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Synthesis and evaluation of the antitumor agent TMC-69-6H and a focused library of analogs

Alois Fürstner,[a,*] Fabian Feyen,[a] Heino Prinz[b] and Herbert Waldmann[b]

[a]*Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany*
[b]*Max-Planck-Institut für Molekulare Physiologie, D-44227 Dortmund, Germany*

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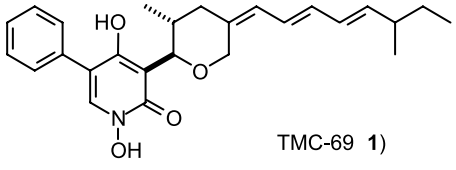
Abstract—A concise, efficient and flexible total synthesis of the potent antitumor agent TMC-69-6H (**2**) is described. Key steps involve the palladium catalyzed regioselective addition of 4-hydroxy-2-pyridone **5** to pyranyl acetate **6** which is accompanied by a spontaneous 1,4-addition of the phenolic –OH group to the emerging enone to give the tricyclic product **7** in excellent yield. When this reaction is carried out with optically enriched (*S*)-**6** (conveniently prepared by a lipase catalyzed kinetic dynamic resolution) in the presence of the chiral ligand (*S*,*S*)-**12** and allylpalladium chloride dimer, the ensuing matched situation delivers the key building block (−)-**7** in 96% ee. Its further elaboration into **2** involves a Julia–Kocienski olefination with tetrazolylsulfone **19** and a final *N*-oxidation effected by the peroxomolybdenum complex [(pyridine)MoO_5(HMPA)] to form the hydroxamic acid motif. The flexibility inherent to this route allows for the preparation of a focused library of analogues for biochemical evaluation. The results obtained show that *N*-hydroxy-2-pyridone derivatives constitute a promising new class of selective phosphatase inhibitors. In contrast to previous reports in the literature, however, TMC-69-6H and congeners are found to exhibit pronounced activities against the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1, while being only weak inhibitors for the dual specific phosphatases Cdc25 A and B. Two key intermediates of the synthesis route have been characterized by X-ray crystallography.

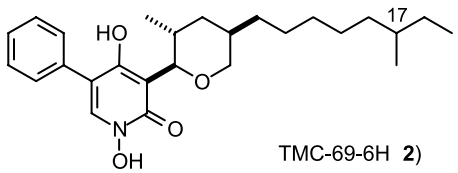
1. Introduction

Reversible phosphorylations of proteins mediate innumerable biological processes, and aberrant phosphorylation can cause the development of human diseases such as cancer and diabetes.[1] As a consequence, all enzymes involved in the regulation of protein phosphorylation sates represent potential targets for current medicinal chemistry and chemical biology research. While the phosphorylating protein kinases have already been intensively studied,[2] it was only recently that their natural antagonists, the protein phosphatases (PPs) responsible for the catalyzed hydrolysis of phosphate esters on tyrosine, serine and threonine, received similar attention.[3–7]

Among them, the dual specific protein phosphatases (PP's) of the Cdc25 family are particularly attractive for their eminent role in cell cycle control.[8] Their physiological substrates are cyclin-dependent kinases which, in turn, trigger key transitions in the process of eukaryotic cellular division. Hence, the homologous Cdc25 enzymes exert crucial regulatory functions at the crossroads between cellular proliferation, cell cycle arrest, and apoptosis. Their oncogenic properties together with the fact that Cdc25A and B are overexpressed in many human tumors render these isoenzymes molecular targets of utmost interest in the quest for anticancer drugs.[7–9]



TMC-69 **1**)



TMC-69-6H **2**)

The number of small molecules that qualify as lead structures in the search for selective inhibitors of Cdc25 phosphatases, however, is rather limited. A particularly promising candidate is the *N*-hydroxy-2-pyridone derivative TMC-69 (**1**) isolated from the culture broth of the fungus

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* Corresponding author. Tel.: +49-208-306-2342; fax: +49-208-306-2994; e-mail: fuerstner@mpi-muelheim.mpg.de

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Chrysosporium sp. TC 1068.[10] According to the literature, this compound is distinguished by IC_{50} values in the low micromolar range as well as by a surprising selectivity for Cdc25 A and B over other phosphatases. While **1** itself is inherently labile and degrades within 2 weeks even at 0 °C, hydrogenation of its triene moiety results in a significantly improved stability and was reported to enhance the inhibitory activity as well as the cytotoxicity even further. Importantly, TMC-69-6H (**2**) thus formed has also proven effective in vivo for the treatment of P388 murine leukemia and B16 melanoma in nude mice, leading to an increase on life span of up to 105.9% at a dose of 1.25 mg/kg i.p.[10]

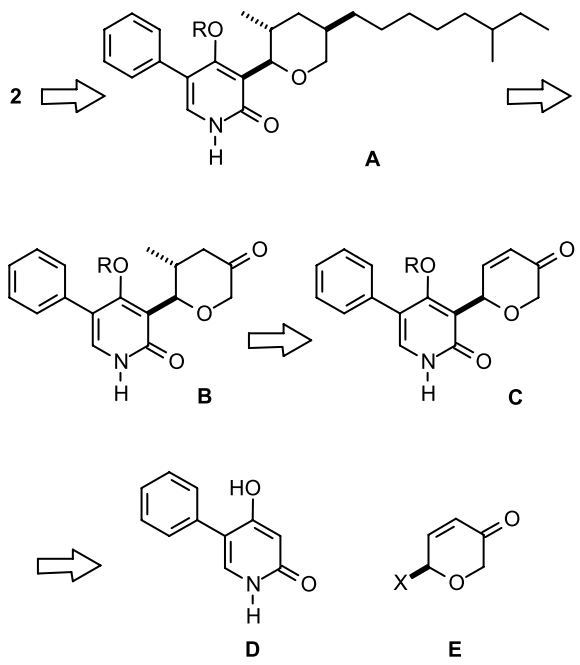
Due to this favorable profile, TMC-69-6H was selected for further study in our program directed at the identification and development of novel classes of phosphatase inhibitors.[11–13] Outlined below is the first total synthesis of both the (17*R*)- and the (17*S*)-configured isomers of **2**, since the absolute stereochemistry at this remote chiral center in the natural product **1** and its derivative **2** has not yet been established.[14] The chosen route is based on a novel palladium catalyzed fragment coupling process for the assembly of the core structure. Moreover, its inherent flexibility allowed for the synthesis of a focused library of analogues which enabled first insights into structure/activity relationships (SAR). Surprisingly though, the consistent set of biochemical data obtained with these samples is not in accord with the claims previously made in the literature.[10] Rather than being potent inhibitors of Cdc25A and B, we find pyridone derivatives of this series to inhibit the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1 much more effectively. The relevance of this finding, which results in the re-definition of the activity profile of TMC-69-6H, is outlined below.

2. Results and discussion

2.1. Retrosynthetic analysis

Since the hydroxamic acid function likely contributes to the lability of **2**, it was decided to install this group at a late stage of the synthesis by *N*-oxidation of the pyridone precursor **A** (Scheme 1). The alkyl side chain of the latter can be attached to the heterocyclic core by an olefination/hydrogenation sequence which provides opportunities for structural variations of this part of the molecule at a later stage. The required precursor **B** featuring two *trans*-disposed substituents might be secured by a 1,4-addition of a suitable methyl donor to the corresponding enone **C** which should derive from pyridone **D** and the pyranone **E**.

Although one might envisage to join these building blocks by established oxo-carbenium cation chemistry,[15] recourse to palladium catalyzed C–C-bond formations should allow to control the absolute stereochemistry at the ring junction and therefore provide a more attractive solution.[16] To this end, however, the metal template has to force the ambident pyridone **D** to act exclusively as a *C*- (rather than *O*- or *N*-) nucleophile and its equally ambident reaction partner **E** to behave solely as an allylcation equivalent rather than as a Michael acceptor. Such a reactivity pattern cannot be taken

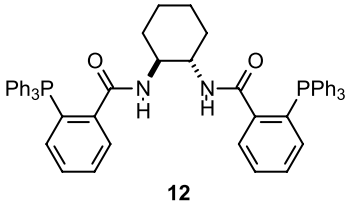


Scheme 1. Retrosynthetic analysis of TMC-69-6H (**2**).

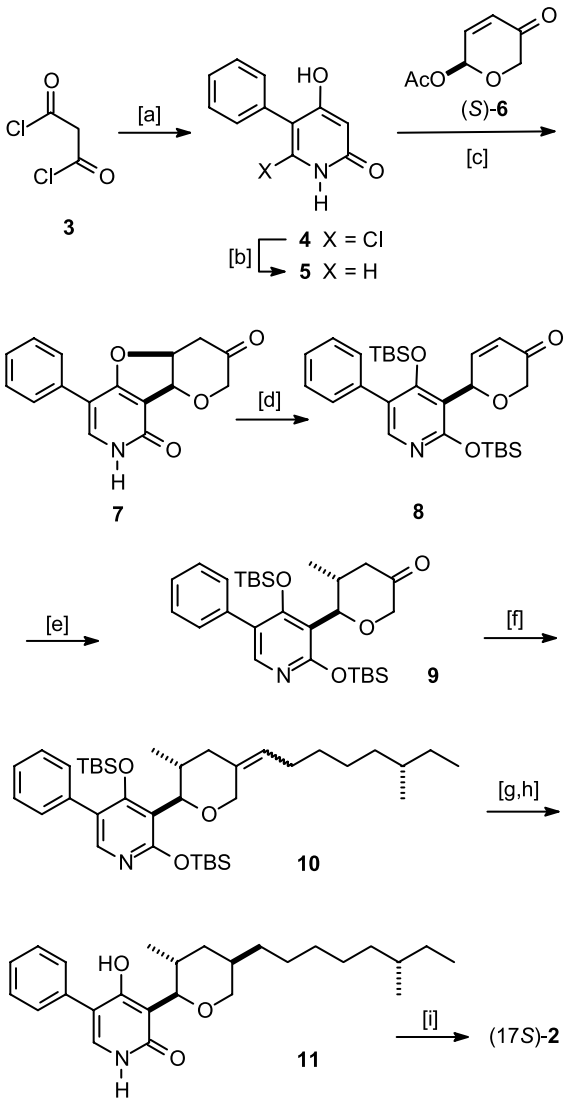
as granted because 2-pyridones tend to react with allylic substrates at their *N*-atom in the presence of palladium catalysts,[17] and palladium catalyzed transformations of 6-hydroxy-6*H*-pyran-3-one **E** (X=OR) derivatives are rather scarce and seem to be restricted to reactions with *O*-nucleophiles.[18] To the best of our knowledge, no Pd-catalyzed *C*-arylation of such a compound with a phenol derivative has previously been described. If successful, however, the envisaged fragment coupling process would greatly contribute to the overall flexibility of the synthesis route and add a new facet to organopalladium chemistry in general.[19,20]

2.2. Total synthesis

The required 4-hydroxypyridone **5** was prepared on a large scale by condensation of malonic acid dichloride **3** with 2-phenylacetonitrile followed by hydrogenolytic removal of the residual chloride in **4** (Scheme 2).[21] We were pleased to see that compound **5** reacted smoothly and regioselectively at its 'enolic' site with *rac*-**6**[22] in the presence of $Pd(PPh_3)_4$ cat. and Et_3N in DMF to give the tricyclic product (±)-**7** in 89% yield. The palladium-catalyzed C–C-bond formation is accompanied by a spontaneous 1,4-addition of the 4-OH group to the enone entity of the emerging product; we are unaware of any precedence for this transformation. Attempts to perform this reaction enantioselectively using *rac*-**6** as the substrate and the chiral diphosphine **12**[23] as ligand to Pd were unrewarding (ee ~30%).



