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Lipase-mediated synthesis of enantiomeric 2,5,6-trideoxy-2,5-iminohexitols☆

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Dedicated to Professor Vicente Gotor on the occasion of his 60th anniversary

ABSTRACT

Syntheses of 2,5,6-trideoxy-2,5-imino-D-alditol (**2**, 6-deoxy-DADP) and its enantiomer (**3**) from tri-orthogonally protected derivatives of DADP have been developed employing lipase-mediated kinetic desymmetrization and protecting group manipulations. Thus, and as an example, the starting DADP derivative (**4**) was transformed into a new symmetrical 2,5-bis(hydroxymethyl)pyrrolidine (**6**) by sequential N-protection and bis-O-desilylation. The lipase-mediated desymmetrization of **6** was best carried out under acetylation conditions to give (2*R*)-acetyloxymethyl derivative **7**. The absolute configuration and ee of **7** were unambiguously established by chemical correlation with a homochiral sample. Compound **7** was straightforwardly transformed into the target 2,5,6-trideoxy-2,5-iminohexitol **3**.

1. Introduction

Several 5-methylpyrrolidine-triols (**1**) of the type displayed in Figure 1 show potent inhibitory activity versus glycosidases in general[2] as well as α-L-fucosidases[3] in particular. They are also rather weak α-[1,3]-fucosyl-transferase inhibitor with a potent synergistic effect in the presence of GDP,[4] and have been prepared employing chemo-enzymatic[2,5] and chemical methods.[1,6]

In the case of 2,5,6-trideoxy-2,5-imino-D-allitol (**2**, 6-deoxy-DADP), only two chemical syntheses have been reported to date, one by Defoin et al.,[7] using a chiral 1,2-oxazines as starting material, and a second by Jäger and Palmer,[8] where a nitrone approach was the methodology of choice. To the best of our knowledge, no synthesis for *ent*-**2** (**3**) has been reported so far, and taking into account the influence of the chirality of this type of compounds on the specificity and inhibition potency,[9] we considered that the synthesis of **3** would be of interest for future enzymatic assays. From a synthetic point of view, the symmetrical character of (2*R*,3*R*,4*S*,5*S*)-3,4-dibenzyloxy-2,5-bis(*tert*-butyldiphenylsilyloxymethyl)pyrrolidine (**4**), recently prepared from the carbohydrate *chiral pool* (D-fructose) by our group,[10] makes it an appropriate starting material, suitable for further desymmetrization, to achieve the previously mentioned iminohexitol **3**. A lipase-mediated regioselective transesterification at the hydroxylmethyl groups on the corresponding *N*-protected, bis-*O*-desilylated derivative **6**, obtained from pyrrolidine **4**, was the methodology of choice in order to obtain the required chirality. Although chemo-enzymatic desymmetrizations have been described on different *N*-protected acyclic[11] and cyclic aminodiols,[12] to the best of our knowledge, the only example of this methodology applied to a pyrrolidinic skeleton has been done by Donohoe et al.[13] on a 2,5-bis(hydroxymethyl)-Δ^3-pyrroline. We described another approach of this method performed on more complex pyrrolidines together with the use of the resulting products in the enantiosynthesis of 2,5,6-trideoxy-2,5-iminohexitols **2** and **3**.

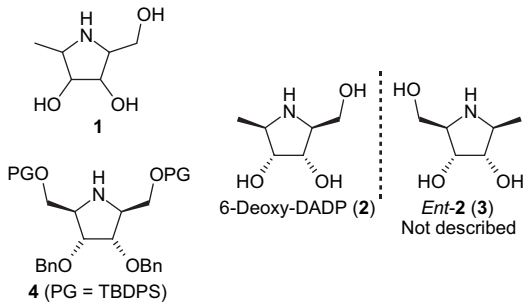

Figure 1. General structure for 5-methylpyrrolidine-triols (**1**), the enantiomers of 6-deoxy-DADP (**2** and **3**), and an orthogonally protected derivative (**4**) of 2,5-dideoxy-2,5-imino-D-allitol.

☆ Part VII: Polyhydroxylated pyrrolidines. For Part VI, see Ref. 1.

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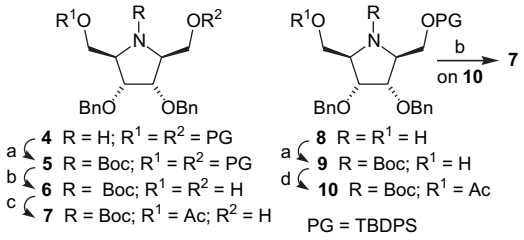
2. Results and discussion

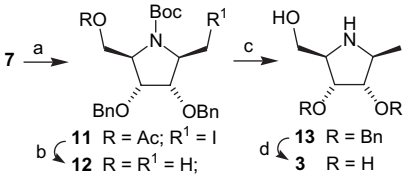
According to Scheme 1, compound **4** was transformed into its *N*-protected derivative **5** after reaction with di-*tert*-butyldicarbonate. Subsequently, bis-O-desilylation afforded (2*R*,3*R*,4*S*,5*S*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2,5-bis(hydroxylmethyl)pyrrolidine (**6**), which was subjected to reaction with vinyl acetate in the presence of Chirazyme® L-2, c.-f., C2, lyo from *Candida antarctica* lipase-B, at room temperature (rt). The chemo-enzymatic reaction caused desymmetrization yielding the (2*R*,3*R*,4*S*,5*S*)-2-acetyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-hydroxymethylpyrrolidine (**7**) isolated in an 81% yield with a 94% ee, determined by its rotatory power[14] $[\alpha]_{405}^{20}$ −15 (*c* 1) (see below).



Scheme 1. Desymmetrization of **4** and absolute configuration assignment of pyrrolidine **7**. Reagents and conditions: (a) $(t\text{-BuOCO})_2O$–TEA–DCM, rt; (b) TBAF·$3H_2O$–THF, rt; (c) vinyl acetate–TBME–Chirazyme® L-2, c.-f., C2, lyo, rt; (d) Ac_2O–DMAP (cat.)–Py, rt.

