperature. Although TES and TBS were removed easily under these conditions, cleavage of the TBDPS group proceeded very slowly finally resulting in massive decomposition. Because of the hydrophilic nature of the highly polar carboxylic acid diol **49** preventing its extraction into dichloromethane, a more polar dichloromethane/EtOH (4:1) mixture was used for its isolation. The dihydroxy acid **49** lactonizes slowly during solvent evaporation and also when stored at ambient temperature. However, when **49** was treated with acid prior to isolation, lactone formation was sluggish and did not go to completion. Unfortunately, the er of **49** (80.5:19.5) was determined to be significantly lower than the dr of **48** (87:13).

Methyl ether cleavage as well as formation of the seven-membered lactone ring were accomplished by 2.1 equiv of aqueous HBr in DME furnishing target molecule **7** in optically pure form (er > 99.95:0.05, chiral HPLC). DE ring building block **7** was thus synthesized over nine linear steps in 11.1% overall yield utilizing one column chromatography.

Summary

In conclusion, we have described two practical routes to DE ring fragment **7**, which have the potential to serve as the basis for a technical synthesis of this key building block required for the synthesis of homocamptothecin derivatives such as diflomotecan **4**. The two approaches, the "acetal route" and the "amide route", starting from both commercially available and inexpensive pyridine building blocks rely on unprecedented efficient and practical asymmetric acetate aldol additions to ketone substrates whereby the auxiliary can be easily recycled in high yield. Optically pure **7** is obtained after the final lactonization step in 8.9% yield via the acetal approach (nine linear steps, no chromatographic purification, one silica gel filtration) or in 11.1% overall yield via the amide approach (nine linear steps, one chromatography required).

Experimental Section

Synthesis of 2-Methoxy-isonicotinonitrile (20).[19] A stirred suspension of NaOMe (17.86 g, 330.7 mmol, 1.22 equiv) in acetonitrile (95 mL) was cooled to 0 °C, and a solution of 2-chloro-4-cyano pyridine (**8**, 37.56 g, 271.1 mmol) in acetonitrile (225 mL) was added over 45 min. Stirring was continued at room temperature for 23 h (HPLC control). Potassium dihydrogen phosphate (11.1 g, 81.56 mmol, 0.30 equiv) was added at 0 °C, and stirring was continued for 3 h at room temperature. The reaction mixture was then evaporated to dryness in a rotary evaporator (40 °C/10 mbar) yielding the crude product (64.94 g, 179 wt %) as a brown solid. The crude product was extracted with toluene (900 mL) for 18 h at reflux temperature using a Soxhlet extraction apparatus yielding product **20** (25.65 g, 71 wt %) as an orange solid. An analytical sample (white solid) was obtained by column chromatography with heptane/ethyl acetate (1:1). Mp: 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, 1H, J = 5.1 Hz), 7.07 (dd, 1H, J = 5.1 Hz, J = 1.2 Hz), 6.99 (br. s, 1H), 3.97 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 148.5, 122.4, 117.5, 116.5, 114.2, 54.0 ppm. IR (ATR-FTIR) 2922, 2853, 2238, 1601, 1547, 1480, 1476, 1450, 1387, 1313, 1151, 1041, 843 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 134 (95), 133 (100), 104 (71). HRMS (ESI POS) calcd for $C_7H_7N_2O$ (MH^+) 135.0558, found 135.0559. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.54; H, 4.57; N, 20.84.

Synthesis of 1-(2-Methoxy-pyridin-4-yl)-propan-1-one (21). A stirred suspension of **20** (25.44 g, 189.7 mmol) in TBME (380 mL) was cooled to 0 °C, and a solution of ethylmagnesium chloride (114 mL, 2.0 M in THF, 228.0 mmol, 1.20 equiv) was added within 45 min. Stirring was continued at 0 °C. After 3 h 40 min, additional ethylmagnesium chloride (5 mL, 10.0 mmol, 0.05 equiv) was added at 0 °C. The reaction was monitored by HPLC. After 4.5 h, the reaction was quenched at 0 °C by addition of water (300 mL). The resulting suspension was stirred for 16 h at room temperature and was then diluted with toluene (200 mL). The aqueous phase was extracted with toluene (400 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl (500 mL) and brine (500 mL), dried over Na_2SO_4 (50 g, 30 min), and filtered. The filter cake was washed with toluene (100 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (28.64 g, 91 wt %) was obtained as an orange solid. An analytical sample (white solid) was obtained by Kugelrohr distillation (85 °C, 0.6 mbar). Mp: 38 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, 1H, J = 5.3 Hz), 7.30 (dd, 1H, J = 5.3 Hz, J = 1.3 Hz), 7.18 (br. s, 1H), 3.98 (s, 3H), 2.96 (q, 2H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 165.1, 148.0, 145.9, 114.0, 109.4, 53.9, 32.3, 7.8 ppm. IR (ATR-FTIR) 2978, 1690, 1603, 1559, 1479, 1391, 1311, 1170, 1038, 1017, 848 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 165 (98), 164 (75), 136 (100), 108 (43). HRMS (ESI POS) calcd for $C_9H_{12}NO_2$ (MH^+) 166.0868, found 166.0870. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.22; H, 6.55; N, 8.50.

Synthesis of 4-(2-Ethyl-[1,3]dioxan-2-yl)-2-methoxy-pyridine (11). Sulfuric acid (96%, 473 μL, 4.63 mmol, 0.02 equiv), *para*-toluenesulfonic acid monohydrate (99%, 889 mg, 4.63 mmol, 0.02 equiv), and 1,3-propanediol (100 mL, 1.39 mol, 6.0 equiv) were added to a stirred solution of **21** (38.23 g, 231.4 mmol) in toluene (575 mL). The reaction mixture was heated for 72 h (NMR control) to reflux (oil bath temperature 160 °C). After cooling to room temperature, saturated aqueous $NaHCO_3$ (500 mL) was added and the phases were separated. The organic phase was washed with brine (2 × 250 mL) and was then dried over Na_2SO_4 (50 g, 30 min) and filtered. The filter cake was washed with toluene (100 mL). After evaporation of solvent in a rotary evaporator (50 °C/10 mbar), the crude product (40.31 g, 78 wt %) was obtained as a brown oil. Purification was achieved using a high-vacuum distillation (bp 95 °C at 0.056 mbar, oil bath temperature 125 °C, 40 cm Vigreux column) furnishing product **11** (31.80 g, 142.4 mmol, 62 wt %) as a colorless liquid. Bp: 95 °C (0.056 mbar).^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (dd, 1H, J = 5.2 Hz, J = 0.8 Hz), 6.91 (dd, 1H, J = 5.3 Hz, J = 1.5 Hz), 6.78 (dd, 1H, J = 1.4 Hz, J = 0.8 Hz), 3.96 (s, 3H), 3.89 (m, 2H), 3.75 (m, 2H), 2.09 (m, 1H), 1.72 (q, 2H, J = 7.5 Hz), 1.26 (m, 1H), 0.81 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 152.3, 147.2, 115.9, 109.8, 101.2, 61.4, 53.5, 36.8, 25.4, 7.1 ppm. IR (ATR-FTIR) 2970, 2870, 1606, 1559, 1477, 1385, 1314, 1141, 1083, 1041, 840 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 223 (2), 194 (100), 136 (44). HRMS (ESI POS) calcd for $C_{12}H_{18}NO_3$ (MH^+) 224.1287, found 224.1285. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.27; H, 7.78; N, 6.05.