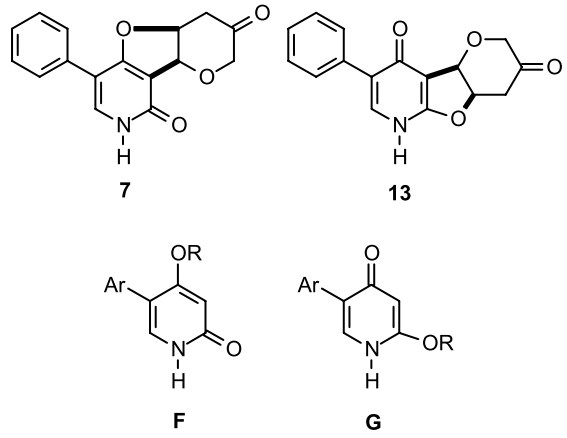
12



Scheme 2. Synthesis of (17*S*)-**2**: [a] phenylacetonitrile, 4d, 50%; [b] H_2 (1 atm), Pd/C, EtOH, 60 °C, 97%; [c] $[(allyl)PdCl]_2$ (0.5%), ligand **12** (1.5%), DMF, 65% (ee=96%); [d] TBSCl, Et_3N, 18 h, 78%; [e] Me_2CuLi, THF, −70 °C; [f] LiHMDS, (*S*)-**19**, THF, −78 °C, 69% (over both steps); [g] H_2, Pd/C, EtOH; [h] TBAF, THF, 69% (over both steps); [i] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 71%.

Gratifyingly though, the use of **12** in combination with enantiomerically enriched (*S*)-**6** (ee=81%), which is easily prepared on a multigram scale by a lipase catalyzed dynamic resolution,[24] served our purpose very well, delivering the tricyclic ketone (−)-**7** in good yield (65%) and excellent optical purity (ee=96%) (Scheme 2). Thereby it is essential to keep the catalyst loading low to avoid partial racemization of the intermediates via ligand transfer processes.

It is worth mentioning that an unambiguous structure assignment of this tricyclic product is not trivial. Specifically, one has to consider that the 2-hydroxy-4-pyridone tautomer of **5** might come into play and lead to the formation of compound **13**, which is difficult to distinguish from **7** by NMR and IR. Recent studies, however, revealed that such tautomeric ethers show distinctly different UV spectra.[21,25] While chromophors of the general type **F** have an absorption maximum in the range of λ_{max}=245–247 nm, their constitutional isomers **G** absorb at λ_{max}=233–235 nm. Since the tricyclic product formed in the palladium-catalyzed fragment coupling process shows a λ_{max} at 245 nm, we ascribe the 2(1*H*)-pyridinone structure **7** to this key building block.



The cyclic ether moiety in **7** acts as a temporary protecting group for the enone, which can be released by a retro-Michael reaction on treatment with oxophilic reagents in the presence of a base.[26] Optimal results were obtained with TBSCl in combination with Et_3N. The bis-TBS-ether **8**, though labile, can be isolated in pure form, whereas its TMS-counterpart is too unstable to be of practical use. The structure of this compound in the solid state is shown in Figure 1. As can be seen, one π-face of the enone (C7A–C8A) is strongly shielded by the bulky silyl group attached to O4A. Although it has not been investigated if this product adopts a similar conformation in solution, this particular steric arrangement augured for a good selectivity in the subsequent 1,4-addition reaction.

In fact, exposure of compound **8** to Me_2CuLi afforded the somewhat sensitive *trans*-disubstituted ketone **9** in good yield and excellent diastereoselectivity (de >90%). Crystals suitable for X-ray analysis could be obtained from the closely related compound **25** carrying a chloride substituent on the pyridone ring (see below). Its structure in the solid state is shown in Figure 2.

Although ketone **9** can be isolated in pure form, it turned out to be rather unstable. Therefore the crude product was immediately subjected to a Julia–Kocienski olefination reaction for the introduction of the aliphatic side chain.[27,28] The required sulfones were prepared from citronellene **14** as shown in Scheme 3 for (*R*)-**19**. Selective ozonolysis of the more highly substituted double bond[29,30] followed by routine elaboration of the resulting aldehyde **15** gave alcohol **17**, which condensed with commercial 1-phenyl-1*H*-tetrazol-5-thiol under Mitsunobu conditions[31] to give sulfide **18**. Oxidation with aqueous H_2O_2 in the presence of catalytic amounts of ammonium molybdate furnished sulfone (*R*)-**19** in good overall yield. Since both isomers of citronellene are commercially available, the antipodal sulfone (*S*)-**19** is equally accessible by this route.

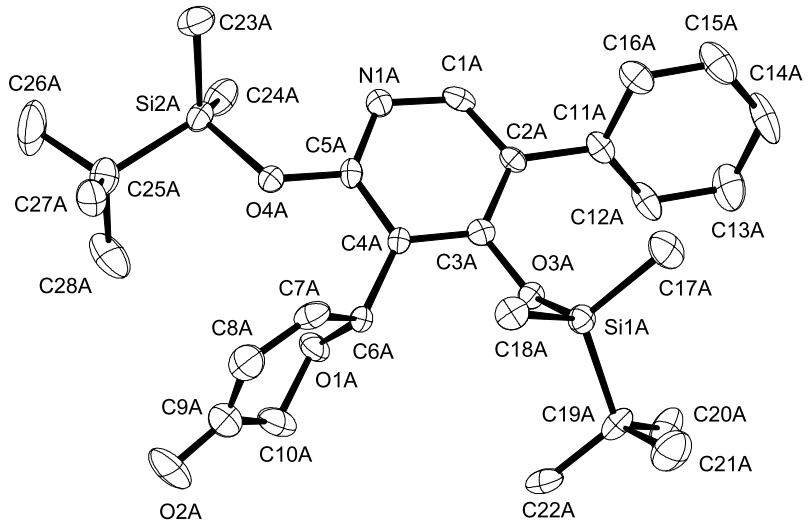
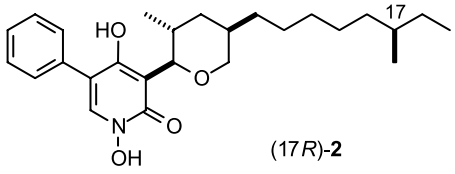


Figure 1. Molecular structure of compound **8** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level, hydrogen atoms are omitted for clarity. Only one of the two independent molecules in the unit cell is depicted. Selected bond length (Å) and angles (°): C(1A)–N(1A) 1.341(6), C(1A)–C(2A) 1.371(7), C(2A)–C(3A) 1.409(7), C(3A)–C(4A) 1.383(6), C(4A)–C(5A) 1.401(6), C(5A)–N(1A) 1.330(6), C(6A)–C(7A) 1.488(7), C(7A)–C(8A) 1.352(7), C(8A)–C(9A) 1.439(8), C(9A)–O(2A) 1.229(7), C(9A)–C(10A) 1.488(9), C(10A)–O(1A) 1.427(6), C(6A)–O(1A) 1.435(5), C(3A)–O(3A) 1.375(6), C(5A)–O(4A) 1.350(5), C(8A)–C(7A)–C(6A) 120.9(5), C(7A)–C(8A)–C(9A) 120.3(6), O(2A)–C(9A)–C(8A) 122.8(7), O(1A)–C(6A)–C(7A) 111.5(4), O(1A)–C(10A)–C(9A) 113.5(5).

Reaction of the lithiated sulfone (*S*)-**19** with the crude ketone **9** provided alkene **10** as a 1:1 mixture of isomers. HPLC analyses on chiral columns and comparison with the racemic series confirmed that no racemization had occurred during this or any of the preceding steps (ee = 97%). Subsequent hydrogenation of the (*E*,*Z*)-mixture of **10** over Pd/C followed by cleavage of the –OTBS groups furnished a separable 5:1 mixture of the desired product **11** and its C-10 diastereomer in 69% yield over both steps. The axial orientation of the alkyl chain on the tetrahydropyran ring in **11** was evident from an analysis of the pertinent coupling constants and NOESY data (Scheme 4).

For the final *N*-oxidation to the desired hydroxamic acid derivative,[33] compound **11** was refluxed with hexamethyldisilazane (HMDS) and the resulting bis-silylether was treated with the peroxomolybdenum complex [(pyridine)MoO_5(HMPA)].[34] An aqueous work-up of the reaction mixture with EDTA to sequester all metal cations completed the first total synthesis of (17*S*)-TMC-69-6H (17*S*-**2**).



(17*R*)-**2**

As mentioned earlier, no secured information concerning the absolute stereochemistry of the remote chiral center on the lateral chain of compound **2** derived from natural sources is presently available.[10] Therefore the same

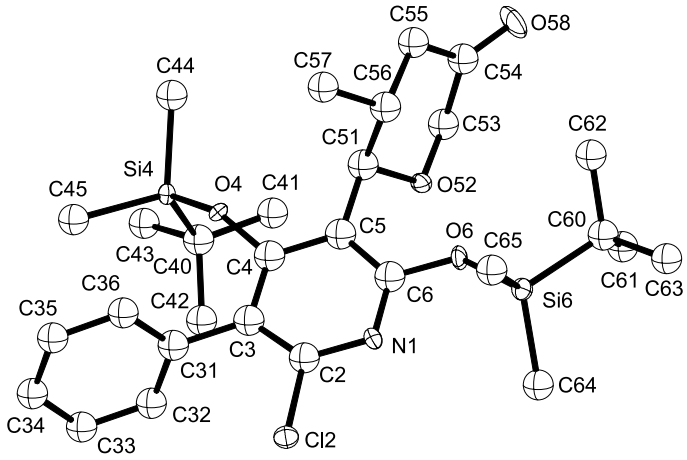
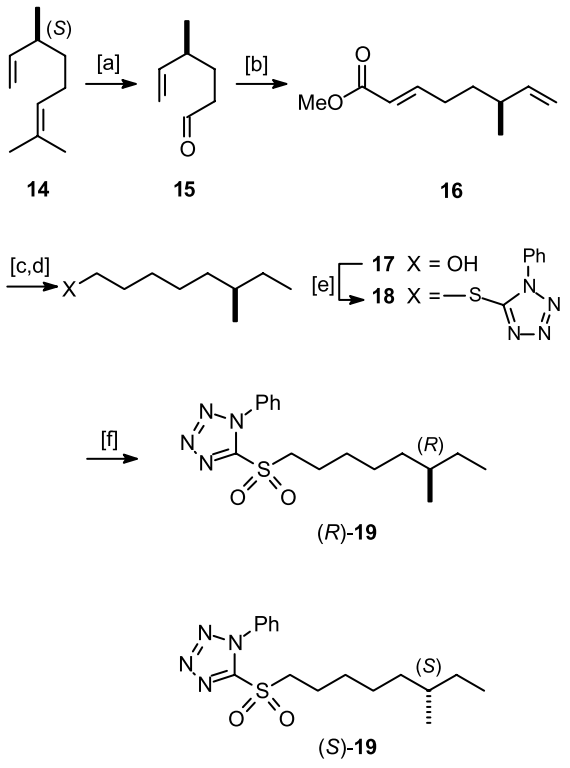


Figure 2. Molecular structure of compound **25** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level, hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (°): N(1)–C(2) 1.335(6), N(1)–C(6) 1.342(6), C(2)–C(3) 1.385(7), C(3)–C(4) 1.408(7), C(4)–C(5) 1.395(7), C(5)–C(6) 1.398(7), O(4)–C(4) 1.361(6), O(6)–C(6) 1.342(6), C(51)–C(56) 1.527(7), C(55)–C(56) 1.533(7), C(54)–C(55) 1.496(8), C(54)–O(58) 1.201(6), C(53)–C(54) 1.504(8), O(52)–C(53) 1.420(6), C(51)–O(52) 1.445(6), C(57)–C(56)–C(51) 110.6(4), C(51)–C(56)–C(55) 108.9(4), C(5)–C(51)–C(56) 113.8(4), O(52)–C(51)–C(5) 106.3(4).

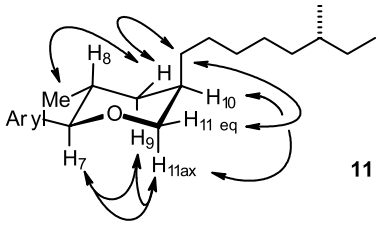


Scheme 3. [a] O_3, CH_2Cl_2, −78 °C, then Me_2S, 98%; [b] $(EtO)_2P(O)CH_2$-COOMe, NaH, THF, −78 °C, 87%; [c] Dibal-H, Et_2O, 91%; [d] H_2, Pd/C, 88%; [e] 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, 68%; [f] $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.1 equiv.), H_2O_2 (10 equiv.), EtOH, 93%.

sequence of reactions was repeated using ketone (−)-**9** and the antipodal sulfone (*R*)-**19** to give (17*R*)-**2** in similar overall yield. The diastereomeric compounds (17*R*)-**2** and (17*S*)-**2** thus obtained, however, are virtually indistinguishable by NMR and match the literature data reported for TMC-69-6H very well. Even a direct comparison of their spectra recorded at 600 MHz with those of an authentic sample does not allow us to rigorously assign the absolute stereochemistry of TMC-69-6H at that distal site (Tables 1 and 2).[35]

2.3. Analogues

In view of the promising biochemical and biological properties of TMC-69 and TMC-69-6H described in the literature,[10] the preparation of analogues was called for. Taking advantage of the flexibility inherent to the synthesis route described above we prepared a small collection of analogues for biological evaluation in order to gain first insights into structure/activity relationships.