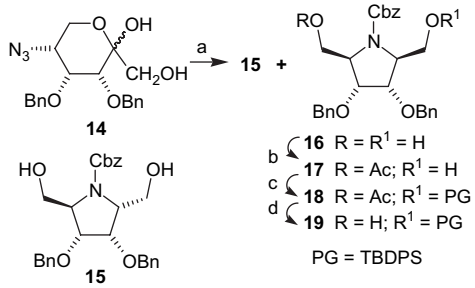
The absolute configuration of desymmetrized pyrrolidine **7** was easily established (Scheme 1 above) by chemical correlation through conventional N-protection of pyrrolidine **8**, previously described by our group,[10] as its *N*-Boc derivative (**9**) followed by acetylation to **10**. Final O-desilylation gave the homochiral **7**, which showed an $[\alpha]_{405}^{20}$ −16 (*c* 1).

Once the absolute configuration of pyrrolidine **7** was established, we continue to the final synthesis of *ent*-6-deoxy-DADP (**3**). According to the indications given in Scheme 2, reaction of (2*R*,3*R*,4*S*,5*S*)-2-acetyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-hydroxymethyl pyrrolidine (**7**) gave the corresponding 5-iodomethyl derivative **11** under Garegg's conditions.[15] Catalytic hydrogenation of **11** with Raney-nickel[16] caused dehalogenation[9d] concomitant with an O-deacetylation, probably due to the weak-basic conditions affording the 5-methylpyrrolidine **12**. Final *N*- and O-deprotection yielded the proposed *ent*-6-deoxy-DADP (**3**), whose spectroscopic data were in closed agreement with those previously reported[7,8] for its enantiomer **2**.



Scheme 2. Synthesis of *ent*-6-deoxy-DADP (**3**) from pyrrolidine **7**. Reagents and conditions: (a) I_2–Ph_3P–imidazole–THF, Δ; (b) H_2 (balloon)–Raney-Ni–MeOH–TEA, rt; (c) 50% TFA–DCM, rt; (d) concd HCl (drops)/10% Pd–C–H_2–MeOH, rt.

We were interested in two aspects of the above synthetic strategy. One was the influence of pyrrolidine N-protection on the desymmetrization process. The second was the possibility of using the 5-azido-5-deoxy-3,4-di-*O*-benzyl-D-fructose (**14**)[10] as precursor in the synthesis of the symmetric pyrrolidine **16**. Straightforward hydrogenation of **14** would lead us to pyrrolidine **16** in one single step shorting out the reaction sequence. As predicted, catalytic hydrogenation of **14** (see Scheme 3) afforded a mixture of 2,5-iminohexitols: D-*altro* (minor) and D-*allo* (major) that could be resolved after chemoselective N-protection to the Cbz derivatives **15** and **16**, respectively. Compound **16** was subjected to chemo-enzymatic transesterification causing its desymmetrization to 2′-*O*-acetyl derivative **17** whose structure was determined by chemical correlation, after O-silylation and subsequent O-deacetylation to pyrrolidine **19**, previously reported by our group.[9f] Comparison of their respective specific rotation indicated a 97% ee for desymmetrized pyrrolidine **17**.



Scheme 3. Synthesis of partially protected DADP (**19**) from a derivative of 5-azido-5-deoxy-D-fructose (**14**). Reagents and conditions: (a) (i) H_2–Raney-Ni–MeOH, rt; (ii) CbzCl–K_2CO_3–Me_2CO, rt; (b) vinyl acetate–TBME–Chirazyme® L-2, c.-f., C2, lyo, rt; (c) TBDPSCl–imidazole–DMF, rt; (d) MeOH–MeONa (cat.), rt.

To explain the formation of D-*altro* (minor) and D-*allo* (major) pyrrolidines, a proposed transition state is shown in Figure 2. The intermediate 5-aminohexulose **A**, produced after the reduction of N_3 function in **14**, reacts in a fast intramolecular process to give Δ^1-pyrroline intermediate **B**, which is finally hydrogenated in a high stereoselective manner to the major D-*allo* diastereomer.

Comment merits the high stereoselectivity found in the hydrogenation of Δ^1-pyrroline intermediate, where compound with the D-*allo* configuration was the major pyrrolidine isolated. Its stereoselective formation can be explained if the hydrogen addition takes place through the same α-face occupied by the substituent next to the N=C bond, giving a product with trans-disposition for the substituents at the C(2)–C(3) positions (see **TS** in Fig. 2). These results are according to ours and other authors.[5a,b,17]

Transformation of the orthogonally protected pyrrolidine **19** was accomplished as for **7** (see Scheme 4 above). Thus, **19** was subjected to OH→I interchange at C(5) to afford halogenated pyrrolidine **20** that was dehalogenated by catalytic hydrogenation, and in this case also produces the loss of the *N*-Cbz protecting group affording the 5-methylpyrrolidine **21**. Straightforward total deprotection of **21** gave the expected 6-deoxy-DADP (**2**), which showed analytical and spectroscopic data in total agreement with those reported in the literature.[7,8]

Finally, we also investigated the influence of *N*-Boc protection on the regioselectivity and enantioselectivity of the enzymatic transesterification reaction. To compare with the previous results, partially protected pyrrolidine **24**, obtained from **23**,[18] was subjected to the same transesterification conditions used for **6** (Scheme 5). The reaction afforded solely the monoacetylated pyrrolidine **25** whose structure was identical to that obtained by acetylation and subsequent O-desilylation of the well known pyrrolidine **26**.[18]

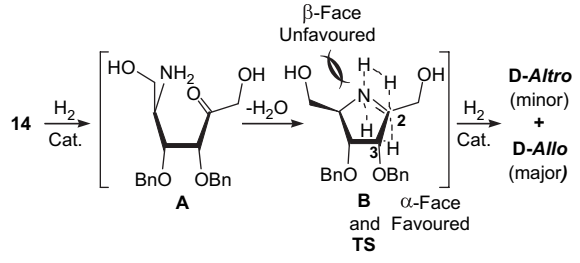
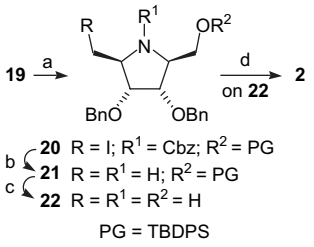
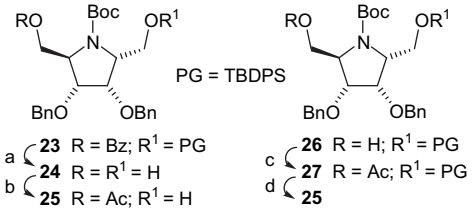


Figure 2. Formation of pyrrolidines from 5-azido-5-deoxy-D-fructose derivative (**14**) and transition state (**TS**) for catalytic hydrogenation of intermediate Δ^1-pyrroline **B**.



