An Access to Chiral β-Benzyl-γ-butyrolactones and Its Application to the Synthesis of Enantiopure (+)-Secoisolariciresinol, (–)-Secoisolariciresinol, and (–)-Enterolactone

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Received 24 January 2011; revised 4 March 2011

Abstract: Both enantiomers of secoisolariciresinol and enantiopure (–)-enterolactone were synthesized through a highly stereoselective convergent synthesis. An Evans diastereoselective alkylation followed by a substrate-induced diastereoselective α-alkylation of the newly formed optically active β-benzyl-γ-butyrolactone gave the β-β′ linkage of the target skeleton. The (*S*,*S*)- and (*R*,*R*)-enantiomers of secoisolariciresinol and (–)-enterolactone were obtained in 12–14% (11 steps) and 20% (7 steps) overall yield, respectively.

Key words: total synthesis, natural product, lactones, asymmetry, diastereoselective alkylation

Lignans form a large class of secondary metabolites widely encountered in plants.[1,2] In 1936, the term lignan was introduced by Harworth[3] to describe a group of plant phenols whose general structure was determined by the oxidase-catalyzed β-β′ radical coupling of two cinnamic acid residues. Many lignans exhibit potent biological activities, mainly due to their antioxidant properties. Therefore, lignans have not only been used in folk remedies for centuries to treat a wide range of disorders but also remain today as promising drug targets.[4] Developing new synthetic methods for lignans is therefore a challenge for synthetic chemists.[1,2,5] Many methods for asymmetric synthesis of chiral lignans involved the intermediacy of enantiomerically pure β-benzyl-γ-butyrolactones (*R*)-**3** and (*S*)-**3** (Figure 1). They allowed – through diastereoselective reactions on (*R*)-**3** and (*S*)-**3** – the synthesis of dibenzylbutyrolactones **2**, dibenzylcyclooctadienes **4**, aryltetralins **5**, and benzylidenebenzylbutyrolactones **6**. Several synthetic approaches for the preparation of optically active butyrolactones have been published.[5i,6] Although these methods have provided elegant routes to the preparation of lignan intermediates, many issues remain. In fact, these methods are limited either in terms of yields, number of steps, enantiomeric purity, or reagents/reactants availability. In 1997, Charlton published a convenient and straightforward approach for the asymmetric synthesis of β-benzyl-γ-butyrolactones (*R*)-**3** and (*S*)-**3** using Evans diastereoselective alkylation through substituted oxazolidinone as chiral auxilliaries.[7] This versatile asymmetric synthesis then allowed the formation of β-benzyl-γ-butyrolactones in a six-step procedure in 45% overall yield and in >95% optical purity. However, a main drawback in this synthetic route lies in the sensitivity of *tert*-butyl ester during the saponification of the oxazolidinone moiety. In fact, despite careful control of the temperature during the workup, we were unable to reproduce their results as the *tert*-butyl ester was partially cleaved, leading to an undesired diacid intermediate.

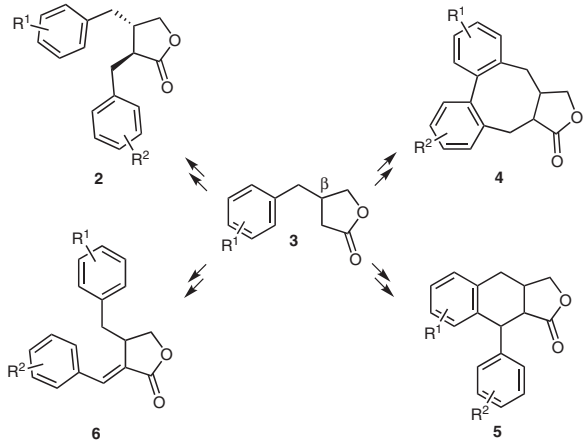
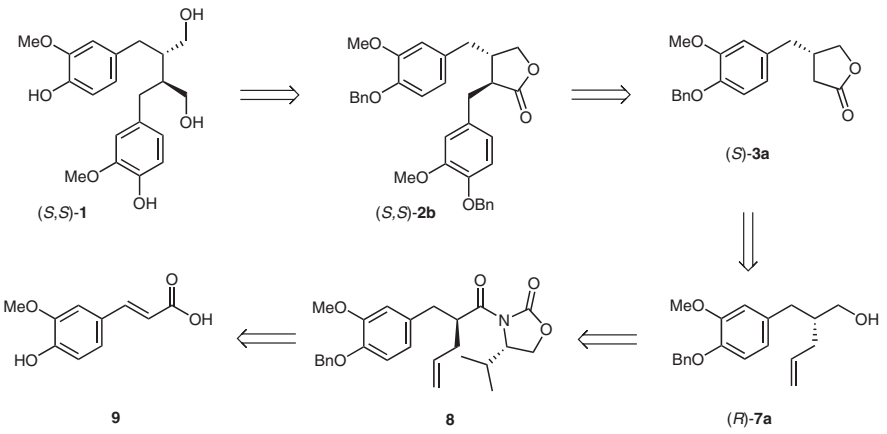


Figure 1 β-Benzyl-γ-butyrolactones as key substructures in lignan synthesis

In the course of our studies dedicated to greener asymmetric syntheses of lignans and phenolic natural substances, a short, cost-limited, and efficient access to chiral β-benzylated γ-butyrolactones was devised and, to prove its utility, was applied to the enantioselective synthesis of secoisolariciresinols **1** and enterolactone (**2a**). This new methodology uses Evans diastereoselective alkylation (allylation) as it allows the formation of both enantiomers in excellent ee's and the possible recovery of the oxazolidinones (recycling).

Our retrosynthetic analysis of **1** and **2a** relied on the control of the chirality of the β-β′ bond via Evans diastereoselective alkylation followed by a substrate-induced diastereoselective α-alkylation of the β-benzyl-γ-butyrolactone intermediate **3** (Scheme 1). First, our efforts were focused on the diastereoselective synthesis of the chiral β-benzylated γ-butyrolactones and the formation of the two enantiomers of diol **1**. Ferulic acid (**9**) was easily converted into its dihydrocinnamic acid derivative **10** in 77% yield through a classical three-step sequence (catalytic hy-

SYNTHESIS 2011, No. 9, pp 1456–1464
Advanced online publication: 01.04.2011
DOI: 10.1055/s-0030-1259982; Art ID: T14311SS



Scheme 1 Retrosynthetic pathway for diol (*S*,*S*)-**1**

drogenation of the olefin over Pd/C, perbenzylation, and saponification of the benzyl ester). Acid **10** was then coupled with chiral oxazolidinones (*S*)-4-isopropyl-2-oxazolidinone (**A**) and (*R*)-4-benzyl-2-oxazolidinone (**B**) using Evans procedure[8] to provide enantiopure **11** and **12** (72% yield) (Figure 2).

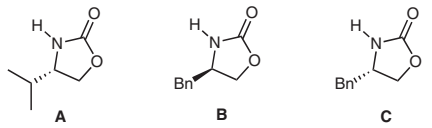
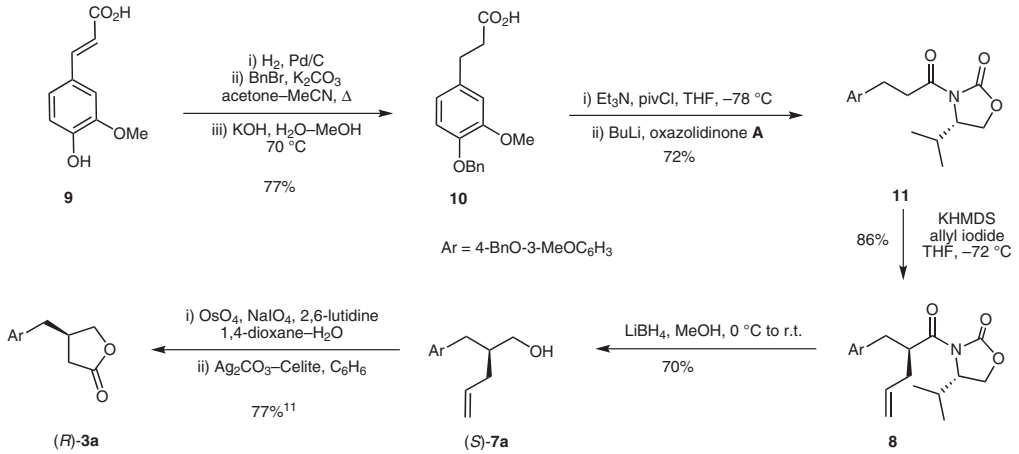


