Article

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Preparation and supporting on solid phase of chiral auxiliary (*S*)-4-(4-hydroxybenzyl)oxazolidin-2-one from *L*-tyrosinol assisted by Microwaves

Adriana Cruz[1] and Ignacio A. Rivero[1,2]*

[1] Centro de Graduados e Investigación en Química, Instituto Tecnológico de Tijuana. C.P. 1166. Tijuana, B.C. 22000, México.
[2] Instituto Nacional de Investigaciones Nucleares, Departamento de Química. Carretera México Toluca S/N, La Marquesa, Ocoyoacac, México, D.F. C.P. 52750, e-mail: irivero@tectijuana.mx

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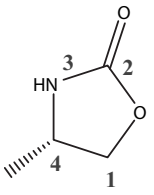
Abstract. An oxazolidinone chiral auxiliary, (*S*)-(4-Hydroxybenzyl)-1,3-oxazolidin-2-one **4** was prepared in 23-80 % yield from *L*-tyrosinol using different methodologies. In solution, compound **4** was protected with a benzyl group on the phenolic hydroxyl **5a**, which allowed the optimization of the solid phase synthesis of **5b-5d**. Chiral auxiliaries **5a** and **5b** reacted in solution with an α,β-unsaturated system to give (*S*)-4-(4-(benzyloxy)benzyl)-1,3-oxazolidin-2-one **6a**. By contrast, in solid phase the same reaction afforded **6b**. Both reactions were carried out under microwave activation. New compounds were characterized by ^{1}H and ^{13}C NMR, infrared spectroscopy and mass spectrometry.
Keywords: Oxazolidinones, chiral auxiliaries, solid phase synthesis.

Resumen. En este trabajo se reporta la preparación del nuevo auxiliar quiral de tipo oxazolidinona, (*S*)-(4-hidroxibencil)-1,3-oxazolidin-2-ona **4** que fue preparado a partir del *L*-tirosinol utilizando diferentes metodologías, con rendimientos que fluctúan en un intervalo de 23-80 %, dependiendo del método. El compuesto **4** fue preparado en solución, protegidos con el grupo benciloxi en el hidroxilo fenólico **5a**, para llevar a cabo la optimización de la síntesis en fase sólida de **5b-5d**. Los auxiliares quirales **5a** y **5b** fueron adicionados en solución a un sistema α,β-insaturado, obteniéndose a la (*S*)-4-(4-(benciloxi)bencil)-1,3-oxazolidin-2-ona **6,** mientras que en fase sólida se observó la formación del compuesto **6b**. Estas reacciones fueron activadas con microondas. Todos los compuestos fueron caracterizados mediante RMN (^{1}H y ^{13}C), IR y EM.
Palabras Claves: Oxazolidinonas, auxiliares quirales, síntesis en fase sólida.

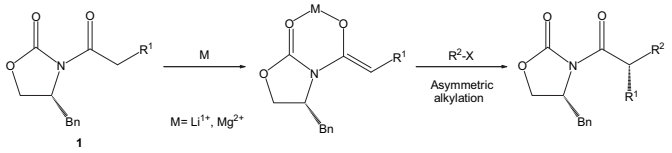
Introduction

The utility of chiral oxazolidinones in organic synthesis is well-documented. The powerful and removable auxiliary has been shown to be effective in the highly stereoselective construction of a wide variety of carbon-carbon and carbon-heteroatom bonds [1]. In particular, Evans' oxazolidinones have proven to be highly selective and efficient chiral auxiliaries [2, 3]. Furthermore, several Oxazolidinone derivatives have attracted growing interest in view of their pharmacological applications [4, 5].

Evans' template [6] is an oxazolidinone ring with a stereogenic center in the fourth position:



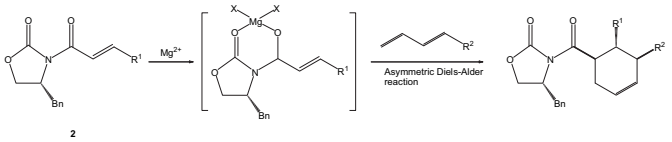
The main objective of the use of these chiral auxiliaries is to facilitate asymmetric induction through the formation of an enolate (Scheme 1). Furthermore, the auxiliary is removable which allows for its recuperation, following construction of the new bond [7].