Scheme 4. Synthesis of 6-deoxy-DADP (**2**) from **19**. Reagents and conditions: (a) I_2–Ph_3P–imidazole–THF, Δ; (b) H_2–Raney-Ni–TEA–MeOH, rt; (c) TBAF·$3H_2O$–THF, rt; (d) concd HCl (drops)/10% Pd–C–H_2–MeOH, rt.



Scheme 5. Chemo-enzymatic acetylation of a partially protected derivative of DALDP (**24**) and structural elucidation of its monoacetylated product (**25**). Reagents and conditions: (a) (i) TBAF·$3H_2O$–THF, rt, (ii) MeONa (cat.)–MeOH, rt; (b) vinyl acetate–TBME–Chirazyme® L-2, c.-f., C2, lyo, rt; (c) Ac_2O–DMAP(cat.)–Py, rt; (d) TBAF·$3H_2O$–THF, rt.

3. Conclusions

Desymmetrization of partially protected symmetric tetrahydroxylated pyrrolidine alkaloids by enzymatic transesterification seems to be an appropriated methodology for the synthesis of key intermediates in the preparation of 2,5,6-trideoxy-2,5-iminohexitols. The nature of the *N*-protecting groups does not appear to play an important role in the enzymatic process and the results show that during the transesterification reaction, it is the left-hand side hydroxymethyl group in **6**, **16** and **24**, which is always chosen for the catalysis. Nevertheless, more experiments on other models are required in order to confirm the scope of this methodology.

4. Experimental

4.1. General

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, ARX-400 and AMX-500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet and br, broad. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum One instrument and mass spectra were recorded with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured, unless otherwise stated, for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} alumnium sheets and detected by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR and HRMS (LSIMS).

*4.1.1. (2R,3R,4S,5S)-3,4-Dibenzyloxy-N-tert-butyloxycarbonyl-2,5-bis(tert-butyldiphenylsilyloxymethyl)pyrrolidine (**5**)*

A stirred solution of **4**[10] (1.77 g, 2.16 mmol) in anhydrous dichloromethane (DCM, 15 mL) was treated with TEA (0.6 mL, 4.32 mmol) and di-*tert*-butyl dicarbonate (706 mg, 3.24 mmol) at rt for 12 h. TLC (Et_2O–hexane, 1:1 v/v) then revealed the presence of a faster-running compound. The reaction mixture was quenched by the addition of MeOH (2 mL), and after 15 min was concentrated and subjected to column chromatography (Et_2O–hexane, 1:3 v/v) to afford pure **5** (1.95 g, 98%) as a white syrup. IR ν_{max}/cm^{-1} (neat): 3070 (aromatic), 1699 (CO, Boc) and 700 (aromatic); ^1H NMR (400 MHz): δ 7.55–7.26 (m, 30H, 6Ph), 4.61 and 4.45 (2d, *J*=12.5 Hz, CH_2Ph), 4.38 and 4.32 (2d, *J*=11.7 Hz, CH_2Ph), 4.15–3.72 (3m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.53 and 1.33 (2s, 9H, $OCMe_3$, two rotamer),[19] 0.98 and 0.94 (2s, 18H, $2SiCMe_3$, two rotamers); ^{13}C NMR (100 MHz, inter alia): δ 155.4 (CO, Boc), 79.9 ($OCMe_3$), 76.9 and 75.5 (C-3,4, two rotamers), 71.8 and 71.4 (CH_2Ph, two rotamers), 63.0 and 62.9 (C-2,5, two rotamers), 61.9 (C-2′,5′), 28.5 ($OCMe_3$), 27.1 ($SiCMe_3$), 19.5 and 19.4 ($SiCMe_3$, two rotamers). HRMS (LSIMS): *m*/*z* 942.4558 [M^++Na]. For $C_{57}H_{69}NO_6NaSi_2$ 942.4561 (deviation +0.3 ppm).

*4.1.2. (2R,3R,4S,5S)-3,4-Dibenzyloxy-N-tert-butyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine (**6**)*

To a stirred solution of **5** (1.9 g, 2.06 mmol) in THF (20 mL) was added TBAF·$3H_2O$ (2 g, 6.3 mmol) and the mixture was kept at rt for 6 h. TLC (Et_2O–hexane, 1:1 v/v) then showed a new slower-running compound. The mixture was concentrated to a residue that was partitioned into Et_2O and brine, the organic phase was separated and concentrated to a residue that was subjected to column chromatography ($Et_2O \rightarrow Et_2O$–MeOH, 20:1 v/v) to afford pure **6** (900 mg, 98%) as a colourless syrup. IR ν_{max}/cm^{-1} (neat): 3400 (OH), 3064 and 3031 (aromatic), 1694 (CO, Boc), 737 and 698 (aromatic); ^1H NMR (400 MHz): δ 7.33–7.28 (m, 10H, 2Ph), 4.55 (br s, 4H, $2CH_2Ph$), 4.13–3.50 (m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, inter alia): δ 156.2 (CO, Boc), 81.0 ($OCMe_3$), 78.3 and 77.8 (C-3,4, two rotamers), 72.1 ($2CH_2Ph$), 66.1 (C-2′,5′), 63.9 (C-2,5), 28.6 (CMe_3). HRMS (LSIMS): *m*/*z* 466.2203 [M^++Na]. For $C_{25}H_{33}NO_6Na$ 466.2206 (deviation +0.6 ppm).