Figure 2 Evans chiral oxazolidinones

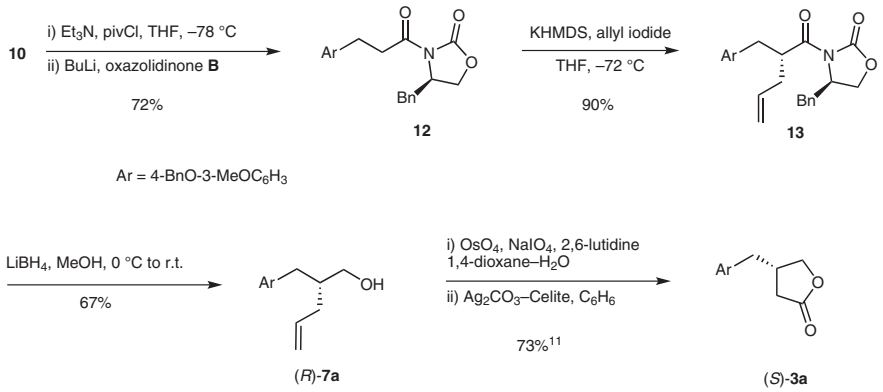
At this stage, we searched for an alternative to Charlton's procedure in order to simplify the formation of butyrolactone **3**. Our main objective being a cost-efficient and straightforward total synthesis of **1** and **2a**, efforts were directed towards the development of a new pathway to **3** using an acid- and base-resistant alkylating agent in order to achieve a selective removal of the oxazolidinone through saponification or reduction. Allyl iodide was chosen as the alkylating agent, which besides its chemical resistance, offered another benefit as it would serve as a masked carbonyl group required latter on in the synthesis.

Therefore, KHMDS-generated enolates of **11** and **12** were alkylated with allyl iodide and provided the corresponding optically active allyl adducts (*S*)-**8** and (*R*)-**13** in 86% and 90% yield, respectively, and in excellent diastereomeric ratios (>97:3 dr) (Schemes 2 and 3).[9a]

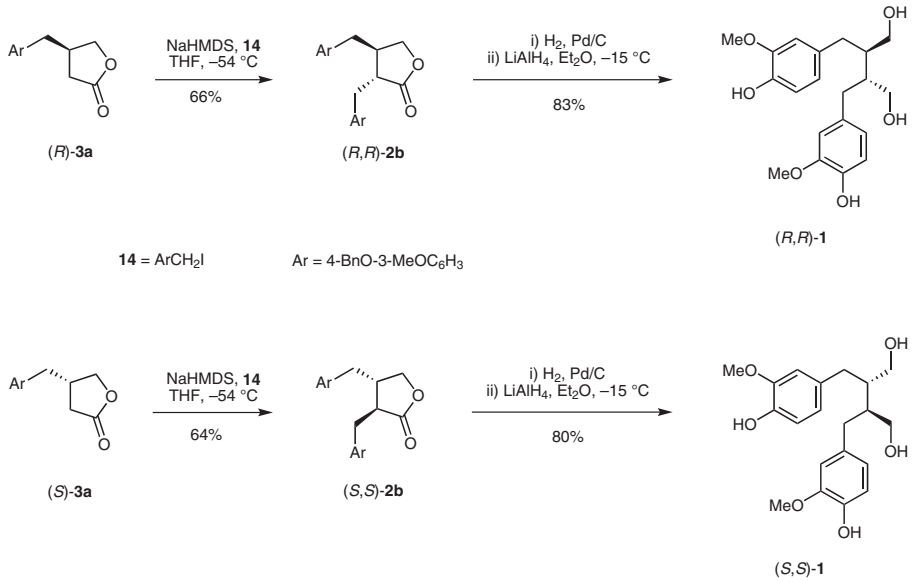
With the butyrolactone precursors in hand, the removal of the chiral auxiliaries was achieved via $LiBH_4$ reduction of (*R*)-**13** and (*S*)-**8** providing, respectively, the optically active primary alcohols (*R*)-**7a** and (*S*)-**7a** in 67 and 70% yield, respectively, and in 98% ee.[9b] Both enantiomers of **7a** were then efficiently transformed into the β-benzyl-γ-butyrolactones (*S*)-**3a** and (*R*)-**3a** in a two-step sequence: the oxidative cleavage of the olefin in (*R*)-**7a** and (*S*)-**7a** (OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane–H_2O) provided a crude hemiacetal,[10] which was directly oxidized into its corresponding lactone with Fetizon's reagent[11] (silver carbonate on Celite) to give (*S*)-**3a** and (*R*)-**3a** in 73 and 77% yield, respectively. In order to complete the synthesis of diols (*S*,*S*)-**1** and (*R*,*R*)-**1**, the next task was the diastereoselective benzylation of both enantiomers of **3a** on the α-position (Scheme 4). Thus, after deprotonation of (*R*)-**3a** and (*S*)-**3a** with NaHMDS and treatment with substituted benzyl iodide **14**,[12,13h] the dibenzylated lactones (*R*,*R*)-**2b** and (*S*,*S*)-**2b** were obtained in 66 and 64% yield, respectively, and in >97:3 dr.[9a] Finally, secoisolariciresinols



Scheme 2 Diastereoselective synthesis of α-benzyl-γ-butyrolactone (*R*)-**3a**



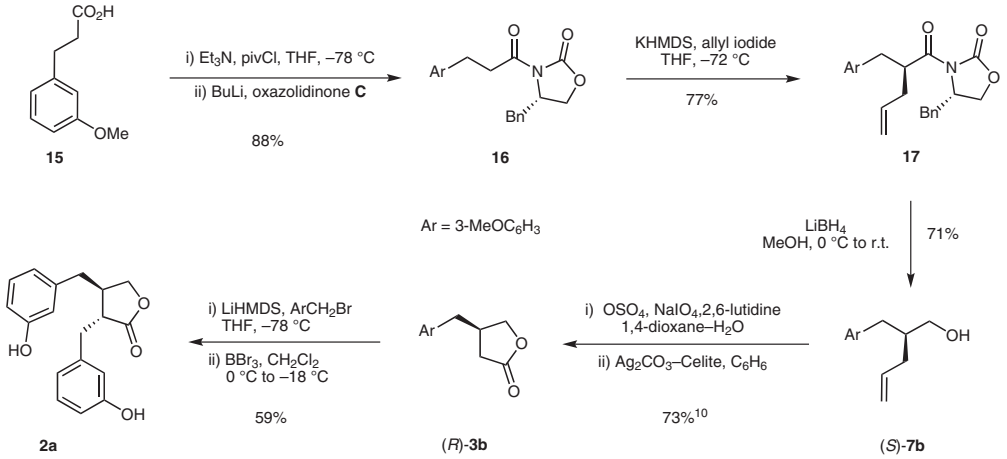
Scheme 3 Diastereoselective synthesis of α-benzyl-γ-butyrolactone (*S*)-**3a**



Scheme 4 Diastereoselective synthesis of secoisolariciresinols (*S*,*S*)-**1** and (*R*,*R*)-**1**

(*S*,*S*)-**1** and (*R*,*R*)-**1** were successfully formed after removal of benzyl protecting groups via hydrogenation directly followed by lithium aluminum hydride reduction of the lactones [80–83% yield; (*S*,*S*)-**1**: 12% overall yield (11 steps), (*R*,*R*)-**1**: 14% overall yield (11 steps)].

