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Ligand creation via linking—a rapid and convenient method for construction of novel supported PyOX-ligands

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Abstract—A novel supported amino alcohol linker was synthesized and utilized for attachment of picolinic acid derivatives onto different supports. When the resin bound molecule was further activated, the PyOX-moiety could be constructed reliably in enantiopure form. Furthermore, an efficient Pd-catalyzed modification of a picolinic acid derivative is presented.

1. Introduction

For economic and environmental reasons, the trend towards the application of enantiopure compounds is undoubtedly increasing. Asymmetric induction with chiral ligands and their transition metal complexes constitutes one of the most versatile methods for the preparation of chiral compounds in enantiopure form.[1] Covalent immobilization of catalysts on insoluble polymer or other supports has received considerable attention in recent years.[2] Heterogeneous catalysis has two major advantages over homogenous catalysis: (1) separation of the catalyst from reagents and products is technically easier and facilitates recycling and recovery of the valuable catalyst material; (2) optimization of either the diversity of the ligand or the reaction conditions is facilitated. In particular, polymer supported ligands have been studied extensively.[3] Whereas the PyOX-core (Fig. 1) has been widely reported in several applications as soluble ligands, solid-supported PyOX-ligands are still very rarely published,[4] despite their obvious usefulness in various catalytic asymmetric reactions.[5–7] More intensively, the C_2-symmetric PyBOX-core has been attached to a solid support using various methods.[8]

In modification processes of the PyOX-core, the modification has traditionally been carried out by altering the amino alcohols, which are used to form the oxazoline part of the PyOX-core (Fig. 1). Much less attention has been focused on the pyridine part.[7c,d] In this paper, we will introduce a new method to simultaneously link picolinic acid derivatives to a solid support and form the PyOX-core via cyclization on the solid support. For this purpose, a novel tyrosine-based aminoalcohol linker **1** was synthesized. This methodology allows the possibility of systematically optimizing the substituents of the pyridine ring in the PyOX. When the pyridine is adorned with a functional tail, the Py-part can be attached to a support and optimization of the oxazoline part can take place.

2. Results and discussion

The main plan for the formation of a novel linker was to utilize the amino alcohol functionality for both linking carboxylic acids and oxazoline formation via varying the substituents of the pyridine ring. Natural tyrosine provides the necessary orthogonal functionalities for linking and oxazoline formation, and was therefore used as the starting material for the linker. As the support we chose the robust Merrifield resin with no additional linkers. Attachment to the resin can be achieved via an ether bond between the resin and the phenolic group of tyrosine. This linking strategy gives us the possibility to prepare additional linkers in the future, if flexibility is needed.

In solution phase model experiments for linker preparation the solid support was replaced with a benzyl group as a soluble analogue of the Merrifield resin. The model reactions were performed in order to optimize the reaction conditions with respect to reaction rate, conversion and retention of stereochemistry. The protected tyrosine **3** was prepared according to published methods (Scheme 1).[9] Benzylation of the protected tyrosine posed some critical technical issues: the use of cesium carbonate in benzylation

Keywords: Supported PyOX-ligand; Amino alcohol linker; Tyrosine; Picolinic acid derivative.
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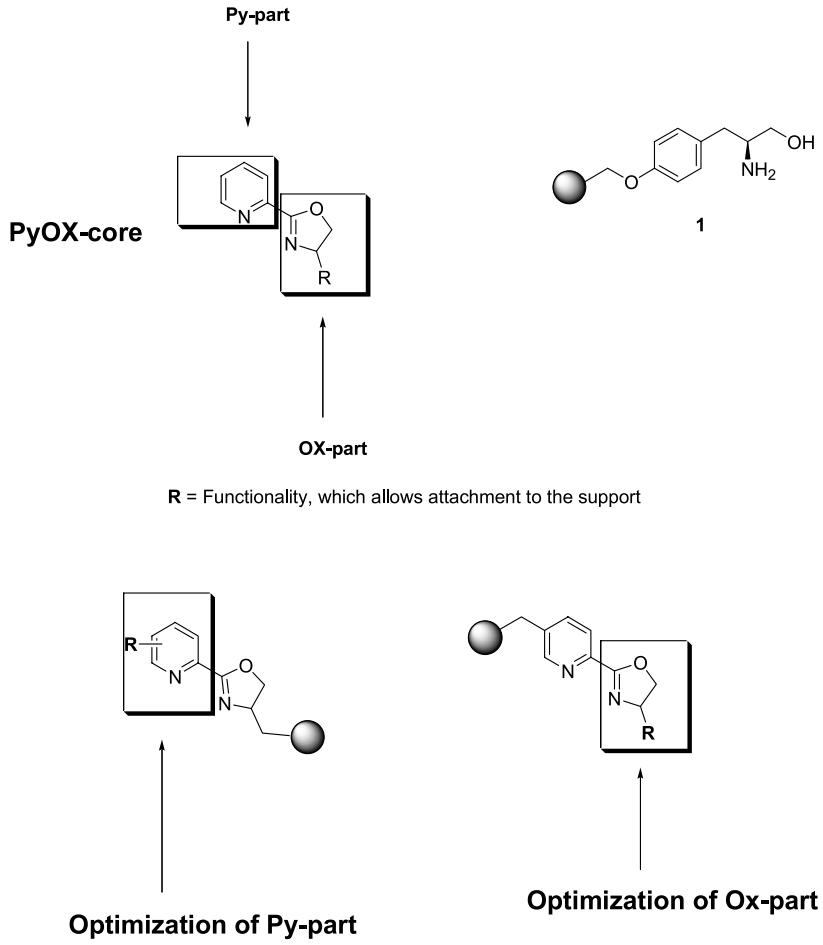
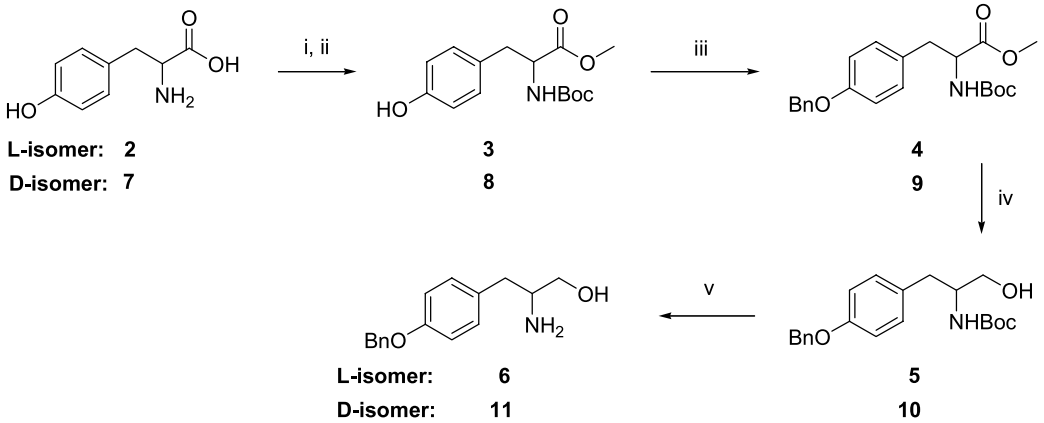


