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Asymmetric syntheses of protected (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline and 4′-*tert*-butoxyamido-2′-deoxythymidine

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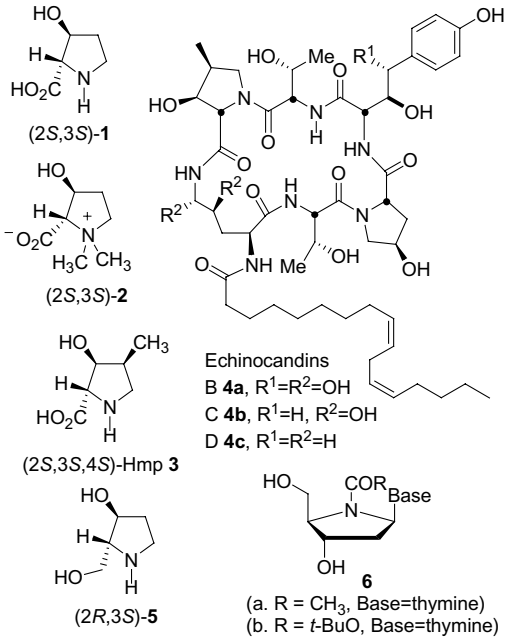
Abstract—Described herein is a versatile approach to (i) (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **3**, a constituent of echinocandins and related oligopeptide antibiotics; (ii) (2*S*,3*S*)-3-hydroxyproline **1**; (iii) (2*R*,3*S*)-3-hydroxyprolinol **5**, and (iv) 4′-*tert*-butoxyamido-2′-deoxythymidine **6b**. The method features a stepwise regio- and diastereoselective reductive furylation of the protected (3*S*,4*S*)-4-methylmalimide **10**, (*S*)-malimide **9**, and a chemoselective oxidative transformation of the furyl group to the carboxyl group as the key steps.

1. Introduction

3-Hydroxyproline and 3-hydroxyprolinol are found as integrality or as sub-unities in a number of bioactive natural products. For example, (2*S*,3*S*)-3-hydroxyproline **1** (*trans*-3-hydroxy-L-proline) is a nonproteinogenic amino acid isolated both from hydrolyzates of Mediterranean sponge[1] and the seeds of *Delonix regia*.[2,3] It is also a component found in a number of bioactive natural peptides, such as mucrorin-D,[4] tetomycin,[5] and cyclic peptide alkaloids;[6] the dimethylated derivative of 3-hydroxyproline, namely 3-hydroxyproline betaines (L-*trans*-3-hydroxystachydrine **2**[7]) was isolated from *Courbonia virgata*;[7a] (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **3** (Hmp), another nonproteinogenic amino acid, is present as a common structural moiety in a class of natural oligopeptide antibiotic (e.g., echinocandins **4**) and the pharmaceutically interesting analogues[8] such as LY303366 and FK-463. The latters are currently being investigated in phase II/III clinical studies against *Candida* and *Aspergillums* species. Hmp **3** is also a constituent found in nostopeptins,[9] which are elastase inhibitors isolated from the cultured freshwater *Cyanobacterium Nostoc minutum* (CNIES-26); (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine (CYB-3 or *trans*-3-hydroxy-L-prolinol, **5**), the reduced form of *trans*-3-hydroxy-L-proline, is also a natural product isolated from the seeds of the legume *Castarospermum australe*.[10] Moreover, azanucleosides,[11] such as **6a**,[12] have been shown to stabilize antisense oligonucleotides toward 3′-exonucleases.[12a]



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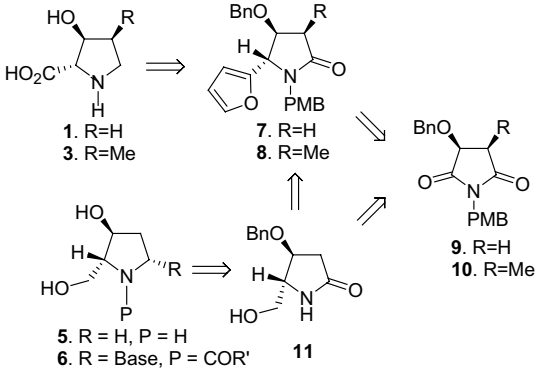
Different strategies have been developed for the syntheses of (2*S*,3*S*)-3-hydroxyproline **1**,[13] (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **3** (Hmp),[14] (2*R*,3*S*)-3-hydroxyprolinol **5**,[13b,g,15] and azanucleosides **6**.[11,12,16] However, none of them has been used to synthesize different kinds of above-mentioned 3-hydroxyprolines and 3-hydroxyprolinols. We report herein a versatile approach for the asymmetric syntheses of protected (2*S*,3*S*,4*S*)-3-hydroxy-4-methylprolines **20** and **21**,[17] protected (2*S*,3*S*)-3-hydroxyproline **23**, protected (2*R*,3*S*)-3-hydroxyprolinol **25**, and azathymidine **6b**.

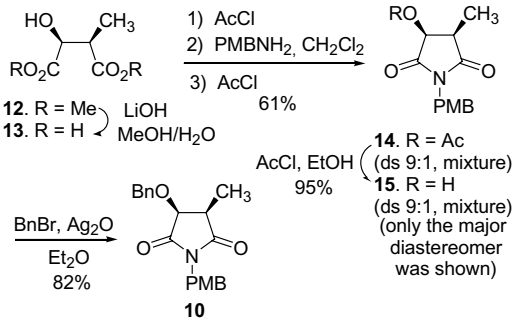
2. Results and discussion

We have long been interested in developing a synthetic methodology based on the stepwise asymmetric reductive alkylation of the cyclic imides.[18] An extension of this strategy to the asymmetric synthesis of (2*S*,3*S*)-3-hydroxyproline **1**, (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **3** (Hmp), (2*R*,3*S*)-3-hydroxyprolinol **5**, and azanucleosides **6**, would require a reductive carboxylation or reductive hydroxymethylation of an appropriate malimide. As 2-lithiofuran is a useful synthetic equivalent to an unpoled carboxyl group,[19] a simple retrosynthetic analysis (Scheme 1) shows that **1**, **3**, and **5** could be derived from 5-(fur-2-yl)-pyrrolidin-2-one **7** or **8**, which could in turn be prepared from the protected malimide **9** or **10** via a stepwise reductive furylation. 2-Pyrrolidinone **11**, useful intermediate for the syntheses of prolinol **5** and azathymidine **6** could be derived either from 5-(fur-2-yl)-pyrrolidin-2-one **7**, or from the protected malimide **9** via a stepwise reductive hydroxymethylation. The key questions resided on the feasibility of both the chemoselective oxidation of the 2-furyl group to the carboxyl group with strong oxidative agent RuO_4, while keeping the easily oxidizable *p*-methoxybenzyl group (PMB)[20] intact, and the regioselective furylation or hydroxymethylation at the C-2 carbonyl of the malimide **9** or **10**.



Scheme 1.

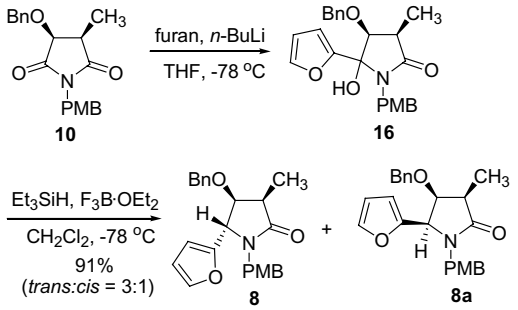
Our first target was (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **3**. The synthesis started with (2*S*,3*S*)-3-methylmalic acid **13**,[21] easily available from the known (2*S*,3*S*)-3-methylmalate **12**[22] (as a 10:1 diastereomeric mixture) by saponification (Scheme 2). Compound **13** was converted (a: 7 equiv AcCl, ~47 °C, 1 h; b: 1.5 equiv $PMBNH_2$, ~47 °C, 2 h; c: 5 equiv AcCl, ~47 °C, 1 h), in one-pot[23] and in an overall yield of 61%, to **14** as an inseparable 9:1 (*cis*/*trans*) diastereomeric mixture as indicated by its ^1H NMR spectrum. Higher reaction temperatures and prolonged reaction times led to epimerization at the C-4 stereogenic center. De-acetylation (AcCl, EtOH, 0–rt, 30 h, yield 95%) followed by recrystallization gave *cis*-**15**. *O*-Benzylation of *cis*-**15** afforded the desired imide **10** {$[\alpha]_D^{28} = +59.6$ (*c* 1.0, $CHCl_3$)} in 82% yield.



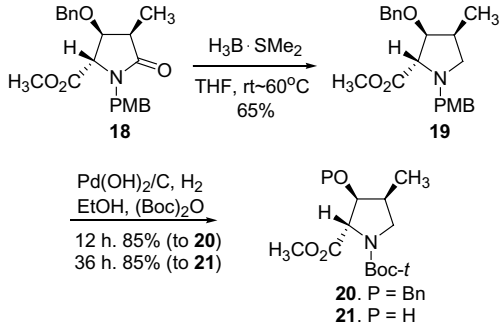
Scheme 2.