To evaluate the scope of this new access to β-benzyl-γ-butyrolactones, the synthesis of the widely known lignan (–)-enterolactone (**2a**) was undertaken, for which numerous total syntheses have been reported to date.[6a,b,12b,13] According to the procedure described in Scheme 2, commercially available 3-methoxydihydrocin-



Scheme 5 Stereoselective synthesis of (–)-enterolactone (**2**)

namic acid (**15**) was coupled with chiral oxazolidinone (*S*)-4-benzyl-2-oxazolidinone (**C**) (Figure 2) using Evans procedure and provided enantiopure **16** (88%) (Scheme 5). Diastereoselective alkylation of **16** was then realized and gave the optically active allylated intermediate **17** in 77% yield and with >97/3 dr.[9a] $LiBH_4$ reduction of **17** gave the corresponding alcohol (*S*)-**7b** (98% ee)[9b] which, after oxidative cleavage and oxidation, provided the β-benzyl-γ-butyrolactone (*R*)-**3b** in 52% yield. Finally, after diastereoselective α-alkylation of (*R*)-**3b** and subsequent O-demethylation,[13l] (–)-enterolactone (**2a**) was obtained in 59% yield (20% overall yield, 7 steps) and its spectral data were in good agreement with those reported in the literature.[6a,b,12b,13]

In conclusion, we have developed an efficient, short, and easy access to enantiopure β-benzyl-γ-butyrolactones via Evans diastereoselective allylation and oxidative cleavage of the allyl moiety as the key steps. This methodology was then successfully applied to the synthesis of (–)-enterolactone and both enantiomers of secoisolariciresinol in good yields and with excellent stereoselectivity.

CH_2Cl_2 (stabilized with amylene) was purified by distillation from CaH_2 under N_2 immediately before use. THF and Et_2O were purified by distillation from sodium/benzoquinone under N_2. Moisture and O_2-sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at temp below 35 °C unless otherwise noted. Column chromatography (CC) was carried out under positive N_2 pressure with 40–63 μm silica gel. Melting points are uncorrected. ^{1}H Spectra of samples in the indicated solvent were recorded at 300 MHz at 20 °C (^{1}H NMR: $CDCl_3$ residual signal at 7.26 ppm). ^{13}C NMR Spectra of samples in the indicated solvent were recorded at 75 MHz at 20 °C (^{13}C NMR: $CDCl_3$ residual signal at 77.26 ppm). All reported yields are uncorrected and refer to purified products. Assignments are given as per the labeling shown below (Figure 3).

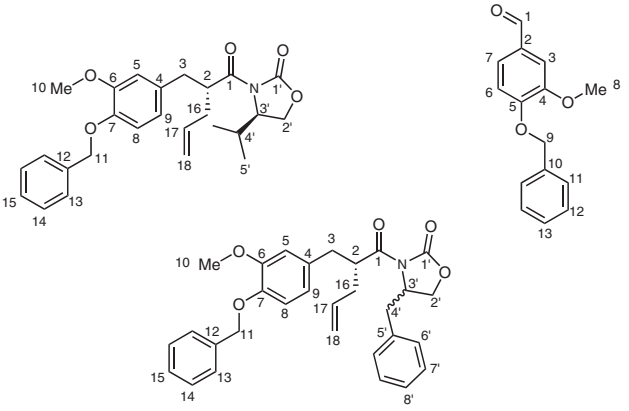


Figure 3 Numbering of the carbon atoms for NMR assignments

3-(4-Benzyloxy-3-methoxyphenyl)propanoic Acid (10)

To a solution of ferulic acid (**9**; 20.0 g, 103 mmol) in EtOAc (500 mL) under argon at r.t. was added 10% Pd/C and the solution was placed under an atmosphere of H_2 (1 atm). The mixture was stirred at r.t. until completion (TLC), filtered over Celite and concentrated in vacuo to afford dihydroferulic acid as a white solid (19.8 g, 98%). To a solution of dihydroferulic acid (19.8 g, 100.9 mmol) in acetone–MeCN (1:1, 600 mL) under argon was added K_2CO_3 (39.6 g, 286.8 mmol) and BnBr (60 mL, 86.28 g, 504.5 mmol). The mixture was refluxed until completion (TLC), filtered over Celite, and concentrated in vacuo to provide crude dibenzylated dihydroferulic acid. To a solution of the crude dibenzylated dihydroferulic acid in MeOH–H_2O (58 mL/580 mL) was added KOH (78.6 g) and the solution was stirred at 70 °C until completion. The mixture was then cooled to r.t. and washed with $CHCl_3$ (3 × 600 mL). The aqueous layer was neutralized with concd HCl until pH 2 and extracted with $CHCl_3$ (5 × 600 mL). The combined organic layers were washed with brine (400 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 3:7) to give **10** as a white solid (22.3 g, 77%). All spectral data were consistent with those reported in the literature.[14]

(*S*)-3-[3-(4-Benzyloxy-3-methoxyphenyl)propanoyl]-4-isopropyloxazolidin-2-one (11)

To a solution of **10** (1.00 g, 3.49 mmol) in THF (9 mL) under argon at –70 °C was successively added, dropwise, Et_3N (0.56 mL, 407 mg, 4.02 mmol) and pivaloyl chloride (0.45 mL, 434 mg, 3.59 mmol). The mixture was then warmed to 0 °C, stirred at this temperature for 1 h, and then recooled to –70 °C. *n*-BuLi (2.24 mL, 1.6 M in hexane, 3.59 mmol) was added dropwise to a solution of (*S*)-4-isopropyl-2-oxazolidinone (451 mg, 3.49 mmol) in THF (20 mL) under argon at –70 C. The resulting lithium salt was then transferred to the above anhydride mixture via a cannula at –70 °C over a 10 min period. The resulting mixture was then stirred for 1 h, warmed to 0 °C, and stirred for 35 min at this temperature. Quenching was realized by adding sat. aq NH_4Cl (2.8 mL). The mixture was concentrated in vacuo to remove THF, diluted with H_2O (14 mL), and extracted with EtOAc (4 × 15 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **11**. Flash chromatography on silica gel (cyclohexane–EtOAc, 8:2) provided pure **11** as a thick oil (1.00 g, 72%); $[\alpha]_D^{16}$ +53.9 (*c* 0.1, $CHCl_3$).

IR (neat): 2965, 1778, 1699, 1514 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.25 (m, 5 H, C_6H_5), 6.81–6.69 (m, 3 H, H-5, H-8, H-9, Ar), 5.12 (s, 2 H, H-11, OCH_2Ph), 4.40 (app quint, *J* = 3.6 Hz, 1 H, H-3′, NC*H*-*i*-Pr), 4.25–4.15 [m, 2 H, H-2′, NC(=O)CH_2CH-*i*-Pr], 3.88 (s, 3 H, H-10, ArOCH_3), 3.18 [m, H-3, C(=O)CH$_2$CH_2Ar], 3.00–2.86 [m, 2 H, H-2, C(=O)CH_2CH$_2$Ar], 2.39–2.27 [m, 1 H, H-4′, CH(CH$_3$)$_2$], 0.89 [d, *J* = 7.0 Hz, 3 H, H-5′, CH(CH_3)$_2$], 0.82 [d, *J* = 7.0 Hz, 3 H, H-5′, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7 (s, C-1, carbon from amide), 154.3 (s, C-1′, carbon from urethane), 149.9 (s, C-6, Ar), 146.9 (s, C-7, Ar), 137.6 (s, C-12, C_6H_5), 134.0 (s, C-4, Ar), 128.7 (d, C-14, C_6H_5), 127.9 (d, C-15, C_6H_5), 127.5 (d, C-13, C_6H_5), 120.6 (d, C-9, Ar), 114.6 (d, C-5, Ar), 112.8 (d, C-8, Ar), 71.4 (t, C-11, OCH_2Ph), 63.6 (d, C-3′, NCH-*i*-Pr), 58.7 [t, C-2′, NC(=O)CH_2CH-*i*-Pr], 56.2 (q, C-10, ArOCH_3), 37.3 [t, C-2, C(=O)CH_2CH$_2$Ar], 30.4 [d, C-4′, CH(CH$_3$)$_2$], 28.6 [t, C-3, C(=O)CH$_2$CH_2Ar], 18.1 [q, C-5′, CH(CH_3)$_2$], 14.8 [q, C-5′, CH(CH_3)$_2$].