Synthesis of 4-(2-Ethyl-[1,3]dioxan-2-yl)-2-methoxy-pyridine-3-carbaldehyde (12). A stirred solution of 2-bromomesitylene (98%, 6.87 mL, 44.78 mmol, 2.0 equiv) in THF (44 mL) was cooled to −45 °C. *n*-Butyllithium (35.8 mL, 2.5 M in hexanes, 89.56 mmol, 4.0 equiv) was added within 20 min. The resulting white suspension

(19) Known compound: Walpole, C. S. J.; Wrigglesworth, R.; Bevan, S.; Campbell, E. A.; Dray, A.; James, I. F.; Perkins, M. N.; Reid, D. J.; Winter, J. *J. Med. Chem.* **1993**, *36*, 2362.

was then allowed to warm to 0 °C within 2.5 h. At −10 °C, the reaction mixture became a clear solution. Stirring was continued for an additional hour at 0 °C. The solution was cooled to −10 °C, and a solution of **11** (5.00 g, 22.39 mmol) in THF (15 mL) was added over 15 min under vigorous stirring. The resulting brown suspension was allowed to warm to 10 °C within 2.5 h. The cooling bath was then removed, and stirring was continued at room temperature for an additional hour. The clear brown solution was then cooled to −23 °C, and DMF (5.19 mL, 67.17 mmol, 3.0 equiv) was added. The mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL). After 15 min, water (50 mL) was added. The mixture was extracted with TBME (3 × 150 mL). The combined organic phases were washed with brine (2 × 300 mL), dried over Na_2SO_4 (20 g, 30 min), and filtered. The filter cake was washed with TBME (40 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (12.048 g, 214 wt %) was obtained as a brown oil, which was then purified by silica gel filtration using a gradient elution with heptane/ethyl acetate (30:1) (to elute mesityl products and **11**) and heptane/ethyl acetate (5:1). Evaporation to dryness of the second fraction in a rotary evaporator (40 °C/10 mbar) yielded product **12** (3.832 g, 15.2 mmol, 68 wt %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.33 (s, 1H), 8.25 (d, 1H, J = 5.5 Hz), 6.96 (d, 1H, J = 5.3 Hz), 3.98 (s, 3H), 3.83 (m, 2H), 3.61 (m, 2H), 2.09 (m, 1H), 1.86 (q, 2H, J = 7.5 Hz), 1.29 (m, 1H), 0.92 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 161.7, 151.7, 148.8, 120.2, 116.2, 101.2, 61.2, 54.0, 36.3, 24.8, 7.1 ppm. IR (ATR-FTIR) 2972, 2871, 1706, 1583, 1562, 1376, 1306, 1137, 1079, 1051, 859 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 251 (9), 222 (12), 192 (100), 164 (30). HRMS (ESI POS) calcd for $C_{13}H_{18}NO_4$ (MH^+) 252.1236, found 252.1238. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.30; H, 6.76; N, 5.48.

Synthesis of [4-(2-Ethyl-[1,3]dioxan-2-yl)-2-methoxy-pyridin-3-yl]-methanol (13). Sodium borohydride (96%, 134.6 mg, 3.416 mmol, 0.27 equiv) was added at 0 °C to a stirred solution of **12** (3.178 g, 12.65 mmol) in 2-propanol (95 mL) and water (15.8 mL). The reaction (grey suspension) was monitored by HPLC. After 30 min, acetone (11 mL) was added and stirring was continued for 30 min at room temperature. Saturated aqueous NH_4Cl (190 mL) was added, and the mixture was extracted with dichloromethane (3 × 180 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 (3.184 g, 99 wt %) was obtained as a yellow oil. Purification was achieved by trituration with heptane (16 mL) for 24 h at room temperature and subsequent standing for 4 days at −20 °C. After cold filtration and removal of residual solvent in a rotary evaporator (40 °C/10 mbar), product **13** (2.827 g, 11.2 mmol, 88 wt %) was obtained as white crystals. Mp: 79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 5.3 Hz), 7.01 (d, 1H, J = 5.3 Hz), 4.93 (d, 2H, J = 6.6 Hz), 4.04 (s, 3H), 3.93 (m, 2H), 3.77 (m, 2H), 2.83 (t, 1H, J = 7.2 Hz), 2.10 (m, 1H), 1.81 (q, 2H, J = 7.5 Hz), 1.30 (m, 1H), 0.85 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 148.7, 145.5, 122.0, 117.6, 102.3, 61.6, 56.9, 53.8, 36.3, 25.2, 7.2 ppm. IR (Nujol) 3333, 2923, 2855, 1595, 1557, 1464, 1388, 1309, 1152, 1079, 837 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 254 (7), 224 (100), 194 (19), 166 (36), 115 (42). HRMS (ESI POS) calcd for $C_{13}H_{20}NO_4$ (MH^+) 254.1392, found 254.1395. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.63; H, 7.28; N, 5.47.