For the addition of 2-lithiofuran to imide **10**, the regioselectivity was the major concern.[24–27] The regioselectivities in the addition of carbon nucleophiles to protected (*S*)-*N*,*O*-diprotected malimides, such as **9**,[18a–f,h] have been shown to be dependent on the organonmetallic reagents used: high regioselectivity at the C-2 carbonyl with Grignard reagents,[18a–g] or lithium enolates,[18h] while modest to high C-5 regioselectivities was obtained with alkyllithiums,[18g,27a] organocerium reagents[27a] or organotitanium reagents.[27b] It was envisioned that 2-lithiofuran, being less active than alkyllithiums, would behave like Grignard reagents and react with imide **10** with C-2 regioselectivity. In this event, treatment of the imide **10** with 2-lithiofuran, which was generated in situ from furan and *n*-BuLi at −78 °C, yielded the desired diastereomeric C-2 adduct **16** in 79% yield. The yield was improved to 90% by using an inverse addition procedure. Attribution of the C-2 addition instead of the C-5 addition during the transformation of **10** to **16** was made based on the observed H-3 resonance appearing at 2.92 ppm of the ^1H NMR spectrum of **8**, which was later confirmed by conversion of **8** to the known compound **21**. The diastereomeric mixture **16** was then treated with boron trifluoride etherate and triethylsilane[28] (−78 °C, 8 h, then rt, 8 h) (Scheme 3) to give, via a presumed *N*-acyliminium intermediate,[29] diastereomers **8** and **8a** in 3:1 ratio and in a combined yield of 91%. The stereochemistries of the lactams **8** and **8a** were assigned based on the observed characteristic vicinal coupling constants[18,30] ($J_{4,5} = 2.0$ Hz for *trans*-isomer **8** and $J_{4,5} = 6.3$ Hz for *cis*-diastereomer **8a**), and were further confirmed by converting **8** to the known **21**.

Compared with previous results where the reductive alkylation of **9** led to at least 94:6 *trans*/*cis* diastereo-

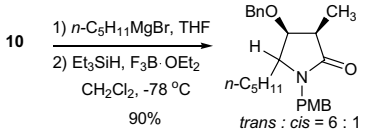


Scheme 3.



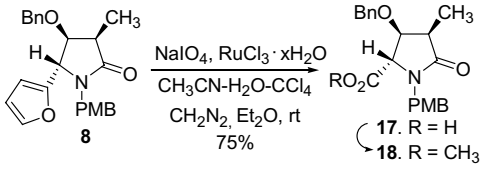
Scheme 6.

selectivities,[18a–f,h] lower diastereoselectivity during the reductive deoxygenation of **16** may be due to the presence of the *cis*-methyl group in **16**.[18a–f,h] To confirm this assumption, reductive *n*-pentanylation of **10** was performed, and indeed, only a 6:1 *trans*/*cis* diastereoselectivity was observed (Scheme 4). Further evidence was gained by performing the reductive furylation of **9** (vide infra).



Scheme 4.

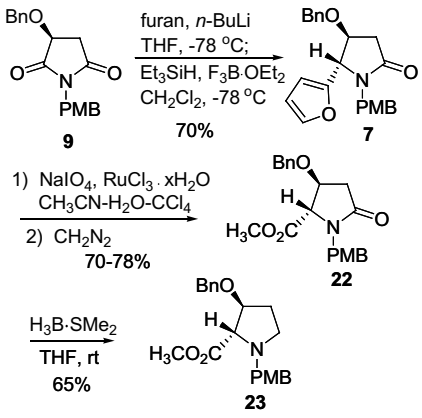
With compound **8** in hand, the chemoselective unmasking of the 2-furyl group to the carboxyl group was undertaken. Treatment of **8** with RuO_4, in situ generated from a $RuCl_3{\cdot}xH_2O$–$NaIO_4$ system in a mixed solvent system (H_2O–MeCN–CCl_4, 3:3:2)[19] at rt led, after esterification (CH_2N_2, Et_2O–THF, 0 °C) of the crude acid, to the desired methyl ester **18** in 56% yield over two steps (Scheme 5). To improve the yield of the chemoselective oxidation of **8**, the oxidation of **8** was conducted at 0–5 °C, and the overall yield from **8** to **18** was improved to 70–78%. Thus remarkable chemoselectivity was achieved during the oxidative cleavage of the furan ring.



Scheme 5.

Chemoselective reduction of the amide carbonyl to methylene in the presence of an ester group[31] was achieved by treatment of **18** with $BH_3{\cdot}SMe_2$, which provided the desired fully protected Hmp **19** in 65% yield (Scheme 6). Finally, chemoselective *N*-de-(*p*-methoxybenzylation) in the presence of both Pearlman's catalyst and $(Boc)_2O$ [$Pd(OH)_2$, H_2, 1 atm, $(Boc)_2O$, EtOH, rt, 12 h] afforded the protected Hmp **20** in 85% yield (Scheme 4). If the catalytic hydrogenolysis was performed under prolonged reaction time (36 h), the known (2*S*,3*S*,4*S*)-*N*-Boc-Hmp-OMe **21**: $\{[\alpha]_D^{25} = -23.4$ (*c* 0.8, $CHCl_3$); lit.[14a] $[\alpha]_D^{25} = -24.2$ (*c* 1.1, $CHCl_3$)$\}$, a compound which has been used in the total synthesis of echinocandin D,[14a] was obtained in 85% yield.

Next, we addressed the synthesis of protected 3-hydroxyproline[13] **23**. Thus, the known imide **9**[18a,f,h] was treated, at −78 °C, with a 0.25 M THF solution of 2-lithiofuran, which was generated from furan and *n*-BuLi, and the reaction was quenched after stirring for 20 min at −78 °C. In this way, the desired adduct was obtained in 78% yield alongside 5% of the C-5 regioisomer. It is noteworthy that a higher concentration of 2-lithiofuran and higher reaction temperature should be avoided to prevent the ring opening side reaction. The diastereomeric adducts were then treated with boron trifluoride etherate and triethylsilane (−78 °C, 8 h, then rt, 8 h) to give *trans*-lactam **7** ($J_{4,5} = 2.1$ Hz) as the only isolable diastereomer (70% overall yield from **9**) (Scheme 7). This result implicates that the diastereoselectivity during the reductive deoxygenation is at least 95%. The high diastereoselectivity observed in the reductive furylation of **9** further confirms the assumption (vide supra) that the methyl groups present in **10** (and thus **16**) are

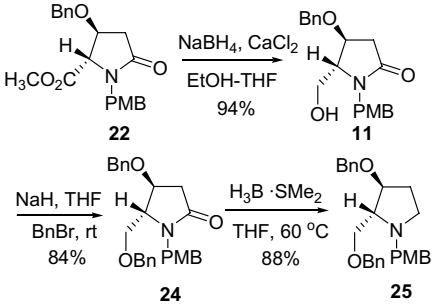


Scheme 7.

responsible for the lower diastereoselectivity in the reductive deoxygenation of **16**.

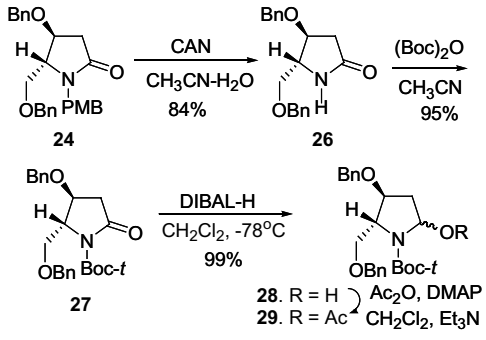
Oxidation of **7** ($RuCl_3{\cdot}xH_2O$–$NaIO_4$, 0–5 °C) followed by esterification (CH_2N_2, Et_2O, 0 °C) gave the desired methyl ester **22** in yields ranging from 70% to 78%. Subsequent chemoselective reduction of the amide carbonyl group in **22** with borane dimethyl sulfide at rt furnished the desired protected (2*S*,3*S*)-3-hydroxyproline **23** in 65% yield.

For the synthesis of protected (2*R*,3*S*)-3-hydroxyprolinol **25** and azanucleoside **6b**, because the attempted direct reductive benzyloxymethylation ($BnOCH_2MgCl$, $HgCl_2$ (cat.);[32] Et_3SiH, $F_3B{\cdot}OEt_2$) of **9** gave a disappointing 1:1 regioisomeric ratio and 20–25% overall yield, we then turned attention to their synthesis from **22**. Thus, treatment of **22** with an excess of sodium borohydride in the presence of anhydrous calcium chloride[33] in EtOH–THF system gave the desired partially reduced product **11** in 94% yield (Scheme 8). Protection of the hydroxyl group (NaH, BnBr, THF, −20 °C, 28 h) afforded **24** in 84% yield. Treatment of **24** with an excess of borane dimethyl sulfide in THF gave the protected (2*R*,3*S*)-3-hydroxyprolinol **25** in 88% yield.