*4.1.3. (2R,3R,4S,5S)-2-Acetyloxymethyl-3,4-dibenzyloxy-N-tert-butyloxycarbonyl-5-hydroxymethylpyrrolidine (**7**)*

To a gently stirred solution of **6** (500 mg, 1.13 mmol) and vinyl acetate (520 μL, 5 equiv) in *tert*-butyl methyl ether (TBME, 10 mL) was added Chirazyme® L-2, c.-f. C2. lyo (150 mg), and the mixture maintained at rt. The reaction was monitored by TLC (Et_2O) and after 72 h revealed the absence of **6** and the presence of a faster-running compound. The enzyme was removed by filtering, thoroughly washed with ether, and the filtrate and washings concentrated to a residue that was subjected to chromatography (Et_2O–hexane, 1:1 v/v) to give **7** (445 mg, 81%, ee 94%) as a colourless syrup. $[\alpha]_D^{27}$ −7, $[\alpha]_{405}^{27}$ −15 (*c* 1); IR ν_{max}/cm^{-1} (neat): 3471 (OH), 3064 and 3031 (aromatic), 1745 (CO, Ac), 1697 (CO, Boc), 738 and 698 (aromatic); ^1H NMR (400 MHz): δ 7.33 (br s, 10H, 2Ph), 4.60–3.40 (5m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.97 (s, 3H, Ac), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, inter alia): δ 170.5 (*C*OMe), 156.6 (CO, Boc), 81.6 (CMe_3), 75.9 (C-3,4), 72.1 ($2CH_2Ph$), 66.1, 64.7 and 62.9 (C-2′5′, two rotamers), 63.6 and 61.2 (C-2,5), 28.5 (CMe_3), 21.0 (CO*Me*). HRMS (LSIMS): *m*/*z* 508.2311 [M^++Na]. For $C_{27}H_{35}NO_7Na$ 508.2311 (deviation 0.0 ppm).

*4.1.4. (2S,3S,4R,5R)-3,4-Dibenzyloxy-N-tert-butyloxycarbonyl-2-tert-butyldiphenylsilyloxymethyl-5-hydroxymethylpyrrolidine (**9**)*

An ice-water cooled and stirred solution of **8**[10] (247 mg, 0.42 mmol) in anhydrous DCM (10 mL) was treated with TEA (118 μL, 0.85 mmol) and di-*tert*-butyl dicarbonate (140 mg, 0.64 mmol) at rt for 24 h. TLC (Et_2O) then revealed the presence of a faster-running compound. The reaction mixture was quenched by the addition of MeOH (0.5 mL), and after 15 min was concentrated and subjected to column chromatography (Et_2O–hexane, 1:1 v/v) to afford pure **9** (205 mg, 71%) as a colourless syrup. $[\alpha]_D^{25}$ +11.4 (*c* 1); IR ν_{max}/cm^{-1}

(neat): 3441 (OH), 3070 and 3031 (aromatic), 1694 and 1674 (CO, Boc), 740 and 700 (aromatic); ^{1}H NMR (400 MHz): δ 7.60–7.32 (2m, 20H, 4Ph), 4.53–3.57 (6m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.33 (s, 9H, OCMe$_3$), 1.03 (s, 9H, SiCMe$_3$); ^{13}C NMR (100 MHz, inter alia): δ 156.8 (CO, Boc), 81.0 (O*C*Me$_3$), 76.7 and 76.0 (C-3,4), 70.8 (*C*H$_2$Ph), 65.4 and 63.1 (C-2′,5′), 64.4 and 63.9 (C-2,5), 27.3 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 19.4 (SiC*Me*$_3$). HRMS (LSIMS): *m*/*z* 704.3386 [M$^+$+Na]. For $C_{41}H_{51}NO_6NaSi$ 704.3383 (deviation −0.3 ppm).

4.1.5. Synthesis of **7** from **9**

Conventional acetylation of compound **9** (250 mg, 0.37 mmol) in dry pyridine (5 mL) with acetic anhydride (0.5 mL, 5.3 mmol) and DMAP (50 mg) afforded after usual work-up and column chromatography (Et$_2$O–hexane, 1:1 v/v) presumably (2*R*,3*R*,4*S*,5*S*)-2-acetyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-*tert*-butyldiphenylsilyloxymethylpyrrolidine (**10**, 215 mg, 81%) that was not investigated but subjected to O-desilylation in THF (10 mL) with TBAF·3H$_2$O (110 mg, 0.35 mmol) at rt for 12 h. Work-up of the reaction mixture as above gave after column chromatography (Et$_2$O) pure homochiral **7** (113 mg, 78%). $[\alpha]_D^{27}$ −8.8, $[\alpha]_{405}^{27}$ −16 (*c* 1.0).

4.1.6. (2R,3R,4S,5R)-2-Acetyloxymethyl-3,4-dibenzyloxy-N-tert-butyloxycarbonyl-5-iodomethylpyrrolidine (**11**)

To a solution of **7** (700 mg, 1.44 mmol) in dry THF (20 mL) were added Ph$_3$P (755 mg, 2.88 mmol), imidazole (392 mg, 5.76 mmol) and I$_2$ (731 mg, 2.88 mmol) at rt. The mixture was refluxed for 2 h. TLC (Et$_2$O) showed not starting material and the presence of a new compound. The solvent was evaporated, the residue redissolved in ether, washed with aqueous 10% $Na_2S_2O_3$ and brine and concentrated. Column chromatography (Et$_2$O–hexane, 1:3 v/v) of the residue gave **11** (690 mg, 82%) as a colourless syrup. $[\alpha]_D^{23}$ −9.3 (*c*, 1.2); IR ν_{max}/cm^{-1} (neat): 3064 and 3031 (aromatic), 1745 (CO, Ac), 1700 (CO, Boc), 738 and 699 (aromatic). ^{1}H NMR (500 MHz): δ 7.30–7.24 (m, 10H, 2Ph), 4.53–3.25 (6m, 12H, 2CH$_2$Ph, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.92 (s, 3H, Ac), 1.39 (s, 9H, CMe$_3$); ^{13}C NMR (125 MHz, inter alia): δ 170.5 (*C*OMe), 154.8 (CO, Boc), 81.2 (*C*Me$_3$), 79.7, 78.3, 76.4 and 74.9 (C-3,4, two rotamers), 72.0, 71.8 and 71.6 (2*C*H$_2$Ph, two rotamers), 63.0 and 62.6 (C-2′, two rotamers), 61.5, 60.9 and 60.3 (C-2,5, two rotamers), 28.5 (C*Me*$_3$), 21.1 (CO*Me*), 10.8 and 8.6 (C-5′, two rotamers). HRMS (LSIMS): *m*/*z* 618.1323 [M$^+$+Na]. For $C_{27}H_{34}INO_6Na$ 618.1329 (deviation +0.9 ppm).