Scheme 1

Oxazolidinones have attracted great attention in organic synthesis [8], in the preparation of natural products [9], antibiotics [7], antibacterials [10] and antimicobacterials [11]. In the literature there are reports about the synthesis of these compounds from amino acids and amino alcohols [12], in addition to other substances such as primary [13] and secondary [14] amines, β-lactams [15], aziridines [16], etc.

The reactivity of Evans template has been tuned when combined with catalytic quantities of magnesium salts, to facilitate the production of cycloaddition products (Scheme 2) [6a].

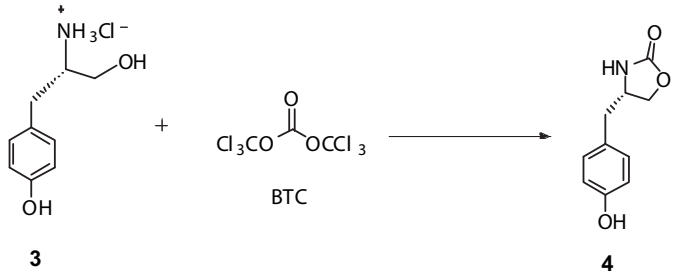


Scheme 1

In the present paper, we report a new synthetic route for the synthesis of (*S*)-4-(4-hydroxybenzyl)oxazolidin-2-one (**4**) in a good and moderate yields from *L*-tyrosinol (**3**). The promising chiral synthon (*E*)-4-[4-(benzyloxy)benzyl]-3-but-2-enoxyloxazolidin-2-one **6**a was derived from **4**. In addition, we established that compound **4** can be conveniently linked to polymeric materials such as Merrifield and Wang resins [6b-d].

Results and Discussion

The synthesis of the (*S*)-4-(4-hydroxybenzyl)-1,3-oxazolidin-2-one (**4**) began with commercially available ***L***-tyrosinol (**3**) and employing triphosgene (BTC) as a reagent for oxazolidin-2-one ring formation, according to the synthetic protocol described in Scheme 3. As shown in Table 1, the cyclization reaction was carried out using different solvents and reaction conditions. Using toluene as solvent, compound **4** was obtained in only 5 min employing microwave activation in 82% yield (entry 4). Alternative synthetic procedures for the synthesis of **4** are reported in entries 2 and 3, making use of the triethylamine (TEA) and triphosgene (BTC) cyclization strategy in THF and CH_2Cl_2 solvents, respectively. Yields varied in the 23-82% range.



Scheme 3. Synthesis of (*S*)-4-(4-hydroxybenzyl)-1,3-oxazolidin-2-one **4.**

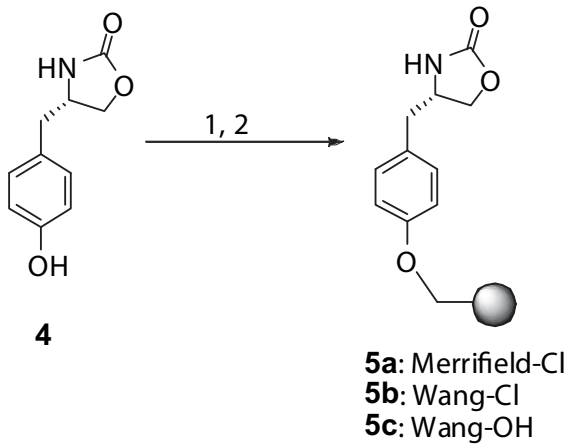
Table 1. Reaction conditions and yields in the preparation of compound **4**.

Entries	Conditions				
	Solvent	Time of reaction	Reagents	Temperature (ºC)	Yield(%)
1	Toluene	4 h	BTC 1 eq	110	80%
2	THF	1.5 h	BTC 1.4 eq TEA 5.6 eq	66	78%
3	DCM	2 h	BTC 2.8 eq TEA 2.2 eq	0	23 %
4*	Toluene	5 min	BTC 1.4 eq	100	82%

*μW 100 W.

Compound **4** was characterized by ^{1}H and ^{13}C NMR spectroscopy, the recorded data are in agreement with previously reported data [17].