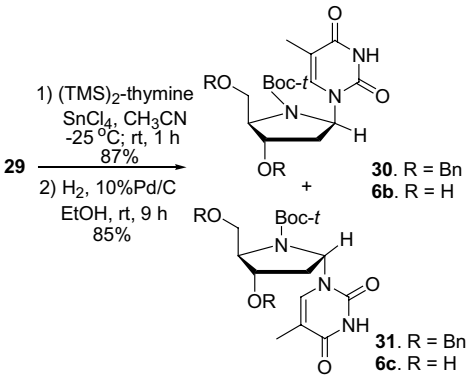
Scheme 8.

In pursuing the synthesis of azathymidine, **24** was first converted to **27** by *N*-deprotection (CAN, rt, yield: 84%) and *N*-activation [(*t*-Boc)$_2$O, DMAP, MeCN, yield: 95%] (Scheme 9). Partial reduction of the C-2 carbonyl of **27** (DIBAL-H, CH_2Cl_2, −78 °C, 30 min, yield: 99%) followed by acetylation (AcCl, Et_3N, DMAP, CH_2Cl_2, rt) gave acetate **29** as a 1:1 diastereomeric mixture in a combined yield of 90%. It is noteworthy that diastereomeric acetates **29** were unstable and decomposed to the starting material during routine flash chromatography purification. However, when the flash chromatography was performed on a short pad of silica gel and pre-cooled eluent was used, the desired acetates **29** can be obtained in high yield.



Scheme 9.

Installation of the thyminyl group was achieved using the Hilbert–Johnson protocol.[12a,34] Thus, treatment of **29** with $SnCl_4$ in the presence of freshly prepared $(TMS)_2$–thymine at −25 °C for 1 h gave a separable mixture of diastereomers **30/31** in 1:1.8 ratio and in a combined yield of 87% (Scheme 10). The two diastereomers were separated by careful flash chromatography on silica gel. The identities of **30** and **31** were determined by means of COSY and NOESY. We observed strong NOEs between H-1′ and H-2′α in **30**, while no NOEs between H-1′ and H-2′β clearly indicate that the thyminyl group is disposed in the β-face, and thus is in *cis* relationship with the C-4′ benzyloxymethyl group. This was confirmed by the observed strong NOEs between H-1′ and H-2′β of the diastereomer **31**, and small NOEs between H-1′ and H-2′α. Thus, in **31**, the C-1′ thyminyl group and C-4′ substituent are in a *trans* disposition.



Scheme 10.

Finally, a controlled catalytic hydrogenation (H_2, 10% Pd/C, EtOH, rt, 9 h) of **30** furnished **6b** in 85% yield. Similarly, chemoselective catalytic hydrogenation of **31** furnished **6c** in 85% yield.

3. Conclusion

In summary, a versatile approach to the protected (2*S*,3*S*)-3-hydroxyproline **23**, (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **21** (Hmp), (2*R*,3*S*)-3-hydroxyprolinol **25**, and azathymidines **6b** was developed via a stepwise regio- and diastereoselective reductive furylation of the protected (3*S*,4*S*)-4-methylmalimide **10** and (*S*)-malimide **9**. The choice of the furyl group as the masked carboxyl group allowed the successful chemoselective unmasking of the former in the presence of the *N*-(*p*-methoxybenzyl) group, which constituted as the second key step of the synthesis.

4. Experimental

The general information is described in Ref. 18f.

4.1. Acetic acid (3*S*,4*S*)-1-(4-methoxybenzyl)-4-methyl-2,5-dioxo-pyrrolidin-3-yl ester 14

A mixture of (2*S*,3*S*)-3-methylmalic acid **13**[22] (7.50 g, 50.67 mmol) and acetyl chloride (26.0 mL, 0.36 mol) was refluxed for 1.5 h and then concentrated in vacuo. The crude anhydride was dissolved in CH_2Cl_2 (30 mL), to which was added a solution of 4-methoxybenzylamine (10.6 mL, 76.01 mmol) in CH_2Cl_2 (24.0 mL). The resultant mixture was stirred at 47 °C for 2 h, and then concentrated in vacuo. The residue was dissolved in acetyl chloride (18 mL, 0.25 mol) and refluxed for 1.5 h. After concentration of the reaction mixture in vacuo, the residue was purified by flash chromatography (EtOAc–PE = 1:3) to give *cis*-**14** and its diastereomer as an inseparable diastereomeric mixture (ratio 9:1) (8.99 g, combined yield 61%). A sample of pure *cis*-**14** was obtained by deacetylation of diastereomeric pure *cis*-**15** (vide infra). *cis*-**14**: colorless oil. $[\alpha]_D^{28} = -2.0$ (*c* 1.0, $CHCl_3$). IR (NaCl): ν = 2925, 1749, 1711, 1651, 1612, 1512, 1432, 1399, 1244, 1220, 1174, 1097, 1025 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 [d, *J* = 7.7 Hz, 3H, C(4)–CH_3], 2.18 (s, 3H, CO_2CH_3), 3.13 [dq, *J* = 8.2, 7.7 Hz, 1H, C(4)–H], 3.80 (s, 3H, OCH_3), 5.6 [d, *J* = 8.2 Hz, 1H, C(3)–H], 4.61 (d, *J* = 14.2 Hz, 1H, NCH_2Ar), 4.62 (d, *J* = 14.2 Hz, 1H, NCH_2Ar), 6.82 (d, *J* = 8.5 Hz, 2H, Ar), 7.35 (d, *J* = 8.5 Hz, 2H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6, 20.3, 38.9, 42.0, 55.2, 69.0, 114.0, 127.4, 130.3, 159.4, 169.8, 173.0, 177.2 ppm. ESI-MS: *m*/*z* (%) = 274 (100), 314 (49) ($M+Na^+$). Elemental analysis calcd for $C_{15}H_{17}NO_5$: C, 61.86; H, 5.84; N, 4.81. Found: C, 62.06; H, 6.03; N, 5.04.

4.2. (3*S*,4*S*)-3-Hydroxy-1-(4-methoxybenzyl)-4-methyl-pyrrolidin-2,5-dione 15

To a solution of diastereomeric **14** (3.08 g, 10.58 mmol) in 65 mL of absolute ethanol was added dropwise AcCl (2.3 mL, 31.5 mmol) at 0 °C. The mixture was stirred at rt for 30 h and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1:2) of the residue afforded *cis*-**15** and its diastereomer (ratio 9:1) as an inseparable diastereomeric mixture (white crystals, 2.50 g, combined yield 95%). A sample of the pure *cis*-diastereomer **15** was obtained after recrystallization. *cis*-Diastereomer **15**: Mp 56 °C (EtOAc/PE). $[\alpha]_D^{28} = -45.5$ (*c* 1.0, $CHCl_3$). IR (KBr): ν = 3450, 2980, 2920, 1610, 1612, 1513, 1434, 1344, 1248, 1178, 1142 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 [d, *J* = 7.7 Hz, 3H, C(4)–CH_3], 1.80 (s, 1H, OH), 3.03 [dq, *J* = 8.3, 7.7 Hz, 1H, C(4)–H], 3.80 (s, 3H, OCH_3), 4.57 [d, *J* = 8.3 Hz, 1H, C(3)–H], 4.58 (s, 2H, NCH_2 Ar), 6.82 (d, *J* = 8.5 Hz, 2H, Ar), 7.35 (d, *J* = 8.5 Hz, 2H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3, 40.9, 41.7, 55.2, 68.5, 114.0, 127.6, 130.1, 159.3, 178.1, 178.3 ppm. ESI-MS: *m*/*z* (%) = 250 (100) ($M+H^+$). Elemental analysis calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.93; H, 6.04; N, 5.85.

4.3. (3*S*,4*S*)-3-Benzyloxy-1-(4-methoxybenzyl)-4-methyl-pyrrolidin-2,5-dione 10

To a solution of diastereomeric **15** (ratio 9:1) (2.37 g, 9.54 mmol) in 50 mL of diethyl ether were added benzyl bromide (3.4 mL, 28.60 mmol) and silver oxide (6.64 g, 28.60 mmol). After being stirred in the dark for 7 days at rt, the mixture was filtered through Celite and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1:4) of the residue afforded **10** (2.65 g, 82% yield) as a colorless oil. $[\alpha]_D^{28} = +59.6$ (*c* 1.0, $CHCl_3$). IR (film): ν = 2937, 1708, 1611, 1520, 1389, 1341, 1301, 1249, 1179, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 7.7 Hz, 3H, CH_3), 2.77 (dq, *J* = 7.8, 7.7 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 4.26 (d, *J* = 7.8 Hz, 1H, H-3), 4.57 (d, *J* = 14.5 Hz, 1H, NCH_2Ar), 4.60 (d, *J* = 14.5 Hz, 1H, NCH_2Ar), 4.78 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.98 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 6.82 (d, *J* = 8.5 Hz, 2H, Ar), 7.32–7.38 (m, 7H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0, 39.6, 41.5, 55.1, 73.0, 73.7, 114.0, 127.7, 127.8, 128.0, 128.4, 130.1, 136.9, 159.2, 175.6, 178.1 ppm. ESI-MS: *m*/*z* (%) = 340 (7) ($M+Na^+$), 300 (100). Elementary analysis calcd for $C_{20}H_{21}NO_4$: C, 70.79; H, 6.19; N, 4.13. Found: C, 70.63; H, 6.26; N, 4.40.