Synthesis of 3-Benzyloxymethyl-4-(2-ethyl-[1,3]dioxan-2-yl)-2-methoxy-pyridine (14). Lithium bis(trimethylsilyl)amide (16.6 mL, 1.0 M in THF, 16.62 mmol, 1.1 equiv) was added within 10 min at −78 °C to a stirred solution of **13** (3.828 g, 15.11 mmol) in THF (21 mL). After an additional 10 min at −78 °C, stirring was continued for 10 min at 0 °C and for 15 min at room temperature. Benzylbromide (2.56 mL, 21.15 mmol, 1.4 equiv) and dry tetrabutylammonium iodide (98%, 570 mg, 1.51 mmol, 0.1 equiv) were subsequently added, and the mixture was heated to 65 °C. The reaction was monitored by HPLC. After 16 h at 65 °C, pyrrolidine (875 μL, 7.55 mmol, 0.7 equiv) was added at room temperature. After 3.5 h, the mixture was poured into heptane (600 mL) and the organic phase was washed with aqueous HCl (0.5 M, 2 × 400 mL) and subsequently with water (500 mL). The organic phases were dried over Na_2SO_4 (20 g, 30 min) and filtered. The solid was washed with heptane (40 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (4.985 g, 96 wt %) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, 1H, J = 5.5 Hz), 7.25−7.41 (m, 5H), 6.98 (d, 1H, J = 5.4 Hz), 4.73 (s, 2H), 4.63 (s, 2H), 3.98 (s, 3H), 3.85 (m, 4H), 2.09 (m, 1H), 1.80 (q, 2H, J = 7.5 Hz), 1.24 (dm, 1H, J = 13.0 Hz), 0.84 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 150.4, 146.2, 138.7, 128.3, 127.9, 127.5, 118.9, 117.4, 102.3, 73.4, 63.5, 61.9, 53.8, 36.7, 25.4, 7.3 ppm. IR (film) 2969, 1592, 1562, 1387, 1311, 1153, 1013, 984, 737 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 343 (6), 252 (10), 234 (100), 176 (45), 91 (46). HRMS (ESI POS) calcd for $C_{20}H_{26}NO_4$ (MH^+) 344.1862, found 344.1865. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.90; H, 7.24; N, 4.03.

Synthesis of 1-(3-Benzyloxymethyl-2-methoxy-pyridin-4-yl)-propan-1-one (15). *para*-Toluenesulfonic acid monohydrate (99%, 461 mg, 2.40 mmol, 0.2 equiv) was added at room temperature to a stirred solution of **14** (4.120 g, 12.00 mmol) in ethanol (96 mL) and water (24 mL). The mixture was subsequently heated to 80 °C, and the reaction was monitored by HPLC. After 6.25 h at 80 °C, the solution was cooled to room temperature and poured into heptane (600 mL). The organic phase was washed with water (600 mL), subsequently with aqueous $NaHCO_3$ solution (600 mL, 0.1 M), and again with water (600 mL). The organic phase was dried over Na_2SO_4 (20 g, 30 min) and filtered. The solid was washed with heptane (40 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (3.302 g, 96 wt %) was obtained as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 5.1 Hz), 7.29−7.37 (m, 5H), 6.75 (d, 1H, J = 5.3 Hz), 4.62 (s, 2H), 4.50 (s, 2H), 3.95 (s, 3H), 2.74 (q, 2H, J = 7.2 Hz), 1.06 (t, 3H, J = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 161.8, 150.7, 146.4, 137.7, 128.4, 128.0, 127.8, 117.0, 113.7, 73.4, 63.6, 53.8, 36.2, 7.5 ppm. IR (ATR-FTIR) 2943, 1706, 1594, 1561, 1450, 1386, 1355, 1303, 1068, 1017, 735, 697 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 286 (2), 194 (100), 179 (41), 176 (81), 91 (32). HRMS (ESI POS) calcd for $C_{17}H_{20}NO_3$ (MH^+) 286.1443, found 286.1442. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.44; H, 6.69; N, 4.94.

Asymmetric Aldol Addition: Synthesis of (4*R*,5*S*)-3-[(*R*)-3-(3-Benzyloxymethyl-2-methoxy-pyridin-4-yl)-3-hydroxy-pentanoyl]-4,5-diphenyl-oxazolidin-2-one (52). A solution of **22** (108.4 mg, 0.385 mmol, 1.1 equiv) in THF (650 μL) was slowly added (addition time: 5 min) at −78 °C to a solution of lithium bis-(trimethylsilyl)amide (389.4 μL, 1.0 M in THF, 0.385 mmol, 1.1 equiv). During the addition, the color changed from colorless to bright yellow. After 2 h at −78 °C, the solution was cooled to −95 °C and **15** (100.0 mg, 0.350 mmol) dissolved in THF (400 μL) was slowly added (addition time: 5 min). The solution was kept for an additional 30 min at −95 °C and then for 45 min at −78 °C. Subsequently, the reaction was quenched by addition of aqueous 0.5 M HCl (5 mL). The mixture was extracted with dichloromethane (3 × 10 mL), and the combined extracts were dried over sodium sulfate (1 g, 30 min) and filtered. The filter cake was washed with dichloromethane (2 mL). After removal of solvent in a rotary evaporator (40 °C/5 mbar), the crude product was obtained as a colorless oil (206.7 mg, 104 wt %, dr = 92:8 (^{1}H NMR)). An analytical sample (dr > 30:1 (^{1}H NMR), white solid) was obtained by column chromatography with heptane/ethyl acetate (7:3). $[\alpha]_D^{20}$ (c = 0.7417 /dL, $CHCl_3$) = −23.9. Mp: 61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, 1H, J = 5.6 Hz), 6.83−7.33 (m, 15H), 6.57 (d, 1H, J = 5.6 Hz), 5.79 (d, 1H, J = 7.7 Hz), 5.51 (d, 1H, J = 7.7 Hz), 5.31 (s, 1H), 4.89 (d, 1H, J = 10.5 Hz), 4.81

(d, 1H, J = 10.6 Hz), 4.42 (d, 1H, J = 11.6 Hz), 4.35 (d, 1H, J = 16.8 Hz), 4.33 (d, 1H, J = 11.8 Hz), 3.90 (s, 3H), 3.22 (d, 1H, J = 16.8 Hz), 1.92 (q, 2H, J = 7.1 Hz), 0.80 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 163.8, 156.2, 153.6, 145.9, 138.5, 133.9, 132.6, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.4, 126.3, 126.3, 117.8, 115.7, 80.3, 78.0, 71.9, 63.1, 62.7, 53.7, 46.0, 36.3, 7.8 ppm. IR (ATR-FTIR) 3444, 2923, 1779, 1694, 1592, 1555, 1455, 1377, 1243, 1185, 1133, 1060, 836, 760, 724 cm^{-1}. MS (ESI) m/z 567.4 (MH^+). HRMS (ESI POS) calcd for $C_{34}H_{35}N_2O_6$ (MH^+) 567.2495, found 567.2493. Anal. Calcd for $C_{34}H_{34}N_2O_6$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.87; H, 6.31; N, 4.54.