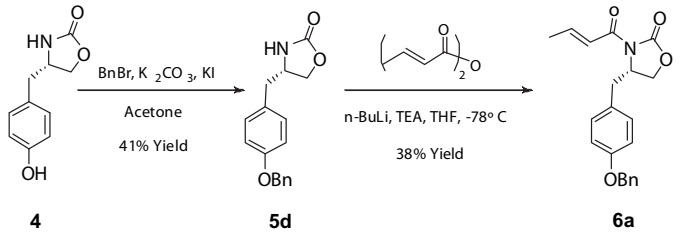
One attractive feature of oxazolidinone **4** is the adequacy of the phenol group for attachment to polymers. Indeed such attachment was accomplished with Merrifield-Cl and Wang-Cl resins *via* nucleophilic displacement of the chloride (9.5 equiv. of 4, NaH, DMF, 3 days) to obtain **5a** and **5b** with loadings of 98 and 91%, respectively. Furthermore, for the Wang resin the desired linkage was also accomplished via Mistsunobu coupling,[19] using eight equiv. of 1,3-oxazolidin-2-one, 10 equiv of triphenylphosphine and 12 equiv of diisopropyl azodicarboxilate (DIAD) in THF, to give *O*-linked-NH-1,3-oxazolidin-2-one polymer **5c**, loading 88% (Scheme 4). These reactions were followed by IR spectroscopy (KBr pellet). For all compounds a strong C=O stretching band for the carbonyl group is found at 1749 cm^{-1}.



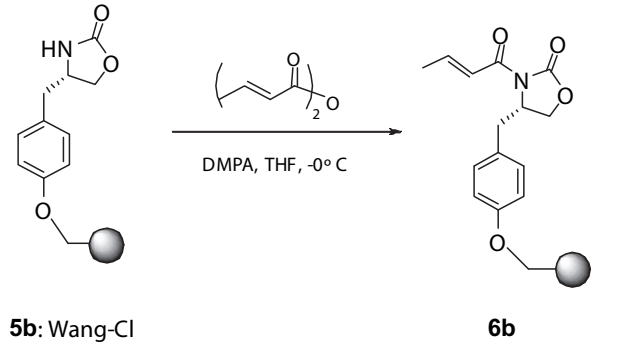
Scheme 4. *Reagents and conditions:* 1, NaH, DMF, 25º C, 3 days for **5a** (98%) and **5b** (91%); 2) PPh_3, DIIAD, THF, 25º C, 3 days for **5c** (88%).

Compound (*E*)-4-[4-(benzyloxy)benzyl]-3-but-2-enoxyloxazolidin-2-one (**6a)** was synthesized in two steps from **4**. The first step of the synthesis consisted in the benzylation of the (*S*)-4-(4-hydroxybenzyl)-1,3-oxazolidin-2-one with an excess of benzyl bromide, K_2CO_3 and KI at 25 ºC in acetone, obtaining the corresponding (*S*)-4-(4-benzyloxybenzyl)-1,3-oxazolidin-2-one (**5d)** in 41% yield. Next, the resulting oxazolidin-2-one **5d** was treated with the lithium salt of *trans*-crotonic anhydride and TEA at –78 ºC in THF, to obtain compound **6a** in 30% yield (Scheme 5).

Additionally, compound **6b** was obtained by solid-phase synthesis using the chiral auxiliary **5b** with dimethylaminopyridine (DMAP), TEA and 4 equiv. of *trans*-crotonic anhydride in THF, loading 82% (Scheme 6). This compound exhibited two strong C=O stretching bands for the carbonyl groups at 1754 and 1713 cm^{-1}.



Scheme 5. Synthesis of **6a** in solution.



Scheme 6. Solid-phase synthesis of **6b**.

X-Ray crystal structure of (*S*)-(4-Hydroxybenzyl)-1,3-oxazolidin-2-one (4)

Good quality crystals for X-ray diffraction studies were obtained of **4**. The structure was determined (Figure 2), which confirms its absolute stereochemistry. Packing within the unit cell is dominated by hydrogen bonds between the donor OH(3) and acceptor carbonylic O(2), and the donor NH(3) and acceptor phenol O(3). These hydrogen bonds connect neighboring molecules to form a 2D network structure which is consistent with the higher stability of the compound, as indicated by its high melting point.