4.4. (3*S*,4*S*,5*S*)-4-Benzyloxy-5-(fur-2-yl)-1-(4-methoxy benzyl)-3-methylpyrrolidin-2-one 8

To a well-stirred cooled solution (−78 °C) of furan (0.64 g, 9.48 mmol) in anhydrous THF (13 mL), was added, under argon, *n*-butyllithium (1.9 mL, 4.74 mmol, 2.5 M solution in hexane). The solution was stirred at 0 °C for 2 h. To a cooled (−78 °C) solution of **10** (1.07 g, 3.16 mmol) in anhydrous THF (43 mL) was added dropwise 2-lithiofuran (15 mL, 4.47 mmol, 0.3 M solution in THF). After being stirred for 20 min at the same temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (14 mL). The mixture was warmed to rt and diluted with Et_2O (14 mL). The organic layer was separated and the aqueous layer extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by column chromatography using ethyl acetate–petroleum ether (1:3) as an eluent to yield a diastereomeric mixture of **16** (1.22 g, yield 95%), which was used in the next step without separation.

To a cooled (−78 °C) solution of the diastereomeric mixture of **16** (1.22 g, 3.00 mmol) in dry CH_2Cl_2 (30 mL) was added successively triethylsilane (4.74 mL, 30.0 mmol) and boron trifluoride etherate (1.3 mL, 10.51 mmol) under argon. After being stirred at −78 °C for 8 h, the reaction was allowed to warm up and the stirring continued at rt for 8 h. The reaction was quenched by saturated aqueous $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 for three times. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was flash chromatographed (EtOAc–PE = 1:4–1:2) to give *trans*-diastereomer **8** (0.80 g, 68%, colorless oil) and *cis*-diastereomer **8a** (0,27 g, 23%, white crystals). *trans*-Diastereomer **8**: $[\alpha]_D^{28} = +31.3$ (*c* 1.2, $CHCl_3$).

IR (film): ν = 2933, 1694, 1611, 15121 1451, 1415, 1246, 1069, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 [d, J = 7.3 Hz, 3H, C(3)–CH_3], 2.92 [qd, J = 7.3, 6.1 Hz, 1H, C(3)–H], 3.61 (d, J = 15.0 Hz, 1H, NCH_2Ar), 3.78 (s, 3H, OCH_3), 4.10 [dd, J = 6.1, 2.0 Hz, 1H, C(4)–H], 4.41 [d, J = 2.0 Hz, 1H, C(5)–H], 4.45 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.51 (d, J = 12.0 Hz, 1H, OCH_2Ph), 5.07 (d, J = 15.0 Hz, 1H, NCH_2Ar), 6.14 [d, J = 3.2 Hz, 1H, C(3′)–H], 6.33 [dd, J = 3.2, 1.8 Hz, 1H, C(4′)–H], 6.82 (d, J = 8.8 Hz, 2H, Ar), 7.11 (d, J = 8.4 Hz, 2H, Ar), 7.19 [d, 1H, J = 1.8 Hz, C(5′)–H], 7.26–7.38 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.0, 40.0, 43.7, 55.2, 71.8, 75.4, 79.0, 108.3, 110.4, 113.9, 127.4, 127.7, 128.1, 128.3, 129.3, 137.6, 142.9, 150.6, 159.0 ppm. ESI-MS: m/z (%) = 392 (100) ($M+H^+$), 414 (4) ($M+Na^+$). Elemental analysis calcd for $C_{24}H_{25}NO_4$: C, 73.66; H, 6.39; N, 3.58. Found: C, 73.68; H, 6.30; N, 3.56.

4.5. (3*S*,4*S*,5*S*)-4-Benzyloxy-1-(4-methoxybenzyl)-3-methyl-2-oxo-proline methyl ester 18

To a solution of $NaIO_4$ (4.31 g, 20.16 mmol) in a mixed solvent system H_2O–CH_3CN–CCl_4 (3:3:2, v/v/v, 73 mL) was added an aqueous solution of $RuCl_3{\cdot}xH_2O$ (2.24 mL, 0.11 mmol, 0.05 M). After being stirred for 20 min at 0 °C, a solution of furanoid derivative **8** (0.95 g, 2.24 mmol) in CH_3CN (24.2 mL) was added. The color of the solution turned instantaneously from light yellow-green to black. After 10 min, the mixture was diluted with water (40 mL) and extracted with EtOAc (5 × 20 mL). The combined organic extracts were washed successively with saturated aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude acid was dissolved in Et_2O–THF (2:1 v/v) and treated with an ethereal solution of diazomethane (0.56 M, 24 mL) at 0 °C. Flash chromatography (EtOAc/PE = 1:2.5) of the residue afforded ester **18** (0.64 g, 75%) as a white solid. Mp 87 °C (EtOAc–PE). $[\alpha]_D^{28} = +17.1$ (c 1.0, $CHCl_3$). IR (film): ν = 2934, 1711, 1696, 1611, 1512, 1450, 1413, 1360, 1247, 1177, 1069, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 [d, J = 7.3 Hz, 3H, C(3)–CH_3], 2.70 [qd, J = 7.3, 5.8 Hz, 1H, C(3)–H], 3.68 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 3.98 (d, J = 15.0 Hz, 1H, NCH_2Ar), 4.00 [s, 1H, C(5)–H], 4.09 [d, J = 5.8 Hz, 1H, C(4)–H], 4.43 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.54 (d, J = 11.9 Hz, 1H, OCH_2Ar), 5.02 (d, J = 15.0 Hz, 1H, NCH_2Ar), 6.82 (d, J = 8.4 Hz, 2H, Ar), 7.11 (d, J = 8.4 Hz, 2H, Ar), 7.20–7.38 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.6, 40.3, 44.8, 52.4, 55.1, 62.7, 71.1, 73.7, 114.0, 127.7, 127.8, 128.4, 130.1, 136.9, 159.0, 170.2, 175.5 ppm. ESI-MS: m/z (%) = 384 (100) ($M+H^+$), 404 (5) ($M+Na^+$). ESI-HRMS: calcd for [$C_{22}H_{25}NO_5+H^+$]: 384.1805; found: 384.1810.

4.6. (2*S*,3*S*,4*S*)-3-Benzyloxy-1-(4-methoxybenzyl)-4-methylproline methyl ester 19

To a solution of **18** (90 mg, 0.23 mmol) in anhydrous THF (4.6 mL) was added $BH_3{\cdot}SMe_2$ (0.2 mL, 2.1 mmol) at 0 °C. The resulting mixture was stirred at 15 °C for 1.5 days. The solution was re-cooled to −10 °C, diluted with EtOAc (8 mL), and then quenched by MeOH (6 mL). The solvent was evaporated under reduced pressure. To the resulting residue were added successively EtOAc (8 mL) and H_2O (6 mL). The resulting solution was stirred at 60 °C for 2 h before being extracted with Et_2O (5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue using ethyl acetate–petroleum ether (1:3.5) as an eluent afforded **19** (55 mg, 65%) as a colorless oil. $[\alpha]_D^{23} = -54.9$ (c 0.9, $CHCl_3$). IR (film): ν = 2960, 2921, 1737, 1613, 1510, 1455, 1259, 1093, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.09 [d, J = 6.6 Hz, 3H, C(4)–CH_3], 2.35–2.41 [m, 1H, C(4)–H], 2.45 [dd, J = 11.0, 8.0 Hz, 1H, C(5)–H], 3.11 [dd, J = 11.0, 6.0 Hz, 1H, C(5)–H], 3.45 [d, J = 2.3 Hz, 1H, C(2)–H], 3.67 (s, 3H, CH_3O), 3.69 (d, J = 12.6 Hz, 1H, NCH_2Ar), 3.82 (d, J = 12.6 Hz, 1H, NCH_2Ar), 3.83 (s, 3H, CO_2CH_3), 3.96 [dd, J = 5.8, 2.3 Hz, 1H, C(3)–H], 4.51 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.69 (d, J = 11.9 Hz, 1H, OCH_2Ph), 6.82 (d, J = 8.5 Hz, 2H, Ar), 7.20–7.39 (m, 7H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.2, 37.2, 44.8, 52.0, 55.2, 59.0, 59.1, 71.2, 72.5, 84.2, 113.5, 127.6, 128.3, 130.2, 130.4, 138.2, 158.7, 173.5 ppm. ESI-MS: m/z (%) = 370 (100) ($M+H^+$). ESI-HRMS: calcd for [$C_{22}H_{27}NO_4+H^+$]: 370.2013; found: 370.2013.