Scheme 4. Schematic representation of compound **11** with characteristic NOESY data. The following coupling constants indicate a chair conformation of the tetrahydropyran ring: $^3J_{H7,H8}=10.4$ Hz, $^3J_{H10,H11ax}=2.5$ Hz, $^3J_{H10,H11eq}\leq 1$ Hz (TMC-69-6H numbering).[32]

The ketone group in **9** provides an opportunity for late stage divergent modification that might allow to probe the importance of the aliphatic tail for binding to the protein. To this end, compound **9** was subjected to Julia–Kocienski olefination reactions with the two unbranched alkyl sulfones **20a**,**b**.[27,36] The olefins **21a**,**b** thus formed were hydrogenated over Pd/C and the major stereoisomers of the resulting products (d.r.=5:1) were separated and *N*-oxidized with [(pyridine)MoO_5(HMPA)] as outlined above to give products **23a**,**b**, respectively, differing from the lead compound **2** only in their lipophilicity (Scheme 5).

Next, the synthesis was repeated with the 6-chloropyridone derivative **4**[21] which was formed as the primary product in the condensation reaction shown in Scheme 2. Gratifyingly, the aryl halide did neither interfere in the palladium-catalyzed fragment coupling step to give optically active tricyclic ketone **24** (ee=95%) nor in the cuprate addition reaction introducing the methyl branch. However, dehalogenation competes with the hydrogenation of the double bond in product **26**; therefore careful monitoring of the reaction was necessary to obtain product **27** in 44% yield, which was oxidized according to the established protocol to give the desired analogue **28** for biological evaluation (Scheme 6).

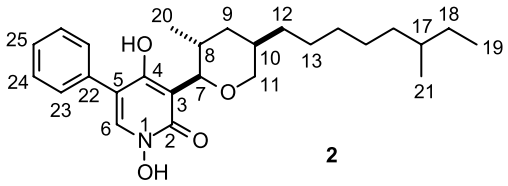
Finally, more substantial structural modifications were made by substituting the entire lipophilic segment of the natural product by bare alkyl chains attached to C-3 of the pyridone (Scheme 7). For this purpose, we investigated if simple allylic esters undergo similar palladium catalyzed cross coupling reactions with pyridone **5** as does the more activated substrate **6** used in the total synthesis of **2**. In fact, acetates **29a**,**b** afforded the desired C-allylated products **30a**,**b**, although more forcing conditions were required and the yields were lower than those obtained with **6**. Subsequent hydrogenation followed by *N*-oxidation proceeded uneventfully and afforded product **32** as a simplified analogue of TMC-69-6H.

2.4. Biochemical investigations: Re-assessment of the phosphatase inhibitory activity of TMC-69-6H and analogues

The excellent match between the analytical and spectroscopic data of (17*R*)-**2** and (17*S*)-**2** prepared by total synthesis with those reported in the literature leaves no doubt about the structural integrity of these compounds. Therefore we were surprised to find that their phosphatase inhibitory activity significantly deviates from the reported profile both in terms of potency and selectivity. In contrast to what has been claimed,[10] the compounds prepared by total synthesis as well as the authentic sample of **2** all turned out to be only rather weak inhibitors for Cdc25A ($IC_{50}>30$ μM) in our assay. Instead, they exhibit promising activities against the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1 (Table 3).

PTP1B is a key negative regulator of insulin-receptor

Table 1. Comparison of the ^{13}C NMR data of (17*R*)-**2** and (17*S*)-**2** in $CDCl_3$ with those of the authentic material published in the literature;[10] the accuracy of the recorded data is ± 0.1 ppm. Arbitrary numbering scheme as shown in the insert



2

Position	(17*S*)-**2**	(17*R*)-**2**	Authentic sample	Literature[10]
2	157.2	157.2	157.4	157.0
3	109.3	109.5	109.3	109.3
4	160.9	161.0	161.0	160.9
5	113.5	113.7	113.7	113.5
6	131.1	130.5	130.8	129.9
7	81.6	81.6	81.6	81.7
8	31.0	31.0	31.0	31.0
9	36.1	36.1	36.1	36.1
10	33.0	34.0	34.0	34.0
11	72.4	72.4	72.4	72.5
12	30.8	30.8	30.8	30.9
13	30.0	29.9	29.9	30.0
14	27.1	27.0	27.0	27.1
15	27.8	27.8	27.8	27.8
16	36.5	36.5	36.5	36.9
17	34.4	34.4	34.4	34.4
18	29.5	29.5	29.5	29.5
19	11.4	11.4	11.4	11.4
20	17.8	17.8	17.8	17.9
21	19.2	19.2	19.2	19.2
22	133.2	133.1	133.2	133.2
23	129.2	129.2	129.2	129.2
24	128.4	128.4	128.4	128.4
25	127.7	127.7	127.7	127.7

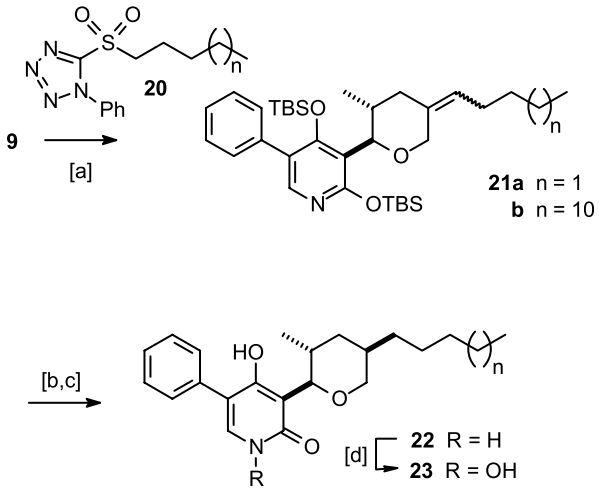
activity, and PTP1B-inhibitors are expected to enhance insulin sensitivity and act as effective therapeutics for the treatment of Type II diabetes, insulin resistance and obesity.[6] The vaccinia VH1-related phosphatase VHR is a physiological regulator of various members of the MAP kinase family and therefore influences signaling cascades via the MAP kinase pathway.[37] PP1 is a major enkaryotic phosphatase that regulates diverse cellular processes such as signal transduction, cell cycle progression, protein synthesis, muscle contraction, carbohydrate metabolism and transcription. All of these phosphatases have been subject to intense research activities aimed at the development of inhibitors for biological studies and drug development.[1–7,38]

The evaluation of TMC-69-6H, its analogues and isomers described above allows us to draw further conclusions. First, the comparison of the IC_{50} values for, e.g. (17*S*)-**2** with those of the precursor amide (17*S*)-**11** indicate that the presence of the *N*-OH group in the heterocycle, though not strictly required for phosphatase inhibition, enhances the potency of such compounds. Secondly, (17*S*)-**2** and (17*R*)-**2** are equally effective inhibitors within the error margins, thus showing that the configuration at the lateral methyl branch is hardly relevant. In line with this notion, analogues **23a**,**b** bearing straight-chain alkyl residues were both active, with the more lipophilic compound **23b** being significantly more potent. Furthermore, alkene groups embedded in the alkyl side chain are tolerated and their configuration is of minor importance since both isomers of **10** and **30b** led to respectable phosphatase inhibition. The chloride substituent on the pyridone ring in **28** is well accommodated, indicating that further variations in the aromatic part of **2** might be worthwhile. Equally promising is the fact that even more severe structural changes as those found in compounds **30**–**32** do not annihilate the inhibitory capacity for relevant phosphatases at all.

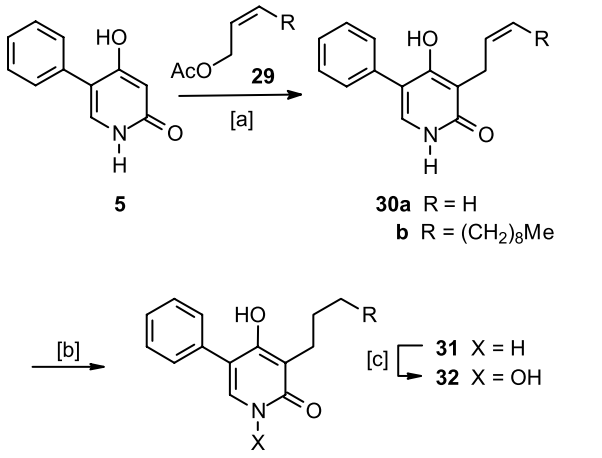
Although we are unable to reconcile our findings concerning

Table 2. Comparison of pertinent ^1H NMR data of (17*R*)-**2** and (17*S*)-**2** in $CDCl_3$ with those of the authentic material published in the literature;[10] the full set of data is compiled in the Section 3; arbitrary numbering scheme as shown in the insert to Table 1

Position	(17*S*)-**2**	(17*R*)-**2**	Literature[10]
–OH	9.52	9.52	9.51
6	7.67	7.67	7.67
7	4.68 (d, $J=10.5$ Hz)	4.68 (d, $J=10.5$ Hz)	4.68 (d, $J=10.5$ Hz)
8	2.06 (m)	2.07 (m)	2.08 (m)
9a	1.76 (d, $J=12.2$ Hz)	1.76 (d, $J=11.0$ Hz)	1.77 (d, $J=12.0$ Hz)
10	1.62 (m)	1.61 (m)	1.63 (m)
11a	3.96 (d, $J=11.5$ Hz)	3.96 (d, $J=11.8$ Hz)	3.96 (d, $J=11.6$ Hz)
11b	3.72 (dd, $J=11.5$, 2.3 Hz)	3.72 (dd, $J=11.6$, 2.5 Hz)	3.72 (dd, $J=11.6$, 2.5 Hz)

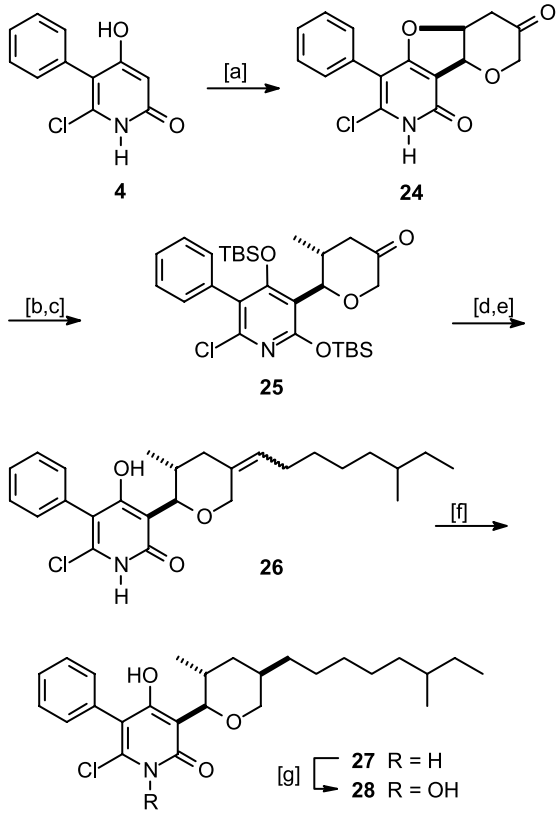


Scheme 5. [a] LiHMDS, **20a**,**b**, THF, −78 °C; [b] H_2, Pd/C, EtOH; [c] TBAF, THF, 32% (**21a** over three steps), 17% (**21b**, over three steps); [d] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 80% (**23a**), 85% (**23b**).