The hydrogen bonding data are summarized in Table 2, which fall within the range reported for related structures [3b, c, 21].

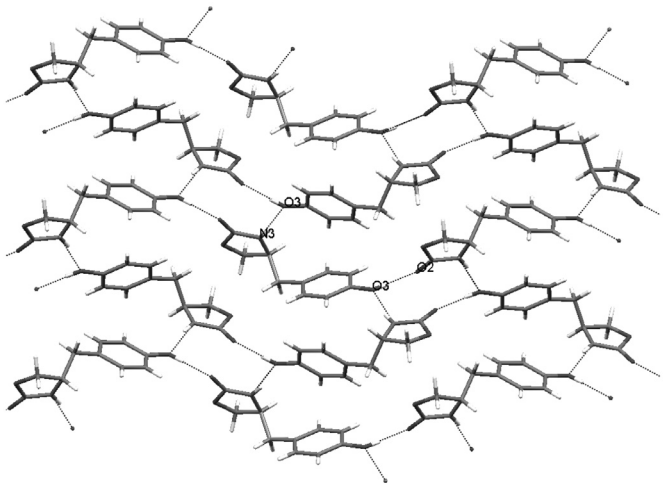


Fig. 2. Crystal packing diagram of compound **4** with the hydrogen bonds indicated by dashed lines [22].

Table 2. Hydrogen bonding data for **4**[a]

D-H···A	D-H	H···A(Å)	D···A(Å)	D-H···A(°)
O(3)-H(3A)···O(2)#1	0.81(3)	1.96(4)	2.763(3)	172(4)
N(3)-H(3)···O(3)#2	0.82(4)	2.23(4)	3.029(4)	168(3)

[a]Symmetry codes: #1 –x+0.5, -y+1, z+0.5; #2 –x+1, y-0.5, -z+0.5

Conclusions

A new synthetic procedure for the preparation of chiral 1,3-oxazolidinones from *L*-tyrosinol in good yield has been developed. The conditions described in this paper, a good and simple method for the preparation of the chiral synthons **5a, 5b,** and **5c** in solid phase and **6a** and **6b**. Finally, 1,3-oxazolidinone (*S*)-**4** is a key intermediate for the preparation of a number of polymer supported Evans'1,3-oxazolidin-2-ones that have been employed previously for solid supported asymmetric synthesis. We show here the advantages of activation by microwaves to get good yields of the desired 1,3-oxazolidin-2-one in only five minutes of reaction time.

Experimental Section

General Procedures. Merrifield (1.4 mmol/g) and Wang (0.6 mmol/g) resins were purchased from Aldrich Chem. Co. The chlorination of Wang resin was performed according to a literature procedure [18]. Melting points were determined on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin Elmer FT-IR 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 MHz Spectrometer in $CDCl_3$ and DMSO solvent with TMS as internal standard. Mass spectra were obtained on an Agilent 1100 MSD Ion Trap spectrometer. Optical rotations were measured using an automatic polarimeter Autopol III. Solvents were dried as reported in the literature [20].

Synthesis of quiral auxiliary* (*S*)-(4-Hydroxybenzyl)-1,3-oxazolidin-2-one (4):*

Entry 1 in Table 1: *L*-Tyrosinol hydrochloride (**3**) (0.25 g, 1.23 mmol) was dissolved in toluene (10 mL), before the addition of BTC (0.2 g, 0.674 mmol) and the resulting mixture was stirred at room temperature 24 h. The mixture was heated to reflux for 4 h. The white solid was filtered and recrystallized from methanol to give 0.19 g of product (80 % yield), mp.