4.1.7. (2R,3R,4S,5S)-3,4-Dibenzyloxy-N-tert-butyloxycarbonyl-2-hydroxymethyl-5-methylpyrrolidine (**12**)

To a solution of compound **11** (650 mg, 1.09 mmol) in MeOH (20 mL), triethylamine (TEA, 0.31 mL, 2.18 mmol) was added. The mixture was hydrogenated (balloon) over wet Raney-nickel (500 mg, Fluka) for 6 h. TLC (Et$_2$O–hexane, 3:1 v/v) then revealed the presence of a slower-running compound. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings were concentrated to a residue that was dissolved in dry methanol (10 mL). NaOMe–MeOH (2 N, 1 mL) was added and the mixture was stirred for 2 h. TLC (Et$_2$O–hexane, 3:1 v/v) then showed a slower-running compound. The reaction mixture was neutralized with AcOH and concentrated to a residue that was subjected to column chromatography (Et$_2$O–hexane, 1:2 v/v) to afford syrup **12** (437 mg, 94%). $[\alpha]_D^{25}$ +13 (*c* 1); IR ν_{max}/cm^{-1} (neat): 3437 (OH), 3064 and 3031 (aromatic), 1691 and 1669 (CO, Boc), 736 and 698 (aromatic); ^{1}H NMR (300 MHz): δ 7.37 (br s, 10H, 2Ph), 4.63–3.57 (3m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.50 (s, 9H, CMe$_3$), 1.20 (d, 3H, $J_{5,Me}$=6.3 Hz, Me-5); ^{13}C NMR (75 MHz, inter alia): δ 157.2 (CO, Boc), 138.2, 128.7, 128.2 and 128.1 (2CH$_2$Ph), 80.8 and 77.8 (*C*Me$_3$, C-3,4), 72.1 (2*C*H$_2$Ph), 65.8 (C-2′), 63.9 and 57.8 (C-2,5), 28.7 (C*Me*$_3$), 19.9 (Me-5). HRMS (LSIMS): *m*/*z* 450.2250 [M$^+$+Na]. For $C_{25}H_{33}NO_5Na$ 450.2256 (deviation +1.4 ppm).

4.1.8. (2R,3R,4S,5S)-3,4-Dibenzyloxy-2-hydroxymethyl-5-methylpyrrolidine (**13**)

Compound **12** (400 mg, 0.94 mmol) was dissolved in a 50% solution of TFA–DCM (25 mL) and the mixture was stirred at rt for 60 min. TLC (Et$_2$O) then revealed a non-mobile compound. The solvent was eliminated and the residue codistilled with toluene to a new residue that was dissolved in DCM and washed with aqueous 10% Na_2CO_3 and concentrated to a residue that was subjected to column chromatography (Et$_2$O–MeOH, 3:1 v/v) to afford **13** (246 mg, 80%) as a white solid. Mp 93–94 °C; $[\alpha]_D^{25}$ −15.2 (*c* 1); IR ν_{max}/cm^{-1} (neat): 3243 (OH), 3065, 3031, 735 and 697 (aromatic); ^{1}H NMR (300 MHz): δ 7.37 (br s, 10H, 2 Ph), 4.66 and 4.57 (2d, 2H, *J*=11.7 Hz, CH$_2$Ph), 4.65 and 4.59 (2d, 2H, *J*=11.7 Hz, CH$_2$Ph), 3.84 (t, 1H, *J*=4.7 Hz, H-3 or 4), 3.62–3.41 (2m, 5H, H-2,2′a,2′b,3 or 4,5), 2.53 (br s, 2H, OH and NH), 1.18 (d, 3H, $J_{5,Me}$=6.2 Hz, Me-5); ^{13}C NMR (75 MHz, inter alia): δ 138.5, 138.4, 128.6, 128.2, 128.1 and 127.9 (2Bn), 84.0 and 78.8 (C-3,4), 72.2 (2CH$_2$Ph), 62.8 (C-2′), 62.7 and 56.3 (C-2,5), 20.6 (Me-5). HRMS (LSIMS): *m*/*z* 350.1734. For $C_{20}H_{25}NO_3Na$ 350.1732 (deviation −0.6 ppm). Anal. calcd for $C_{20}H_{25}NO_3$: C 73.37, H 7.70, N 4.28; found: C 73.46, H 7.56, N 4.45.

4.1.9. (2R,3R,4S,5S)-3,4-Dihydroxy-2-hydroxymethyl-5-methylpyrrolidine (**3**, ent-6-deoxy-DADP)

A solution of **13** (205 mg, 0.63 mmol) in MeOH (10 mL) was acidified with concd HCl (0,2 mL) and hydrogenated at 60 psi over with 10% Pd–C (80 mg) for 24 h. The catalyst was filtered off and washed with MeOH. The mixture was neutralized with Amberlite IRA-400 (OH$^-$ form) and concentrated to a residue that was retained onto a column of Dowex® 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH (30 mL), water (30 mL) and then with 1 N NH$_4$OH (20 mL) to afford pure **3** (90 mg, 98%) as colourless syrup; $[\alpha]_D^{27}$ +1.9 (*c* 1.5, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4): δ 3.87 (dd, 1H, $J_{2,3}$=4.8, $J_{3,4}$=6.2 Hz, H-3), 3.68 (d, 2H, $J_{2,2'}$=4.4 Hz, H-2′,2′), 3.44 (t, 1H, $J_{4,5}$=7.0 Hz, H-4), 3.02 (q, 1H, H-2), 3.00 (quin, 1H, H-5), 1.24 (d, 3H, $J_{5,Me}$=6.6 Hz, Me-5); ^{13}C NMR (75 MHz, inter alia): δ 77.7 (C-4), 72.3 (C-3), 65.9 (C-2), 61.6 (C-2′), 58.3 (C-5), 17.1 (Me-5). MS (EI): *m*/*z* 116 (M$^+$−CH$_2$OH, 100%).