Scheme 7. [a] $Pd(PPh_3)_4$ (5 mol%), Et_3N, DMF, 110 °C, 59% (**30a**, R=H); or: $Pd(PPh_3)_4$ (7.5 mol%), NaH, DMF, 125 °C, 49% (**30b**, R=$(CH_2)_8$Me); [b] H_2 (1 atm), Pd/C, EtOH, quant. 60% (R=$(CH_2)_8$Me); [c] (i) HMDS, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc.

the physiological activity profile of TMC-69-6H with the literature reports,[10] the excellent reproducibility of our results, the internal control against authentic **2**, the consistency within the individual series, and the established validity of our Cdc25-assay[11–13] leave no room for interpretation. More importantly, these data make clear that *N*-hydroxy-2-pyridone derivatives constitute a promising new class of selective phosphatase inhibitors which allow for substantial structural variations and therefore constitute relevant lead compounds for further optimization.[39] Notably, TMC-69-6H incorporates a structural framework not present in any of the PTP1B- and PP1 inhibitors developed so far. Its proven activity in cellular assays as well as in vivo[10] renders further research activities in this field promising. In particular it seems lucrative to investigate the inhibitory profile of other natural products containing an *N*-hydroxy-2-pyridone motif similar to the one found in TMC-69.[40]



Scheme 6. [a] Compound (*S*)-**6**, [(allyl)PdCl]$_2$ (0.5%), ligand **12** (1.5%), DMF, 71% (ee=95%); [b] TBSCl, Et_3N, 1 h, 39%; [c] Me_2CuLi, THF, −70 °C; [d] LiHMDS, **19**, THF, −78 °C; [e] TBAF, THF, *E*/*Z*=1:1, 82% (over three steps); [f] H_2, Pd/C, EtOH, 44%, d.r.=3:1; [g] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 77%.

3. Experimental

3.1. General

All reactions were carried out under Argon in flame-dried glassware using Schlenk techniques. The solvents were dried by distillation over the indicated drying agents and were stored and transferred under Argon: CH_2Cl_2, Et_3N, DMF (CaH_2), toluene, THF, DME (Na), MeOH, EtOH (Mg), Et_2O (Mg-anthracene). Flash chromatography: Merck silica gel (230–400 mesh) using either hexanes/ethyl acetate or pentanes/diethyl ether in various proportions as the eluents. NMR: Spectra were recorded on a Bruker DPX 300, AMX 400, DMX 600 spectrometer in $CDCl_3$ or CD_2Cl_2 as indicated. Chemical shifts (δ) are given in ppm relative to the residual peak of $CHCl_3$ or $CHDCl_2$; coupling constant (J) in Hz. IR: Nicolet FT-7199, wavenumbers in cm^{-1}. MS: Varian CH-5 (70 eV), HRMS: Finnigan MAT SSQ 7000 (70 eV). Elemental analyses: H. Kolbe, Mülheim. Commercialy available reagents (Aldrich, Fluka, Strem, Lancaster) were used as received.

3.1.1. 1-Phenyl-3,4b(*S*),8,8a(*R*)-tetrahydro-5,9-dioxa-3-aza-flouren-4,7-dione (7). A solution of pyridone **5** (1.00 g, 5.34 mmol)[21] in DMF (25 mL) and Et_3N (0.5 mL) was stirred for 10 min before [(allyl)PdCl]$_2$ (9.8 mg, 0.03 mmol) and (−)-1,2-bis-N-[2′-(diphenylphosphino)-

Table 3. IC_{50} values [μM] of authentic and synthetic TMC-69-6H, its immediate precursors and analogues against different phosphatases[a]

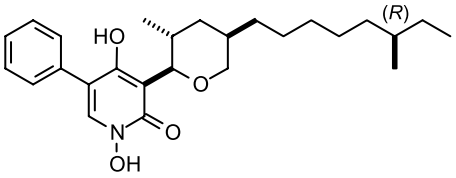
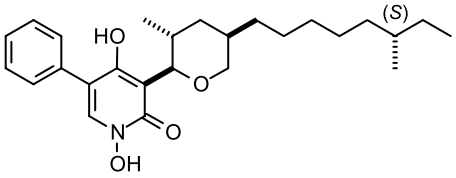
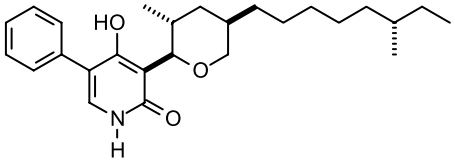
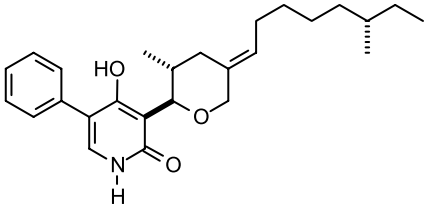
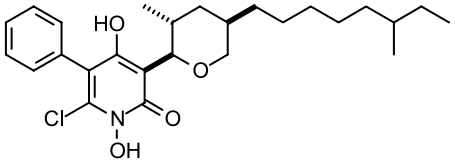
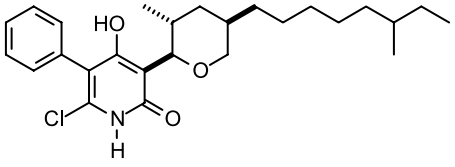
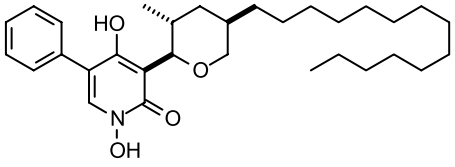
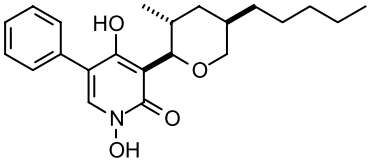
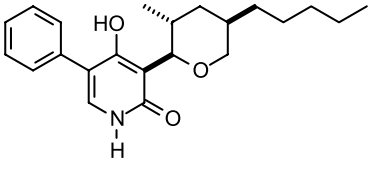
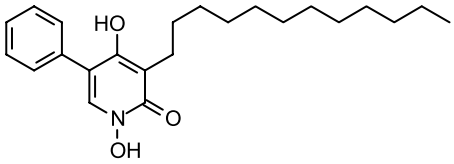
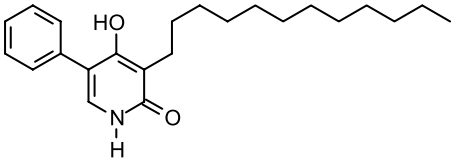
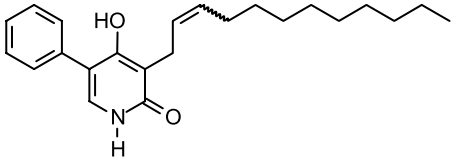
Compound		Cdc25A	PTP1B	VHR	PP1
Authentic **2**		≥50	3.2±1.6	7.0±3.5	6±3
	(17*R*)-**2**	45±23	4±2.0	6±3	8.5±4.5
	(17*S*)-**2**	32±16	3.5±1.7	5.5±3	8±4
	(17*S*)-**11**	≥50	11±5.5	9±5	30±5
	(17*S*)-**10a**	≥50	23±11	11±5.5	32±16
	**28**	>50	5.9±4.2	26±16.5	38.5±13
	**27**	>50	11.3±5.6	18.9±14	47±6
	**23b**	>50	2.8±1.5	26±13	
	**23a**	>50	12±6	19±8	
	**22a**	>50	14.1±8.3	3.1±1.4	>50

Table 3 (*continued*)

Compound		Cdc25A	PTP1B	VHR	PP1
	**32**	>50	4.7±1.2	3.1±1.6	47
	**31b**	>50	6.1±3.3	9.5±8.6	33±15
	**30b**[b]	>50	9.2±4.6	26±13	>50

[a] The enzymatic activity was determined by hydrolysis of *para*-nitrophenyl phosphate in standard buffers for PTP1B, VHR and PP1.
[b] 1:1 Mixture of isomers.

benzoyl]-1(*S*),2(*S*)-diaminocyclohexane (*S*,*S*)-**12** (55.5 mg, 0.08 mmol) were introduced. The resulting mixture was added dropwise to a solution of acetate (*S*)-**6** (1.12 g, 7.20 mmol, ee=81%)[24] in DMF (15 mL) and stirring was continued for 25 min before the reaction was quenched with aq. sat. NH_4Cl. A standard extractive work up followed by flash chromatography of the crude product (EtOAc/EtOH, 20:1+Et_3N (0.1%, v/v)) afforded compound **7** as a pale yellow solid (834 mg, 65%). The enantiomeric excess (ee=96%) was determined by HPLC on a chiral column (Chiralcel OJ-R, ∅ 4.6×150 mm; MeCN/water 20:80, 0.5 mL min^{-1}; 308 K; 3.6 MPa; retention times: (−)-**7**: 9.435 min, (+)-**7**: 10.237 min). $[\alpha]_D^{20}=-185°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^1H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.64 (s, 1H), 7.50–7.30 (m, 5H), 5.47 (d, J=7.3 Hz, 1H), 5.37 (dt, J=7.0, 4.0 Hz, 1H), 4.01 (d, J=18.1 Hz, 1H), 3.64 (d, J=18.1 Hz, 1H), 3.19 (dd, J=16.2, 4.0 Hz, 1H), 2.88 (dd, J=16.2, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.5, 167.9, 160.3, 137.8, 132.9, 128.7, 127.5, 127.2, 107.7, 105.5, 82.0, 73.8, 68.5, 39.6; IR (KBr) 3144, 3055, 2973, 2875, 1739, 1662, 1438, 1199, 1086, 775, 698; UV [ε_{max} (λ)]: 14200 (245 nm), 11600 (210 nm); MS (EI) *m*/*z* (rel. intensity) 283 ([M^+], 72), 224 (41), 212 (55), 211 (100), 196 (12), 144 (5), 102 (7), 77 (5); HR-MS (ESI-pos) ($C_{16}H_{13}NO_4$) calcd 283.084270, found 283.084457.

3.1.2. 2-Chloro-1-phenyl,3,4b(*S*),8,8a(*R*)-tetrahydro-5,9-dioxa-3-aza-flouren-4,7-dione (24). Prepared as described above from pyridone **4** (200 mg, 0.90 mmol) and acetate (*S*)-**6** (210 mg, 1.34 mmol). Pale yellow powder (205 mg, 71%). ee=95.3% (Chiralcel OD-R, ∅ 4.6×250 mm; MeCN/water 35:65, 0.5 mL/min; 298 K; 3.3 MPa; retention times: (+)-(**24**): 14.465 min, (−)-(**24**): 16.119 min). $[\alpha]_D^{20}=-222°$ ($c=0.52$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.46–7.25 (m, 5H), 5.69 (d, J=7.3 Hz, 1H), 5.28 (m, 1H), 4.11 (d, J=18.1 Hz, 1H), 3.86 (d, J=18.3 Hz, 1H), 3.06 (dd, J=16.3, 3.9 Hz, 1H), 2.99 (dd, J=15.3, 3.9 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.5, 170.2, 161.6, 139.8, 130.2, 129.9, 128.6, 128.4, 109.9, 104.5, 83.0, 73.8, 69.1, 39.3; IR (film) 2869, 1737, 1650, 1613, 1544, 1432, 1211, 1094, 1074, 1025, 957, 900, 772, 702; UV [ε_{max} (λ)]: 12300 (240 nm), 11600 (219 nm); MS (EI) *m*/*z* (rel. intensity) 317 ([M^+], 88), 258 (35), 245 (100), 222 (22), 209 (45), 167 (7), 153 (12), 115 (13), 89 (19), 43 (27); HR-MS (ESI-pos) ($C_{16}H_{12}NO_4Cl$) calcd 317.0455, found 317.0450.