4.7. (2*S*,3*S*,4*S*)-3-Benzyloxy-1-(*tert*-butoxycarbonyl)-4-methylproline methyl ester 20

A suspension of **19** (44 mg, 0.12 mmol), 20% $Pd(OH)_2/C$ (13 mg), and $(Boc)_2O$ (0.1 mL, 0.9 mmol) in 4 mL of 95% ethanol was stirred under an atmosphere of hydrogen for 12 h. The mixture was filtered through Celite and the filtrate evaporated in vacuo. Flash chromatography (EtOAc–PE = 1:4.5) of the residue afforded **20** (26 mg, 85%) as a colorless oil. $[\alpha]_D^{17} = -26.7$ (c 0.9, $CHCl_3$). IR (film): ν = 2967, 1746, 1711, 1612, 1511, 1452, 1357, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, two rotamers): δ = 1.11, 1.12 [two rotamers, each d, J = 6.8, 6.9 Hz, 3H, C(4)–CH_3], 1.44, 1.49 (each s, 9H, Boc), 2.35–2.45 [m, 1H, C(4)–H], 3.18, 3.22 [each dd, J = 10.1, 9.8 Hz, 1H, C(5)–H], 3.70 [dd, J = 8.2, 10.1 Hz, 0.5H, C(5)–H, rotamer 1], 3.74 [dd, J = 10.1, 8.2 Hz, 0.5H, overlapped with CO_2CH_3, C(5)–H, rotamer 2], 3.75, 3.76 [each s, 3H, overlapped with H–5, CO_2CH_3], 3.88, 3.91 [each dd, J = 1.1, 4.5 Hz, 1H, C(3)–H], 4.38 [d, J = 1.1 Hz, 0.5H, C(2)–H, rotamer 1], 4.51 [s, 0.5H, C(2)–H, rotamer 2], 4.54, 4.56 (each d, J = 11.4 Hz, 1H, OCH_2Ph), 4.76, 4.78 (each d, J = 11.4 Hz, 1H, OCH_2Ph), 7.28–7.40 (m, 5H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers): δ = 11.0, 11.1, 28.2, 28.4, 29.7, 35.8, 36.7, 50.9, 51.4, 52.1, 52.3, 64.2, 64.7, 71.2, 71.3, 79.9, 82.6, 83.3, 127.5, 127.7, 127.8, 128.4, 137.6, 154.6, 153.7, 171.6, 171.3 ppm. ESI-MS: m/z (%) = 274 (100) ($M-Bu^t-H_2O^+$). ESI-HRMS: calcd for [$C_{12}H_{21}NO_5+H^+$]: 350.1967; found: 350.1964.

4.8. (2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-4-methylproline methyl ester 21

A suspension of **19** (44 mg, 0.12 mmol), 20% $Pd(OH)_2/C$ (13 mg), and $(Boc)_2O$ (0.09 mL, 0.9 mmol) in 4 mL of 95% ethanol was stirred under an atmosphere of hydro-

gen for 36 h. The mixture was filtered through Celite and the filtrate evaporated in vacuo. Flash chromatography (EtOAc–PE = 1:3) of the residue afforded **21** (26 mg, 85%) as a colorless oil. $[\alpha]_D^{15} = -23.4$ (*c* 0.8, $CHCl_3$). IR (film): ν = 3420, 2970, 1750, 1710, 1690, 1680 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, two rotamers): δ = 1.07 [each d, J = 6.9 Hz, 3H, C(4)–CH_3], 1.40, 1.44 (each s, 9H, Boc), 1.78 (s, 1H, OH), 2.32–3.28 [m, 1H, C(4)–H], 3.13, 3.16 [each d, J = 10.3 Hz, 1H, C(5)–H], 3.68 [dd, J = 10.3, 8.2 Hz, 0.5H, C(5)–H, rotamer 1], 3.74 [m, 0.5H, C(5)–H, rotamer 2, overlapped with CO_2CH_3], 3.74, 3.75 (each s, 3H, CO_2CH_3), 4.20, 4.21 [each dd, J = 4.5 Hz, 1H, C(3)–H], 4.22, 4.33 [each br s, 1H, C(2)–H] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 10.8, 28.2, 28.4, 36.1, 36.8, 50.2, 50.8, 52.2, 52.4, 68.0, 68.2, 76.1, 80.1, 153.8, 154.6, 171.2, 171.6 ppm. ESI-MS: *m*/*z* (%) = 260 (100) ($M+H^+$). ESI-HRMS: calcd for [$C_{12}H_{21}NO_5+H^+$]: 260.1492; found: 260.1488.

4.9. (4*S*,5*S*)-4-Benzyloxy-5-(fur-2-yl)-1-(4-methoxybenzyl)pyrrolidin-2-one 7

To a cooled (−78 °C) solution of furan (1.25 g, 18.45 mmol) in anhydrous THF (26 mL) was added *n*-butyllithium (3.69 mL, 9.23 mmol, 2.5 M solution in hexane) under argon and the resulting solution stirred at 0 °C for 2 h. To a cooled (−78 °C) solution of **9** (2.00 g, 6.15 mmol) in anhydrous THF (70 mL) was added dropwise a diluted 2-lithiofuran (37 mL, 9.23 mmol, 0.25 M solution in THF). After being stirred for an additional 20 min at the same temperature, the reaction was quenched by saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate–petroleum ether (1:3) as an eluent yielded the furylated product as a mixture of two diastereomers.

To a cooled (−78 °C) solution of the diastereomeric mixture the furylated product in dry CH_2Cl_2 (51 mL) were added triethylsilane (8.1 mL, 50.87 mmol) and boron trifluoride etherate (1.9 mL, 15.22 mmol). After being stirred at −78 °C for 8 h, the reaction was allowed to warm up and stirred for an additional 8 h at rt. The reaction was quenched by a saturated aqueous $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude was flash chromatographed (EtOAc–PE = 1:4–1:2) to give **7** (1.63 g, 70%, over two steps) as colorless crystals. Mp 55 °C (EtOAc/PE). $[\alpha]_D^{14} = +50.2$ (*c* 1.1, $CHCl_3$). IR (KBr): ν = 2926, 1683, 1511, 1427, 1245, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.59 [dd, J = 17.3, 2.7 Hz, 1H, C(3)–H], 2.92 [dd, J = 17.3, 6.7 Hz, 1H, C(3)–H], 3.57 [d, J = 14.9 Hz, 1H, NCH_2Ar], 3.80 (s, 3H, OCH_3), 4.20 [ddd, J = 6.7, 2.7, 2.1 Hz, 1H, C(4)–H], 4.46 (s, 2H, OCH_2Ph), 4.50 [d, J = 2.1 Hz, 1H, C(5)–H], 5.03 (d, J = 14.9 Hz, 1H, NCH_2Ar), 6.14 [d, J = 3.1 Hz, 1H, C(3′)–H], 6.35 [dd, J = 3.1, 1.8 Hz, 1H, C(4′)–H], 6.81 (d, J = 8.5 Hz, 2H, Ar), 7.11 (d, J = 8.4 Hz, 2H, Ar), 7.19 [d, J = 1.8 Hz, 1H, C(5′)–H], 7.23–7.35 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.5, 43.5, 55.2, 60.8, 71.1, 76.4, 108.6, 110.3, 113.9, 127.5, 127.8, 127.9, 128.4, 129.3, 137.2, 143.0, 150.6, 159.0, 172.3 ppm. ESI-MS: *m*/*z* = 378 (100) ($M+H^+$). Elemental analysis calcd for $C_{23}H_{23}NO_4$: C, 73.21; H, 6.10; N, 3.71. Found: C, 73.52; H, 6.06; N 3.90.

4.10. [(4*S*,5*S*)-4-Benzyloxy-1-(4-methoxybenzyl)-2-oxoproline methyl ester 22

To a stirred solution of $NaIO_4$ (8.34 g, 38.97 mmol) in H_2O–CH_3CN–CCl_4 3:3:2 (195 mL) was added an aqueous solution of $RuCl_3$–xH_2O (4.33 mL, 0.22 mmol, 0.05 M). After being stirred for 20 min at 0 °C, 2-furyl derivative **7** (1.63 g, 4.33 mmol) in CH_3CN (27 mL) was added. The color of the solution changed instantaneously from light yellow-green to black. After 5 min, the mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed successively with saturated aqueous $NaHSO_3$ (until the solution become colorless) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude acid was dissolved in Et_2O–THF (2:1 v/v) and treated with an ethereal solution of diazomethane (0.56 M, 62 mL) at 0 °C. Flash chromatography (EtOAc–PE = 1:2) of the residue afforded ester **22** (1.24 g, 78%) as a white solid. Mp 65 °C (EtOAc/PE). $[\alpha]_D^{14} = +29.8$ (*c* 1.0, $CHCl_3$). IR (KBr): ν = 2934, 1713, 1689, 1607, 1512, 1448, 1251, 1219, 1078, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.53 [dd, J = 17.5, 1.1 Hz, 1H, C(3)–H], 2.76 [dd, J = 17.5, 6.4 Hz, 1H, C(3)–H], 3.68 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 4.00 (d, J = 14.9 Hz, 1H, NCH_2Ar), 4.09 [s, 1H, C(5)–H], 4.14 [dd, J = 6.4, 1.1 Hz, 1H, C(4)–H], 4.46 (d, J = 11.8 Hz, 1H, OCH_2Ph), 4.50 (d, J = 11.8 Hz, 1H, OCH_2Ph), 4.99 (d, J = 14.9 Hz, 1H, NCH_2Ar), 6.81 (d, J = 8.4 Hz, 2H, Ar), 7.15 (d, J = 8.4 Hz, 2H, Ar), 7.20–7.38 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.5, 44.7, 55.2, 64.9, 70.8, 74.5, 113.9, 127.2, 127.6, 127.9, 128.4, 129.5, 136.8, 159.0, 170.2, 172.9 ppm. ESI-MS: *m*/*z* (%) = 370 (100) ($M+H^+$). Elemental analysis calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.73; H, 6.42; N, 3.94.