4.1.10. (2R,3R,4S,5S)-3,4-Dibenzyloxy-N-benzyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine (**16**)

Compound **14** (1.5 g, 2.41 mmol) in MeOH (20 mL) was hydrogenated at 60 psi over wet Raney-Ni (2 g) overnight. TLC (Et$_2$O–hexane, 1:1 v/v) then revealed the absence of starting material and the presence of a non-mobile compound. When TLC was performed with Et$_2$O–MeOH 2:1 v/v, two compounds of similar mobility were observed. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings were concentrated to a residue that was dissolved in dry acetone (15 mL) and the resulting solution treated with anhydrous K_2CO_3 (2.4 g) and benzyl chloroformate (575 μL, 3.37 mmol) at rt with stirring for 12 h. TLC (Et$_2$O–MeOH, 2:1 v/v) then showed the presence of two faster-running compounds. The reaction mixture was filtered and concentrated to a residue that was subjected to column chromatography (Et$_2$O–hexane, 5:1 v/v → Et$_2$O → Et$_2$O–MeOH, 20:1 v/v) to afford first (2*R*,3*R*,4*S*,5*R*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine (**15**, 90 mg, 8% from **14**) as a colourless syrup. $[\alpha]_D^{24}$ −21, $[\alpha]_{405}^{24}$ −53 (*c* 0.8); IR ν_{max}/cm^{-1} (neat): 3430 (OH), 3032 (aromatic), 1701 (CO, Cbz), 739 and 699 (aromatic); ^{1}H NMR (500 MHz): δ 7.30–7.20 (m, 15H, 3Ph), 5.25–3.30 (4m, 14H, 3CH$_2$Ph and H-2,2′a,2′b,3,4,5,5′a,5′b, two rotamers); ^{13}C NMR (125 MHz, inter alia): δ 156.0 (CO, Cbz), 77.6, 76.5, and 76.1 (C-3,4, two rotamers), 72.5 and 72.3 (2*C*H$_2$Ph), 67.8 (Cbz), 63.7, 62.8, 60.3 and 58.7 (C-2,5, two rotamers), 61.9, 61.2, 58.8 and 58.5 (C-2′,5′, two rotamer). HRMS (LSIMS): *m*/*z* 500.2055 [M$^+$+Na]. For $C_{28}H_{31}NO_6Na$ 500.2049 (deviation −1.2 ppm).

Eluted second was **16** (760 mg, 66% from **14**) as a colourless syrup. IR ν_{max}/cm^{-1} (neat): 3411 (OH), 3064 and 3032 (aromatic), 1682 (CO, Cbz), 737 and 698 (aromatic); ^1H NMR (500 MHz): δ 7.27–7.24 (m, 15H, 3Ph), 5.06 and 4.49 (2s, 6H, $3CH_2Ph$), 4.10–3.86 (m, 6H, H-2′a,2′b,3,4,5′a,5′b), 3.52 (br s, 2H, H-2,5); ^{13}C NMR (125 MHz, inter alia): δ 156.5 (CO, Cbz), 78.2 and 77.9 (C-3,4, two rotamers), 72.2 ($2CH_2Ph$), 67.7 (Cbz), 64.2 and 63.9 (C-2,5, two rotamers), 62.8 and 62.2 (C-2′,5′, two rotamers). HRMS (LSIMS): *m*/*z* 500.2045 [M^++Na]. For $C_{28}H_{31}NO_6Na$ 500.2049 (deviation +0.8 ppm).

4.1.11. (2R,3R,4S,5S)-2-Acetyloxymethyl-3,4-dibenzyloxy-N-benzyloxycarbonyl-5-hydroxymethylpyrrolidine (*17*)

To a gently stirred solution of **16** (760 mg, 1.59 mmol) and vinyl acetate (734 μL, 5 equiv) in TBME (15 mL) was added Chirazyme® L-2, c.-f. C2. lyo (200 mg), and the mixture maintained at rt with stirring. The reaction was monitored by TLC (Et_2O) and after 18 h revealed the absence of **16** and the presence of a faster-running compound. The enzyme was removed by filtering, thoroughly washed with ether and the filtrate and washings concentrated to a residue that was subjected to chromatography (Et_2O–hexane, 1:2 v/v→Et_2O) to afford pure **17** (620 mg, 75%) as a colourless thick syrup. $[\alpha]_D^{24}$ −8, $[\alpha]_{405}^{28}$ −19.6 (*c* 1.1); IR ν_{max}/cm^{-1} (neat): 3467 (OH), 3064 and 3032 (aromatic), 1743 (CO, Ac),1702 (CO, Cbz), 737 and 698 (aromatic); ^1H NMR (400 MHz): δ 7.36 (br s, 15H, 3Ph), 4.64–4.52 (m, 4H, $2CH_2Ph$), 4.28–3.59 (m, 10H, CH_2Ph, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.94 (br s, 3H, Ac). HRMS (LSIMS): *m*/*z* 542.2159 [M^++Na]. For $C_{30}H_{33}NO_7Na$ 542.2155 (deviation −0.9 ppm).

4.1.12. (2R,3R,4S,5S)-2-Acetyloxymethyl-3,4-dibenzyloxy-N-benzyloxycarbonyl-5-tert-butyldiphenylsilyloxymethyl pyrrolidine (*18*)

To a stirred solution of **17** (590 mg, 1.13 mmol) in dry DMF (10 mL) were added imidazole (165 mg, 2.43 mmol) and *tert*-butylchlorodiphenylsilane (500 μL, 1.9 mmol) and the mixture was left at rt overnight. TLC (Et_2O–hexane, 1:1 v/v) then showed a faster-running compound. MeOH (1 mL) was added and after 15 min the reaction mixture was diluted with water (30 mL) and extracted with ether (3×15 mL), then concentrated to a residue that was subjected to chromatography (Et_2O–hexane, 1:2 v/v→1:1 v/v) to afford **18** (710 mg, 82%) as a colourless syrup. $[\alpha]_D^{24}$ +29 (*c* 1); IR ν_{max}/cm^{-1} (neat): 3069 and 3032 (aromatic), 1747 (CO, Ac), 1699 (CO, Cbz), 741 and 698 (aromatic); ^1H NMR (400 MHz): δ 7.61–7.29 (m, 25H, 5Ph), 5.20–3.60 (3m, 14H, $3CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b, two rotamers), 1.82 and 1.74 (2br s, 3H, Ac, two rotamers), 1.06 (br s, 9H, CMe_3); ^{13}C NMR (100 MHz, inter alia): δ 170.5 (*C*OMe), 155.7 (CO, Cbz), 77.1, 76.3, 76.0 and 75.3 (C-3,4, two rotamers), 71.9 ($2CH_2Ph$), 67.4 and 62.1 (Cbz, C-2′,5′), 63.5, 63.0, 60.4 and 60.0 (C-2,5, two rotamers), 27.1 (C*Me*$_3$), 20.7 (CO*Me*), 19.5 (*C*Me$_3$). HRMS (LSIMS): *m*/*z* 780.3339 [M^++Na]. For $C_{46}H_{51}NO_7NaSi$ 780.3333 (deviation −0.8 ppm).