3.1.3. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-pyridin-3-yl]-6*H*-pyran-3-one (8). A solution of compound **7** (50 mg, 0.18 mmol), TBSCl (140 mg, 0.93 mmol) and Et_3N (0.5 mL) was stirred for 18 h at ambient temperature. The mixture was adsorbed on silica and the product was purified by flash chromatography (hexanes/Et_2O, 10:1+Et_3N (0.5%, v/v)) to give compound **8** as a colorless, moisture-sensitive solid (70 mg, 78%). $[\alpha]_D^{20}=-8.35°$ ($c=3.5$, THF). ^1H NMR (400 MHz, CD_2Cl_2) δ 7.97 (s, 1H), 7.45–7.34 (m, 5H), 7.17 (dd, J=10.4, 1.7 Hz, 1H), 6.20 (dd, J=10.5, 2.7 Hz, 1H), 5.76 (dd, J=4.4, 2.2 Hz, 1H), 4.31 (d, J=16.4 Hz, 1H), 4.20 (dd, J=16.2, 2.1 Hz, 1H), 0.95 (s, 9H), 0.93 (s, 9H), 0.34 (s, 3H), 0.30 (s, 3H), −0.26 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2, 162.4, 160.0, 153.4, 149.0, 136.6, 130.0, 129.5, 128.4, 126.7, 124.9, 113.1, 72.8, 68.2, 25.8, 25.6, 18.4, 18.2, −4.0, −4.3, −4.5, −4.9; IR (film) 3063, 2955, 2929, 2885, 2858, 1702, 1582, 1461, 1255, 1066, 976, 843, 787, 701; MS (EI) *m*/*z* (rel. intensity) 511 ([M^+], <1) 496 (3), 456 (13), 454 (100), 424 (12), 396 (4), 368 (3), 338 (7), 294 (2), 199 (1), 156 (5), 129 (3), 73 (19); HR-MS (ESIpos) ($C_{28}H_{42}NO_4Si_2$) calcd 512.265241, found 512.265080 (M+H).

3.1.4. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-pyridin-3-yl]-(*R*)-5-methyl-tetrahydro-pyran-3-one (9). A cooled solution (−78 °C) of enone **8** (140 mg, 0.27 mmol) in THF (4 mL) was slowly added to a solution

of Me_2CuLi [freshly prepared from $CuBr \cdot Me_2S$ (259 mg, 1.26 mmol) and MeLi (1.6 M in Et_2O, 1.57 mL) in THF (8 mL) at 0 °C] and the resulting mixture was stirred for 2 h at −70 °C. Addition of aq. NH_4OH/NH_4Cl (pH 8–9) followed by a standard extractive work up provided crude **9** (205 mg, dr >9:1) which is moisture sensitive and therefore used without further purification in the next step. Characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42–7.30 (m, 5H), 4.79 (d, J=10.0 Hz, 1H), 4.22 (dd, J=15.9, 1.7 Hz, 1H), 3.97 (d, J=15.9 Hz, 1H), 3.07 (m, 1H), 2.78 (ddd, J=16.0, 5.3, 1.5 Hz, 1H), 2.20 (dd, J=16.0, 11.2 Hz, 1H), 0.98 (s, 9H), 0.94 (s, 9H), 0.86 (m, 3H), 0.36 (s, 3H) 0.35 (s, 3H), −0.01 (s, 3H), −0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 161.8, 159.7, 148.0, 136.7, 129.9, 128.3, 127.1, 124.5, 113.6, 76.5, 74.3, 46.5, 33.1, 26.0, 26.0, 18.4, 18.2, 18.2, −3.9, −3.9, −4.4, −4.9; IR (film) 3061, 2956, 2930, 2895, 2858, 1733, 1582, 1456, 1445, 1256, 1056, 976, 840, 784, 700; MS (EI) *m/z* (rel. intensity) 527 ([M^+], <1), 512 (4), 470 (100), 442 (5), 412 (22), 340 (13), 314 (21), 258 (5), 207 (2), 157 (2), 73 (21); HR-MS (ESI-pos) ($C_{29}H_{46}NO_4Si_2$) calcd 528.296541, found 528.296878 (M+H).

3.1.5. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-6-chloro-pyridin-3-yl]-(*R*)-5-methyl-tetrahydro-pyran-3-one (25). Prepared analogously. Characteristic data: $[\alpha]_D^{20}=-28°$ (c=0.14, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47–7.25 (m, 5H), 4.70 (d, J=10.0 Hz, 1H), 4.15 (dd, J=15.7, 1.7 Hz, 1H), 3.98 (d, J=15.7 Hz, 1H), 3.02 (m, 1H), 2.74 (ddd, J=15.9, 5.1, 1.5 Hz, 1H), 2.20 (dd, J=15.9, 11.6 Hz, 1H), 1.01 (s, 9H), 0.89 (s, 9H), 0.83 (m, 3H), 0.38 (s, 3H), 0.38 (s, 3H), 0.02 (s, 3H), −0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 162.0, 160.2, 147.2, 134.8, 132.4, 128.0, 127.9, 122.8, 113.2, 76.3, 74.3, 46.4, 33.2, 25.9, 25.9, 18.5, 18.1, 17.9, −4.0, −4.1, −4.3, −5.0; IR (film) 2956, 2931, 2897, 2859, 1733, 1571, 1541, 1428, 1251, 1158, 1140, 1105, 1077, 951, 841, 824, 812, 785, 701; MS (EI) *m/z* (rel. intensity) 561 ([M^+], <1), 548 (2), 507 (15), 506 (46), 504 (100), 448 (12), 446 (26), 374 (13), 350, (9), 348 (23), 292 (3), 224 (2), 174 (3), 129 (3), 73 (35); HR-MS (ESI-pos) ($C_{29}H_{45}NO_4Si_2Cl$) calcd 562.257569, found 562.257635 (M+H).

3.1.6. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-((*S*)-6-methyl-octyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (10). A solution of LiHMDS (100 mg, 0.60 mmol) in DME (2 mL) was added to a solution of sulfone (*S*)-**19** (160 mg, 0.48 mmol) in DME (4 mL) at −78 °C. The resulting, bright yellow mixture was stirred for 15 min before a solution of ketone **9** (200 mg, 0.38 mmol) in DME (4 mL) was introduced and stirring was continued at that temperature for 30 min. The reaction was quenched with aq. NH_4Cl/NH_4OH (pH=8, 10 mL), the aqueous layer was repeatedly extracted with EtOAc, the combined organic layers were dried and evaporated, and the crude product was purified by flash chromatography (Et_2O/Et_3N/pentane, 1:1:100) to give product **10** as a colorless syrup which is moisture sensitive and immediately used in the next step (120 mg, 69% over two steps, *E*/*Z*=1:1). Characteristic data: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.89 (s, 2H), 7.45–7.30 (m, 12H), 5.30–5.25 (m, 2H), 4.63 (d, J=12.4 Hz, 1H), 4.54 (m, 2H), 4.05 (d, J=12.0 Hz, 1H), 4.00 (d, J=11.9 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 2.80 (dd, J=13.5, 2.7 Hz, 1H), 2.58 (m, 2H), 2.40, (d, J=13.5, 2.6 Hz, 1H), 2.15–0.80 (m, 30H), 1.00 (s, 18H) 0.96 (s, 18H), 0.74, (d, J=6.7 Hz, 6H), 0.70 (d, J=6.7 Hz, 6H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.65 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 162.1, 159.6, 147.2, 137.2, 134.3, 134.0, 130.0, 128.3, 128.1, 127.0, 124.6, 124.2, 115.2, 115.1, 78.0, 74.1, 66.5, 42.7, 36.6, 35.0, 34.5, 34.5, 34.2, 33.4, 30.6, 30.3, 29.8, 29.7, 29.6, 27.3, 27.1, 27.0, 27.0, 26.1, 26.0, 25.9, 25.8, 19.1, 18.4, 18.2, 17.8, 17.5, 11.3, 11.3, −4.1, −4.2, −4.2, −4.3, −4.6, −5.3; IR (film) 2956, 2928, 2857, 1582, 1455, 1444, 1254, 1136, 1058, 1004, 842, 784, 699; MS (EI) *m/z* (rel. intensity) 637 ([M^+], <1), 622 (2), 582 (18), 580 (100), 562 (8), 550 (14), 448 (5), 398 (12), 332 (3), 284 (4), 256 (2), 95 (2), 73 (17), 57 (2), 43 (2); HR-MS (ESI-pos) ($C_{38}H_{65}NO_3Si_2$) calcd 638.442476, found 638.442434 (M+H).

3.1.7. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-(pentyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (21a). Prepared analogously using sulfone **20a**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.88 (s, 2H), 7.46–7.27 (m, 10H), 5.30–5.25 (m, 2H), 4.63 (d, J=12.4 Hz, 1H), 4.53 (dd, J=9.8, 9.7 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 3.99 (d, J=11.9 Hz, 1H), 3.74 (d, J=12.4 Hz, 1H), 2.78 (dd, J=13.5, 2.7 Hz, 1H), 2.58 (m, 2H), 2.40 (d, J=13.5, 2.6 Hz, 1H), 2.08 (m, 4H), 1.70 (m, 1H), 1.42–1.26 (m, 10H), 1.10–0.80 (m, 42H), 0.74 (d, J=6.7 Hz, 3H), 0.70 (d, J=6.7 Hz, 3H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.65 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 162.0, 159.6, 147.2, 137.1, 134.3, 134.0, 130.0, 128.2, 126.9, 124.5, 124.1, 115.1, 78.0, 74.0, 66.4, 65.7, 42.6, 35.0, 34.2, 34.0, 33.4, 32.3, 32.1, 29.8, 29.7, 26.9, 26.6, 25.9, 25.8, 25.8, 22.5, 22.5, 18.4, 18.1, 17.7, 17.5, 15.2, 13.9, −4.2, −4.3, −4.3, −4.7, −5.3; IR (film) 2956, 2929, 2858, 1582, 1455, 1443, 1254, 1136, 1057, 1004, 839, 783, 699; MS (EI) *m/z* (rel. intensity) 581 ([M^+], <1), 566 (2), 526 (16), 525 (43), 524 (100), 506 (9), 494 (13), 398 (10), 386 (5), 342 (3), 332 (3), 284 (4), 256 (2), 75 (2), 73 (19), 67 (2); HR-MS (ESI-pos) ($C_{34}H_{56}NO_3Si_2$) calcd 582.37988, found 582.37987 (M+H).

3.1.8. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-(tetradecyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (21b). Prepared analogously using sulfone **20b**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.88 (s, 2H), 7.45–7.26 (m, 10H), 5.30–5.25 (m, 2H), 4.62 (d, J=12.4 Hz, 1H), 4.53 (dd, J=9.8, 9.7 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 3.98 (d, J=11.9 Hz, 1H), 3.75 (d, J=12.5 Hz, 1H), 2.78 (dd, J=13.5, 2.7 Hz, 1H), 2.57 (m, 2H), 2.38, (d, J=13.5, 2.6 Hz, 1H), 2.02 (m, 5H), 1.68 (m, 1H), 1.43–1.21 (m, 45H), 0.98 (s, 18H), 0.96 (s, 18H), 0.88 (t, J=6.5 Hz, 6H), 0.72 (d, J=6.7 Hz, 3H), 0.69 (d, J=6.7 Hz, 3H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.67 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.0, 159.6, 147.2, 137.1, 133.9, 130.0, 128.2, 126.9, 124.5, 124.2, 115.1, 78.0, 74.0, 66.4, 65.7, 42.6, 35.0, 34.2, 34.0, 33.4, 32.3, 32.0, 30.2, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 29.5, 27.2, 27.0, 25.9, 25.8, 25.8, 22.8, 18.4, 18.1, 17.7, 17.5, 14.0, −4.2, −4.3, −4.3, −4.7, −5.3; IR (film) 2956, 2926, 2855, 1582, 1455, 1444, 1406, 1254, 1136, 1057, 1004, 840, 810, 784, 699; MS (EI) *m/z* (rel. intensity) 707 ([M^+], <1), 652 (21), 651 (53), 650 (100), 632 (6), 620 (11), 536 (2), 518 (4), 398 (11), 386 (6), 332 (2), 314 (2), 284 (3), 256 (2), 73 (14), 57 (2); HR-MS

(ESIpos) ($C_{43}H_{74}NO_3Si_2$) calcd 708.72053, found 708.71976 (M+H).