178-179 °C (Lit. [23] 175-178 °C) $[\alpha]^{20}_D$ = +15.2 (*c* 0.0155, $(CH_3)_2SO$); [Lit. [23] +8.6 (c 0.5, ethanol)]. IR (KBr): 3334, 3138, 2917, 1733, 1595, 1515, 1414, 1237, 1014 cm^{-1}. ^1H NMR (DMSO-$CDCl_3$, 200 MHz): δ 9.29 (s, 1H, -OH), 8.24 (s, 1H, -NH), 7.00 (d, 2H, *J* = 8.6 Hz, A_2B_2 syst.), 6.69 (d, 2H, *J* = 8.6 Hz, A_2B_2 syst.), 4.24 (dd, 1H, *J* = 6.3, 5.4 Hz, OCHaH), 3.96 (m, 2H, OCHbH, CH), 2.76 (dd, 1H, *J* = 13.6, 6.6 Hz, CHaH), 2.60 (dd, 1H, *J* = 13.6, 6.7 Hz, CHHb). ^{13}C NMR ($CDCl_3$-DMSO, 50 MHz): δ 158.3 (C=O), 155.6 (C), 129.8 (2CH), 126.0 (C), 114.9 (2CH), 67.8 (CH_2), 52.6 (CH), 39.8 (CH_2). ESIMS *m*/*z* 194(100) $[M+H]^+$, 192 (100) $[M-H]^-$.

Entry 2 in Table 1: Compound **3** (0.256 g, 1.26 mmol) was dissolved in anhydrous THF (10 mL), before the addition of TEA (7.14 mmol, 0.726 g) at 0 ºC, and the resulting mixture was stirred for 10 min. A solution of BTC (0.2 g, 0.674 mmol) in 3 mL of THF was added dropwise stirring for 36 h, and then, the mixture was heated to reflux for 1.5 h. The crude product was filtered and washed with 5% aqueous HCl (3 × 5 mL). The expected product **4** (0.15 g, 78 % yield) was obtained as crystalline material.

Entry 3 in Table 1: Compound **3** (1g, 4.91 mmol) was dissolved on DCM (3 mL) and the resulting mixture was cooled to 0 ºC and stirred for 5 min, before the slow addition of TEA (1.08 g, 10.65 mmol). The reaction mixture was stirred for 10 min and then a solution of BTC (500 mg, 1.72 mmol) in 2 mL of DCM was added dropwise. The reaction as allowed to proceed during 2 h at this temperature, before a solution of BTC (500 mg, 1.72 mmol in 2 mL of DCM) was added. Stirring was continued for 2 h at 0 ºC. Five mL of water and 3 mL of MeOH was added and the stirring was continued for 30 min. The solvent was eliminated and 5 mL of water was added with continued stirring for 5 additional min. The precipitate obtained was filtered and washed with a solution of 0.1 M HCl and 5 mL of water. A crystalline colorless solid was obtained (0.22g, 23 % yield).

Entry 4 in Table 1: Compound **3** (1g, 4.91 mmol) was dissolved in 2 mL of toluene solvent, and the resulting mixture was cooled to 0 ºC, before the addition of TEA and the mixture was stirred for 10 min. BTC (0.78 g, 2.63 mmol) in 3 mL of THF was added and the reaction mixture as stirred for 2 min. After this, the mixture was heated under microwave irradiation at 100 ºC, 100 W for 5 min. The product was washed with 10% HCl aqueous solution and filtered; finally the product was purified by crystallization in MeOH obtaining a colorless solid (0.78g, 82 % yield).

Supported chiral auxiliary, (*S*)-(4-Hydroxybenzyl)-1,3-oxazolidin-2-one (4) on resins:

Merrifield-Cl resin (5a): Merrifield resin (0.1 g, 0.14 mmol) was swollen in 10 mL of dry DMF, before the addition of compound **4** (0.51 g, 0.27 mmol, 9.5 equiv). The resulting mixture was stirred for 15 min and cooled on an ice bath. A sodium hydride solution (0.011mg, 0.27 mmol, 9.5 equiv, in 2mL of dry DMF) was added dropwise under inert conditions. The mixture was stirred at room temperature for three days. Finally, the solution was filtered and washed several times with DMF, MeOH and DCM. The final product was dried under vacuum. A pale yellow solid (0.95 g, 91 %) was obtained. IR (KBr): 3435, 3052, 3023, 2914, 2861, 1942, 1871, 1749, 1599, 1506 cm^{-1}.