4.1.13. (2S,3S,4R,5R)-3,4-Dibenzyloxy-N-benzyloxycarbonyl-2-tert-butyldiphenylsilyloxymethyl-5-hydroxymethylpyrrolidine (*19*)

Conventional Zemplen deacetylation of **18** (695 mg, 0.91 mmol) in anhydrous MeOH (15 mL) with 2 N MeONa (0.5 mL) for 12 h gave after usual work-up and column chromatography (Et_2O–hexane, 1:1 v/v→Et_2O) pure **19** (576 mg, 86%, ee 97%) as a colourless syrup, which had spectroscopic data in total agreement with those previously reported.[9f] $[\alpha]_D^{24}$ +9.7 (*c* 1) [lit.[9f] $[\alpha]_D^{25}$ +10 (*c* 1.8)].

4.1.14. (2S,3S,4R,5S)-3,4-Dibenzyloxy-N-benzyloxycarbonyl-2-tert-butyldiphenylsilyloxymethyl-5-iodomethylpyrrolidine (*20*)

To a solution of **19** (630 mg, 0.88 mmol) in dry THF (15 mL) were added Ph_3P (482 mg, 1.76 mmol), imidazole (240 mg, 3.52 mmol) and I_2 (448 mg, 1.76 mmol) at rt. The mixture was refluxed for 2 h. TLC (Et_2O–hexane, 1:1 v/v) then showed the end of the reaction and the presence of a new compound. The solvent was evaporated, the residue redissolved in DCM, washed with aqueous 10% $Na_2S_2O_3$ and brine and concentrated. Column chromatography (Et_2O–hexane, 1:1 v/v) of the residue gave **20** (690 mg, 95%) as a colourless syrup. $[\alpha]_D^{23}$ +19 (*c*, 1); IR ν_{max}/cm^{-1} (neat): 3068 and 3031 (aromatic), 1709 (CO, Cbz), 739 and 699 (aromatic). HRMS (LSIMS): *m*/*z* 848.2242 [M^++Na]. For $C_{44}H_{48}INO_5NaSi$ 848.2244 (deviation +0.3 ppm).

4.1.15. (2S,3S,4R,5R)-3,4-Dibenzyloxy-2-tert-butyldiphenylsilyloxymethyl-5-methylpyrrolidine (*21*)

To a solution of compound **20** (680 mg, 0.82 mmol) in MeOH (15 mL), TEA (0.23 mL, 1.64 mmol) was added. The mixture was hydrogenated at 60 psi over wet Raney-nickel (500 mg, Fluka) for 20 h. TLC (Et_2O–hexane, 1:1 v/v) then revealed the presence of a slower-running compound. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings were concentrated to a residue that was subjected to column chromatography (Et_2O–hexane, 2:1 v/v) to afford colourless syrup **21** (400 mg, 86%). $[\alpha]_D^{24}$ +29.1 (*c* 1.4); IR ν_{max}/cm^{-1} (neat) 3360 (NH), 3069, 3030, 739 and 700 (aromatic); ^1H NMR (300 MHz): δ 7.68–7.33 (2m, 10H, 2Ph), 4.66 and 4.55 (2d, 2H, *J*=12.0 Hz, CH_2Ph), 4.56 (s, 2H, CH_2Ph), 3.88 (t, 1H, *J*=4.7 Hz, H-3), 3.76 (dd, 1H, $J_{2,2'a}$=3.8 Hz, $J_{2'a,2'b}$=10.6 Hz, H-2′a), 3.71 (dd, 1H, $J_{2,2'b}$=4.1 Hz, H-2′b), 3.41–3.33 (m, 3H, H-2,4,5), 1.66 (br s, 1H, NH), 1.23 (d, 3H, $J_{5,Me}$=5.9 Hz, Me-5), 1.08 (s, 9H, CMe_3); ^{13}C NMR (75 MHz, inter alia): δ 84.6 (C-4), 78.6 (C-3), 72.2 and 71.9 (2 *C*H_2Ph), 64.5 (C-2′), 64.2 (C-2), 56.8 (C-5), 27.2 (C*Me*$_3$), 19.7 (Me-5), 19.5 (*C*Me$_3$). HRMS (LSIMS): *m*/*z* 566.3093 [M^++H]. For $C_{36}H_{44}NO_3$ 566.3090 (deviation −0.4 ppm).

4.1.16. (2S,3S,4R,5R)-3,4-Dibenzyloxy-2-hydroxymethyl-5-methylpyrrolidine (*22*)

To a stirred solution of **21** (370 mg, 0.65 mmol) in THF (15 mL) was added TBAF·$3H_2O$ (310 mg, 0.98 mmol) and the mixture was kept at rt for 16 h. TLC (Et_2O) then showed a new compound of lower mobility. The mixture was concentrated to a residue that was subjected to column chromatography (Et_2O→Et_2O–MeOH, 10:1 v/v) to yield impure **22** that was retained onto a column of Dowex® 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **22** (200 mg, 93%) as a white solid. Mp 96–98 °C; $[\alpha]_D^{25}$ +15.1 (*c* 1.1). The spectroscopic data were identical to that of the above enantiomer (−)-**13**.

4.1.17. (2S,3S,4R,5R)-3,4-Dihydroxy-2-hydroxymethyl-5-methyl-pyrrolidine [*2*, (−)-6-deoxy-DADP]

A solution of **22** (190 mg, 0.58 mmol) in MeOH was acidified with concd HCl and hydrogenated at 60 psi with 10% Pd–C (80 mg) for 16 h. The catalyst was filtered off and washed with MeOH. The mixture was neutralized with Amberlite IRA-400 (OH^- form), the resin filtered off, washed with MeOH and the filtrate and washing concentrated to a residue that was retained onto a column of Dowex® 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **2** (72 mg, 85%) as colourless syrup. $[\alpha]_D^{30}$ −1.7 (*c* 1, MeOH) [lit.[7] $[\alpha]_D^{20}$ −2 (*c* 1, MeOH), lit.[8] $[\alpha]_D^{20}$ −1 (*c* 1.5, MeOH)], which had analytical and spectroscopic data in accordance to those previously reported.[7,8]

4.1.18. (2R,3R,4S,5R)-3,4-Dibenzyloxy-N-tert-butyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine (*24*)