3.1.9. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-((*S*)-6-methyl-octyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-6-chloro-pyridine. Prepared analogously as a *E*/*Z*=1:1 mixture of isomers. Characteristic data: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.50–7.28 (m, 10H), 7.25 (s, br, 2H), 5.30–5.25 (m, 2H), 4.62 (d, J=12.5 Hz, 1H), 4.53 (t, J=9.7 Hz, 1H), 4.07 (d, J=12.0 Hz, 1H), 3.98 (d, J=11.9 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 2.78 (d, J=13.5 Hz, 1H), 2.60 (m, 2H), 2.39 (d, J=13.5 Hz, 1H), 2.08 (m, 3H), 1.78 (m, 1H), 1.45–1.22 (m, 9H), 1.20–0.79 (m, 58H), 0.74 (d, J=6.7 Hz, 3H), 0.70 (d, J=6.7 Hz, 3H), 0.38 (s, 6H), 0.34 (s, 6H), 0.06 (s, 6H), −0.61 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 161.8, 160.4, 146.4, 135.1, 134.0, 133.7, 132.4, 131.8, 127.9, 127.7, 124.4, 122.5, 114.5, 77.8, 74.0, 66.4, 42.5, 36.6, 34.9, 34.5, 34.5, 34.2, 33.4, 30.6, 30.3, 29.6, 27.3, 27.1, 27.0, 27.0, 26.1, 25.9, 25.8, 25.8, 22.5, 19.1, 18.5, 18.1, 17.7, 17.5, 11.3, −4.3, −4.4, −4.45, −4.5, −5.0; IR (film) 2957, 2928, 2857, 1572, 1541, 1427, 1399, 1255, 1158, 1140, 1070, 1004, 953, 841, 825, 812, 784, 700; MS (EI) *m*/*z* (rel. intensity) 671 ([M$^+$], <1), 616 (47), 614 (100), 586 (9), 584 (18), 482 (5), 434 (8), 432 (14), 270 (6), 73 (23); HR-MS (ESI-pos) ($C_{38}H_{63}NO_3Si_2Cl$) calcd 672.40350, found 672.40365 (M+H).

3.1.10. 3-((2*R*,3*R*)-Tetrahydro-3-methyl-5-(6-methyl-octyliden)-2*H*-pyran-2-yl)-4-hydroxy-5-phenyl-6-chloro-pyridin-2(1*H*)-one (26). TBAF (1 M in THF, 0.36 ml, 0.36 mmol) was added to a solution of the pyridone described above (115 mg, 0.171 mmol) in THF (5 mL) and the resulting mixture was stirred for 30 min. The solution was adsorbed on Celite and the product was purified by flash chromatography (hexanes/EtOAc, 5:1) to afford product **26** as a colorless solid (74 mg, 99%, *E*/*Z*=1:1). Characteristic data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (br, 2H), 7.50–7.27 (m, 10H), 5.28 (m, 2H), 4.85 (m, 2H), 4.71 (d, J=12.5 Hz, 1H), 4.12 (m, 2H), 3.91 (d, J=12.7 Hz, 1H), 3.00 (m, 1H), 2.72 (d, J=11.5 Hz, 1H), 2.35 (dd, J=13.0, 2.1 Hz, 2H), 2.20–1.75 (m, 10H), 1.40–0.70 (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 162.8, 138.3, 132.6, 132.3, 132.1, 130.7, 128.1, 127.9, 126.0, 116.0, 107.0, 80.2, 67.1, 41.6, 38.3, 37.6, 36.4, 34.3, 34.3, 34.2, 30.2, 29.8, 29.5, 29.4, 27.1, 26.8, 26.6, 19.1, 18.0, 17.8, 11.4, 11.3; IR (film) 3200, 2959, 2926, 2854, 1635, 1614, 1449, 1359, 1236, 1050, 954, 838, 762, 697; MS (EI) *m*/*z* (rel. intensity) 443 ([M$^+$], 57), 427 (9), 425 (23), 408 (5), 387 (17), 358 (9), 330 (12), 326 (16), 261 (51), 250 (100), 237 (12), 234 (43), 221 (22), 144 (8), 82 (14), 55 (21); HR-MS (ESI-pos) ($C_{26}H_{34}NO_3ClNa$) calcd 466.21249, found 466.21292 (M+Na).

3.1.11. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*S*)-6-methyloctyl)-2*H*-pyran-2-yl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (11). A suspension of compound **10** (*E*/*Z* mixture, 120 mg, 0.19 mmol) and Pd/C (10% *w*/*w*, 30 mg) in EtOH (6 mL) was stirred under an atmosphere of H_2 (1 atm) for 24 h. The catalyst was filtered off and was carefully washed with hot EtOH (containing 1% Et_3N) and EtOAc (containing 1% Et_3N), the combined filtrates were evaporated and the crude product was directly subjected to the subsequent desilylation reaction. Characteristic data: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.86 (s, 1H), 7.43–7.28 (m, 5H), 4.34 (d, J=10.2 Hz, 1H), 3.81 (d, J=11.3 Hz, 1H), 3.58 (dd, J=11.3, 2.6 Hz, 1H), 2.60 (m, 1H), 1.80 (d, J=10.4 Hz, 1H), 1.63–1.46 (m, 4H), 1.40–1.20 (m, 9H), 1.15–1.05 (m, 2H), 1.02 (s, 9H), 0.96 (s, 9H), 0.94–0.76 (m, 6H), 0.61 (d, J=6.7 Hz, 3H), 0.38 (s, 3H), 0.35 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H); IR (film) 3058, 2955, 2926, 2856, 1646, 1582, 1454, 1444, 1256, 1060, 839, 785, 700; MS (EI) *m*/*z* (rel. Intensität) 639 ([M$^+$], <1), 624 (3), 584 (19), 583 (48), 582 (100), 468 (20), 398 (3), 314 (1), 272 (2), 73 (30), 55 (7); HR-MS (ESI-pos) ($C_{38}H_{66}NO_3Si_2$) calcd 640.458126, found 640.457570 (M+H). For this purpose, TBAF (1 M in THF, 0.40 mL, 0.38 mmol) was added to a solution of the crude product in THF (5 mL) and the resulting mixture was stirred for 5 min. The reaction mixture was adsorbed on Celite and the product was purified by flash chromatography (EtOAc/hexanes, 2:1) to give product **11** as a mixture of diastereomers (52 mg, 69% over two steps, d.r.=5:1). The major isomer was separated by preparative HPLC (Nucleosil-5-120-C18/A, ∅ 4.5×125 mm; MeOH/water 80:20, 0.8 mL min^{-1}; 308 K; 8.6 MPa; retention time: 51.64 min). $[\alpha]_D^{20}=+94.5°$ (c=1.0, MeOH). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 12.77 (s, br, 1H), 9.65 (s, br, 1H), 7.44–7.30 (m, 5H), 7.26 (s, 1H), 4.67 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.5 Hz, 1H), 2.10 (m, 1H), 1.80 (d, J=13.1 Hz, 1H), 1.68–1.47 (m, 4H), 1.40–1.20 (m, 9H), 1.15–1.05 (m, 2H), 0.89–0.80 (m, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.4, 164.1, 134.2, 133.5, 129.2, 128.2, 127.3, 115.5, 110.1, 81.4, 72.5, 36.6, 36.2, 34.5, 34.2, 31.2, 30.9, 30.1, 29.5, 27.8, 27.1, 19.0, 17.9, 11.2; MS (EI) *m*/*z* (rel. intensity) 411 ([M$^+$], 61), 393 (33), 368 (18), 366 (23), 284 (34), 266 (15), 226 (31), 216 (30), 201 (100), 187 (40), 146 (6), 118 (11), 91 (4), 57 (18), 55 (16), 43 (20), 41 (18); HR-MS (EI) ($C_{26}H_{37}NO_3$) calcd 411.277343, found 411.277067.

3.1.12. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-pentyl-2*H*-pyran-2-yl)-4-hydroxy-5-phenyl-pyridin-2(1*H*)-one (22a, *n*=1). Prepared analogously. The major isomer was purified by preparative HPLC (Nucleosil-100-5-C18/A, ∅ 4.5×125 mm; MeOH/water 75:25; 0.8 mL min^{-1}; 308 K; 12.1 MPa). $[\alpha]_D^{20}=98.5°$ (c=0.51, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 12.65 (s, br, 1H), 9.70 (s, br, 1H), 7.48–7.26 (m, 5H), 7.25 (s, 1H), 4.66 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.4 Hz, 1H), 2.10 (m, 1H), 1.78 (d, J=11.7 Hz, 1H), 1.68–1.40 (m, 3H), 1.40–1.20 (m, 7H), 0.95–0.80 (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.3, 164.1, 134.2, 133.5, 129.2, 128.2, 127.3, 115.5, 110.1, 81.4, 72.5, 36.2, 34.2, 32.0, 31.2, 30.8, 27.5, 22.7, 17.9, 14.0; IR (film) 3131, 2956, 2926, 2855, 1646, 1600, 1457, 1233, 1053, 698; MS (EI) *m*/*z* (rel. intensity) 355 ([M$^+$], 43), 337 (24), 325 (7), 312 (18), 310 (17), 284 (24), 266 (17), 242 (22), 229 (12), 226 (32), 216 (29), 201 (100), 200 (76), 187 (44), 155 (10), 146 (6), 144 (5), 130 (6), 118 (10), 91 (7), 55 (14), 41 (13); HR-MS (EI) ($C_{22}H_{29}NO_3$) calcd 355.214744, found 355.214445.

3.1.13. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-tetradecyl-2*H*-pyran-2-yl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (22b, *n*=10). Prepared analogously. The major isomer was purified by preparative HPLC (Nucleosil-100-5-C18/A ∅ 4.5×125 mm; MeOH/water 95:5; 0.8 mL min^{-1}; 308 K; 6.1 MPa; retention time 14.271 min). $[\alpha]_D^{20}=68.6°$ (c=0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 9.82 (s, br, 1H),

7.48–7.26 (m, 6H), 4.68 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.3 Hz, 1H), 2.10 (m, 1H), 1.79 (d, J=12.3 Hz, 1H), 1.68–1.44 (m, 4H), 1.40–1.18 (m, 24H), 0.95–0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.2, 133.6, 133.4, 129.1, 128.4, 127.7, 116.9, 109.6, 81.2, 72.5, 36.1, 34.0, 31.9, 31.0, 30.9, 29.7 (m), 29.6, 29.6, 29.3, 27.8, 22.7, 18.0, 14.1; IR (film) 3143, 2958, 2922, 2852, 1645, 1601, 1457, 1435, 1380, 1230, 1051, 801, 759, 697; MS (EI) m/z (rel. intensity) 481 ([M^+], 21), 463 (23), 451 (6), 438 (13), 436 (14), 382 (2), 298 (9), 284 (20), 266 (11), 242 (23), 229 (10), 228 (17), 227 (9), 226 (22), 216 (21), 201 (100), 200 (64), 187 (20), 146 (3), 118 (4), 97 (3), 95 (2), 91 (3), 67 (2), 43 (14); HR-MS (ESI-pos) ($C_{31}H_{48}NO_3$) calcd 482.363419, found 482.36352 (M+H).

3.1.14. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(6-methyloctyl)-2H-pyran-2-yl)-4-hydroxy-5-phenyl-6-chloropyridin-2(1*H*)-one (27). Prepared analogously. The major isomer was purified by preparative HPLC (Asahipak, ∅ 4.5×250 mm; MeCN/TEAA buffer (pH 6.96)=70:30; 0.8 mL min^{-1}; 308 K; 6.5 MPa). $[\alpha]_D^{20}=-83.0°$ (c=0.7, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50–7.29 (m, 5H), 4.64 (d, J=10.5 Hz, 1H), 3.94 (d, J=11.8 Hz, 1H), 3.72 (dd, J=11.8, 2.6 Hz, 1H), 2.04 (m, 1H), 1.77 (d, J=12.7 Hz, 1H), 1.70–1.38 (m, 4H), 1.35–1.17 (m, 10H), 1.19–1.00 (m, 2H), 0.93–0.78 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.7, 139.2, 132.9, 130.8, 128.2, 128.1, 128.0, 116.4, 107.5, 81.0, 72.4, 36.6, 36.2, 34.4, 34.0, 31.1, 30.8, 29.4, 27.8, 27.0, 19.2, 18.0, 11.4; IR (film) 3189, 2959, 2926, 2855, 1634, 1614, 1590, 1460, 1380, 1263, 1235, 1076, 1056, 982, 762, 698; MS (EI) m/z (rel. intensity) 445 ([M^+], 100), 427 (17), 402 (14), 400 (14), 318 (16), 276 (19), 275 (10), 274 (11), 223 (17), 221 (42), 211 (19), 144 (11), 129 (5), 116 (6), 115 (6), 82 (7), 57 (19), 43 (28), 41 (29); HR-MS (ESI-pos) ($C_{26}H_{37}NO_3Cl$) calcd 446.24619, found 446.24617.