HRMS (TOF, ES+): *m*/*z* calcd for $C_{23}H_{27}NO_5$ + Na [M + Na]: 420.1787; found: 420.1789.

(*S*)-3-[(*S*)-2-(4-Benzyloxy-3-methoxybenzyl)pent-4-enoyl]-4-isopropyloxazolidin-2-one (8)

To a solution of **11** (1.00 g, 2.51 mmol) in THF (26 mL) under argon at –72 °C was added KHMDS (5.3 mL, 0.5 M in hexane, 2.64 mmol) over a 10 min period. The mixture was stirred at this temperature for 1 h, and then allyl iodide (0.69 mL, 1.27 g, 7.55 mmol) was added over a 5 min period. The mixture was stirred at –72 °C for 2 h before quenching with sat. aq NH_4Cl (10 mL). The mixture was concentrated in vacuo to remove THF and extracted with EtOAc (4 × 20 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **8**. Flash chromatography on sil-

ica gel (cyclohexane–EtOAc, 8:2) provided pure **8** as a thick oil (942 mg, 86%); $[\alpha]_D^{22}$ +75.5 (*c* 0.1, CH_2Cl_2).

IR (neat): 2967, 1775, 1697, 1513 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 5 H, C_6H_5), 6.76 (d, *J* = 7.5 Hz, 2 H, Ar), 6.63 (d, *J* = 7.2 Hz, 1 H, Ar), 5.81 (m, 1 H, H-17, CH_2CH=CH_2), 5.12 (s, 2 H, H-11, OCH_2Ph), 5.13–5.01 (m, 2 H, H-18, CH_2CH=CH_2), 4.34 (m, 1 H, H-3′, NC*H*-*i*-Pr), 4.16 [m, 1 H, H-2, C(=O)CH_2CH_2Ar], 4.01 [d, *J* = 8.7 Hz, 1 H, H-2′, NC(=O)CH_2CH-*i*-Pr], 3.87 (s, 3 H, H-10, $ArOCH_3$), 3.81 [app t, *J* = 8.9 Hz, 1 H, H-2′, NC(=O)CH_2CH-*i*-Pr], 2.88–2.69 [m, 2 H, H-3, C(=O)CH_2CH_2Ar], 2.50 (m, 1 H, H-16, CH_2CH=CH_2), 2.33–2.27 [m, 2 H, H-4′, $CH(CH_3)_2$ and H-16, CH_2CH=CH_2], 0.85 [d, *J* = 7.0 Hz, 3 H, H-5′, $CH(CH_3)_2$], 0.81 [d, *J* = 7.0 Hz, 3 H, H-5′, $CH(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5 (s, C-1, carbon from amide), 153.9 (s, C-1′, carbon from urethane), 149.7 (s, C-6, Ar), 146.8 (s, C-7, Ar), 137.5 (s, C-12, C_6H_5), 135.3 (d, C-17, CH_2CH=CH_2), 132.4 (s, C-4, Ar), 128.6 (d, C-14, C_6H_5), 127.9 (d, C-15, C_6H_5), 127.5 (d, C-13, C_6H_5), 121.2 (d, C-9, Ar), 117.3 (t, C-18, CH_2CH=CH_2), 114.3 (d, C-5, Ar), 113.1 (d, C-8, Ar), 71.2 (t, C-11, OCH_2Ph), 63.3 (d, C-3′, NC*H*-*i*-Pr), 58.8 [t, C-2′, NC(=O)CH_2CH-*i*-Pr], 56.1 (q, C-10, $ArOCH_3$), 44.0 [t, C-2, C(=O)CH_2CH_2Ar], 38.1 [t, C-3, C(=O)CH_2CH_2Ar], 36.6 (t, C-16, CH_2CH=CH_2), 28.8 [d, C-4′, $CH(CH_3)_2$], 18.1 [q, C-5′, $CH(CH_3)_2$], 15.0 [q, C-5′, $CH(CH_3)_2$].

HRMS (TOF, ES+): *m*/*z* calcd for $C_{26}H_{31}NO_5$ + Na [M + Na]: 460.2100; found: 460.2121.

(*S*)-2-(4-Benzyloxy-3-methoxybenzyl)pent-4-en-1-ol [(*S*)-7a]

To a rapidly stirred solution of **8** (228 mg, 0.52 mmol) in Et_2O (15 mL) were added $LiBH_4$ (0.52 mL, 2.0 M, 1.04 mmol) and anhyd MeOH (44 μL, 1.04 mmol) dropwise. After stirring at r.t. until completion, the reaction mixture was cooled to 0 °C and 1 M aq NaOH (2 mL) and EtOAc (15 mL) were added. The organic layer was separated, washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude alcohol, which was then purified by flash chromatography (cyclohexane–EtOAc, 6:4) providing pure (*S*)-**7a** as a thick oil (114 mg, 70%); $[\alpha]_D^{25}$ –17.9 (*c* 0.1, CH_2Cl_2).

IR (neat): 3400, 2910, 1512 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.25 (m, 5 H, C_6H_5), 6.82–6.63 (m, 3 H, Ar), 5.84 (m, 1 H, H-17, CH_2CH=CH_2), 5.12 (s, 2 H, H-11, OCH_2Ph), 5.13–5.00 (m, 2 H, H-18, CH_2CH=CH_2), 3.88 (s, 3 H, H-10, $ArOCH_3$), 3.55 [d, *J* = 5.4 Hz, 2 H, H-1, $ArCH_2CH$(allyl)CH_2OH], 2.57 [m, 2 H, H-3, $ArCH_2CH$(allyl)CH_2OH], 2.13 (app t, *J* = 6.0 Hz, 2 H, H-16, CH_2CH=CH_2), 1.89 [m, 1 H, H-2, $ArCH_2CH$(allyl)CH_2OH], 1.58 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9 (s, C-6, Ar), 146.8 (s, C-7, Ar), 137.7 (s, C-12, C_6H_5), 137.1 (d, C-17, CH_2CH=CH_2), 134.0 (s, C-4, Ar), 128.7 (d, C-14, C_6H_5), 128.0 (d, C-15, C_6H_5), 127.5 (d, C-13, C_6H_5), 121.4 (d, C-9, Ar), 116.8 (t, C-18, CH_2CH=CH_2), 114.6 (d, C-5, Ar), 113.4 (d, C-8, Ar), 71.5 (t, C-11, OCH_2Ph), 65.1 [t, C-1, $ArCH_2CH$(allyl)CH_2OH], 56.3 (q, C-10, $ArOCH_3$), 42.7 [d, C-2, $ArCH_2CH$(allyl)CH_2OH], 37.2 [t, C-3, $ArCH_2CH$(allyl)CH_2OH], 35.8 (t, C-16, CH_2CH=CH_2).

HRMS (TOF, ES+): *m*/*z* calcd for $C_{20}H_{24}O_3$ + Na [M + Na]: 335.1623; found: 335.1637.

(*R*)-4-(4-Benzyloxy-3-methoxybenzyl)dihydrofuran-2(3*H*)-one [(*R*)-3a]

To a solution of (*S*)-**7a** (203 mg, 0.65 mmol) in 1,4-dioxane–H_2O mixture (3:1, 5.4 mL/1.8 mL) at r.t. were successively added OsO_4 (0.013 mmol), 2,6-lutidine (0.15 mL, 1.29 mmol), and $NaIO_4$ (555 mg, 2.59 mmol). The solution was stirred at r.t. until completion, then quenched by the addition of H_2O (10 mL) followed by the addition of CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude hemiacetal (lactol) was used directly without further purification. Ag_2CO_3 on Celite[11b] (972 mg, 1.62 mmol) was added to a solution of crude lactol in benzene (6.9 mL). The mixture was refluxed for 4 h, cooled to r.t., filtered on Celite and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to afford pure lactone (*R*)-**3a** as a thick oil (156 mg, 77%) with spectral data in good agreement with literature values;[15] $[\alpha]_D^{20}$ –16.0 (*c* 0.2, $CHCl_3$) {Lit.[2b] $[\alpha]_D^{20}$ –16.0 (*c* 0.4, $CHCl_3$)}.