4.11. (2*S*,3*S*)-3-Benzyloxy-1-(4-methoxybenzyl)proline methyl ester 23

To a solution of **22** (46 mg, 0.12 mmol) in anhydrous THF (1.3 mL) was added $BH_3{\cdot}SMe_2$ (0.1 mL, 1.12 mmol) at 0 °C. The resulting mixture was stirred at 25 °C overnight. The solution was re-cooled to −10 °C, diluted with EtOAc (8 mL), and quenched with MeOH (0.5 mL). The solvent was evaporated under reduced pressure. To the residue were added successively EtOAc (2 mL) and H_2O (2 mL). The resulting solution was stirred at 60 °C for 2 h before being extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1:3.5) of the residue afforded **23** (29 mg, 65%) as a colorless oil. $[\alpha]_D^{25} = -13.3$ (*c* 0.6, $CHCl_3$). IR (film): ν = 2960, 2921, 1737, 1613, 1510, 1455, 1259, 1093, 1028 cm^{-1}. ^1H

NMR (500 MHz, $CDCl_3$): δ = 1.86–1.91 [m, 1H, C(4)–H], 2.06–2.11 [m, 1H, C(4)–H], 2.67 [ddd, J = 16.0, 6.5, 2.0 Hz, 1H, C(5)–H], 3.03 [ddd, J = 16.0, 9.0, 2.0 Hz, 1H, C(5)–H], 3.36 [d, J = 3.5 Hz, 1H, C(2)–H], 3.63 (d, J = 13.0 Hz, 1H, NCH_2Ar), 3.65 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 3.83 (d, J = 13.0 Hz, 1H, NCH_2Ar), 4.15–4.18 [m, 1H, C(3)–H], 4.51 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.69 (d, J = 11.9 Hz, 1H, OCH_2Ph), 6.82 (d, J = 8.5 Hz, 2H, Ar), 7.22–7.39 (m, 7H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.4, 51.7, 51.9, 55.2, 58.2, 71.0, 72.2, 82.7, 113.5, 127.6, 128.3, 130.0, 130.4, 137.9, 158.9, 173.3 ppm. ESI-HRMS: calcd for [$C_{21}H_{25}NO_4$+H^+]: 356.1865; found: 356.1876. Calcd for [$C_{21}H_{25}NO_4$+Na^+]: 378.1681; found: 378.1690.

4.12. (4*S*,5*R*)-4-Benzyloxy-5-hydroxymethyl-1-(4-methoxybenzyl)pyrrolidin-2-one 11

To a suspension of **22** (0.30 g, 0.81 mmol) and $CaCl_2$ (0.38 g, 3.4 mmol) in EtOH–THF (1:2) (3.24 mL) was added $NaBH_4$ (0.25 mg, 6.48 mmol). The mixture was stirred for 3 h at rt, then cooled to 0 °C and diluted with EtOAc (10 mL). To the resultant mixture was added $Na_2SO_4{\cdot}10H_2O$ until the evolution of gas ceased. The mixture was filtered through Celite. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with aqueous NH_4Cl, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed (EtOAc–PE = 3: 1) to give **11** (0.26 g, 95%) as a white solid. Mp 101 °C (EtOAc/PE). $[\alpha]_D^{14} = +74.6$ (c 1.1, $CHCl_3$). IR (KBr): ν = 3322, 2904, 1678, 1652, 1511, 1250, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.49 [dd, J = 17.4, 2.0 Hz, 1H, C(3)–H], 2.62 (br s, 1H, OH), 2.78 [dd, J = 17.4, 6.7 Hz, 1H, C(3)–H], 3.53 [dd, J = 3.7, 2.4 Hz, 1H, C(5)–H], 3.57 [ddd, J = 11.2, 4.1, 2.4 Hz, 1H, C(6)–H], 3.72 [ddd, J = 11.2, 4.0, 3.7 Hz, 1H, C(6)–H], 3.80 (s, 3H, OCH_3), 4.13 [dd, J = 6.7, 2.0 Hz, 1H, C(4)–H, overlapped with one of N–CH_2], 4.17 (d, J = 14.9 Hz, 1H, NCH_2Ar), 4.42 (d, J = 11.7 Hz, 1H, OCH_2Ph), 4.49 (d, J = 11.7 Hz, 1H, OCH_2Ph), 4.83 (d, J = 14.9 Hz, 1H, NCH_2Ar), 6.81 (d, J = 8.5 Hz, 2H, Ar), 7.21 (d, J = 8.5 Hz, 2H, Ar), 7.23–7.35 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.1, 43.8, 55.2, 60.4, 65.2, 70.6, 74.4, 114.1, 127.6, 127.8, 128.3, 128.4, 129.0, 137.5, 159.0, 173.9 ppm. ESI-MS: m/z (%) = 342 (100) ($M+H^+$). Elemental analysis calcd for $C_{20}H_{23}NO_4$: C, 70.38; H, 4.10; N, 6.74. Found: C, 70.11; H, 4.25; N, 6.67.

4.13. (4*S*,5*S*,5*R*)-4-Benzyloxy-5-benzyloxymethyl-1-(4-methoxybenzyl)pyrrolidin-2-one 24

To a suspension of NaH (40 mg, 60% in mineral oil, 1.00 mmol) in dry THF (4.3 mL) was added dropwise a solution of **11** (0.29 g, 0.84 mmol) in THF (4.5 mL) at −20 °C. The reaction was stirred for 30 min at −20 °C, then to the mixture was added BnBr (0.15 mL, 1.26 mmol) and the stirring continued for 40 h at the same temperature before being quenched with NH_4Cl. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1:3) of the residue afforded **24** (0.30 g, 84%) as an oil. $[\alpha]_D^{20} = -31.7$ (c 0.8, $CHCl_3$). IR (film): ν = 2922, 1686, 1611, 1512, 1453, 1246 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.51 [dd, J = 17.3, 1.9 Hz, 1H, C(3)–H], 2.81 [dd, J = 17.3, 6.6 Hz, 1H, C(3)–H], 3.43 [dd, J = 10.0, 3.5 Hz, 1H, C(6)–H], 3.45 [dd, J = 10.0, 4.1 Hz, 1H, C(6)–H, overlapped with other C(6)–H], 3.61 [ddd, J = 4.1, 3.5, 3.5 Hz, 1H, C(5)–H], 3.80 (s, 3H, OCH_3), 4.00 (d, J = 15.1 Hz, 1H, NCH_2Ar), 4.08 [ddd, J = 6.6, 3.5, 1.9 Hz, 1H, C(4)–H], 4.38 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.41 (d, J = 11.7 Hz, 1H, OCH_2Ph), 4.42 (d, J = 11.7 Hz, 1H, OCH_2Ph), 4.48 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.89 (d, J = 15.1 Hz, 1H, NCH_2Ar), 6.81 (d, J = 8.5 Hz, 2H, Ar), 7.16 (d, J = 8.5 Hz, 2H, Ar), 7.22–7.39 (m, 10H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.8, 43.8, 55.2, 63.2, 67.2, 70.6, 74.5, 113.9, 127.5, 127.7, 127.8, 128.3, 128.4, 129.1, 137.5, 158.9, 173.2 ppm. ESI-MS: m/z (%) = 342 (100) ($M+H^+$). ESI-HRMS: calcd for ($C_{27}H_{29}NO_4$+H^+): 432.2169; found: 432.2155. Calcd for ($C_{27}H_{29}NO_4$+Na^+): 454.1994; found: 454.1981.

4.14. (2*R*,3*S*)-3-Benzyloxy-2-benzyloxymethyl-1-(4-methoxybenzyl)prolinol 25

To a solution of **24** (37 mg, 0.09 mmol) in anhydrous THF (0.9 mL) was added $BH_3{\cdot}SMe_2$ (0.07 mL, 0.8 mmol) at 0 °C. The resulting mixture was stirred at 25 °C overnight and quenched by the addition of MeOH (0.5 mL) and H_2O (2 mL). The resulting mixture was stirred at 60 °C for 3 h before being extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1:4.5) of the residue afforded **25** (32 mg, 88%) as a colorless oil. $[\alpha]_D^{25} = -21.6$ (c 0.7, $CHCl_3$). IR (film): ν = 2922, 1611, 1512, 1453, 1246 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.85–1.91 [m, 2H, C(4)–H], 2.57 [ddd, J = 7.0, 4.5, 2.0 Hz, 1H, C(2)–H], 2.87–2.93 [m, 2H, C(5)–H], 3.36 [dd, J = 9.5, 7.0 Hz, 1H, C(6)–H], 3.47 [dd, J = 9.5, 4.5 Hz, 1H, C(6)–H], 3.53 (d, J = 13.0 Hz, 1H, NCH_2Ar), 3.81 (s, 3H, OCH_3), 3.94–3.97 [m, 1H, C(3)–H], 3.98 (d, J = 13.0 Hz, 1H, NCH_2Ar), 4.51 (d, J = 12.0 Hz, 2H, OCH_2Ph), 4.54 (d, J = 12.0 Hz, 2H, OCH_2Ph), 6.83 (d, J = 8.5 Hz, 2H, Ph), 7.22–7.38 (m, 12H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.5, 52.2, 55.2, 59.1, 69.2, 70.5, 71.4, 73.2, 82.0, 113.5, 127.4, 127.5, 127.6, 127.6, 128.3, 130.1, 131.4, 138.4, 138.7, 158.6 ppm. ESI-HRMS: calcd for ($C_{27}H_{31}NO_3^+$+H^+): 418.2382; found: 418.2394. Calcd for ($C_{27}H_{31}NO_3$+Na^+): 440.2236; found: 440.2216.