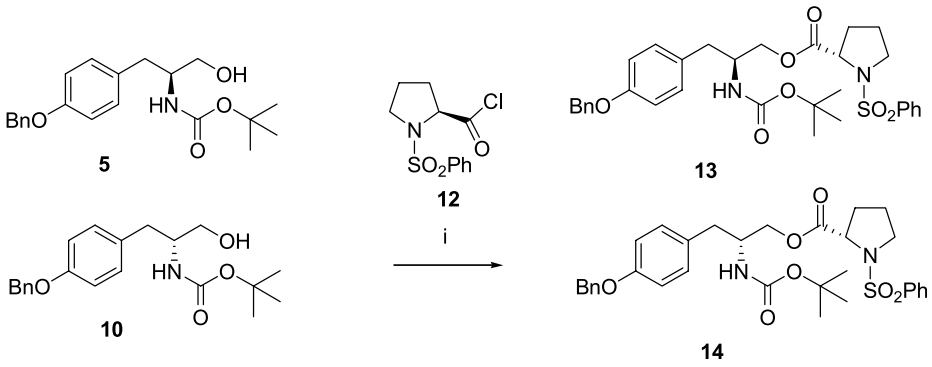
Figure 1. The PyOX-core and its possibilities for optimization.



Scheme 1. Model experiments with soluble analogues, starting from (L)-tyrosine (**2**–**6**) and (D)-tyrosine (**7**–**11**). (i) $SOCl_2$, MeOH, −72 °C to reflux, 20 h; (ii) NEt_3, Boc_2O, MeOH, rt, 17 h, 89% (two steps); (iii) BnBr, K_2CO_3, KI, acetone, reflux, 4 h, 100%; (iv) $NaBH_4$, LiI, THF, reflux, 3 h, 87%; (v) *p*-TsOH, CH_2Cl_2, THF, rt, 20 h, 68% (1 crop).

is reported to lead to racemization.[10] On the other hand, it has been reported that the use of K_2CO_3 in acetone evades the racemization in liquid-phase experiments.[6a] However, acetone cannot be used with the Merrifield resin due to poor swelling. We soon discovered that the optical rotation of **4** remained identical, when the solvent was changed from acetone to DMF.[11]

Reduction of **4** could be carried out using the standard $LiAlH_4$-procedure, but we chose $NaBH_4$/LiI-reduction[12] for milder conditions and more convenient work-up with resins. The procedure used for Boc removal was designed for solid phase use.[13] Standard Boc cleavage (50% TFA/CH_2Cl_2) caused some cleavage of the phenolic ether in **5**, whereas *p*-TsOH proved mild enough to avoid this side reaction. The



Scheme 2. (i) **12**, DIPEA, CH_2Cl_2, rt, **5**→**13**: 18 h; **10**→**14**: 20 min.

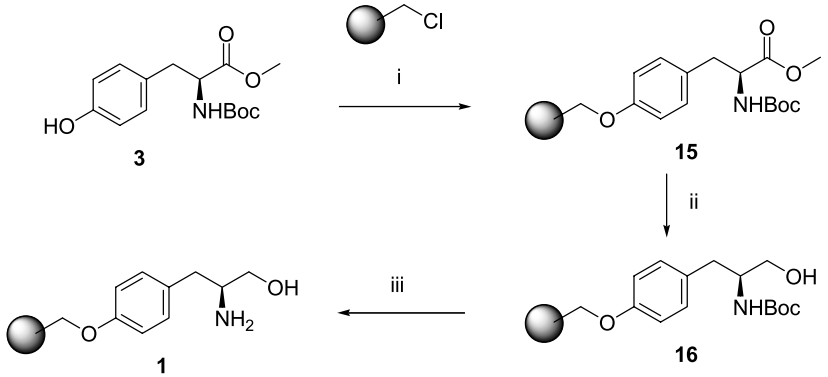
synthesis was repeated with D-tyrosine to ascertain that no racemization had occurred during the steps (compounds **7**–**11**). Compounds **4**–**6** were analyzed by IR and the characteristic signals mapped for comparison with the solid phase analogues.

Enantiomers **5** and **10** were derivatized with the chiral proline derivative **12** to form diastereomers **13** and **14** (Scheme 2).[14] These were shown to be pure by achiral HPLC and NMR.

The optimized reaction conditions from liquid phase experiments (Scheme 1) were applied with the supported **4**. Phenol **3** was attached to the Merrifield resin using the benzylation protocol developed above. Reaction monitoring on solid support could easily be performed by FTIR, as the characteristic signals were found by model experiments in solution. The easiest region to follow is the carbonyl region ($\nu = 1750$–$1600\ cm^{-1}$) due to the strong signals and characteristic changes.[15] Scheme 3 illustrates the formation of linker **1**.

Picolinic acid derivatives were attached to **1** to form the amido alcohol functionality. We focused our attention on acids substituted also at the 5-position, because the corresponding picolinic acids (e.g., **18** and **19**, Fig. 2) can be prepared utilizing the differing reactivities of the 2- and 5-positions. The picolinic acid derivatives **18** and **19** were selected so that they have electronically different substituents. Furthermore, these functionalities could be utilized as attachment sites (Fig. 1). Picolinic acid (**17**) was selected as 'standard' with neither electron withdrawing nor donating groups. 5-(Methoxycarbonyl)picolinic acid **18** was prepared using a known procedure through exhaustive esterification and selective hydrolysis (Scheme 6).[16]

Methyl 5-bromopicolinate **22** was prepared according to known procedures by selective lithiation (Scheme 4).[17,18] We attempted to prepare the acetylenic adduct **19** using standard Sonogashira-conditions[19] in various solvents, but a reproducible protocol was not achieved. Excluding the copper, however, gave excellent results, in contrast to previous literature studies regarding pyridine ring coupling at the 5-position.[20] In that paper, a strict Cu/Pd-ratio was required to achieve acetylenic coupling at the 5-position.