Asymmetric Aldol Addition: Synthesis of (*R*)-3-(3-Benzyloxymethyl-2-methoxy-pyridin-4-yl)-3-hydroxy-pentanoic Acid (17). A solution of **22** (4.733 g, 16.82 mmol, 1.2 equiv) in THF (19 mL) prepared at 65 °C was cooled to −78 °C, and lithium bis(trimethylsilyl)amide solution (17.00 mL, 1.0 M in THF, 16.82 mmol, 1.2 equiv) was slowly added (addition time: 10 min). During the addition, the color changed from colorless to bright yellow. After 2 h at −78 °C, the clear solution was cooled to −95 °C. A solution of **15** (4.00 g, 14.02 mmol) in THF (16 mL) was slowly added (syringe pump, addition time: 30 min), and the solution was kept for an additional 30 min at −95 °C and then for 45 min at −78 °C. Subsequently, aqueous LiOH solution (87.6 mL, 0.8 M, 70.1 mmol, 5.0 equiv) and aqueous H_2O_2 solution (7.01 mL, 10 M, 70.1 mmol, 5.0 equiv) were added, and stirring of the resulting suspension was continued at 0 °C for 30 min and at room temperature for 1 h. The precipitated auxiliary was collected by filtration, and the solid was washed with water (15 mL). The filtrate was poured on aqueous NaOH solution (200 mL, 2.0 M). A second portion of precipitated auxiliary was collected by filtration, and the solid was washed with water (3 mL) [Auxiliary recycling: the combined filter cakes (4.16 g) were triturated at reflux temperature in toluene (20.8 mL, 30 min). After cooling to room temperature overnight while stirring, 3.63 g of auxiliary was recycled (15.17 mmol, 90 wt %, white crystals).] The filtrate was extracted with TBME (3 × 200 mL) to remove unreacted **15**, unprecipitated auxiliary, and impurities. The aqueous phase was then acidified with aqueous HCl (2.0 M) until pH 3. The resulting white suspension was extracted with dichloromethane (2 × 200 mL). The combined dichloromethane extracts were washed with saturated aqueous NH_4Cl (80 mL) and brine (16 mL) and were subsequently dried over sodium sulfate (20 g, 30 min) and filtered. The solid was washed with dichloromethane (40 mL). After removal of solvent in a rotary evaporator (40 °C/5 mbar), the crude product was obtained as a light yellow oil (3.61 g, 75 wt %, er = 87.2:12.8 [chiral HPLC; sample preparation: ethanol solution: Chiralcel-ODH column, 250 × 4.6; temperature of 25 °C; mobile phase, 99.9% heptane/ethanol (24:1); 0.1% trifluoroacetic acid; flow of 0.8 mL/min; injection volume of 5 μL; detection, UV 275 nm; retention time of 12.75 min **(*S*)-17**, 14.51 min **(*R*)-17**]). $[\alpha]_D^{20}$ (c = 0.9884 g/dL, $CHCl_3$) = −23.3 (for ee = 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 1H, J = 5.5 Hz), 7.35 (m, 5H), 6.78 (d, 1H, J = 5.5 Hz), 6.16 (s, 1H), 4.97 (d, 1H, J = 11.3 Hz), 4.86 (d, 1H, J = 11.3 Hz), 4.65 (d, 1H, J = 11.7 Hz), 4.60 (d, 1H, J = 11.7 Hz), 3.93 (s, 3H), 2.96 (d, 1H, J = 15.5 Hz), 2.84 (d, 1H, J = 16.1 Hz), 1.86 (m, 2H), 0.76 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 163.5, 155.3, 146.4, 137.2, 128.5, 128.4, 128.1, 128.1, 117.1, 115.7, 72.8, 63.2, 54.0, 46.3, 35.8, 7.9 ppm. IR (ATR-FTIR) 3455, 2968, 2600, 1709, 1593, 1555, 1453, 1383, 1312, 1191, 1061, 1027, 1006, 824, 736, 698 cm^{-1}. MS (ESI) m/z 344.2 ($M - H^+$). HRMS (ESI POS) calcd for $C_{19}H_{24}NO_5$ (MH^+) 346.1654, found 346.1658. Microanalysis: C was not in the range <0.4%, even after purification by preparative HPLC (HPLC purity 100.0%).

Synthesis of (*R*)-5-Ethyl-5-hydroxy-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene (7). Aqueous HBr (2.01 mL, 48%, 17.89 mmol, 2.06 equiv) was added to a stirred solution of **17** (3.00 g, 8.69 mmol) in 1,2-dimethoxyethane (11 mL). After 15 min at room temperature, the solution was heated to 50 °C. After 4 h, the first product crystals appeared. The reaction was monitored by HPLC. After 27 h at 50 °C, the reaction was cooled to room temperature. The mixture was allowed to stir at room temperature for 72 h and was then filtered. The solid was washed with TBME (2 × 2.2 mL) and subsequently washed with acetone (2.2 mL), water (2 × 2.2 mL), and finally with acetone (2 × 2.2 mL). After drying in vacuo, product **7** (1.040 g, 4.66 mmol, 54 wt %, er = 99.95:0.05 [chiral HPLC; sample preparation: ethanol solution; Chiralcel-ODH column, 250 × 4.6; temperature of 25 °C; mobile phase, 75% heptane, 25% ethanol/trifluoroacetic acid (99:1); flow of 0.8 mL/min; injection volume of 5 μL, detection, UV 308 nm; retention time, 9.68 min **(*S*)-7**, 13.28 min **(*R*)-7**]) was obtained as white crystals. $[\alpha]_D^{20}$ (c = 1.1000 g/dL, DMSO) = +134.4. 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 = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, DMSO): δ 171.9, 161.1, 155.6, 133.7, 122.6, 104.9, 72.7, 61.0, 42.2, 35.7, 8.1 ppm. IR (ATR-FTIR) 3279, 3106, 2968, 1742, 1621, 1562, 1528, 1422, 1281, 1177, 1040, 1020, 879, 809, 798 cm^{-1}. MS (EI) m/z (rel intensity) 223 (26), 205 (3), 194 (17), 181 (10), 166 (18), 163 (26), 152 (100). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.95; H, 5.73; N, 6.24.