Wang-Cl (5b): Chiral auxiliary **1** (1.45 g, 7.52 mmol, 4.9 equiv) and resin **4** (3.0 g, 1.545 mmol) swollen in dry DMF (50 mL) were stirred for 15 min. The mixture was cooled on an ice bath and treated with a solution of NaH (0.224 g, 9.3 mmol 6 equiv, in 4 mL of dry DMF). The reaction mixture was stirred at room temperature for three days and then was washed with DMF (3 × 60 mL), MeOH (3 × 60 mL) and DCM (3 × 60 mL). The final product was dried under vacuum to obtain a pale yellow resin (3.2 g, 98 %). IR (KBr): 3424, 3023, 2918, 2851, 1742, 1604, 1504, 1226 cm^{-1}.

Wang-OH resin (5c): Compound **1** (0.93 g, 0.48 mmol, 8 equiv), triphenylphosphine (0.16 mg, 0.6 mmol, 10 eq) and Wang resin (0.1 mg, 0.6 mmol), was swollen in dry THF (15 mL). The mixture was stirred for 15 min while bubbling argon through the solution. A solution of diisopropyl azodicarboxilate (0.146 mg, 0.72 mmol, 12 equiv, in 2 mL of dry THF) previously cooled in an ice bath, was added dropwise. The resulting mixture was stirred at room temperature for three days and then washed several times with DMF, MeOH and DCM and dried under vacuum. The final product was a pale yellow liquid (0.92 g, 88 %). IR (KBr): 3415, 3021, 2913, 2848, 1749, 1711, 1599, 1507 cm^{-1}.

Protection of the quiral auxiliary:

(*S*)-4-[4-(Benzyloxy)benzyl]-1,3-oxazolidin-2-one (5d): Acetone (70 mL) was added to a flask containing chiral auxiliary **4** (2.27 g, 11.76 mmol), K_2CO_3 (8.13 g, 58.8 mmol) and potassium iodide (0.98 g, 5.9 mmol). The resulting mixture was stirred for 5 min before the addition of benzyl bromide (2.21 g, 12.94 mmol). The reaction was allowed to proceed at room temperature during 20 h. The solvent was removed by distillation, water (50 mL) was added to the mixture and washed with ethyl acetate (3 × 70 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under vacuum. The product was purified by column chromatography using petroleum ether:ethyl acetate (1:1) as eluent, to obtain a white solid (1.37 g, 41 % yield), mp 135-137°C. [lit. [23] 136-138°C]; $[\alpha]^{21}_D$ =-85.2 (*c* 0.0175, EtOAc), Lit. [23] = -84.8 (c, 5.0, $CHCl_3$); IR (KBr): 3253, 2928, 2845, 1738, 1609, 1247, 1023 cm^{-1}. ^1H NMR ($CDCl_3$-*d*, 200 MHz): δ 8.17 (m, 5H, OC_5H_5), 7.06 (d, 2H, *J* = 8.7 Hz, A_2B_2 syst.), 6.91 (d, 2H, *J* = 8.7 Hz, A_2B_2 syst.), 5.58 (s, 1H, N-H), 5.02 (s, 1H, OCH_2-Bn), 4.41 (pt, 1H, *J* = 8.4, 8.1 Hz, OCHaH), 4.11 (dd, 1H, *J* = 8.1, 5.5 Hz, OCHHb), 3.99 (ddt, 1H, *J* = 8.4, 6.6, 5.5 Hz, CH), 2.78 (d, 2H, *J* =6.7 Hz, CH_2) ppm. ^1H-^1H COSY: CHA_2-CHB_2 (*J* = 8.7 Hz), CHa–CHb (*J* = 8.1 Hz), CHa–CH (*J* = 8.4

Hz), CHb–CH_2 (J = 6.7 Hz), CH–CH_2 (J = 6.7 Hz). ^{13}C NMR ($CDCl_3$-*d*, 200 MHz): δ 158.1 (C=O), 156.9 (C), 135.8 (CBn), 129.0 (2CHBn), 127.6 (CHBn), 127.1 (CHBn), 127.0 (2CH), 126.4 (C), 114.4 (2CH), 69.2 (CH_2Bn), 69.7 (CH_2), 53.1 (CH), 39.8 (CH_2) ppm. ESIMS *m*/*e* 284 (100) $[M+Na]^+$, 282 (100) $[M-H]^-$.