Scheme 3. (i) Merrifield resin, loading 1.59 mmol/g, K_2CO_3, KI, DMF, 70 °C, 19 h; (ii) $NaBH_4$, LiI, THF, reflux, 7 h; (iii) *p*-TsOH, CH_2Cl_2, THF, rt, 1.5 h.

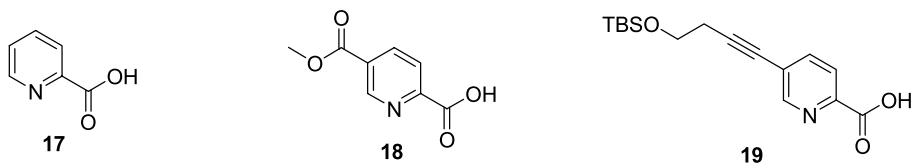
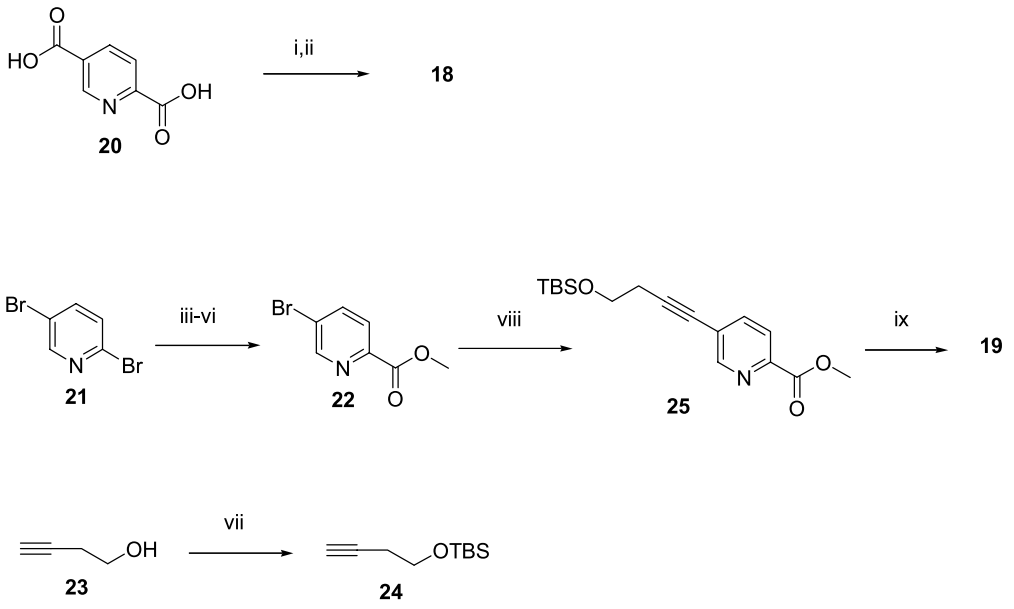
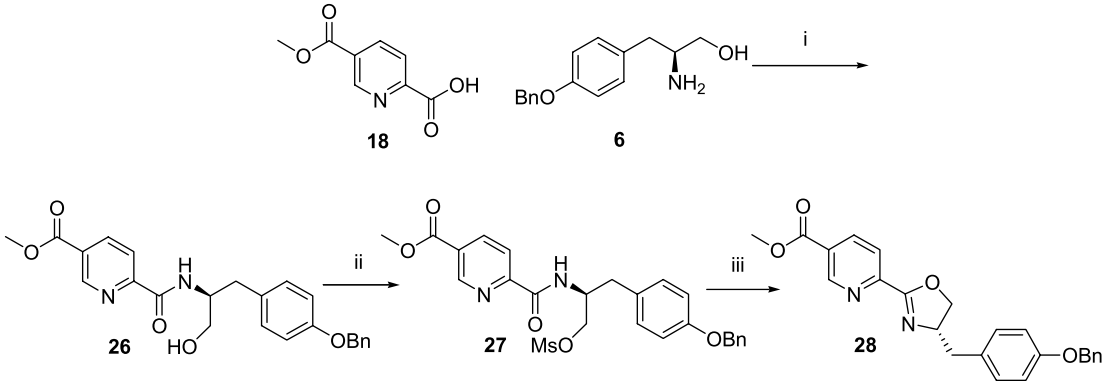


Figure 2. The picolinic acid derivatives used in linking and PyOX formation.



Scheme 4. (i) MeOH, H_2SO_4, reflux, 22 h; (ii) NaOH, MeOH, reflux, 2 h, 62% (from **20**); (iii) *n*-BuLi, PhMe, −77 °C, 3 h; (iv) CO_2; (v) $SOCl_2$, reflux, 4 h; (vi) MeOH, NEt_3, rt, 46% (over four steps); (vii) TBSCl, NEt_3, DMAP, CH_2Cl_2, rt, 20 h, 85%; (viii) **24**, $Pd(PPh_3)_2Cl_2$, NEt_3, THF, reflux, 24 h, 92%; (ix) NaOH, aqueous MeOH, reflux, 6 h, 64%.



Scheme 5. Model compounds for FTIR analysis. (i) (a) **18**, $SOCl_2$, reflux, 2.5 h, (b) **6**, NEt_3, CH_2Cl_2, rt, 15 min, 62% (from **18**); (ii) MsCl, NEt_3, DMAP, CH_2Cl_2, rt, 1 min, 81%; (iii) DBU, THF, 40 °C, 24 h, 43%.