Synthesis of (4*R*,5*S*)-3-Acetyl-4,5-diphenyl-oxazolidin-2-one (22).[20] *n*-Butyllithium (13.65 mL, 1.5 M in pentane, 20.47 mmol, 0.98 equiv) was added at −78 °C during 6 min to a stirred suspension of (4*R*,5*S*)-(+)-*cis*-4,5-diphenyl-2-oxazolidinone (98%, 5.100 g, 20.89 mmol, recycled material) in THF (102 mL). The resulting dark red solution was stirred for an additional 70 min at −78 °C. During this period, the solution became colorless. Stirring was continued for 15 min at −25 °C, before it was cooled again to −78 °C. A solution of acetyl chloride (1.536 mL, 21.31 mmol, 1.02 equiv) in THF (15.3 mL) was then added within 5 min. After 50 min, the mixture was poured on water (510 mL) and the product was extracted with dichloromethane (3 × 305 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (715 mL, 1.0 M) and with brine (715 mL). The solution was dried over sodium sulfate (25 g, 30 min) and filtered. The filter cake was washed with dichloromethane (50 mL). After removal of solvent in a rotary evaporator (40 °C/30 mbar), the crude product (5.899 g, 100 wt %) was obtained as a white solid. Purification was accomplished by recrystallization from toluene (13 mL). The heterogeneous mixture was heated to reflux until a clear solution was obtained, which was then allowed to slowly cool to room temperature. After 2 days, product **22** was collected by filtration as white crystals (5.157 g, 18.332 mmol, 88%). $[\alpha]_D^{20}$ (c = 0.453 g/dL, $CHCl_3$) = +80.4. Mp: 142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 6H), 6.97 (m, 2H), 6.86 (m, 2H), 5.91 (d, 1H, J = 7.5 Hz), 5.67 (d, 1H, J = 7.5 Hz), 2.62 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 154.0, 134.4, 132.8, 128.5, 128.3, 128.2, 128.1, 126.6, 126.1, 80.3, 62.7, 23.9 ppm. IR (ATR-FTIR) 2923, 1778, 1712, 1702, 1604, 1497, 761, 699 cm^{-1}. MS (EI) m/z (rel intensity) 281 (3), 237 (39), 149 (100), 132 (78), 107 (95), 43 (35). HRMS (ESI POS) calcd for $C_{17}H_{15}NO_3Na$ (MNa^+) 304.0950, found 304.0950. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.78; H, 5.53; N, 4.75.

Synthesis of 2-Chloro-*N*-isopropyl-isonicotinamide (42).[21] Thionyl chloride (99%, 11.77 mL, 160.2 mmol, 1.3 equiv) and DMF (762 μL, 9.86 mmol, 0.08 equiv) were added to a stirred suspension of 2-chloroisonicotinic acid (97%, 20.00 g, **41**, 123.2 mmol) in acetonitrile (200 mL). The mixture was heated to reflux (clear dark red solution) and was monitored by HPLC (sample preparation: 5 μL of the reaction mixture was added to 0.2 mL of MeOH). After

(20) The enantiomer is known: Ferroci, M.; Inesi, A.; Palombi, L.; Sotgiu, G. *J. Org. Chem.* **2002**, *67*, 1719.

(21) Known compound: Pavlova, M. V.; Mikhalev, A. I.; Kon'shin, M. E.; Vasilyuk, M. V.; Kotegov, V. P. *Pharm. Chem. J.* **2002**, *36*, 425.

60 min, 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 (200 mL), and the solution was cooled to 0 °C. Triethylamine (20.6 mL, 147.8 mmol, 1.20 equiv) and isopropylamine (99.5%, 11.7 mL, 135.5 mmol, 1.10 equiv) were subsequently added, and stirring was continued for 2 h at 0 °C (almost black solution). The mixture was poured on water (200 mL), and the phases were separated. The organic phase was 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/20 mbar), the crude product (24.83 g, 102 wt %) was obtained as a brown solid. Mp: 99 °C (decomp). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (dd, 1H, J = 4.9 Hz, J = 0.6 Hz), 7.62 (dd, 1H, J = 1.3 Hz, J = 0.6 Hz), 7.51 (dd, 1H, J = 5.1 Hz, J = 1.5 Hz), 5.94 (br. s, 1H), 4.27 (m, 1H), 1.28 (d, 6H, J = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 152.4, 150.4, 145.1, 122.0, 119.8, 42.5, 22.6 ppm. IR (Nujol) 3278, 3061, 2969, 1636, 1532, 1460, 1365, 1297, 1077, 905 cm^{-1}. MS (ESI) *m*/*z* 199.1 (MH^+). HRMS (ESI POS) calcd for $C_9H_{12}ClN_2O$ (MH^+) 199.0638, found 199.0639. Anal. Calcd for $C_9H_{11}ClN_2O$: C, 54.42; H, 5.58; N, 14.10. Found: C, 54.21; H, 5.71; N, 14.10.

Synthesis of *N*-Isopropyl-2-methoxy-isonicotinamide (43). NaOMe (95%, 27.82 g, 489.3 mmol, 5.0 equiv) was added to a stirred solution of **42** (19.44 g, 97.86 mmol) in methanol (165 mL) in four equal portions over 60 min. The solution was then heated to 80 °C (oil bath temperature), and the reaction was monitored by HPLC. After 23 h, the mixture was cooled to room temperature and quenched by addition of saturated aqueous NH_4Cl (200 mL). The product was extracted with dichloromethane (3 × 150 mL). The combined organic phases were dried over sodium sulfate (40 g, 30 min) and filtered. The filter cake was washed with dichloromethane (80 mL). After removal of solvent in a rotary evaporator (40 °C/22 mbar), the crude product (15.856 g, 83 wt % (84% over two steps from **41**)) was obtained as a white solid. An analytical sample was obtained by column chromatography with heptane/ethyl acetate (7:3). Mp: 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (dd, 1H, J = 5.3 Hz, J = 0.6 Hz), 7.15 (dd, 1H, J = 5.3 Hz, J = 1.3 Hz), 7.02 (dd, 1H, J = 1.3 Hz, J = 0.6 Hz), 5.89 (br. s, 1H), 4.28 (m, 1H), 3.96 (s, 3H), 1.26 (d, 6H, J = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.34, 165.26, 148.3, 145.6, 114.5, 109.1, 54.3, 42.7, 23.2 ppm. IR (Nujol) 3297, 2924, 1633, 1616, 1539, 1466, 1450, 1394, 1234, 1156, 1133, 1050, 895, 801 cm^{-1}. MS (ESI) *m*/*z* 195.3 (MH^+). HRMS (ESI POS) calcd for $C_{10}H_{14}N_2O_2$ (M^+) 194.1055, found 194.1055. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.61; H, 7.12; N, 14.38.