To a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-benzoyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-*tert*-butyldiphenylsilyloxymethylpyrrolidine (**23**)[18] (3.34 g, 4.26 mmol) in THF (20 mL) was added TBAF·$3H_2O$ (2 g, 6.4 mmol) and the mixture was kept at rt until disappearance of the starting material for 2 days. TLC (Et_2O–hexane, 1:2 v/v) then showed two new slower-running compounds,

probably **24** and its 2′-*O*-benzoyl derivative. MeONa solution in MeOH (2 N, 2 mL) was added and the reaction monitored until only **24** was observed. The reaction mixture was neutralized with acetic acid and concentrated to a residue that was subjected to column chromatography (Et_2O) to afford pure **24** (1.74 g, 92%) as a colourless syrup. $[\alpha]_D^{26}$ −42 (*c* 1.1); IR ν_{max}/cm^{-1} (neat): 3428 (OH), 3064 and 3032 (aromatic), 1694 (CO, Boc), 738 and 699 cm^{-1} (aromatic); ^1H NMR (400 MHz): δ 7.40 (br s, 10H, 2Ph), 4.81–3.69 (2m, 12H, $2CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, inter alia): δ 155.8 (CO, Boc), 81.26 (CMe_3), 79.1, 77.7 and 77.4 (C-3,4, two rotamers), 72.4 and 72.2 ($2CH_2Ph$), 64.6 and 60.0 (C-2,5), 64.3, 62.7, 60.8 and 59.2 (C-2′,5′, two rotamers), 28.6 (CMe_3). HRMS (LSIMS): *m*/*z* 466.2206 [M^++Na]. For $C_{25}H_{33}NO_6Na$ 466.2206 (deviation −0.1 ppm).

4.1.19. (2*R*,3*R*,4*S*,5*R*)-2-Acetyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-hydroxymethylpyrrolidine (**25**)

To a gently stirred solution of **24** (415 mg, 0.94 mmol) and vinyl acetate (500 μL, 5 equiv) in TBME (15 mL) was added Chirazyme® L-2, c.-f. C2. lyo (160 mg) and the mixture maintained at rt for 3 days. The reaction was monitored by TLC (Et_2O) and after 72 h revealed the absence of **24** and the presence of a faster-running compound. The enzyme was removed by filtering, thoroughly washed with ether and the filtrate and washings concentrated to a residue that was subjected to chromatography (Et_2O–hexane, 1:1 v/v) to give **25** (315 mg, 69%) as a colourless syrup. $[\alpha]_D^{25}$ −26, $[\alpha]_{405}^{25}$ −57 (*c* 1); IR ν_{max}/cm^{-1} (neat): 3462 (OH), 3064 and 3031 (aromatic), 1746 (CO, Ac), 1696 (CO, Boc), 738 and 699 (aromatic); ^1H NMR (400 MHz): δ 7.39–7.29 (m, 10H, 2Ph), 4.80–3.82 (2m, 12H, $2CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.95 and 1.94 (2br s, 3H, Ac, two rotamers), 1.51 and 1.50 (2 s, 9H, CMe_3, two rotamers); ^{13}C NMR (100 MHz, inter alia): δ 170.5 and 170.4 (*C*OMe, two rotamers), 155.0 and 154.2 (CO, Boc, two rotamers), 81.3 and 81.2 (CMe_3, two rotamers), 78.6, 77.2 and 76.6 (C-3,4, two rotamers), 72.8, 72.4 and 72.1 ($2CH_2Ph$, two rotamers), 63.2, 62.8, 61.2 and 59.3 (C-2′,5′, two rotamers), 61.1, 60.8 and 59.5 (C-2,5, two rotamers), 28.6 (CMe_3), 20.9 (CO*Me*). HRMS (LSIMS): *m*/*z* 508.2316 [M^++Na]. For $C_{27}H_{35}NO_7Na$ 508.2311 (deviation −1 ppm).

4.1.20. (2*R*,3*R*,4*S*,5*R*)-2-Acetyloxymethyl-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5-*tert*-butyldiphenylsilyloxymethylpyrrolidine (**27**)

Conventional acetylation of (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2-*tert*-butyldiphenylsilyloxymethylpyrrolidine[18] (**26**, 300 mg, 0.44 mmol) in dry pyridine (5 mL) with acetic anhydride (0.5 mL, 5.3 mmol) and DMAP (50 mg) afforded after usual work-up and column chromatography (Et_2O–hexane, 1:2 v/v) pure **27** (270 mg, 85%). $[\alpha]_D^{28}$ +18 (*c* 1.1); IR ν_{max}/cm^{-1} (neat): 3069 and 3031 (aromatic), 1746 (CO, Ac), 1698 (CO, Boc), 738 and 700 (aromatic); ^1H NMR (300 MHz): δ 7.80–7.30 (2m, 20H, 4Ph), 4.90–3.75 (m, 12H, $2CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.88 (s, 3H, Ac), 1.33 (s, 9H, $OCMe_3$), 1.11 (s, 9H, $SiCMe_3$); ^{13}C NMR (75 MHz, inter alia): δ 170.6 (CO, Ac), 154.1 and 153.5 (CO, Boc, two rotamers), 80.5 ($OCMe_3$), 80.7, 79.3, 77.8 and 77.1 (C-3,4, two rotamers), 72.7 ($2CH_2Ph$), 63.6 and 62.4 (C-2′,5′), 60.4 (C-2,5), 28.5 ($OCMe_3$), 27.2 ($SiCMe_3$), 20.9 (CO*Me*), 19.4 ($SiCMe_3$). HRMS (LSIMS): *m*/*z* 746.3593 [M^++Na]. For $C_{43}H_{53}NO_7NaSi$ 746.3591 (deviation −2.6 ppm).

4.1.21. Synthesis of **25** from **27**

To a stirred solution of **27** (230 mg, 0.32 mmol) in THF (10 mL) was added TBAF·$3H_2O$ (130 mg, 0.41 mmol) and the mixture was kept at rt for 14 h. TLC (Et_2O–hexane, 1:2 v/v) then showed a new slower-running compound. The reaction mixture was concentrated and subjected to column chromatography (Et_2O–hexane, 1:3 → 1:1 v/v) to afford pure **25** (127 mg, 82%). $[\alpha]_D^{26}$ −28, $[\alpha]_{405}^{26}$ −59 (*c* 1.4).

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Supplementary data

^1H, ^{13}C and DEPT NMR spectra of *ent*-6-deoxy-DADP (**3**) (two pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.089.

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