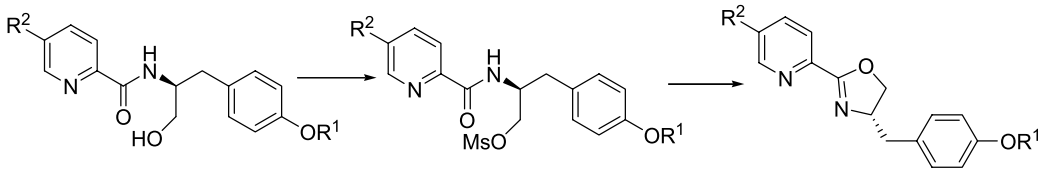
An explanation for this controversial result is probably the methyl ester group at the 2-position in our case (compound **22**, Scheme 4). In our hands, coupling of **22** and **23** proceeded, but did not reach complete conversion. Instead, coupling of **22** and **24**[21] gave a total conversion and excellent yield. The ester **25** was then hydrolyzed[16] to give **19** (Scheme 4).

The PyOX core on solid support was constructed by first coupling the picolinic acid and the amine followed by cyclization of the formed amido alcohol using suitable reagents.[22] We optimized the cyclization to suit all PyOX-precursors tested thus far using mesylate activation and DBU assisted cyclization.[23]

Model experiments were performed to examine the signals on FTIR and define characteristic signals for a facile monitoring of the reaction progress on solid support. The most informative signal turned out to be the amide signal: the signal of amido alcohol **26** was present, as the coupling of **6** and **18** was made. Mesylation of **26** shifted the amide signal to a higher wave number, as expected. The mesyl signal was in the fingerprint region and thus very hard to detect and define, especially in the case of the resins. The slowest reaction step, that is, cyclization to **28** (Scheme 5), could also be monitored using FTIR, because of the apparent signal shift towards a lower wavenumber. A summary of changes in the IR shift is shown in Table 1.

To our knowledge, this is the first time a solid-supported PyOX-ligand has been prepared by simultaneous linking and cyclization. In the rare reported cases, the solid-supported PyOX-ligands have been prepared by forming the PyOX-core and then attaching the compound to a solid support.[4a,8] We reasoned that formation of the PyOX on the solid support allows to use efficient reactions and monitor the reactions reliably. The picolinic acid derivatives **18–19** were all attached using a peptide coupling protocol, viz.

Table 1. The IR signals of either the amide or the C=N-group of oxazoline



R^1	R^2	Amido alcohol	Mesylate	PyOX
Bn	CO_2Me	1651	1666	1637
	H	1662	1669	1641
	CO_2Me	1664	1668	1635
		1656	1671	1636

HOBt/DIC-activation.[24] Acid chloride formation turned out to be too vigorous, since the use of acid chlorides also gave rise to double coupling, that is, also the corresponding amido ester was formed. In the case of picolinic acid **17** attachment, however, this was not the case and the acid chloride protocol could be used. Activation of the amido alcohols **29–31** was achieved with the usual mesylation protocol and cyclization was efficiently performed with DBU to form the PyOX-ligands **35–37** (Scheme 6).[22] In none of the cases could the cyclization be brought to completion using the one-step cyclization by Meyers,[25] involving either the tosylate or the mesylate activation. The general reaction path is shown in Scheme 6.

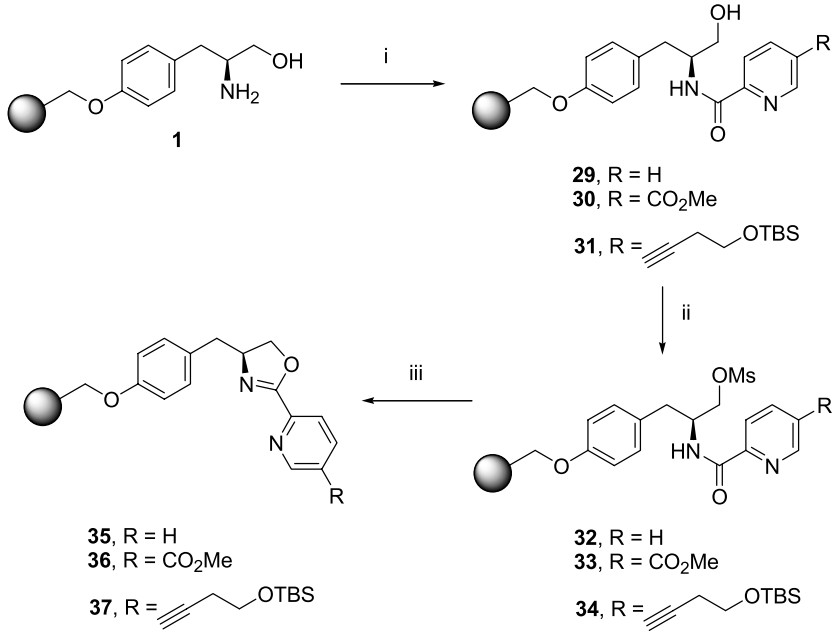
3. Conclusions

A new and general method to form PyOX-ligands on solid support is presented. It involves a simple path to link picolinic acids and functionalize them as the PyOX-core in three steps. Functionalization at the 5-position of the pyridine ring has also been carried out. The aim of functionalizing the 5-position was to build further functional groups for various needs. It is also surprisingly easy to differentiate between the 2-position and the 5-position of the pyridine ring due to the reactivity gap between these positions. This gives nearly unlimited resources, when variation around the PyOX-core is needed. Our strategy gives also the opportunity to link the PyOX-core from either the oxazoline or the pyridine ring. New support materials will also be used in the formation of supported PyOX-ligands. We are currently exploring one application, the use of the mercapto ester derived PyOX in nanotechnology,[23] which will be reported in due course.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe and dried prior to use. Toluene was distilled from Na, THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. Other solvents and reagents were used as



Scheme 6. Formation of the PyOX-ligands. (i) 5-R-picolinic acid, HOBt, DIC, CH_2Cl_2, DMF, rt; (ii) MsCl, NEt_3, DMAP, CH_2Cl_2, rt; (iii) DBU, THF, 50 °C.

obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with $KMnO_4$-solution (1.0 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 ml 5% aqueous NaOH-solution, 100 ml H_2O) or ninhydrin solution (1.0 g ninhydrin, 0.2 ml glacial AcOH, 100 ml EtOH). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The ^{1}H and ^{13}C NMR spectra were recorded in either $CDCl_3$ or d_6-DMSO on a Bruker Avance 400 (^{1}H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ 7.26) or d_6-DMSO (δ 2.50)[26] for ^{1}H NMR. For the ^{13}C NMR spectra, the residual $CDCl_3$ (δ 77.0) or d_6-DMSO (δ 39.5) were used as the internal standard. The optical purity of products **13** and **14** were determined by HPLC in comparison to the corresponding racemic samples using Waters 501 pump and Waters 486 detector, ThermoHypersil column and *i*-PrOH/hexane as eluent. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer using KBr-disc. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. High-resolution mass spectrometric data were obtained at the University of Oulu on Micromass LCT spectrometer. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