Synthesis of 3-Hydroxy-2-isopropyl-4-methoxy-2,3-dihydro-pyrrolo[3,4-*c*]pyridin-1-one (44). TMEDA (99.5%, 17.2 mL, 113.3 mmol, 2.2 equiv) was added to a stirred suspension of **43** (10.00 g, 51.40 mmol) in TBME (300 mL) at room temperature resulting in the formation of a clear solution, which was then cooled to −78 °C. Subsequently, *n*-butyllithium (102.8 mL, 1.5 M in hexane, 154.4 mmol, 3.0 equiv) was added over 35 min and stirring was continued at the same temperature for an additional 3 h and subsequently at −22 °C for another 3 h. DMF (13.9 mL, 180.0 mmol, 3.5 equiv) was added to the slightly brown suspension, at −78 °C. The resulting suspension was quenched after 16 h 45 min by addition of saturated aqueous NH_4Cl (200 mL). The mixture was extracted with dichloromethane (3 × 150 mL). The combined organic phases were dried over Na_2SO_4 (20 g, 30 min) and filtered. The filter cake was washed with dichloromethane (40 mL). After evaporation of solvent in a rotary evaporator (40 °C/20 mbar), the crude product (19.400 g, 170 wt %, regioselectivity: 11.68:1 (^{1}H NMR)) was obtained as a brown oil. An analytical sample was obtained by silica gel chromatography (heptane/ethyl acetate = 1:1). Mp: 117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, 1H, J = 5.1 Hz), 7.26 (dd, 1H, J = 5.1 Hz), 6.05 (d, 1H, J = 7.5 Hz), 4.40 (sept, 1H, J = 6.8 Hz), 4.07 (s, 3H), 2.44 (d, 1H, J = 8.5 Hz), 1.44 (d, 3H, J = 6.8 Hz), 1.42 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 159.3, 149.2, 143.1, 124.6, 110.8, 79.9, 53.9, 44.4, 21.8, 20.1 ppm. IR (Nujol) 3290, 2921, 1684, 1667, 1605, 1468, 1418, 1329, 1082, 1047, 868, 854 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 222 (6), 207 (80), 164 (100). HRMS (ESI POS) calcd for $C_{11}H_{14}N_2O_3$ (M^+) 222.1004, found 222.1005. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.26; H, 6.31; N, 12.53.

Synthesis of 4-Methoxy-3*H*-furo[3,4-*c*]pyridin-1-one (45). Sodium borohydride (96%, 5.160 g, 130.9 mmol, 1.5 equiv) was added to a stirred solution of crude **44** (19.40 g, 87.29 mmol) in 2-propanol (300 mL) and water (100 mL) at room temperature. The reaction was monitored by HPLC. After 3 h 10 min, the reduction was quenched at 0 °C by addition of acetone (34.0 mL, 474.4 mmol, 5.3 equiv) and stirring was continued for 35 min at room temperature. The mixture was poured on aqueous 2 M HCl (415 mL, 829.3 mmol, 9.5 equiv) at 0 °C, and stirring was continued for 20 min at room temperature. The mixture was then heated to 50 °C overnight and was subsequently cooled to 0 °C. Dipotassium hydrogen phosphate was added to adjust the pH to 3.0, and ca. 95% of the 2-propanol was removed in a rotary evaporator (40 °C/10 mbar). Water was added until the salts were dissolved, and the mixture was extracted with dichloromethane (3 × 300 mL). The combined organic phases were dried over Na_2SO_4 (50 g, 30 min) and filtered. The solid was washed with dichloromethane (100 mL). After evaporation of solvent in a rotary evaporator (40 °C/25 mbar), the crude product (9.963 g, 69 wt %) was obtained as a light brown solid. Purification was achieved by trituration with ethyl acetate (30 mL) for 24 h at room temperature and subsequent addition of heptane (60 mL). The suspension was then allowed to stand for 24 h at 5 °C yielding the product (5.486 g, 33.22 mmol, 40 wt % (68% over two steps)) as a beige solid. Mp: 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, 1H, J = 5.1 Hz), 7.36 (d, 1H, J = 5.3 Hz), 5.29 (s, 2H), 4.07 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 159.3, 148.1, 136.3, 129.0, 111.7, 68.1, 54.0 ppm. IR (ATR-FTIR) 1785, 1769, 1606, 1465, 1441, 1402, 1360, 1256, 1173, 1036, 845 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 165 (100), 164 (61), 136 (35). HRMS (ESI POS) calcd for $C_8H_7NO_3$ (M^+) 165.0426, found 165.0429. Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.89; H, 4.39; N, 8.57.

Synthesis of 1-Ethyl-4-methoxy-1,3-dihydro-furo[3,4-*c*]pyridin-1-ol (46). Ethyllithium (40.0 mL, 0.5 M in cyclohexane/benzene, 20.0 mmol, 1.1 equiv) was added dropwise to a triethylaluminum solution (10.5 mL 1.9 M in toluene, 20.0 mmol, 1.1 equiv) at 0 °C. After 15 min at 0 °C, THF (50 mL, precooled to −40 °C) was added rapidly via a cannula. A solution of **45** (3.000 g, 18.17 mmol) in THF (75 mL) was subsequently added rapidly at −40 °C (orange suspension). After 10 min at −40 °C, additional ethyllithium (40.0 mL, 20.0 mmol, 1.1 equiv) was added slowly (clear yellow−orange solution). The mixture was allowed to warm to −15 °C within 3 h, and the reaction was afterward quenched by addition of methanol (3.68 mL, 100 mmol, 5 equiv). After 30 min, the mixture was poured in saturated aqueous potassium sodium tartrate (1.5 L) and was extracted with dichloromethane (3 × 500 mL). The combined organic phases were dried over Na_2SO_4 (100 g, 30 min) and filtered. The solid was washed with dichloromethane (200 mL). After evaporation of solvent in a rotary evaporator (40 °C/10 mbar), the crude product (3.77 g, 106 wt %) was obtained as a brown oil, which was purified by column chromatography with heptane/ethyl acetate (7:3) yielding product **46** (1.877 g, 9.61 mmol, 53 wt %) as yellow solid. Mp: 145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) lactol-form: δ 8.15 (d, 1H, J = 5.3 Hz), 6.90 (d, 1H, J = 5.2 Hz), 5.13 (d, 1H, J = 13.2 Hz), 4.95 (d, 1H, J = 13.2 Hz), 3.99 (s, 3H), 2.86 (s, 1H), 2.06 (m, 2H), 0.86 (t, 3H, J = 7.4 Hz) ppm. ^{1}H NMR (300 MHz, $CDCl_3$) hydroxy-ketone-form: δ 8.21 (d, 1H, J = 5.3 Hz), 6.99 (d, 1H, J = 5.2 Hz), 4.63 (d, 2H, J = 7.2 Hz), 4.00 (s, 3H), 3.07 (t, 1H, J = 7.1 Hz), 2.92 (q, 2H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) lactol-form: δ 159.9, 151.9, 146.9, 121.6, 110.7, 110.6, 69.4, 53.5, 32.2, 8.0 ppm. IR (ATR-FTIR) 3280, 1597, 1473, 1458, 1411, 1340, 1096,

1003, 917, 823 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 195 (11), 178 (10), 166 (100), 136 (27). HRMS (ESI POS) calcd for $C_{10}H_{14}NO_3$ (MH^+) 196.0974, found 196.0973. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.38; H, 6.78; N, 7.06.