(*R*)-4-Benzyl-3-[3-(4-benzyloxy-3-methoxyphenyl)propanoyl]oxazolidin-2-one (12)

To a solution of **10** (1.00 g, 3.49 mmol) in THF (9 mL) under argon at –70 °C were successively added, dropwise, Et_3N (0.56 mL, 407 mg, 4.02 mmol) and pivaloyl chloride (0.45 mL, 434 mg, 3.59 mmol). The mixture was then warmed to 0 °C and stirred at this temperature for 1 h, then recooled to –70 °C. *n*-BuLi (2.24 mL, 1.6 M in hexane, 3.59 mmol) was added dropwise to a solution of (*R*)-4-benzyl-2-oxazolidinone (618 mg, 3.49 mmol) in THF (20 mL) under argon at –70 °C. The resulting lithium salt was then transferred to the above anhydride mixture via a canula at –70 °C over a 10 min period. The resulting mixture was then stirred for 1 h, warmed to 0 °C, and stirred for 35 min at this temperature. Quenching was realized by adding sat. aq NH_4Cl (2.8 mL). The mixture was concentrated in vacuo to remove THF, diluted with H_2O (14 mL), and extracted with EtOAc (4 × 15 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **12**. Flash chromatography on silica gel (cyclohexane–EtOAc, 8:2) provided pure **12** as a thick oil (1.12 g, 72%); $[\alpha]_D^{22}$ –52.9 (*c* 1, CH_2Cl_2).

IR (neat): 2879, 1782, 1695, 1514 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.15 (m, 10 H, C_6H_5), 6.84–6.72 (m, 3 H, Ar), 5.13 (s, 2 H, H-11, OCH_2Ph), 4.65 (m, 1 H, H-3′, NC*H*CH_2Ph), 4.16 [m, 2 H, H-2′, NC(=O)CH_2CHCH_2Ph], 3.89 (s, 3 H, H-10, $ArOCH_3$), 3.25 [m, 3 H, H-3, C(=O)CH_2CH_2Ar and H-4′, NCHCH_2Ph], 2.96 [m, 2 H, H-2, C(=O)CH_2CH_2Ar], 2.74 (m, 1 H, H-4′, NCHCH_2Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 (s, C-1, carbon from amide), 153.6 (s, C-1′, carbon from urethane), 149.9 (s, C-6, Ar), 146.9 (s, C-7, Ar), 137.6 (s, C-5′, C_6H_5), 135.4 (s, C-12, C_6H_5), 133.9 (s, C-4, Ar), 129.6 (d, C-7′, C_6H_5), 129.1 (d, C-8′, C_6H_5), 128.7 (d, C-14, C_6H_5), 127.9 (d, C-15, C_6H_5), 127.6 (d, C-6′, C_6H_5), 127.5 (d, C-13, C_6H_5), 120.7 (d, C-9, Ar), 114.5 (d, C-5, Ar), 112.8 (d, C-8, Ar), 71.4 (t, C-11, OCH_2Ph), 66.3 [t, C-2′, NC(=O)CH_2CHCH_2Ph], 56.2 (q, C-10, $ArOCH_3$), 55.3 (d, C-3′, NCHCH_2Ph), 38.0 (t, C-4′, NCHCH_2Ph), 37.4 [t, C-2, C(=O)CH_2CH_2Ar], 30.2 [t, C-3, C(=O)CH_2CH_2Ar].

HRMS (TOF, ES+): *m*/*z* calcd for $C_{27}H_{27}NO_5$ + Na [M + Na]: 468.1787; found: 468.1795.

(*R*)-4-Benzyl-3-[(*S*)-2-(4-benzyloxy-3-methoxybenzyl)pent-4-enoyl]oxazolidin-2-one (13)

To a solution of **12** (1.12 g, 2.51 mmol) in THF (26 mL) under argon at –72 °C was added KHMDS (5.3 mL, 0.5 M in hexane, 2.64 mmol) over a 10 min period. The mixture was stirred at this temperature for 1 h, then allyl iodide (0.69 mL, 1.27 g, 7.55 mmol) was added over a 5 min period. The mixture was stirred at –72 °C for 2 h before quenching with sat. aq NH_4Cl (10 mL). The mixture was concentrated in vacuo to remove THF, and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **15**. Flash chromatography on silica gel (cyclohexane–EtOAc, 9:1) provided pure **13** as a thick oil (1.10 g, 90%); $[\alpha]_D^{21}$ –89.7 (*c* 1, CH_2Cl_2).

IR (neat): 2908, 1776, 1696, 1513 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.16 (m, 10 H, C_6H_5), 6.80–6.63 (m, 3 H, Ar), 5.86 (m, 1 H, H-17, CH_2CH=CH_2), 5.12 (s, 2 H, H-11, OCH_2Ph), 5.16–5.01 (m, 2 H, H-18, CH_2CH=CH_2), 4.36 [m, 2 H, H-2, C(=O)C*H*(allyl)CH_2Ar and H-3′, NC*H*CH_2Ph], 3.96 [d, *J* = 6.9 Hz, 1 H, H-2′, NC(=O)CH_2CHCH_2Ph], 3.87 (s, 3 H, H-10, ArOCH_3), 3.72 [app t, *J* = 8.4 Hz, 1 H, H-2′, NC(=O)CH_2CHCH_2Ph], 3.21 (dd, *J* = 2.7, 13. 2 Hz, 1 H, H-4′, NCHCH_2Ph), 2.91–2.76 [m, 2 H, H-3, C(=O)CH(allyl)CH_2Ar], 2.68–2.49 (m, 2 H, H-4′, NCHCH_2Ph and H-16, CH_2CH=CH_2), 2.40–2.30 (m, 1 H, H-16, CH_2CH=CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6 (s, C-1, carbon from amide), 153.3 (s, C-1′, carbon from urethane), 149.8 (s, C-6, Ar), 146.9 (s, C-7, Ar), 137.5 (s, C-5′, C_6H_5), 135.6 (d, C-17, CH_2CH=CH_2), 135.3 (s, C-12, C_6H_5), 132.3 (s, C-4, Ar), 129.6 (d, C-7′, C_6H_5), 129.1 (d, C-8′, C_6H_5), 128.7 (d, C-14, C_6H_5), 128.0 (d, C-15, C_6H_5), 127.5 (d, C-6′, C-13, C_6H_5), 121.2 (d, C-9, Ar), 117.5 (t, C-18, CH_2CH=CH_2), 114.3 (d, C-5, Ar), 113.1 (d, C-8, Ar), 71.3 (t, C-11, OCH_2Ph), 66.0 [t, C-2′, NC(=O)CH_2CHCH_2Ph], 56.2 (q, C-10, ArOCH_3), 55.8 (d, C-3′, NCHCH_2Ph), 44.1 [t, C-2, C(=O)CH(allyl)CH_2Ar], 38.4 [t, C-4′, NCHCH_2Ph or C-3, C(=O)CH(allyl)CH_2Ar], 38.3 [t, C-3, C(=O)CH_2CH_2Ar or C-4′, NCHCH_2Ph], 36.6 (t, C-16, CH_2CH=CH_2).

HRMS (TOF, ES+): *m*/*z* calcd for $C_{30}H_{31}NO_5$ + Na [M + Na]: 508.2100; found: 508.2109.

(*R*)-2-(4-Benzyloxy-3-methoxybenzyl)pent-4-en-1-ol [(*R*)-7a]

To a rapidly stirred solution of **13** (320 mg, 0.66 mmol) in Et_2O (19 mL) were added $LiBH_4$ (0.66 mL, 2.0 M, 1.32 mmol) and anhyd MeOH (56 μL, 1.32 mmol) dropwise. After stirring at r.t. until completion, the reaction mixture was cooled to 0 °C and 1 M aq NaOH (2.5 mL) and EtOAc (19 mL) were added. The organic layer was separated, washed with H_2O (6 mL) and brine (6 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude alcohol, which was then purified by flash chromatography (cyclohexane–EtOAc, 6:4) providing pure (*R*)-**7a** as a thick oil (138 mg, 67%); $[\alpha]_D^{25}$ +18.2 (*c* 0.3, CH_2Cl_2).