4.1.1. Phenylsulfonylproline *O*-benzyl-*tert*-butyloxycarbonyltyrosinyl esters 13 and 14. Compound **12** was prepared according to a literature procedure[14] by dissolving (*S*)-phenylsulfonyl proline (1.27 g, 5.0 mmol) in 10 ml CH_2Cl_2. Oxalyl chloride (1.0 ml, 11.5 mmol, 230 mol%) was added, followed by two drops of DMF. This caused a violent heat evolution, which settled after 5 min. The volatiles were evaporated after 1.5 h and the slurry product was dissolved in benzene and washed with saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, **12** solidified at vacuum pump overnight.

Compounds **5** and **10** were treated with the identical procedure. Tyrosinol derivative **5** or **10** (16 mg, 0.045 mmol, 100 mol%) was dissolved in 2 ml CH_2Cl_2. To this solution was added phenylsulfonylproline **12** (25 mg, 0.091 mmol, 200 mol%) dissolved in 1 ml CH_2Cl_2 and 0.035 ml DIPEA. According to TLC, the starting material was totally consumed after 18 h. The reaction was quenched with 10% aqueous citric acid and extracted twice with CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. Baseline impurities were removed by filtration through a short pad of silica (EtOAc/hexane 1:2) to yield the compounds **13** and **14** for analysis of enantiopurity.

Compound **13**. White solid. R_f=0.50 (EtOAc/hexane 1:1, UV); $[\alpha]_D^{22}$ −60.0 (*c* 0.2; CH_2Cl_2); mp=121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ($CDCl_3$) 7.89 (m, 2H, Ar-*H*), 7.61–7.51 (m, 3H, Ar-*H*), 7.44–7.31 (m, 5H, Ar-*H*), 7.13 (d, *J*=8.5 Hz, 2H, Ar-*H*), 6.91 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.84 (d, *J*=7.3 Hz, 1H, –N*H*Boc), 4.34 (dd, *J*=5.1, 7.1 Hz, 1H, –CH_2C*H*(NHBoc)(CH_2OCOR)), 4.12 (m, 3H, –CHCH_2OCOR, 2-Pro-C*H*), 3.51 (m, 1H, Ar-CH_2CHR$_2$-A), 3.31 (m, 1H, Ar-CH_2CHR$_2$-B), 2.81 (m, 2H, 5-Pro-CH_2), 2.03 (m, 3H, 3-Pro-CH_2, 4-Pro-CH_2-A), 1.78 (m, 1H, 4-Pro-CH_2-B), 1.40 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ($CDCl_3$) 172.0 (2-Pro-C(*O*)OR), 157.7 (RNHC(*O*)OC(CH$_3$)$_3$), 138.3 (Ar), 137.1 (Ar), 132.8 (Ar), 130.4 (Ar), 129.5 (Ar), 129.1 (Ar), 128.6 (Ar), 127.9 (Ar), 127.4 (Ar), 115.0 (Ar), 79.4 (–NHCO$_2$*C*(CH$_3$)$_3$), 70.1 (Ph*C*H$_2$OAr), 65.4 (–CH*C*H$_2$OCOR), 60.5 (2-Pro-*C*H), 51.1 (–CH$_2$*C*H(NHBoc)(CH$_2$OCOR)), 48.4 (Ar-*C*H$_2$CHR$_2$), 30.9 (5-Pro-*C*H$_2$), 29.7 (3-Pro-*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 24.7 (4-Pro-*C*H$_2$); HRMS (ESI) calcd for $C_{32}H_{38}N_2O_7SNa$ 617.2297, found 617.2281 (M+Na); Enantiomeric purity was determined by HPLC (ThermoHypersil column, 1% *i*-PrOH/hexanes, flow rate 1.5 ml/min): τ=25.59 min.

Compound **14**. Colourless oil. R_f=0.50 (EtOAc/hexane 1:1, UV); $[\alpha]_D^{22}$ −102 (*c* 0.15; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H, Ar-*H*), 7.61–7.51 (m, 3H, Ar-*H*), 7.44–7.31 (m, 5H, Ar-*H*), 7.14 (d, *J*=8.5 Hz, 2H, Ar-*H*), 6.91 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.94 (d, *J*=8.1 Hz, 1H, –N*H*Boc), 4.30 (dd, *J*=5.9, 6.2 Hz, 1H, –CH_2C*H*(NHBoc)(CH_2OCOR)), 4.20 (m, 1H, 2-Pro-C*H*), 4.04 (m, 2H, –CHCH_2OCOR), 3.57 (m, 1H, Ar-CH_2-CHR$_2$-A), 3.30 (m, 1H, Ar-CH_2CHR$_2$-B), 2.83 (m, 2H, 5-Pro-CH_2), 2.02 (m, 3H, 3-Pro-CH_2, 4-Pro-CH_2-A), 1.77 (m, 1H, 4-Pro-CH_2-B), 1.41 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (2-Pro-C(*O*)OR), 157.6 (RNHC(*O*)OC(CH$_3$)$_3$), 138.1 (Ar), 137.1 (Ar), 132.8 (Ar), 130.3 (Ar), 129.6 (Ar), 129.1 (Ar), 128.5 (Ar), 127.9 (Ar), 127.4 (Ar), 127.3 (Ar), 114.9 (Ar), 77.2 (–NHCO$_2$*C*(CH$_3$)$_3$), 70.0 (Ph*C*H$_2$OAr), 65.5 (–CH*C*H$_2$OCOR), 60.6 (2-Pro-*C*H), 51.1 (–CH$_2$*C*H(NHBoc)(CH$_2$OCOR)), 48.4 (Ar-*C*H$_2$CHR$_2$), 30.9 (5-Pro-*C*H$_2$), 29.6 (3-Pro-*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 24.6 (4-Pro-*C*H$_2$); HRMS (ESI) calcd for $C_{32}H_{38}N_2O_7SNa$ 617.2297, found 617.2297 (M+Na); Enantiomeric purity was determined by HPLC (ThermoHypersil column, 1% *i*-PrOH/hexanes, flow rate 1.5 ml/min): τ=27.61 min.