Synthesis of 1-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methoxy-pyridin-4-yl]-propan-1-one (47). TBSCl (3.475 g, 23.05 mmol, 3.0 equiv) was added to a solution of **46** (1.500 g, 7.68 mmol) and imidazole (1.831 g, 26.89 mmol, 3.5 equiv) in DMF (12.5 mL) at 0 °C. The solution was allowed to slowly warm to room temperature overnight. Heptane (285 mL) was added, and the solution was washed with water (445 mL). The organic phase was separated, dried over Na_2SO_4 (20 g, 30 min), and filtered. The solid was washed with heptane (40 mL). After evaporation in a rotary evaporator (40 °C/10 mbar) and subsequently under high vacuum (40 °C, 0.01 mbar), product **47** (2.34 g, 7.56 mmol, 98 wt %) was obtained as a slighty yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 5.1 Hz), 6.72 (d, 1H, J = 5.2 Hz), 4.77 (s, 2H), 3.96 (s, 3H), 2.82 (t, 2H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.2 Hz), 0.88 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 160.2, 149.2, 144.8, 118.6, 112.9, 56.3, 52.7, 35.4, 24.9, 17.6, 6.7, −6.6 ppm. IR (ATR-FTIR) 2952, 1710, 1594, 1561, 1450, 1371, 1252, 1066, 1018, 835 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 309 (2), 252 (100), 178 (52), 75 (18). HRMS (ESI POS) calcd for $C_{16}H_{28}NO_3Si$ (MH^+) 310.1840, found 310.1838. Anal. Calcd for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found: C, 62.12; H, 8.83; N, 4.47.

Synthesis of (*R*)-3-{3-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methoxy-pyridin-4-yl]-3-hydroxy-pentanoyl}-(*R*)-4-phenyl-oxazolidin-2-one (48). A solution of **39** (1.989 g, 9.69 mmol, 3.0 equiv) in THF (7.5 mL) was slowly added (addition time: 10 min) to a solution of lithium bis(trimethylsilyl)amide (9.79 mL, 1.0 M in THF, 9.69 mmol, 3.0 equiv) at −78 °C. Upon addition, the color changed from colorless to bright yellow. After 2 h at −78 °C, the solution was cooled to −95 °C and **47** (1.000 g, 3.231 mmol) dissolved in THF (6.7 mL) was slowly added (addition time: 60 min) using a syringe pump. The solution was kept for an additional 30 min at −95 °C and then for 1 h at −78 °C. Subsequently, the reaction was quenched by addition of aqueous 0.5 M HCl (50 mL). The mixture was extracted with dichloromethane (3 × 50 mL), and the combined extracts were dried over sodium sulfate (10 g, 30 min) and filtered. The filter cake was washed with dichloromethane (20 mL). After removal of solvent in a rotary evaporator (40 °C/5 mbar), the crude product was obtained as an orange solid (3.12 g, 188 wt %, dr = 87:13 (^{1}H NMR)). An analytical sample (dr > 50:1; colorless oil) was obtained by semipreparative HPLC (Extend C18, 21.2 × 150 mm). $[\alpha]_D^{20}$ (c = 0.285 g/dL, $CHCl_3$) = −98.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 1H, J = 5.4 Hz), 7.23 (m, 3H), 7.03 (m, 2H), 6.67 (d, 1H, J = 5.5 Hz), 5.42 (s, 1H), 5.35 (dd, 1H, J = 8.7 Hz, J = 4.0 Hz), 4.97 (d, 1H, J = 11.6 Hz), 4.93 (d, 1H, J = 11.6 Hz), 4.62 (t, 1H, J = 8.7 Hz), 4.18 (dd, 1H, J = 8.6 Hz, J = 4.2 Hz), 4.07 (d, 1H, J = 16.2 Hz), 3.91 (s, 3H), 3.23 (d, 1H, J = 16.2 Hz), 1.90 (m, 2H), 0.87 (s, 9H), 0.78 (t, 3H, J = 7.4 Hz), 0.06 (s, 3H), 0.01 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 162.8, 155.4, 153.7, 145.3, 138.4, 129.0, 128.4, 125.4, 120.3, 115.5, 78.1, 69.8, 57.5, 56.5, 53.5, 46.0, 36.4, 25.9, 18.3, 7.9, −5.3, −5.4 ppm. IR (MTIR) 3480, 2928, 1779, 2698, 1380, 1249, 1044, 1003, 835, 762, 696 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 515 (2), 457 (2), 439 (1), 365 (31), 262 (96), 252 (54), 202 (100), 178 (69). HRMS (ESI POS) calcd for $C_{27}H_{38}N_2O_6NaSi$ (MNa^+) 537.2397, found 537.2396. Anal. Calcd for $C_{27}H_{38}N_2O_6Si$: C, 63.01; H, 7.44; N, 5.44. Found: C, 62.68; H, 7.62; N, 5.44.