IR (neat): 3400, 2910, 1512 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.25 (m, 5 H, C_6H_5), 6.82–6.63 (m, 3 H, Ar), 5.84 (m, 1 H, H-17, CH_2CH=CH_2), 5.12 (s, 2 H, H-11, OCH_2Ph), 5.13–5.00 (m, 2 H, H-18, CH_2CH=CH_2), 3.88 (s, 3 H, H-10, ArOCH_3), 3.55 [d, *J* = 5.4 Hz, 2 H, H-1, ArCH_2CH(allyl)CH_2OH], 2.57 [m, 2 H, H-3, ArCH_2CH(allyl)CH_2OH], 2.13 (app t, *J* = 6.0 Hz, 2 H, H-16, CH_2CH=CH_2), 1.89 [m, 1 H, H-2, ArCH_2C*H*(allyl)CH_2OH], 1.58 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9 (s, C-6, Ar), 146.8 (s, C-7, Ar), 137.7 (s, C-12, C_6H_5), 137.1 (d, C-17, CH_2CH=CH_2), 134.0 (s, C-4, Ar), 128.7 (d, C-14, C_6H_5), 128.0 (d, C-15, C_6H_5), 127.5 (d, C-13, C_6H_5), 121.4 (d, C-9, Ar), 116.8 (t, C-18, CH_2CH=CH_2), 114.6 (d, C-5, Ar), 113.4 (d, C-8, Ar), 71.5 (t, C-11, OCH_2Ph), 65.1 [t, C-1, ArCH_2CH(allyl)CH_2OH], 56.3 (q, C-10, ArOCH_3), 42.7 [d, C-2, ArCH_2C*H*(allyl)CH_2OH], 37.2 [t, C-3, ArCH_2CH(allyl)CH_2OH], 35.8 (t, C-16, CH_2CH=CH_2).

HRMS (TOF, ES+): *m*/*z* calcd for $C_{20}H_{24}O_3$ + Na [M + Na]: 335.1623; found: 335.1626.

(4*S*)-4-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2-ol [(*S*)-3a]

To a solution of (*R*)-**7a** (322 mg, 1.03 mmol) in 1,4-dioxane–H_2O mixture (3:1, 8.6 mL/2.9 mL) at r.t. were successively added OsO_4 (0.021 mmol, 0.02 equiv), 2,6-lutidine (0.24 mL, 2.05 mmol, 2 equiv), and $NaIO_4$ (880 mg, 4.11 mmol, 4 equiv). The solution was stirred at r.t. until completion, then quenched by addition of H_2O (16 mL), followed by the addition of CH_2Cl_2 (24 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 32 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude hemiacetal (lactol) was used directly without further purification. Ag_2CO_3 on Celite[11b] (1.54 g, 2.57 mmol) was added to a solution of crude lactol in benzene (11 mL). The mixture was refluxed for 4 h, cooled to r.t., filtered on Celite, and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to afford pure lactone (*S*)-**3a** as a thick oil (235 mg, 73%) with spectral data in good agreement with literature values;[15] $[\alpha]_D^{20}$ +16.2 (*c* 0.3, $CHCl_3$).

1-Benzyloxy-4-(iodomethyl)-2-methoxybenzene (14)

To a solution of vanillin (7.70 g, 50.67 mmol) in EtOH (40 mL) was added K_2CO_3 (7.90 g, 57.35 mmol) and BnBr (6.0 mL, 50.67 mmol), and the mixture was stirred at r.t. overnight. The reaction mixture was filtered through Celite and the filtrate concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (250 mL), washed with aq 5% w/v NaOH (2 × 100 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The recrystallization of the residue obtained from EtOH gave 4-benzyloxy-3-methoxybenzaldehyde as a white powder (11.2 g, 91%); mp 63–64 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1 H, H-1, CHO), 7.42–7.36 (m, 7 H, C_6H_5, H-6, H-7, Ar), 6.98 (d, *J* = 8.1 Hz, 1 H, H-3, Ar), 5.23 (s, 2 H, H-9, OCH_2Ph), 3.93 (s, 3 H, H-8, ArOCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0 (s, C-1, CHO), 153.9 (s, C-5, Ar), 150.4 (s, C-4, Ar), 136.3 (s, C-10, C_6H_5), 130.6 (s, C-2, Ar), 128.9 (d, C-12, C_6H_5), 128.4 (d, C-13, C_6H_5), 127.4 (d, C-11, C_6H_5), 126.7 (d, C-7, Ar), 112.8 (d, C-6, Ar), 109.8 (d, C-3, Ar), 71.1 (t, C-9, OCH_2Ph), 56.3 (q, C-8, ArOCH_3).

To a solution of 4-benzyloxy-3-methoxybenzaldehyde (5.00 g, 20.64 mmol) in anhyd CH_2Cl_2 (25 mL) was added a suspension of $NaBH_4$ (0.97 g, 25.59 mmol) in MeOH (12 mL), and the mixture was stirred at r.t. until completion (ca. 1 h). The mixture was carefully poured into H_2O (50 mL), extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were dried ($MgSO_4$). Concentration in vacuo gave a white residue. Recrystallization from Et_2O–petroleum ether provided 4-(benzyloxy)-3-methoxyphenyl)methanol as colorless needles (4.91 g, 97%); mp 72–73 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.19 (m, 5 H, C_6H_5), 6.94 (s, 1 H, H-3, Ar), 6.84–6.82 (m, 2 H, H-6, H-7, Ar), 5.15 (s, 2 H, CH_2Ph), 4.59 (d, *J* = 4.2 Hz, 2 H, H-1, ArCH_2OH), 3.89 (s, 3 H, H-8, ArOCH_3), 1.70 (d, *J* = 4.2 Hz, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1 (s, C-4, Ar), 147.9 (s, C-5, Ar), 137.4 (s, C-10, C_6H_5), 134.5 (s, C-2, Ar), 128.7 (d, C-12, C_6H_5), 128.0 (d, C-13, C_6H_5), 127.5 (d, C-11, C_6H_5), 119.5 (d, C-7, Ar), 114.4 (d, C-3, Ar), 111.3 (d, C-6, Ar), 71.4 (t, OCH_2Ph), 65.4 (t, C-1, ArCH_2OH), 56.2 (q, C-8, ArOCH_3).

To a stirred solution of (4-benzyloxy-3-methoxyphenyl)methanol (2.33 g, 9.54 mmol) in THF (50 mL) at 0 °C was added I_2 (2.68 g, 10.56 mmol), imidazole (0.85 g, 12.49 mmol), and PPh_3 (2.82 g, 10.75 mmol). The mixture was stirred for 50 min at 0 °C before the addition of a solution of $Na_2S_2O_3·5H_2O$ (1.90 g) in H_2O (15mL) followed by Et_2O (50 mL). The organic phase was separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic extracts were then washed with aq $Na_2S_2O_3$ (11% w/v, 15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc, 20:1) gave the compound **14** as white needles (2.70 g, 80%) with spectral data in good agreement with literature values;[12c] mp 82–83 °C.

(3*R*,4*R*)-3,4-Bis(4-benzyloxy-3-methoxybenzyl)dihydrofuran-2(3*H*)-one [(*R*,*R*)-2b]

To a solution of lactone (*R*)-**3a** (550 mg, 1.76 mmol) in THF (6.5 mL) cooled to –78 °C was added NaHMDS (2.64 mL, 1.0 M in THF, 2.64 mmol) dropwise over a period of 5 min under N_2. After stirring at this temperature for 1.25 h, a solution of 3-methoxyben-

zyl iodide (**14**; 941 mg, 3.17 mmol) in THF (3.2 mL) was added dropwise over a period of 5 min. The reaction mixture was then warmed up to –54 °C and stirred at this temperature for 22 h. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to afford the alkylated product (*R*,*R*)-**2b** as a pale yellow oil (626 mg, 66%) with spectral data in good agreement with literature values;[16,17] $[\alpha]_D^{21}$ –14.5 (*c* 0.1, $CHCl_3$) {Lit.[16] $[\alpha]_D^{20}$ –14.0 (*c* 0.5, $CHCl_3$)}.