4.1.2. *N-tert*-butoxycarbonyl tyrosine methyl ester resin 15. Merrifield resin (4.61 g, 7.33 mmol based on reported loading, 100 mol%) and KI (430 mg, 2.59 mmol, 40 mol%) were suspended in 20 ml DMF. In another flask, **3** (4.10 g, 13.9 mmol, 190 mol%) was dissolved in 40 ml DMF and K_2CO_3 (3.55 g, 25.7 mmol, 350 mol%) was added. After 15 min, the suspension of **3**/K_2CO_3 was added to the resin and the mixture was heated on a 70 °C oil bath for 19 h. The resin was filtered and washed subsequently with DMF, DMF/H_2O 1:1, DMF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1717.

4.1.3. *N-tert*-butoxycarbonyl tyrosinol resin 16. Functionalised resin **15** (2.10 g, 3.34 mmol, 100 mol%) was suspended in 50 ml THF. LiI (4.47 g, 33.4 mmol, 1000 mol%) was added, followed by $NaBH_4$ (1.26 g, 33.3 mmol, 1000 mol%).The mixture was set for reflux for 7 h and filtered. It was washed subsequently with THF/H_2O 1:1, THF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1685.

4.1.4. Tyrosinol resin 1. To **16** (2.00 g, 3.18 mmol, 100 mol%) was added a stock solution[13] of *p*-TsOH

(10.57 g, 55.6 mmol, 1700 mol%), 11 ml CH_2Cl_2 and 21 ml THF. The resin was filtered after 1.5 h, followed by subsequent wash with NEt_3/DMF 1:2, DMF, DMF/H_2O 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 3385.

4.1.5. 5-(1′-*tert*-Butyldimethylsilyloxy-3-butynyl)methyl picolinate 25. Bromopyridine **22** (590 mg, 2.73 mmol, 100 mol%), 18 ml dry THF, NEt_3 (0.58 ml, 4.16 mmol, 150 mol%) and **24** (1003 mg, 5.44 mmol, 200 mol%) were loaded into a Schlenk apparatus. Retaining the oxygen-free atmosphere, $Pd(PPh_3)_2Cl_2$ (100 mg, 0.14 mmol, 5 mol%) was added to the solution. The mixture was heated to reflux for 24 h and diluted with CH_2Cl_2. It was quenched with saturated aqueous $NaHCO_3$ and extracted three times with CH_2Cl_2. The organics were washed with brine and dried over Na_2SO_4 to give 1.56 g of a dark brown oil. It was purified by FC (EtOAc/hexane 1:4) to give **25** (800 mg, 2.50 mmol, 92%) as an almost colourless oil. R_f=0.29 (EtOAc/hexane 1:1, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J=0.8, 2.0 Hz, 1H, 6-Py-C*H*), 8.04 (dd, J=0.8, 8.0 Hz, 1H, 4-Py-C*H*), 7.77 (dd, J=2.0, 8.0 Hz, 1H, 3-Py-C*H*), 3.98 (s, 3H, –CO_2Me), 3.81 (t, J=6.8 Hz, 2H, –$CH_2CH_2OSiR_3$), 2.65 (t, J=6.8 Hz, 2H, –$CH_2CH_2OSiR_3$), 0.89 (s, 9H, –C(CH_3)$_3$), 0.07 (s, 6H, –Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (–CO_2CH_3), 152.2 (6-Py-*C*), 145.7 (2-Py-*C*–CO_2Me), 139.2 (4-Py-*C*), 124.4 (3-Py-*C*), 124.3 (5-Py-*C*-R), 94.6 (Ar-C≡*C*–CH_2R), 77.9 (Ar-*C*≡C–CH_2R), 61.4 (–$CH_2CH_2OSiR_3$), 52.8 (–CO_2CH_3), 25.8 (–$SiR_2C(CH_3)_3$), 24.0 (–C≡C–CH_2CH_2–), 18.3 (–$SiR_2C(CH_3)_3$), −5.3 (–Si(CH_3)$_2$C(CH_3)$_3$); HRMS (ESI) calcd for $C_{17}H_{25}NO_3Si$ 320.1682, found 320.1690 (M+1).

4.1.6. 5-(1′-*tert*-Butyldimethylsilyloxy-3-butynyl)picolinic acid 19. Ester **25** (620 mg, 1.94 mmol, 100 mol%) was dissolved in 30 ml of 90% aqueous methanol. Finely ground NaOH (82 mg, 2.05 mmol, 110 mol%) was added and the mixture was set for reflux for 6 h. The solution was concentrated to a small volume and acidified carefully with 1 M aqueous HCl at 0 °C. The formed solid was filtered and dried at pump to yield **19** (380 mg, 1.24 mmol, 64%) as a white solid; mp 104–105 °C (dec); IR (KBr, cm^{-1}) 2229, 1703; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.62 (s, 1H, 6-Py-C*H*), 7.97 (d, J=7.9 Hz, 1H, 4-Py-C*H*), 7.90 (d, J=8.0 Hz, 1H, 3-Py-C*H*), 3.80 (t, J=6.4 Hz, 2H, –CH_2CH_2-$OSiR_3$), 2.68 (t, J=6.4 Hz, 2H, –$CH_2CH_2OSiR_3$), 2.08 (s, 1H, –CO_2H), 0.89 (s, 9H, –C(CH_3)$_3$), 0.08 (s, 6H, –Si(CH_3)$_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.8 (–CO_2H), 151.1 (6-Py-*C*), 147.9 (2-Py-*C*–CO_2H), 139.3 (4-Py-*C*), 124.1 (3-Py-*C*), 122.7 (5-Py-*C*-R), 94.5 (Ar-C≡*C*–CH_2R), 77.9 (Ar-*C*≡C–CH_2R), 61.0 (–CH_2-CH_2OSiR_3), 25.7 (–$SiR_2C(CH_3)_3$), 23.3 (–C≡C–CH_2CH_2–), 17.9 (–$SiR_2C(CH_3)_3$), −5.3 (–Si(CH_3)$_2$C(CH_3)$_3$); HRMS (ESI) calcd for $C_{16}H_{23}NO_3SiNa$ 328.1345, found 328.1342 (M+Na).