(*S,E*)-4-[4-(Benzyloxy)benzyl]-3-but-2-enoyl-1,3-oxazolidin-2-one (6a): Under inert conditions, product **5d** (0.17 g, 0.6 mmol) was dissolved with anhydrous THF (5 mL). The resulting mixture was cooled to **-**78 °C before the slow addition of *n*-BuLi in hexanes (0.4 mL, 0.6 mmol) maintaining the reaction mixture under these conditions for 30 min. In a separate flask *trans*-crotonic anhydride (0.097 g, 0.63 mmol) was dissolved in anhydrous THF (8 mL), and then TEA (0.073 g, 0.72 mmol) was added. The reaction mixture was cooled to **-**78 °C and then the chiral auxiliary was added through a cannula. The reaction was stirred under these conditions for 1 h before the addition of a saturated solution of NH_4Cl and then the mixture was allowed to warm to room temperature. The organic phase was distilled, and the aqueous phase was extracted with DCM (3 × 40 mL), dried over $MgSO_4$ and the solvent removed under vacuum. The combined product was purified by column chromatography using petroleum ether:ethyl acetate (8:2) as eluent to obtain a white solid (0.0581 g, 30 % yield), mp 112-114 °C. $[\alpha]^{20}_D$ = **-**2.1 (*c* 0.0146, $(CH_3)_2SO$); IR (KBr): 2925, 2845, 1782, 1678, 1630, 1383, 1216 cm^{-1}. ^{1}H NMR ($CDCl_3$-*d*, 200 MHz): δ 7.38 (m, 5H, CHBn), 7.25-7.19 (m, 2H, CH=CH), 7.11 (d, 2H, J = 8.7 Hz, A_2B_2 syst.), 6.93 (d, 2H, J = 8.7 Hz, A_2B_2 syst.), 5.04 (s, 2H, CH_2Bn), 4.68 (dddd, 1H, J = 12.8, 9.3, 7.0, 3.3 Hz, CH), 4.21 (dd, 1H, J = 9.1, 7.0 Hz, OCHaH), 4.14 (dd, 1H, J = 12.8, 9.1 Hz, OCHHb), 3.25 (dd, 1H, J = 13.6, 3.3 Hz, CH-CHaH), 2.75 (dd, 1H, J = 13.6, 9.3 Hz, CH-CHHb), 1.98 (d, 3H, J = 5.1 Hz, CH_3) ppm. ^{1}H-^{1}H COSY: CHA_2-CHB_2 (J = 8.7 Hz), CH-OCHa (J = 12.0 Hz), CHaH–CHHb (J = 13.6 Hz), CH–CHaH (J = 3.3 Hz), CH–CHHb (J = 9.3 Hz), CH=CH–CH_3 (J = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): d164.6 (C=O), 157.7 (C=O), 153.1 (C), 146.6 (CH), 136.5 (C), 130.2 (2CH), 128.3 (2CH), 127.7 (CH), 127.2 (CH), 127.1 (C), 121.6 (CH), 114.9 (CH), 69.8 (CH_2), 65.9 (CH_2), 55.2 (CH), 36.9 (CH_2), 18.5 (CH_3) ppm. ESIMS *m*/*z* 374 (100) $[M+Na]^+$, 351 (70) $[M-H]^-$.

Functionalization of (*S*)-(4-hydroxybenzyl)-1,3-oxazolidin-2-one in solid phase (6b).

Chiral auxiliary **5b** (2.98 g, 1.41 mmol) was swollen on dry THF (100 mL) and stirred for 15 min before the addition of DMAP (0.344 g, 2.82 mmol, 2 equiv) and TEA (0.71 g, 7.05 mmol, 5 equiv). A solution of *trans*-crotonic anhydride (0.87 g, 5.64 mmol, 4 eq) was added dropwise, keeping the temperature at 0 °C, and the reaction mixture was stirred vigorously at room temperature for 1 h, and then heated to reflux for 72 h. The solvent was removed and the resin washed with THF (3 × 30 mL), MeOH (3 × 30 mL) and DCM (3 × 30 mL). A pale yellow solid was obtained, which was dried under vacuum to afford the expected product (2.83 g, 82 %). IR (KBr): 3022, 2907, 1754, 1713, 1603, 1502, 1226, 1018 cm^{-1}.

Acknowledgments

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