Synthesis of (*R*)-3-Hydroxy-3-(3-hydroxymethyl-2-methoxy-pyridin-4-yl)-pentanoic Acid (49). An aqueous solution of LiOH (37.8 mL, 0.8 M, 30.2 mmol, 5.0 equiv) and an aqueous solution of H_2O_2 (3.02 mL, 10 M, 30.2 mmol, 5.0 equiv) was added to a solution of crude **48** (3.11 g, 6.04 mmol) in THF (35 mL) at 0 °C. After 30 min, aqueous NaOH solution (220 mL, 2.0 M) was added and the ice bath was removed. The reaction was monitored by HPLC. After 2 h, the resulting emulsion was extracted with TBME (7 × 100 mL) to remove unreacted **47** and the auxiliary. [Auxiliary recycling: the TBME extracts were evaporated to dryness in a rotary evaporator (40 °C/5 mbar) yielding a yellow semisolid (1.61 g), which was purified by dissolving in ethyl acetate (3 mL) at reflux temperature and subsequent dropwise addition of heptane (7.5 mL). The resulting suspension was filtered, and the isolated crystals were washed with heptane (2 mL) yielding the pure auxiliary (1.07 g, 87 wt %).] The aqueous phase was acidified with aqueous HCl (2.0 M) to adjust the pH to 3.0 and was extracted with dichloromethane/ethanol (4:1, 9 × 100 mL). After evaporation in a rotary evaporator (40 °C/5 mbar), product **49** was obtained as a colorless semisolid (700 mg, 2.74 mmol, 45 wt % (85% over two steps from **47**), er = 80.5:19.5) (chiral HPLC method, sample preparation: ethanol solution; Chiralpak-ADH column, 250 × 4.6; temperature of 25 °C; mobile phase, 90% heptane, 10% ethanol/trifluoroacetic acid (99:1); flow of 0.8 mL/min; injection volume of 5 μL, detection, UV 308 nm; retention time, 22.20 min **(*R*)-49**, 24.78 min **(*S*)-49**). **49** lactonizes partly during solvent evaporation and also when stored at ambient temperature, thus ruling out a correct microanalysis. $[\alpha]_D^{20}$ (c = 1.3154 g/dL, $CHCl_3$) = +9.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, 1H, J = 5.5 Hz), 6.76 (d, 1H, J = 5.4 Hz), 5.04 (d, 1H, J = 12.2 Hz), 4.89 (d, 1H, J = 12.2 Hz), 3.97 (s, 3H), 3.07 (d, 1H, J = 16.2 Hz), 2.85 (d, 1H, J = 16.2 Hz), 1.92 (br. q, 2H, J = 7.5 Hz), 0.82 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 163.5, 154.2, 145.5, 120.9, 115.3, 77.4, 56.5, 54.1, 44.7, 35.3, 8.1 ppm. IR (ATR-FTIR) 3404, 2949, 1725, 1596, 1567, 1450, 1370, 1267, 1188, 1044 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 237 (19), 208 (20), 166 (100). HRMS (ESI POS) calcd for $C_{12}H_{17}NO_5Na$ (MNa^+) 278.1004, found 278.1004. HRMS (ESI POS) calcd for $C_{12}H_{18}NO_5$ (MH^+) 256.1185, found 256.1184. Microanalysis: C was not in the range <0.4%, even after purification by preparative HPLC (HPLC purity 100.0%).

Synthesis of (*R*)-5-Ethyl-5-hydroxy-2,5,6,9-tetrahydro-8-oxa-2-aza-benzocycloheptene (7). Aqueous HBr (48%, 1.01 mL, 9.0 mmol, 2.1 equiv) was added to a stirred solution of **49** (1.097 g, 4.298 mmol) in 1,2-dimethoxyethane (15 mL). After 15 min at room temperature, the solution was heated to 50 °C. After 18 h at 50 °C, the resulting suspension was allowed to stir at room temperature for an additional 24 h and subsequently to stand at 5 °C for 18 h. The precipitate was collected by filtration using no vacuum and was subsequently washed with TBME (2 × 2.6 mL), then with acetone (2.6 mL), water (2 × 3.2 mL), and finally again with acetone (2 × 2.6 mL). After evaporation of residual solvent in a rotary evaporator (40 °C/10 mbar), product **7** (418.1 mg, 1.873 mmol, 44 wt %, er > 99.95:0.05 (chiral HPLC, sample preparation: ethanol solution; Chiralcel-ODH column, 250 × 4.6; temperature of 25 °C, mobile phase, 75% heptane, 25% ethanol/trifluoroacetic acid (99:1); flow of 0.8 mL/min; injection volume of 5 μL; detection, UV 308 nm; retention time, 9.68 min **(*S*)-7**, 13.28 min **(*R*)-7**)) was obtained as white crystals. $[\alpha]_D^{20}$ (c = 1.178 g/dL, DMSO) = +127.9. 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 = 7.5 Hz) ppm. The other analytical data are in accordance with those described above.

Synthesis of (*R*)-3-Acetyl-4-phenyl-oxazolidin-2-one (39).[22] *n*-Butyllithium (21.0 mL, 1.5 M in pentane, 31.53 mmol, 1.05 equiv) was added to a stirred suspension of (4*R*)-(−)-4-phenyl-2-oxazolidinone (98%, 5.000 g, 30.03 mmol) in THF (100 mL) at 0 °C within 10 min. The resulting colorless solution was stirred for an additional 50 min at 0 °C. Acetyl chloride (2.57 mL, 36.0 mmol, 1.2 equiv) was then added within 1 min. After 3 h 30 min, the reaction was stopped by addition of saturated aqueous NH_4Cl (25 mL) and the mixture was extracted with ethyl acetate (75 mL). The organic phase was washed with aqueous $NaHCO_3$ (50 mL,

(22) Known compound: Ferroci, M.; Inesi, A.; Palombi, L.; Rossi, L.; Sotgiu, G. *J. Org. Chem.* **2001**, *66*, 6185.

1.0 M) and with brine (50 mL). The solution was dried over sodium sulfate (5 g, 30 min) and filtered. The filter cake was washed with ethyl acetate (10 mL). After removal of solvent in a rotary evaporator (40 °C/18 mbar), the crude product (6.13 g, 100 wt %) was obtained as white crystals. Purification was achieved by dissolving in 10.6 mL of ethyl acetate at reflux temperature and subsequent dropwise addition of heptane (26.6 mL). The resulting suspension was allowed to slowly cool to 5 °C, and after standing overnight, the precipitate was collected by filtration. After washing with heptane (3 mL), product **39** (5.26 g, 25.6 mmol, 85 wt %) was obtained as white crystals. $[\alpha]_D^{20}$ ($c = 0.083$ g/dL, $CHCl_3$) = −58.8. Mp: 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.42 (m, 5H), 5.42 (dd, 1H, $J = 8.8$ Hz, $J = 3.5$ Hz), 4.69 (t, 1H, $J = 8.8$ Hz), 4.29 (dd, 1H, $J = 8.8$ Hz, $J = 3.5$ Hz), 2.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 153.9, 139.1, 129.2, 128.8, 126.0, 70.0, 57.5, 23.8 ppm. IR (Nujol) 2923, 1789, 1707, 1332, 769, 703 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 205 (7), 162 (47), 161 (100), 43 (77). HRMS (ESI POS) calcd for $C_{11}H_{12}NO_3$ (MH^+) 206.0817, found 206.0818. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.39; N, 6.75.

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Supporting Information Available: General experimental methods and ^{1}H/^{13}C NMR spectra of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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