(3*S*,4*S*)-3,4-Bis(4-benzyloxy-3-methoxybenzyl)dihydrofuran-2(3*H*)-one [(*S*,*S*)-2b]

To a solution of lactone (*S*)-**3a** (678 mg, 2.17 mmol) in THF (8 mL) cooled to –78 °C was added NaHMDS (3.25 mL, 1.0 M in THF, 3.25 mmol) dropwise over a period of 5 min under N_2. After stirring at this temperature for 1.25 h, a solution of 3-methoxybenzyl iodide (**14**; 1.16 g, 3.91 mmol) in THF (4 mL) was added dropwise over a period of 5 min. The reaction mixture was then warmed up to –54 °C and stirred at this temperature for 22 h. The reaction was quenched with sat. aq $NaHCO_3$ (6 mL) and extracted with Et_2O (3 × 18 mL). The combined organic layers were washed with brine (12 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to afford the alkylated product (*S*,*S*)-**2b** as a pale yellow oil (748 mg, 64%) with spectral data in good agreement with literature values;[16,17] $[\alpha]_D^{21}$ +14.3 (*c* 0.1, $CHCl_3$).

(2*R*,3*R*)-2,3-Bis(4-hydroxy-3-methoxybenzyl)butane-1,4-diol [(*R*,*R*)-1]

To a solution of lactone (*R*,*R*)-**2b** (700 mg, 1.30 mmol) in EtOAc (26 mL) under argon at r.t. was added 10% Pd/C (138 mg) and the solution was placed under an atmosphere of H_2 (1 atm). The mixture was stirred at r.t. until completion (TLC), filtered over Celite, and concentrated in vacuo. The crude product was then redissolved in anhyd THF (50 mL) and a suspension of $LiAlH_4$ (0.78 mL, 2.0 M in THF, 1.56 mmol) was added at –15 °C. The mixture was stirred at the same temperature for 2 h. Then the reaction was quenched with H_2O (10 mL), extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by column chromatography (cyclohexane–EtOAc, 5:5) to give (*R*,*R*)-**1** (391 mg, 83%). All spectral data were consistent with those reported in the literature;[18] $[\alpha]_D^{25}$ –32.2 (*c* 0.1, acetone) {Lit.[18e] $[\alpha]_D^{25}$ –32.0 (*c* 0.1, acetone)].

(2*S*,3*S*)-2,3-Bis(4-hydroxy-3-methoxybenzyl)butane-1,4-diol [(*S*,*S*)-1]

To a solution of lactone (*S*,*S*)-**2b** (580 mg, 1.08 mmol) in EtOAc (22 mL) under argon at r.t. was added 10% Pd/C (115 mg) and the solution was placed under an atmosphere of H_2 (1 atm). The mixture was stirred at r.t. until completion (TLC), filtered over Celite, and concentrated in vacuo. The crude product was then redissolved in anhyd THF (41 mL) and a suspension of $LiAlH_4$ in THF (0.65 mL, 2.0 M, 1.29 mmol) was added at –15 °C. The mixture was stirred at the same temperature for 2 h. Then, the reaction was quenched with H_2O (12 mL), extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (25 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by column chromatography (cyclohexane–EtOAc, 5:5) to give (*S*,*S*)-**1** (313 mg, 80%). All spectral data were consistent with those reported in the literature;[18] $[\alpha]_D^{25}$ +32.3 (*c* 0.1, acetone).

(*S*)-4-Benzyl-3-[3-(3-methoxyphenyl)propanoyl]oxazolidin-2-one (16)

To a solution of **15** (629 mg, 3.49 mmol) in THF (9 mL) under argon at –70 °C were successively added dropwise, Et_3N (0.56 mL, 407 mg, 4.02 mmol) and pivaloyl chloride (0.45 mL, 434 mg, 3.59 mmol). The mixture was then warmed to 0 °C and stirred at this temperature for 1 h, then recooled to –70 °C. *n*-BuLi (2.24 mL, 1.6 M in hexane, 3.59 mmol) was added dropwise to a solution of (4*S*)-benzyl-2-oxazolidinone (618 mg, 3.49 mmol) in THF (20 mL) under argon at –70 °C. The resulting lithium salt was then transferred to the above anhydride mixture via a canula at –70 °C over a 10 min period. The resulting mixture was then stirred for 1 h, warmed to 0 °C, and stirred for 35 min at this temperature. Quenching was realized by adding sat. aq NH_4Cl (2.8 mL). The mixture was concentrated in vacuo to remove THF, diluted with H_2O (14 mL), and extracted with EtOAc (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **16**. Flash chromatography on silica gel (cyclohexane–EtOAc, 8:2) provided pure **16** as a thick oil (1.00 g, 88%); $[\alpha]_D^{28}$ +35.9 (*c* 0.6, $CHCl_3$).

IR (neat): 2835, 1778, 1699, 1601, 1490 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 6 H, C_6H_5 + Ar), 6.89–6.75 (m, 3 H, Ar), 4.67 (m, 1 H, H-3′, NC*H*CH_2Ph), 4.17 [m, 2 H, H-2′, NC(=O)OCH_2CHCH_2Ph], 3.82 (s, 3 H, H-10, ArOCH_3), 3.30–3.21 [m, 3 H, H-3, C(=O)CH_2CH_2Ar and H-4′, NCHCH_2Ph], 3.01 [m, 2 H, H-2, C(=O)CH_2CH_2Ar and H-4′, NCHCH_2Ph], 2.77 [app t, *J* = 10.0 Hz, 1 H, H-2, C(=O)CH_2CH_2Ar].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 (s, C-1, carbon from amide), 160.0 (s, C-6, Ar), 153.6 (s, C-1′, carbon from urethane), 142.3 (s, C-4, Ar), 135.4 (s, C-5′, C_6H_5), 129.7 (d, C-8, Ar), 129.2 (d, C-6′, C-7′, C_6H_5), 127.6 (d, C-8′, C_6H_5), 121.2 (d, C-9, Ar), 114.5 (d, C-5, Ar), 112.0 (d, C-7, Ar), 66.4 [t, C-2′, NC(=O)CH_2CHCH_2Ph], 55.4 (q, C-10, ArOCH_3 and d, C-3′, N*C*HCH_2Ph), 38.1 (s, C-4′, NCHCH_2Ph), 37.3 [t, C-2, C(=O)CH_2CH_2Ar], 30.6 [t, C-3, C(=O)CH_2CH_2Ar].

HRMS (TOF, ES+): *m*/*z* calcd for $C_{20}H_{21}NO_4$ + Na [M + Na]: 362.1368; found: 362.1374.

(*S*)-4-Benzyl-3-[(*S*)-2-(3-methoxybenzyl)pent-4-enoyl]oxazolidin-2-one (17)

To a solution of **16** (852 mg, 2.51 mmol) in THF (26 mL) under argon at –72 °C was added KHMDS (5.3 mL, 0.5 M in hexane, 2.64 mmol) over a 10 min period. The mixture was stirred at this temperature for 1 h, then allyl iodide (0.69 mL, 1.27 g, 7.55 mmol) was added over a 5 min period. The mixture was stirred at –72 °C for 2 h before quenching with sat. aq NH_4Cl (10 mL). The mixture was concentrated in vacuo to remove THF, and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **17**. Flash chromatography on silica gel (cyclohexane–EtOAc, 9:1) provided pure **17** as a thick oil (734 mg, 77%); $[\alpha]_D^{20}$ +99.2 (*c* 0.1, CH_2Cl_2).