3.1.15. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*S*)-6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one, (17*S*)-TMC-69-6H, ((17*S*)-2). A mixture of pyridone **11** (25 mg, 0.06 mmol), HMDS (0.50 mL) and freshly distilled TMSCl (9 μL) was refluxed for 6 h before all volatile components were removed in vacuo. The remaining yellow syrup was dissolved in CH_2Cl_2 (1 mL) and treated with (pyridine)MoO_5(HMPA) (52.5 mg, 0.12 mmol).[34] After the mixture had been stirred for 16 h, the mixture was diluted with EtOAc (2.5 mL) and sat. aq. EDTA-Na_4 (2.5 mL), causing a color change from dark red to pale yellow. The pH of the solution was adjusted to 7–7.5 upon addition of aq. HCl (0.1 M) before the aqueous phase was separated and repeatedly extracted with EtOAc. The combined organic layers were evaporated and the residue was dried in vacuo (10^{-4} Torr) to provide compound (17*S*)-**2** as a colorless powder (18.9 mg, 71%). $[\alpha]_D^{20}=88.6°$ (c=0.95, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.47–7.29 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 3.72 (dd, J=11.5, 2.3 Hz, 1H), 2.06 (m, br, 1H), 1.76 (d, J=12.2 Hz, 1H), 1.62 (m, br, 1H), 1.58–1.40 (m, 3H), 1.35–1.19 (m, 9H), 1.13–1.00 (m, 2H), 0.89–0.81 (m, 6H), 0.79 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.2, 133.2, 131.1, 129.2, 128.4, 127.7, 113.5, 109.3, 81.6, 72.4, 36.5, 36.1, 34.4, 33.9, 31.0, 30.8, 30.0, 29.5, 27.8, 27.1, 19.2, 17.8, 11.4; IR (film) 3180, 2958, 2925, 2854, 1640, 1580, 1556, 1455, 1381, 1220, 1054, 775, 698, 658; MS (EI) m/z (rel. intensity) 427 ([M^+], 32), 410 (72), 392 (60), 382 (14), 380 (11), 368 (10), 314 (5), 284 (12), 282 (4), 266 (11), 258 (10), 244 (11), 242 (16), 240 (15), 238 (11), 232 (11), 226 (27), 216 (59), 214 (34), 211 (13), 200 (100), 187 (19), 144 (4), 97 (5), 67 (4), 55 (15), 43 (14), 41 (13); HR-MS (EI) ($C_{26}H_{37}NO_4$) calcd 427.272259, found 427.272083.

3.1.16. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*R*)-6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one, (17*R*)-TMC-69-6H, ((17*R*)-2). Prepared analogously. $[\alpha]_D^{20}=102.3°$ (c=0.6, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.47–7.31 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.8 Hz, 1H), 3.72 (dd, J=11.6, 2.5 Hz, 1H), 2.07 (m, br, 1H), 1.76 (d, J=11.0 Hz, 1H), 1.63 (m, br, 1H), 1.58–1.44 (m, 3H), 1.35–1.18 (m, 9H), 1.13–1.02 (m, 2H), 0.87–0.81 (m, 6H), 0.79 (d, J=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 157.2, 133.1, 130.5, 129.2, 128.4, 127.7, 113.7, 109.5, 81.6, 72.4, 36.5, 36.1, 34.4, 34.0, 31.0, 30.8, 29.9, 29.5, 27.8, 27.0, 19.2, 17.8, 11.4; IR (film) 3187, 2958, 2924, 2854, 1643, 1580, 1557, 1456, 1381, 1220, 1054, 984, 775, 699; MS (EI) m/z (rel. intensity) 427 ([M^+], 45), 410 (100), 392 (74), 382 (15), 380 (12), 367 (9), 314 (6), 284 (5), 282 (5), 266 (7), 258 (13), 244 (13), 242 (10), 240 (17), 238 (11), 232 (16), 226 (18), 216 (66), 214 (37), 211 (14), 200 (87), 187 (12), 144 (5), 97 (6), 57 (15), 55 (22), 43 (22), 41 (21); HR-MS (EI) ($C_{26}H_{37}NO_4$) calcd 427.272259, found 427.271906.

3.1.17. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(pentyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenyl-pyridin-2(1*H*)-one (23a, *n*=1). Prepared analogously. $[\alpha]_D^{20}=88.8°$ (c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.50–7.30 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 3.73 (dd, J=11.6, 2.5 Hz, 1H), 2.08 (br, m, 1H), 1.76 (d, J=11.0 Hz, 1H), 1.68–1.42 (m, 4H), 1.38–1.19 (m, 6H), 0.92–0.86 (t, J=7.0 Hz, 3H), 0.82 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 157.1, 133.1, 130.3, 129.2, 128.4, 127.7, 113.7, 109.5, 81.6, 72.4, 36.1, 34.0, 31.0, 30.8, 29.7, 27.6, 22.4, 17.9, 14.0; IR (film) 3181, 2957, 2922, 2852, 1736, 1639, 1579, 1556, 1455, 1381, 1260, 1218, 1048, 801, 775, 697; MS (EI) m/z (rel. intensity) 371 ([M^+], 24), 354 (39), 336 (29), 312 (13), 284 (17), 266 (15), 242 (17), 216 (43), 200 (100), 187 (30), 155 (13), 118 (9), 97 (10), 69 (12), 55 (22); HR-MS (EI) ($C_{22}H_{29}NO_4$) calcd 371.209659, found 371.209745.

3.1.18. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(tetradecyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one (23b, *n*=10). Prepared analogously. $[\alpha]_D^{20}=66.0°$ (c=1.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, br, 1H), 7.67 (s, 1H), 7.48–7.27 (m, 5H), 4.69 (d, J=10.5 Hz, 1H), 3.98 (d, J=11.4 Hz, 1H), 3.73 (d, J=11.7, 1H), 2.10 (m, 1H), 1.78 (d, J=12.5 Hz, 1H), 1.69–1.42 (m, 4H), 1.37–1.18 (m, 24H), 0.92–0.80 (m, 6H); IR (film) 3136, 2923, 2853, 1644, 1601, 1581, 1555, 1456, 1381, 1221, 1053, 801, 698; MS (ESI) m/z (rel. intensity) 497 ([M^+], <1), 482 (100), 433 (6), 390 (4), 180 (13); HR-MS

(ESI-pos) ($C_{31}H_{48}NO_4$) calcd 498.35833, found 498.35885 (M+H).

3.1.19. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenyl-6-chloropyridin-2(1*H*)-one (28). Prepared analogously. $[\alpha]_D^{20}=+24.0°$ ($c=0.5$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, br, 1H), 9.38 (s, br, 1H), 7.50–7.25 (m, 5H), 4.62 (d, $J=10.2$ Hz, 1H), 3.91 (d, $J=11.0$ Hz, 1H), 3.67 (d, $J=11.0$ Hz, 1H), 2.02 (m, br, 1H), 1.73 (d, $J=12.1$ Hz, 1H), 1.62–1.37 (m, 4H), 1.36–1.00 (m, 11H), 0.86–0.70 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 156.8, 130.8, 128.4, 128.3, 128.2, 113.0, 107.0, 81.5, 72.4, 36.5, 36.1, 34.4, 33.9, 31.1, 30.8, 30.2, 29.9, 29.5, 27.8, 27.0, 19.2, 17.8, 11.4; IR (film) 3168, 2959, 2924, 2854, 1625, 1532, 1453, 1379, 1260, 1215, 1090, 1054, 912, 802, 698; MS (EI) *m/z* (rel. intensity) 461 ([M$^+$], 16), 446 (35), 445 (48), 444 (73), 428 (12), 427 (13), 426 (26), 416 (11), 400 (6), 398 (5), 320 (2), 318 (6), 302 (4), 300 (8), 276 (13), 274 (11), 260 (12), 252 (12), 250 (44), 234 (100), 221 (20), 211 (13), 180 (4), 144 (7), 55 (14), 43 (12), 41 (11); HR-MS (ESI-pos) ($C_{26}H_{37}NO_4Cl$) calcd 462.24111, found 462.24080 (M+H).

3.1.20. 3-Dodecyl-1,4-dihydroxy-5-phenyl-1*H*-pyridin-2-one (32). Prepared analogously from pyridone **31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.29 (m, 6H), 2.68 (m, 2H), 2.10–1.50 (m, 2H), 1.40–1.15 (m, 18H) 0.88 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (signals for C-2 and C-4 were not detected), 132.3, 129.8, 128.7, 128.2, 127.8, 118.0, 113.9, 42.0, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 22.7, 22.7, 14.1; IR (film) 3252, 2921, 2852, 1716, 1622, 1543, 1497, 1463, 1344, 1262, 1198, 1088, 771, 697; MS (EI) *m/z* (rel. intensity) 371 ([M$^+$], 33), 354 (3), 272 (2), 216 (7), 200 (6), 176 (12), 175 (100), 146 (20), 118 (10), 91 (5), 55 (6), 43 (9); HR-MS (ESI-pos) ($C_{23}H_{33}NO_3Na$) calcd 394.23581, found 394.23593 (M+Na).

3.1.21. (*S*)-4-Methylhex-5-enal (15).[29] Ozone was bubbled through a solution of (+)-(*S*)-citronellene **14** (8.2 g, 59 mmol, 91% ee) in CH_2Cl_2 (120 mL) at −78 °C until TLC showed complete consumption of the starting material. At this point, Me_2S (7.0 mL, 148 mmol) was added and the resulting mixture was stirred for 1 h at −30 °C. Excess Me_2S was pumped off in vacuo at that temperature before all volatile components were evaporated at ambient temperature and the crude product was purified by distillation (bp 52–55 °C, 50 mbar) to give aldehyde **15** as a colorless liquid (6.45 g, 98%). $[\alpha]_D^{20}=+3.5°$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.70–5.58 (m, 1H), 5.02–4.94 (m, 2H), 2.46–2.40 (m, 2H), 2.20–2.10 (m, 1H), 1.72–1.53 (m, 2H), 1.02 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 143.3, 113.8, 41.8, 37.4, 28.5, 20.2.

3.1.22. (*S*,*E*)-Methyl 6-methylocta-2,7-dienoat (16). Methyl diethylphosphonoacetate (1.41 g, 6.69 mmol) was added dropwise to a suspension of NaH (160 mg, 6.69 mmol) in THF (15 mL) at 0 °C and the resulting mixture was stirred for 30 min at ambient temperature. The solution was cooled to −78 °C before aldehyde **15** (500 mg, 4.46 mmol) was introduced via syringe and the resulting mixture was allowed to reach ambient temperature. A standard extractive work up followed by flash chromatography (hexanes/Et_2O, 10:1) afforded product **16** as a colorless liquid (650 mg, 87%). $[\alpha]_D^{20}=+16.2°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, $J=15.6$, 7.0 Hz, 1H), 5.81 (m, 1H), 5.70–5.60 (m, 1H), 5.01–4.90 (m, 2H), 3.72 (s, 3H), 2.18–2.05 (m, 3H), 1.47–1.40 (m, 2H), 1.01 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.8, 149.2, 143.4, 120.6, 113.0, 51.0, 37.0, 34.4, 29.6, 19.8; IR (film) 3077, 2954, 2928, 1728, 1658, 1436, 1273, 994, 913; MS (EI) *m/z* (rel. intensity) 168 ([M$^+$], <1), 153 (17), 139 (16), 126 (8), 113 (53), 111 (23), 109 (35), 100 (84), 94 (50), 87 (19), 81 (43), 79 (27), 71 (13), 69 (65), 59 (21), 55 (78), 41 (100), 29 (23); HR-MS (ESI-pos) ($C_{10}H_{16}O_2$) calcd 169.122855, found 169.122843 (M+H).