4.15. (4*S*,5*R*)-4-Benzyloxy-5-benzyloxymethylpyrrolidin-2-one 26

To a solution of **24** (0.35 g, 0.81 mmol) in CH_3CN–H_2O (9:1, 41 mL) was added cerium(IV) ammonium nitrate (2.22 g, 4.05 mmol). The mixture was stirred for 3 h at rt and then diluted with water (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed successively with sat-

urated sodium bicarbonate and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (EtOAc–PE = 1.5:1) of the residue afforded **26** (0.14 g, 84%) as a colorless oil. $[\alpha]_D^{18} = +51.7$ (*c* 1.1, $CHCl_3$). IR (film): 3238, 3030, 2861, 1697, 1497, 1453, 1092, 1068, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *v* = 2.44 [dd, *J* = 17.4, 3.5 Hz, 1H, C(3)–H], 2.66 [dd, *J* = 17.4, 7.0 Hz, 1H, C(3)–H], 3.39 [dd, *J* = 9.5, 6.7 Hz, 1H, C(6)–H], 3.51 [dd, *J* = 9.5, 4.5 Hz, 1H, C(6)–H], 3.85 [ddd, *J* = 6.7, 4.5, 3.5 Hz, 1H, C(5)–H], 4.03 [ddd, *J* = 7.0, 3.5, 3.5 Hz, 1H, C(4)–H], 4.50 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.51 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.53 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.55 (d, 1H, *J* = 11.8 Hz, OCH_2Ph), 6.28 (s, 1H, NH), 7.25–7.38 (m, 10H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.1, 60.2, 71.1, 71.3, 73.4, 75.9, 127.6, 127.7, 127.8, 128.4, 137.3, 137.5, 175.4 ppm. ESI-MS: *m*/*z* (%) = 288 (100), 312 (63) ($M+H^+$). ESI-HRMS: calcd for ($C_{19}H_{21}NO_3+H^+$): 312.1593; found: 312.1609. Calcd for ($C_{19}H_{21}NO_3+Na^+$): 334.1419; found: 334.1435.

4.16. (4*S*,5*R*)-4-Benzyloxy-5-benzyloxymethyl-1-(*tert*-butoxycarbonyl)pyrrolidin-2-one 27

A solution of **26** (0.11 g, 0.35 mmol), di-*tert*-butyl dicarbonate (0.2 mL, 0.83 mmol), and DMAP (cat.) in CH_3CN (1.2 mL) was stirred for 1 h under N_2. The residue obtained after removal of the solvent was purified by column chromatography (EtOAc–PE = 1:4) to afford **27** (0.14 g, 95%) as a colorless oil $[\alpha]_D^{14} = -37.4$ (*c* 0.3, $CHCl_3$). IR (film): *v* = 2977, 2924, 2860, 1785, 1748, 1715, 1671, 1604, 1454, 1367 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9H, *t*-Boc), 2.44 [d, *J* = 18.0 Hz, 1H, C(3)–H], 2.91 [dd, *J* = 18.0, 6.1 Hz, 1H, C(3)–H], 3.64 [d, *J* = 3.7 Hz, 2H, C(6)–H], 4.08 [d, *J* = 6.1 Hz, 1H, C(4)–H], 4.30 [t, *J* = 3.7 Hz, 1H, C(5)–H], 4.48 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.52 (d, *J* = 12.2 Hz, 2H, OCH_2Ph), 4.55 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 7.25–7.38 (m, 10H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 29.7, 39.3, 63.8, 68.9, 70.5, 73.4, 73.6, 83.0, 127.5, 127.7, 127.8, 127.9, 128.4, 137.3, 137.5, 149.7, 172.8 ppm. ESI-MS: *m*/*z* (%) = 312 (100) ($M+H^+-Boc$), 434 (32) ($M+Na^+$). Elementary analysis calcd for $C_{24}H_{29}NO_5$: C, 70.07; H, 7.05; N 3.40. Found: C, 69.96; H,7.11; N, 3.25.

4.17. (2*R*/*S*,4*S*,5*R*)-4-Benzyloxy-5-benzyloxymethyl-1-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidine 28

A solution of DIBAL-H (0.85 M in toluene, 0.68 mmol, 0.8 mL) was added dropwise under argon to a stirred solution of **27** (0.14 g, 0.34 mmol) in dry THF (1.7 mL) at −78 °C. After being stirred for 30 min at −78 °C, a saturated aqueous NH_4Cl solution was added dropwise. The resultant mixture was warmed to rt and filtered through Celite. The aqueous layer was extracted with dichloromethane, and the combined organic phases dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc–PE = 1:4) to give **28** as a diastereomeric mixture (0.14 g, diastereomeric ratio 1:1, combined yield 99%). $[\alpha]_D^{14} = -14.8$ (*c* 0.8 $CHCl_3$, diastereomeric mixture). IR (film): *v* = 3465, 2973, 2925, 2856, 1693, 1454, 1392, 1366, 1169, 1096 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 (2s, 9H, *t*-Boc), 1.95 [ddd, *J* = 15.4, 5.0, 2.5 Hz, 1H, C(3)–H], 2.26 [ddd, *J* = 15.4, 6.4, 1.9 Hz, 1H, C(3)–H], 3.42–3.50 (m, 1H, C(6)–H), 3.60 [dd, *J* = 9.5, 2.8 Hz, 1H, C(5)–H], 3.90–3.97 [m, 1H, C(6)–H], 4.14 [dd, *J* = 6.4, 2.5 Hz, 1H, C(4)–H], 4.48 (d, *J* = 12.2 Hz, 1H, OCH_2Ph), 4.50 (d, *J* = 12.2 Hz, 1H, OCH_2Ph), 4.54 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.57 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 5.48 [dd, *J* = 11.4, 5.0 Hz, 1H, C(2)–H], 7.28–7.39 (m, 10H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 28.4, 29.7, 40.1, 37.9, 36.8, 62.8, 62.5, 69.5, 69.1, 70.8, 73.2, 73.4, 78.9, 79.2, 80.5, 81.7, 82.1, 127.4, 127.7, 127.7, 127.8, 128.4, 137.7, 137.9, 153.4, 154.6 ppm. ESI-MS: *m*/*z* (%) = 296 (100) ($M+H^+-H_2O-Boc$), 396 (72) ($M+H^+-H_2O$), 436 (10) ($M+Na^+$). ESI-HRMS: calcd for ($C_{24}H_{31}N_3O_5+Na^+$): 436.2099; found: 436.2091.

4.18. Acetic acid (2*RS*,4*S*,5*R*)-4-benzyloxy-5-benzyloxymethyl-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl ester 29

To a solution of **28** (0.12 g, 0.28 mmol) and Ac_2O (0.16 mL, 1.68 mmol) and DMAP (cat.) in dichloromethane was added Et_3N (1.68 mmol, 0.23 mL) at 0 °C. The mixture was stirred at 23 °C overnight and then cooled to −15 °C. Saturated aqueous $NaHCO_3$ was added and the aqueous layer extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Short column chromatography purification of the residue on SiO_2 using pre-cooled eluent (EtOAc–PE = 1:5) afforded **29** as a diastereomeric mixture, that was immediately used in the next step.