4.1.7. 5-Methoxycarbonylpicolinyl-(1′-(*S*)-(*p*-benzyloxyphenyl)-2′-hydroxy)ethylamide 26. Acid **18** (70 mg, 0.39 mmol, 100 mol%) was refluxed in 3 ml $SOCl_2$ for 2.5 h. The mixture was evaporated to dryness. Aminoalcohol **6** (100 mg, 0.39 mmol, 100 mol%) was dissolved in 4 ml CH_2Cl_2 and 0.30 ml NEt_3. The residue of **18** was dissolved in 2 ml CH_2Cl_2 and this solution was added to the solution of **6**. After 15 min, ice water was added to the mixture and it was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product recrystallized from EtOAc/hexane to yield 100 mg (0.24 mmol, 62%) of **26** as a white solid. R_f=0.15 (EtOAc/hexane 1:1, $KMnO_4$); $[\alpha]_D^{22}$ −25.5 (*c* 0.07; $CHCl_3$); mp 165–165.5 °C; IR (KBr, cm^{-1}) 1717, 1651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (dd, J=0.9, 2.0 Hz, 1H, 6-Py-C*H*), 8.44 (dd, J=2.0, 8.0 Hz, 1H, 4-Py-C*H*), 8.30 (d, J=8.2 Hz, 1H, –N*H*COAr), 8.25 (dd, J=0.8, 8.0 Hz, 1H, 3-Py-C*H*), 7.43–7.30 (m, 5H, Ar-*H*), 7.19 (d, J=8.6 Hz, 2H, Ar-*H*), 6.92 (d, J=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.32 (m, 1H, –CH_2CH(NHCOAr)(CH_2OH)), 3.99 (s, 3H, –CO_2CH_3), 3.81 (m, 1H, –R_2CHCH_2OH-A), 3.73 (m, 1H, –R_2CHCH_2OH-B) 2.96 (m, 2H, Ar-CH_2-CHR_2), 2.47 (t, J=5.4 Hz, 1H, –CH_2O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (Ar-CO_2CH_3), 163.7 (–NH*C*OAr), 157.6 (C_{Ar}-OR), 152.6 (2-Py*C*-CONHR), 149.4 (6-Py-*C*), 138.5 (C_{Ar}–CH2OAr), 137.0 (4-Py-*C*), 130.2 (Ar), 129.7 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.4 (Ar), 121.8 (Ar), 115.0 (Ar), 70.0 (PhCH_2OAr), 64.3 (–R_2CHCH_2OH), 53.5 (–R_2CHCH_2OH), 52.6 (–CO_2CH_3), 36.3 (ArCH_2CHR_2); HRMS (ESI) calcd for $C_{24}H_{24}N_2O_5Na$ 443.1583, found 443.1576 (M+Na).

4.1.8. 5-Methoxycarbonylpicolinyl-(1′-(*S*)-(*p*-benzyloxyphenyl)-2′-mesyloxy)ethylamide 27. Amide **26** (50 mg, 0.12 mmol, 100 mol%) was dissolved in 3 ml CH_2Cl_2. NEt_3 (0.10 ml, 0.72 mmol, 600 mol%) and DMAP (3 mg, 0.03 mmol, 20 mol%) were added, followed by MsCl (30 μl, 0.39 mmol, 320 mol%). This caused a spontaneous heating of the mixture. TLC monitoring showed total conversion after 3 min. The reaction was quenched with water 10 min later. The mixture was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude mixture filtered through a short pad of silica and recrystallized from EtOAc/hexane to yield 48 mg (0.10 mmol, 81%) of **27** as a white solid. R_f=0.15 (EtOAc/hexane 1:1, $KMnO_4$); $[\alpha]_D^{22}$ +21.0 (*c* 0.07; CH_2Cl_2); mp 115–117.5 °C; IR (KBr, cm^{-1}) 1725, 1666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (dd, J=0.8, 2.0 Hz, 1H, 6-Py-C*H*), 8.44 (dd, J=2.0, 8.0 Hz, 1H, 4-Py-C*H*), 8.25 (d, J=8.2 Hz, 1H, –N*H*COAr), 8.23 (dd, J=0.8, 8.2 Hz, 1H, 3-Py-C*H*), 7.43–7.29 (m, 5H, Ar-*H*), 7.19 (d, J=8.6 Hz, 2H, Ar-*H*), 6.93 (d, J=8.6 Hz, 2H, Ar-*H*), 5.03 (s, 2H, PhCH_2OAr), 4.59 (m, 1H, R_2CH(CH_2OSO_2Me)-(NHCOAr)), 4.36 (m, 1H, $R_2CHCH_2OSO_2$Me-A), 4.26 (m, 1H, $R_2CHCH_2OSO_2$Me-B), 3.99 (s, 3H, 5-Py-CO_2CH_3), 3.00 (m, 2H, Ar-CH_2CHR_2), 3.00 (s, 3H, –$CH_2OSO_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (Ar-CO_2CH_3), 163.2 (–NH*C*OAr), 157.9 (C_{Ar}-OR), 152.2 (2-Py*C*-CONHR), 149.5 (6-Py-*C*), 138.6 (4-Py-*C*), 136.9 (Ar), 130.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 127.4 (Ar), 121.9 (Ar), 115.2 (Ar), 70.0 (R_2CHCH_2-OSO_2Me), 69.4 (PhCH_2OAr), 52.7 (–CO_2CH_3), 50.0 (–R_2CHCH_2OH), 37.3 (–$CH_2OSO_2CH_3$), 36.1 (ArCH_2-CHR_2); HRMS (ESI) calcd for $C_{25}H_{27}N_2O_7S$ 499.1539, found 499.1521 (M+1).