3.1.23. (*R*)-6-Methyloctan-1-ol (17). Dibal-H (1.0 M in hexane, 25.6 mL, 25.6 mmol) was added dropwise to a solution of ester **16** (1.50 g, 8.92 mmol) in Et_2O (20 mL) at 0 °C. After stirring for 2 h, the reaction was carefully quenched with MeOH at −78° C. A standard extractive work up followed by flash chromatography (Et_2O/hexanes, 1:2) afforded (*S*,*E*)-6-methylocta-2,7-dien-1-ol as a colorless liquid (1.13 g, 91%) which showed the following analytical and spectroscopic properties: $[\alpha]_D^{20}=+14.0°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72–5.58 (m, 3H), 5.01–4.90 (m, 2H), 4.10–4.05 (m, 2H), 2.18–1.97 (m, 3H), 1.43–1.33 (m, 2H), 0.99 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 133.3, 129.0, 112.8, 63.8, 37.2, 35.9, 29.8, 20.1; IR (film) 3329, 3077, 2961, 2925, 1640, 1454, 1373, 971; MS (EI) *m/z* (rel. intensity) 140 ([M$^+$], <1), 122 (3), 109 (17), 107 (22), 93 (37), 83 (28), 79 (25), 70 (22), 68 (64), 67 (70), 57 (30), 55 (97), 51 (5), 41 (100), 31 (11), 29 (41); HR-MS (CI) ($C_9H_{16}O$) calcd 141.127940, found 141.127788 (M+H). A suspension of this alcohol (100 mg, 0.70 mmol) and Pd/C (10% w/w, 20 mg) in MeOH (5 mL) was stirred for 6 h under an atmosphere of H_2 (1 atm). The catalyst was filtered off and was carefully rinsed with CH_2Cl_2, the combined filtrates were evaporated and the crude product was purified by flash chromatography (Et_2O/hexanes, 2:1) to give product **17** as a colorless liquid (90 mg, 88%). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 3.59 (m, 2H), 1.56–1.51 (m, 3H), 1.37–1.25 (m, 4H), 1.20–1.07 (m, 4H), 0.92–0.86 (m, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 63.0, 36.7, 34.5, 33.1, 29.6, 27.0, 26.2, 19.1, 11.3.

3.1.24. 5-((*R*)-6-Methyloctylthio)-1-phenyl-1*H*-tetrazol ((*R*)-18).[41] DEAD (202 mg, 1.00 mmol) was added to a solution of alcohol **17** (80 mg, 0.55 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (**45**) (198 mg, 1.10 mmol) and PPh_3 (218 mg, 0.83 mmol) in THF (5 mL) and the resulting mixture was stirred for 10 min. A standard extractive work up followed by flash chromatography (hexanes/EtOAc=30:1) afforded sulfide **18** as a colorless syrup (114 mg, 68%) which was immediately subjected to the subsequent oxidation. Characteristic data: $[\alpha]_D^{20}=-2.5°$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 5H), 3.38 (m, 2H), 1.83–1.78 (m, 2H), 1.44–1.06 (m, 9H), 0.86–0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 133.8, 130.0, 129.7, 123.8, 36.3, 34.2, 33.4, 29.4, 29.1, 28.9, 26.5, 19.1, 11.3; IR (film) 2958, 2927, 2856, 1597, 1500, 1462, 1386, 1243, 761, 694, 552.

3.1.25. 5-((*R*)-6-Methyloctylsulfonyl)-1-phenyl-1*H*-tetrazol ((*R*)-19). A solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (550 mg, 0.45 mmol) in aq. H_2O_2 (30%, 5.84 g, 51.50 mmol) was added to a solution of sulfide (*R*)-**18** (1.60 g, 5.26 mmol) in EtOH (25 mL) and the resulting mixture was stirred for 18 h at ambient temperature. For work up, the mixture was diluted with water and EtOAc, the organic phase was washed with aqueous sodium thiosulfate (5%, w/w) before it was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc/hexanes, 1:8) to give sulfone (*R*)-**19** as a colorless syrup (1.64 g, 93%). $[\alpha]_D^{20}=-2.7°$ ($c=3.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.55 (m, 5H), 3.73 (m, 2H), 1.96 (m, 2H), 1.56–1.42 (m, 2H), 1.41–1.23 (m, 5H), 1.20–1.06 (m, 2H), 0.90–0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 133.0, 131.4, 129.7, 125.1, 56.1, 36.1, 34.3, 29.4, 28.5, 26.4, 22.0, 19.1, 11.3; IR (film) 2958, 2928, 2872, 2859, 1498, 1463, 1341, 1152, 763, 688, 629; MS (EI) *m/z* (rel. intensity) 336 ([M^+], <1), 243 (2), 173 (9), 160 (3), 147 (12), 145 (10), 119 (17), 118 (100), 117 (28), 97 (6), 91 (7), 77 (9), 70 (6), 65 (11), 57 (25), 55 (23), 43 (33), 41 (23), 29 (11); HR-MS (CI) ($C_{16}H_{24}N_4SO_2$) calcd 337.169409, found 337.169423 (M+H); Anal. calcd for $C_{16}H_{23}N_4SO_2$: C 57.12, H 7.19, N 16.65, found: C 57.19, H 7.11, N 16.73.

3.1.26. 3-Allyl-4-hydroxy-5-phenylpyridin-2(1*H*)-one (30a). A solution of allyl acetate **29a** (59 mg, 0.59 mmol) in DMF (2 mL) was slowly added to a solution of pyridone **5** (100 mg, 0.53 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) in DMF (3 mL) and Et_3N (0.91 ml, 0.57 mmol), and the resulting mixture was stirred at 110 °C for 2 h. A standard extractive work up followed by flash chromatography of the crude product (EtOAc→EtOAc/MeOH, 20:1) provided product **30a** as a colorless solid (71 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, br, 1H), 9.45 (s, br, 1H), 7.68–7.24 (m, 6H), 5.82 (m, 1H), 5.01 (dd, $J=2.1$, 17.2 Hz, 1H), 4.92 (dd, $J=2.1$, 10.1 Hz, 1H), 3.30 (d, $J=6.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 160.4, 136.1, 135.3, 132.0, 129.2, 128.3, 126.8, 114.4, 113.9, 109.4, 27.1; IR (film) 3051, 1643, 1479, 1433, 1270, 1095, 756, 728, 694; MS (EI) *m/z* (rel. intensity) 227 ([M^+], 61), 212 (100), 200 (5), 144 (3), 128 (4), 118 (14), 106 (2), 63 (4), 51 (4); HR-MS (EI) ($C_{14}H_{13}NO_2$) calcd 227.094629, found 227.094368.

3.1.27. 3-(Dodec-2-enyl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (30b). Prepared analogously as a mixture of isomers (*E*/*Z*=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.20 (m, 12H), 5.62 (m, 4H), 3.43 (d, $J=6.1$, 4H), 2.00 (m, 4H), 1.47–1.13 (m, 24H), 0.87 (t, $J=7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.0, 132.1, 132.0, 129.1, 128.9, 128.8, 128.5, 128.4, 127.8, 126.3, 115.7, 110.2, 31.4, 31.8, 29.5, 29.4, 29.3, 29.2 (m), 27.3, 26.4, 22.6, 14.0; MS (EI) *m/z* (rel. intensity) 353 ([M^+], 35), 336 (4), 324 (3), 282 (4), 241 (11), 240 (35), 226 (25), 224 (5), 212 (29), 200 (100), 187 (7), 146 (4), 118 (6), 91 (7), 77 (3), 55 (6), 43 (10); HR-MS (EI) ($C_{23}H_{31}NO_2$): calcd 353.235479, found 353.235538.

3.1.28. 3-Dodecyl-4-hydroxy-5-phenyl-1*H*-pyridin-2-one (31). A suspension of olefin **30b** (83 mg, 0.23 mmol) and Pd/C (20 mg, 10%, w/w) in MeOH (2.5 mL) was stirred under an atmosphere of H_2 (1 atm) for 72 h. The catalyst was filtered off through a short pad of Celite and was successively washed with hot MeOH and hot EtOAc, the combined filtrates were evaporated and the crude product was purified by HPLC (Nucleosil-100-5-C18/A, ∅ 4.5× 125 mm; MeOH/water 90:10; 0.8 mL min^{-1}; 308 K; 12.5 MPa; retention time: 4.88 min) to give compound **31** as a colorless solid (60%). ^{1}H NMR (400 MHz, CD_2Cl_2+CD_3OD) δ 7.45–7.32 (m, 6H), 2.55 (m, 2H), 1.51–1.40 (m, 2H), 1.42–1.17 (m, 18H), 0.83 (t, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CD_2Cl_2+CD_3OD$) δ 166.1, 162.8, 135.5, 132.1, 130.5, 129.8, 128.9, 117.3, 114.6, 33.1, 31.0, 30.9, 30.8, 30.6, 29.6 (m), 24.5, 23.9, 14.9; IR (film) 2923, 2852, 1640, 1620, 1600, 1455, 1434, 1208, 1132, 1082, 881, 760, 699; MS (EI) *m/z* (rel. intensity) 355 ([M^+], 17), 338 (10), 214 (13), 201 (100), 200 (46), 188 (1), 173 (1), 146 (2), 130 (3), 118 (2), 91 (3), 55 (3), 43 (3), 41 (2); HR-MS ($C_{23}H_{33}NO_2$+Na) calcd 378.24054, found 378.24059 (M+Na).

3.2. Enzymatic assays

PTP1B-inhibition. PTP1B was purchased from Calbiochem (human recombinant). The enzyme (0.001 U) was pre-incubated with the inhibitors in a buffer (pH 7.2)[42] containing HEPES (25 mM), EDTA (2.5 mM), NaCl (50 mM), DTT (2 mM) and BSA (0.1%) for 15 min at room temperature. Then p-NPP was added (end concentration 50 μM) and the read-out (405 nm) was recorded on a microplate-reader at 37 °C continuously for 80 min. The reaction rate was determined from the absorption difference between 30 and 60 min reaction time.

Cdc25A-inhibition. The clone pET9d/His-Cdc25A was expressed in the *E. coli* strain BL21-DE3 and purified in the presence of 8M urea. 30 μg of the purified enzyme was pre-incubated with the inhibitors in a buffer pH 8.0 containing 50 mM Tris, 50 mM NaCl and 2 mM DTE for 15 min at room temperature.[43,44]

3.3. X-ray crystallographic study

Suitable crystals were obtained by recrystallization from *n*-hexane (**8**) and *n*-heptane (**25**). Data were recorded using an Enraf-Nonius KappaCCD diffractometer with graphite-monochromated Mo K_α-radiation ($\lambda=0.71073$ Å). The crystal was mounted in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97)[45] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[46] Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236780 (**8**) and 236781 (**25**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Selected X-ray crystallographic data for compound **8**. $C_{28}H_{41}NO_4Si_2$, $M_r=511.80$ g mol^{-1}, colorless, crystal size $0.44\times0.08\times0.06$ mm, orthorhombic, $P2_12_12$ [No. 18], $a=18.2689(2)$, $b=26.2118(3)$, $c=12.40800(10)$ Å,

$V=5941.70(11)$ Å^3, $Z=8$, $D_{calc}=1.144$ Mg m^{-3}, $\mu=0.150$ mm^{-1}, $T=100$ K, 74260 reflections collected, 13582 independent reflections, 8780 reflections with $I>2\sigma(I)$, $\theta_{max}=27.45°$, 651 refined parameters, $R=0.0686$, $R_w=0.1666$, $S=1.492$, largest diff. peak and hole $=0.547/-0.503$ e Å^{-3}.

Selected X-ray crystallographic data for compound **25**. $C_{29}H_{44}ClNO_4Si_2$, $M_r=562.28$ g mol^{-1}, colorless, crystal size $0.34\times0.04\times0.03$ mm^3, monoclinic, $P2_1$ [No. 4], $a=7.8949(3)$, $b=15.8034(6)$, $c=12.3838(5)$ Å, $\beta=92.396(2)°$, $V=1543.73(10)$ Å^3, $Z=2$, $D_{calc}=1.210$ Mg m^{-3}, $\mu=0.234$ mm^{-1}, $T=100$ K, 18212 reflections collected, 4405 independent reflections, 3171 reflections with $I>2\sigma(I)$, $\theta_{max}=23.25°$, 189 refined parameters, $R=0.0598$, $R_w=0.1175$, $S=1.032$, largest diff. peak and hole $=0.479/-0.431$ e Å^{-3}.

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