IR (neat): 2977, 1777, 1697, 1489 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 6 H, Ar + C_6H_5), 6.84–6.74 (m, 3 H, Ar), 5.89 (m, 1 H, H-17, CH_2CH=CH_2), 5.19–5.09 (m, 2 H, H-18, CH_2CH=CH_2), 4.49 (m, 1 H, H-3′, NC*H*CH_2Ph), 4.36 [m, 1 H, H-2, C(=O)C*H*(allyl)CH_2Ar], 4.28 [app d, *J* = 6.9 Hz, 1 H, H-2′, NC(=O)OCH_2CHCH_2Ph], 3.86 [app d, *J* = 7.8 Hz, 1 H, H-2′, NC(=O)OCH_2CHCH_2Ph], 3.78 (s, 3 H, H-10, ArOCH_3), 3.24 (app d, *J* = 11.1 Hz, 1 H, H-4′, NCHCH_2Ph), 3.01–2.80 [m, 2 H, H-3, C(=O)CH(allyl)CH_2Ar], 2.72–2.50 (m, 2 H, H-4′, NCHCH_2Ph and H-16, CH_2CH=CH_2), 2.41–2.35 (m, 1 H, H-16, CH_2CH=CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.3 (s, C-1, carbon from amide), 159.7 (s, C-6, Ar), 153.1 (s, C-1′, carbon from urethane), 140.6 (s, C-4, Ar), 135.5 (s, C-5′, C_6H_5), 135.2 (d, C-17, CH_2CH=CH_2),

129.5 (d, C-7′, C_6H_5), 129.4 (d, C-8, Ar), 129.0 (d, C-6′, C_6H_5), 127.4 (d, C-8′, C_6H_5), 121.5 (d, C-9, Ar), 117.4 (t, C-18, $CH_2CH{=}CH_2$), 114.6 (d, C-5, Ar), 112.2 (d, C-7, Ar), 66.0 [t, C-2′, $NC(=O)CH_2CHCH_2Ph$], 55.6 (q, C-10, $ArOCH_3$), 55.2 (d, C-3′, $NCHCH_2Ph$), 43.9 [d, C-2, $C(=O)CH(allyl)CH_2Ar$], 38.4 (t, C-4′, $NCHCH_2Ph$), 38.1 [t, C-3, $C(=O)CH(allyl)CH_2Ar$], 36.4 (t, C-16, $CH_2CH{=}CH_2$).

HRMS (TOF, ES+): *m*/*z* calcd for $C_{23}H_{25}NO_4$ + Na [M + Na]: 402.1681; found: 402.1665.

(*S*)-2-(3-Methoxybenzyl)pent-4-en-1-ol [(*S*)-7b]

To a rapidly stirred solution of **17** (797 mg, 2.1 mmol) in Et_2O (60 mL) were added $LiBH_4$ (2.1 mL, 2.0 M, 4.2 mmol) and anhyd MeOH (178 μL, 4.2 mmol) dropwise. After stirring at r.t. until completion, the reaction mixture was cooled to 0 °C and 1 M aq NaOH (8 mL) and EtOAc (60 mL) were added. The organic layer was separated, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude alcohol, which was then purified by flash chromatography (cyclohexane–EtOAc, 6:4) providing pure (*S*)-**7b** as a thick oil (308 mg, 71%); $[\alpha]_D^{21}$ –22.8 (*c* 0.1, CH_2Cl_2).

IR (neat): 3393, 2913, 1600, 1488 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 1 H, H-8, Ar), 6.82–6.66 (m, 3 H, H-5, H-7, H-9, Ar), 5.84 (m, 1 H, H-17, $CH_2CH{=}CH_2$), 5.13–5.05 (m, 2 H, H-18, $CH_2CH{=}CH_2$), 3.80 (s, 3 H, H-10, $ArOCH_3$), 3.54 [d, *J* = 5.1 Hz, 2 H, H-1, $ArCH_2CH(allyl)CH_2OH$], 2.63 [m, 2 H, H-3, $ArCH_2CH(allyl)CH_2OH$], 2.35 (br s, 1 H, OH), 2.15 (m, 2 H, H-16, $CH_2CH{=}CH_2$), 1.93 [m, 1 H, H-2, $ArCH_2CH(allyl)CH_2OH$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7 (s, C-6, Ar), 142.3 (s, C-4, Ar), 136.9 (d, C-17, $CH_2CH{=}CH_2$), 129.4 (d, C-8, Ar), 121.8 (d, C-9, Ar), 116.6 (t, C-18, $CH_2CH{=}CH_2$), 115.1 (d, C-5, Ar), 111.3 (d, C-7, Ar), 64.6 [t, C-1, $ArCH_2CH(allyl)CH_2OH$], 55.2 (q, C-10, $ArOCH_3$), 42.4 [d, C-2, $ArCH_2CH(allyl)CH_2OH$], 37.3 [t, C-3, $ArCH_2CH(allyl)CH_2OH$], 35.4 (t, C-16, $CH_2CH{=}CH_2$).

HRMS (TOF, ES+): *m*/*z* calcd for $C_{13}H_{18}O_2$ + Na [M + Na]: 229.1204; found: 229.1196.

(*R*)-4-(3-Methoxybenzyl)dihydrofuran-2(3*H*)-one [(*R*)-3b]

To a solution of (*S*)-**7b** (134 mg, 0.65 mmol) in 1,4-dioxane–H_2O mixture (3.1, 5.4 mL/1.8 mL) at r.t. were successively added OsO_4 (0.013 mmol), 2,6-lutidine (0.15 mL, 1.29 mmol), and $NaIO_4$ (555 mg, 2.59 mmol). The solution was stirred at r.t. until completion, then quenched by the addition of H_2O (10 mL), followed by the addition of CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude hemiacetal (lactol) was used directly without further purification. Ag_2CO_3 on Celite[11b] (972 mg, 1.618 mmol) was added to a solution of crude lactol in benzene (6.9 mL). The mixture was refluxed for 4 h, cooled to r.t., filtered on Celite and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 6:4) to afford pure lactone (*R*)-**3b** as a thick oil (148 mg, 73%) with spectral data in good agreement with literature values;[13] $[\alpha]_D^{25}$ +6.5 (*c* 0.2, $CHCl_3$) {Lit.[13l] $[\alpha]_D^{25}$ +6.4 (*c* 1.0, $CHCl_3$)}.

(3*R*,4*R*)-3,4-Bis(3-hydroxybenzyl)dihydrofuran-2(3*H*)-one (2a)

To a cold (–78 °C) solution of lactone (*R*)-**3b** (200 mg, 0.97 mmol) in THF (4 mL) under argon atmosphere was added dropwise LiHMDS (1.45 mL, 1.0 M in THF, 1.45 mmol) over a period of 5 min. After stirring at that temperature for 1 h, a solution of 3-methoxybenzyl bromide (1.746 mmol, 351 mg) in THF (2 mL) was added dropwise over a period of 5 min. The reaction mixture was then slowly warmed up to –54 °C and stirred at this temperature for 20 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated to provide crude dibenzyl lactone. To a rapidly stirred solution of the crude lactone in anhyd CH_2Cl_2 (17 mL) at 0 °C was added BBr_3 (3.3 mL, 1.0 M in CH_2Cl_2, 3.3 mmol) dropwise during 5 min. The stirring was continued at 0 °C for 1 h and then at –18 °C. After 10 h, the reaction mixture was quenched with H_2O (10 mL), the CH_2Cl_2 layer was separated, and the aqueous layer was extracted Et_2O. The CH_2Cl_2 layer and the combined Et_2O layers were separately washed with brine, combined, dried (Na_2SO_4), and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (Et_2O–CH_2Cl_2) to provide **2a** as a colorless semisolid (171 mg, 59%). All spectral data were consistent with those reported in the literature;[13] $[\alpha]_D^{25}$ –38.4 (*c* 0.2, $CHCl_3$) {Lit.[13l] $[\alpha]_D^{27}$ –38.5 (*c* 0.5, $CHCl_3$)}.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

The authors would like to thank the INRA for financial support.

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