4.19. (1′*S*,3′*S*,4′*R*)-4′-(*tert*-Butoxyamido)-3′,5′-dibenzyloxy-2′-deoxythymidine 30 and (1′*R*,3′*S*,4′*R*)-4′-(*tert*-butoxyamido)-3′,5′-dibenzyloxy-2′-deoxythymidine 31

A mixture of thymine (44 mg, 0.35 mmol), $(NH_4)_2SO_4$ (15 mg, 0.12 mmol), and hexamethydisilazane (2 mL) was refluxed at 125 °C for 5 h. The excess HMDS was removed by co-distillation with xylene (3 × 1 mL) under reduced pressure. To the residue was added MeCN (2 mL), the resultant solution was transferred to compound **29** (45 mg, 0.1 mmol). To the resultant mixture was added dropwise a solution of $SnCl_4$ (0.1 mL, 0.15 mmol) in MeCN (0.6 mL) at −25 °C under argon. The resultant mixture was stirred for 1 h at the same temperature. Saturated $NaHCO_3$ aqueous was added and the resultant mixture warmed to rt, and filtered through Celite. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography (Et_2O–PE = 2:1) of the residue gave β-anomer **30** (colorless oil, 16 mg, 31%) and α-anomer **31** (colorless oil, 29 mg, yield 56%). β-Anomer **30**: $[\alpha]_D^{15} = -77.5$ (*c* 0.4, $CHCl_3$). IR (film): *v* = 3186, 2976, 2927, 2863, 1711, 1694, 1681, 1472, 1454, 1367 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 (br s, 9H, *t*-Boc), 1.50, 1.65 (2s, 3H, CH_3–Thy.), 2.24 [ddd, *J* = 13.5, 8.0, 5.0 Hz, 1H, C(2′)–H], 2.54 [dd, *J* = 13.5, 7.0 Hz, 1H, C(2′)–H], 3.65 [dd, *J* = 5.0, 2.5 Hz, 1H, C(5′)–H], 3.25 [m, 0.3H, C(5′)–H, C(4′)–H, C(3′)–H,

min.], 4.08 [d, $J = 5.0$ Hz, 0.9H, C(3′)–H, maj.], 4.03, 4.17 [2br s, 1.8H, C(6′)–H, C(4′)–H, maj.], 4.52 (d, $J = 11.0$ Hz, 1H, OCH_2Ph), 4.54 (d, $J = 11.0$ Hz, 1H, OCH_2Ph), 4.56 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 4.60 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 6.35 [dd, $J = 7.0$, 8.0 Hz, 1H, C(1′)–H], 7.25, 7.39 (m, 10H, Ph), 8.48 [br s, 0.8H, C(6)–H, maj.], 8.56 [d, $J = 4.5$ Hz, 0.2H, C(6)–H, min.] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.9$, 28.1, 29.6, 37.7, 64.4, 68.5, 70.8, 70.4, 73.5, 78.7, 81.5, 110.6, 127.4, 127.5, 127.6, 127.9, 128.0, 128.6, 136.1, 137.3, 137.4, 150.3, 154.2, 163.6 ppm. ESI-MS: *m/z* (%) = 423 (100), 445 (76), 544 (43) ($M+Na^+$). ESI-HRMS: calcd for [$C_{29}H_{35}N_3O_6+H^+$]: 522.2597; found: 522.2592.

α-Anomer **31**: $[\alpha]_D^{15} = -1.3$ (*c* 0.4, $CHCl_3$). IR (film): $\nu = 3186$, 2976, 2927, 2863, 1711, 1694, 1681, 1472, 1454, 1367 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.45$ (br s, 9H, *t*-Boc), 1.50, 1.65 (2s, 3H, CH_3–Thy.), 2.10 [2d, $J = 15.0$ Hz, 1H, C(2′)–H], 2.66 [ddd, $J = 15.0$, 8.5, 5.5 Hz, 0.3H, C(2′)–H, min.], 2.76 [ddd, $J = 15.0$, 8.5, 5.5 Hz, 0.7H, C(2′)–H, maj.], 3.48 [m, 0.2H, C(5′)–H, C(4′)–H, min.], 3.58–3.66 [m, 1.8H, C(5′)–H, C(4′)–H, maj.], 3.69 [dd, $J = 5.5$, 5.5 Hz, 0.8H, C(5′)–H, maj.], 4.13 [d, $J = 5.5$ Hz, 0.8H, C(3′)–H, maj.], 4.17 [d, $J = 5.5$ Hz, 0.2H, C(3′)–H, min.], 4.21 [d, $J = 5.5$ Hz, 0.2H, C(5′)–H, maj.], 4.45 (d, $J = 11.0$ Hz, 1H, OCH_2Ph), 4.47 (d, $J = 11.0$ Hz, 1H, OCH_2Ph), 4.50 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 4.54 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 6.25 [d, $J = 8.5$ Hz, 1H, C(1′)–H], 7.22–7.38 (m, 10H, Ph), 8.60 [br s, 0.2H, C(6)–H, min.], 8.72 [s, 0.8H, C(6)–H, maj.] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 12.1$, 29.6, 28.1, 38.0, 64.5, 68.0, 68.5, 70.9, 73.4, 79.4, 81.6, 109.7, 127.4, 127.5, 127.7, 127.8, 128.0, 128.5, 136.9, 137.1, 137.8, 150.6, 152.7, 163.7 ppm. ESI-MS: *m/z* (%) = 423 (100), 445 (76), 544 (43) ($M+Na^+$). ESI-HRMS: calcd for [$C_{29}H_{35}N_3O_6+H^+$]: 522.2597; found: 522.2598.

4.20. (1′*S*,3′*S*,4′*R*)-4′-*tert*-Butoxyamido-2′-deoxythymidine 6b

To 18 mg of 20% Pd/C (18 mg) was added a solution of **30** (26 mg, 0.05 mmol) in 3 mL of 95% ethanol. The mixture was hydrogenated under 1 atm hydrogen pressure and stirred at room temperature for 9 h. The mixture was filtered through Celite and the filtrate evaporated in vacuo. Flash chromatography of the residue using ethyl acetate as an eluent afforded **6b** (14 mg, 85%) as a white foam. $[\alpha]_D^{20} = -91.4$ (*c* 1.1, MeOH). IR (KBr): $\nu = 3390$, 2924, 1684, 1473, 1392, 1369, 1267, 1162, 1038 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.38$ (br s, 9H, Boc), 1.88 (s, 3H, CH_3–Thy.), 2.30 [m, 1.8 H, C(2′)–H, maj.], 2.65 [d, $J = 9.5$ Hz, 0.2H, C(2′)–H, min.], 3.78 [m, 1.4H, C(5′)–H, maj.], 3.81 [d, $J = 2.5$ Hz, 0.6H, C(5′)–H, min.], 3.93 [d, $J = 9.5$ Hz, 0.5H, C(4′)–H], 3.95 [d, $J = 9.5$ Hz, 0.5H, C(4′)–H], 4.34 [br s, 1H, C(3′)–H], 6.30 [br s, 1H, C(1′)–H], 8.07 [br s, 1H, C(6)–H] ppm. ^{13}C NMR (125 MHz, CD_3OD): $\delta = 12.6$, 28.6, 40.9, 61.6, 62.5, 70.3, 72.5, 82.5, 111.6, 138.5, 152.7, 156.2, 166.5 ppm. ESI-MS: *m/z* (%) = 364 (100) ($M+Na^+$). ESI-HRMS: calcd for [$C_{15}H_{23}N_3O_6+H^+$]: 342.1658; found: 342.1659.

4.21. (1′*R*,3′*S*,4′*R*)-4′-*tert*-Butoxyamido-2′-deoxythymidine 6c

To 13 mg of 20% Pd/C (13 mg) was added a solution of **31** (18 mg, 0.034 mmol) in 3 mL of 95% ethanol. The mixture was hydrogenated under 1 atm hydrogen pressure and stirred at room temperature for 78 h. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. Flash chromatography of the residue using ethyl acetate as an eluent afforded **6c** (10 mg, 85%) as a colorless oil. $[\alpha]_D^{20} = +6.6$ (*c* 0.9, MeOH). IR (film): $\nu = 3390$, 2924, 1684, 1473, 1392, 1369, 1267, 1162, 1038 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): 1.38 (br s, 9H, *t*-Boc), 1.87 [m, 3.5H, C(2′)–H, CH_3–Thy., maj.], 1.91 [m, 0.5H, C(2′)–H, CH_3–Thy., min.], 2.71 [ddd, $J = 14.0$, 8.5, 5.0 Hz, 0.3H, C(2′)–H, min.], 2.76 [ddd, $J = 14.0$, 8.5, 5.0 Hz, 0.7H, C(2′)–H, maj.], 3.58–3.71 [m, 2H, C(5′)–H], 3.95 [m, 0.3H, C(4′)–H, min.], 4.01 [t, $J = 3.5$ Hz, 0.7H, C(4′)–H, maj.], 4.35 [d, $J = 5.0$ Hz, 0.7H, C(3′)–H], 4.37 [d, $J = 5.0$ Hz, 0.3H, C(3′)–H], 6.13 [d, $J = 8.5$ Hz, 0.3H, C(1′)–H], 6.18 [d, $J = 8.5$ Hz, 0.7H, C(1′)–H], 7.63 [s, 0.3H, C(6)–H, min.], 7.82 [s, 0.7H, C(6)–H, maj.] ppm. ^{13}C NMR (125 MHz, CD_3OD): $\delta = 12.6$, 28.5, 28.6, 40.6, 41.4, 61.1, 62.0, 70.6, 71.1, 72.8, 73.8, 82.6, 82.7, 110.2, 110.7, 138.9, 139.4, 152.9, 154.6, 166.6 ppm. ESI-MS: *m/z* (%) = 364 (100) ($M+Na^+$). ESI-HRMS: calcd for [$C_{15}H_{23}N_3O_6+H^+$]: 342.1659; found: 342.1658.

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