4.1.9. 5-Methoxycarbonyl-2-(4′-(*S*)-*p*-benzyloxybenzyl-2′-oxazolinyl)-pyridine 28. Mesylate **27** (26 mg, 52 μmol, 100 mol%) was dissolved in 4 ml THF. DBU (35 μl, 230 μmol, 450 mol%) was added and the mixture was heated on a 40 °C oil bath for 24 h. The reaction was quenched with water and extracted three times with EtOAc. The combined organics were washed with water and brine and dried over Na_2SO_4. The crude product was purified by FC (EtOAc/hexane 2:1) to yield 9 mg (22 μmol, 43%) of **28** as a white solid. R_f=0.45 (EtOAc/hexane 2:1, UV); $[\alpha]_D^{22}$ +18.0 (*c* 0.07; CH_2Cl_2); mp 165–170 °C (dec); IR (KBr, cm^{-1}) 1716, 1637; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (dd, *J*=0.5, 2.0 Hz, 1H, 6-Py-C*H*), 8.38 (dd, *J*=2.1, 8.2 Hz, 1H, 4-Py-C*H*), 8.13 (dd, *J*=0.5, 8.2 Hz, 1H, 3-Py-C*H*), 7.44–7.30 (m, 5H, Ar-*H*), 7.17 (d, *J*=8.6 Hz, 2H, Ar-*H*), 6.92 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.05 (s, 2H, PhCH_2OAr), 4.65 (app dq, *J*=5.3, 8.7 Hz, 1H, 4-oxazoline-C*H*), 4.48 (app t, *J*=8.7 Hz, 1H, 5-oxazoline-CH_2-A), 4.25 (app t, *J*=8.7 Hz, 1H, 5-oxazoline-CH_2-B), 3.98 (s, 3H, –CO_2CH_3), 3.22 (dd, *J*=5.3, 13.9 Hz, 1H, Ar-CH_2-oxazoline-A), 2.74 (dd, *J*=8.7, 13.9 Hz, 1H, Ar-CH_2-oxazoline-B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (–*C*O_2CH_3), 162.5 (RN=*C*-OR), 157.7 (C_{Ar}-OR), 150.8 (2-Py-*C*-oxazoline), 150.0 (6-Py-*C*), 137.8 (Ar), 137.1 (Ar), 130.2 (Ar), 129.9 (Ar), 128.6 (Ar), 127.9 (Ar), 127.4 (Ar), 127.4 (Ar), 123.5 (Ar), 115.0 (Ar), 72.7 (5-oxazoline-*C*), 70.1 (Ph*C*H_2OAr), 68.4 (4-oxazoline-*C*), 52.6 (–CO_2CH_3), 40.6 (Ar-*C*H_2-oxazoline); HRMS (ESI) calcd for $C_{24}H_{22}N_2O_4$ 403.1658, found 403.1653 (M+1).

4.1.10. Picolinyl amido alcohol resin 29. Resin **1** (203 mg, 0.32 mmol based on the reported Merrifield resin loading 1.59 mmol/g, 100 mol%) was suspended in 3 ml CH_2Cl_2 and 0.2 ml NEt_3. To the solution was added 46 mg (0.32 mmol, 100 mol%) of picolinyl chloride (prepared from **17**). The solution turned dark blue in a matter of minutes. The resin was filtered 3 h later and washed subsequently with DMF/H_2O 3:1, DMF, methanol and CH_2Cl_2. Resin **29** was dried, first at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1662.

4.1.11. (5-Methoxycarbonyl)picolinyl amido alcohol resin 30. Acid **18** (46 mg, 0.25 mmol, 110 mol%) was dissolved in 3 ml CH_2Cl_2 and 1 ml DMF. HOBt (35 mg, 0.26 mmol, 110 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin **1** (150 mg, 0.24 mmol, 100 mol%) in 5 ml CH_2Cl_2, followed by DIC (40 μl, 0.26 mmol, 110 mol%). The solution turned orange after 30 min. After 24 h stirring, the resin was filtered and washed subsequently with CH_2Cl_2, DMF/H_2O 3:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1733, 1664.

4.1.12. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)picolinyl amido alcohol resin 31. Acid **19** (97 mg, 0.32 mmol, 100 mol%) was dissolved in 4 ml CH_2Cl_2 and 1 ml DMF. HOBt (43 mg, 0.32 mmol, 100 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin **1** (200 mg, 0.32 mmol, 100 mol%) in 6 ml CH_2Cl_2, followed by DIC (50 μl, 0.32 mmol, 100 mol%). The solution turned orange after a few hours. After 23 h stirring, the resin was filtered and washed subsequently with DMF, DMF/H_2O 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2238, 1656.

4.1.13. Picolinyl amido mesylate resin 32. Amide resin **29** (50 mg, 80 μmol, 100 mol%) was suspended in 6 ml CH_2Cl_2 and 0.2 ml NEt_3. DMAP (3 mg, 25 μmol, 30 mol%) was added, followed by MsCl (30 μl, 0.39 mmol, 490 mol%). The reaction mixture turned bright yellow with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1669.

4.1.14. (5-Methoxycarbonyl)picolinyl amido mesylate resin 33. Resin **30** (70 mg, 110 μmol, 100 mol%) was suspended in 6 ml CH_2Cl_2 and 0.2 ml NEt_3. DMAP (5 mg, 40 μmol, 40 mol%) was added, followed by MsCl (50 μl, 0.64 mmol, 580 mol%). The reaction mixture turned orange with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1727, 1668.

4.1.15. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)picolinyl amido mesylate resin 34. Resin **31** (190 mg, 0.30 mmol, 100 mol%) was suspended in 5 ml CH_2Cl_2 and 0.3 ml NEt_3. DMAP (10 mg, 82 μmol, 30 mol%) was added, followed by MsCl (70 μl, 0.90 mmol, 300 mol%). The reaction mixture turned orange with slight reflux. After 25 min, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2238, 1671.

4.1.16. Pyridine 2-(2′-oxazolinyl)resin 35. Resin **32** (40 mg, 60 μmol, 100 mol%) was suspended in 3 ml THF. DBU (0.24 ml, 1.60 mmol, 2500 mol%) was added and the mixture was heated in a 50 °C oil bath for 48 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, THF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1641.

4.1.17. (5-Methoxycarbonyl)pyridine 2-(2′-oxazolinyl) resin 36. Resin **33** (65 mg, 100 μmol, 100 mol%) was suspended in 4 ml THF. DBU (0.12 ml, 0.80 mmol, 800 mol%) was added and the mixture was heated on a 45 °C oil bath for 20 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1728, 1635.

4.1.18. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)pyridine 2-(2′-oxazolinyl)resin 37. Resin **34** (175 mg, 280 μmol, 100 mol%) was suspended in 5 ml THF. DBU (0.23 ml, 1.54 mmol, 550 mol%) was added and the mixture was heated in a 50 °C oil bath for 22 h and filtered. The resin was washed successively with THF, THF/H_2O 2:1, THF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2237, 1636.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.073

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