Stereoselective syntheses of piperidinones and their modification by organometallic coupling reactions

Birgit Kranke and Horst Kunz*

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Dehydropiperidinones stereoselectively obtained from *N*-arabinosyl imines were iodinated at the enaminone structure. Knochel iodine–magnesium exchange afforded Grignard compounds of these piperidinone derivatives which reacted, either directly or after transmetalation to zinc or copper intermediates, with alkyl-, aryl- or acylhalides to give correspondingly substituted piperidinones. Stereoselective conjugate allyl cuprate addition to a thus obtained 5-allyl dehydropiperidinone and ring-closing metathesis of the product gave a hydroquinolinone containing three stereogenic centers.

Introduction

Numerous natural products feature the piperidine ring as an essential pharmacophoric motif. Due to various substitution patterns of piperidine compounds they exhibit a wide variety of pharmacological properties. Therefore, efficient stereoselective syntheses of highly functionalized piperidine derivatives are of major interest to medicinal chemistry.

Recently, we reported the stereoselective synthesis of 2-substituted *N*-arabinosyl dehydropiperidinones and their application in the construction of chiral 2,3-, 2,5- and 2,6-substituted piperidinones.[1] We here describe the extension of this chemistry to the preparation of 2,5-disubstituted piperidinones *via* iodine–magnesium exchange and its use for the introduction of a range of functionalities.

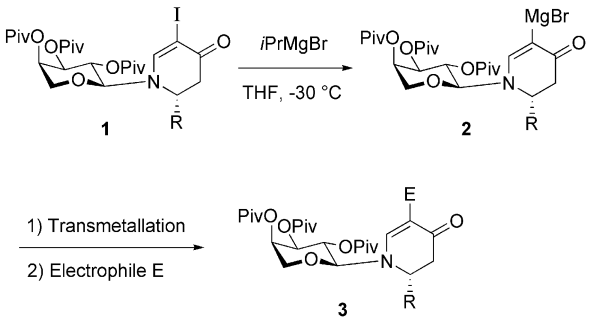
Results and discussions

The halogen–magnesium exchange[2] provides mild conditions for the synthesis of aryl,[3] alkenyl[4] and heterocyclic[5] magnesium species bearing sensitive reactive groups.

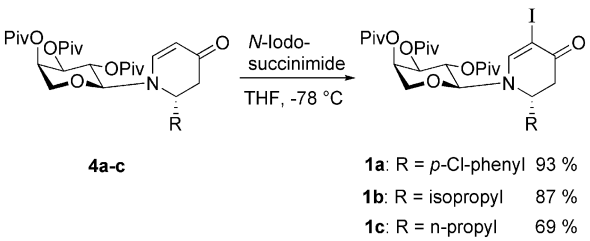
These organomagnesium derivatives on the one hand react with various electrophiles, and on the other hand, easily undergo metal–metal exchange reactions. During studies on the synthesis of functionalized piperidines we observed that 2-substituted *N*-arabinosyl-5-iodo-5,6-dehydropiperidin-4-ones **1** readily undergo iodine-magnesium exchange at −30 °C within one hour when treated with isopropyl magnesium bromide in THF. The corresponding Knochel–Grignard compounds **2** react with various electrophiles leading to 2,5-disubstituted piperidine derivatives of type **3** (Scheme 1).

The required halogenated dehydropiperidinones **1a**–**c** are accessible from dehydropiperidinones **4a**–**c**[1] by electrophilic iodination with *N*-iodosuccinimide exploiting the enamine moiety of **4** (Scheme 2).

Transformation of 5-iododehydropiperidinones **1a** and **1b** to 5-allyl dehydropiperidinone derivatives **5a** and **5b** was achieved

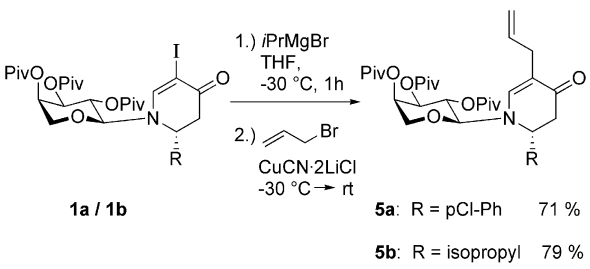


Scheme 1 Iodine magnesium exchange.



Scheme 2 Iodination.

via an iodine–magnesium exchange, subsequent transmetalation by treating the Grignard reagents with the THF-soluble copper salt CuCN·2LiCl,[6] and reaction of the formed cuprate with allylbromide (Scheme 3).

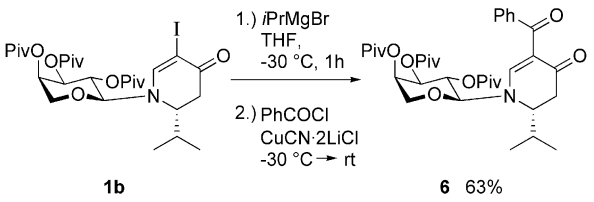


Scheme 3 Copper mediated allylation.

Benzoylation of dehydropiperidinone was carried out in a similar manner. After iodine–magnesium exchange and subsequent

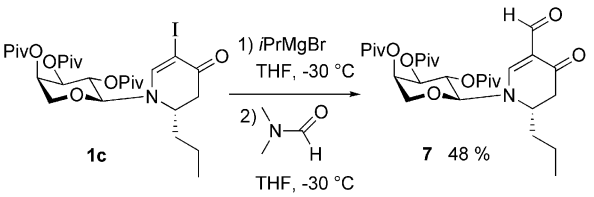
Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, 55128, Mainz, Germany. E-mail: hokunz@uni-mainz.de; Fax: +49 (0)6131 392 4786; Tel: +49 (0)6131 392 2334

transmetalation with CuCN·2LiCl, the intermediate copper compound was treated with benzoyl chloride affording 5-benzoyl derivative **6** (Scheme 4).



Scheme 4 Copper mediated benzoylation.

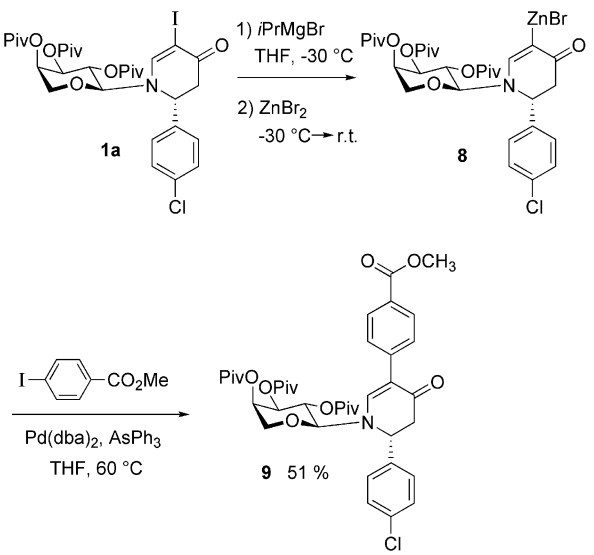
In contrast, formylation was achieved directly without preceding transmetalation of the formed Grignard reagent.[7] Thus, **1b** was first treated with *i*PrMgBr at −30 °C for 1 h followed by addition of *N*,*N*-dimethyl formamide leading to 5-formyl dehydropiperidinone **7** (Scheme 5).



Scheme 5 Formylation of the organomagnesium species.

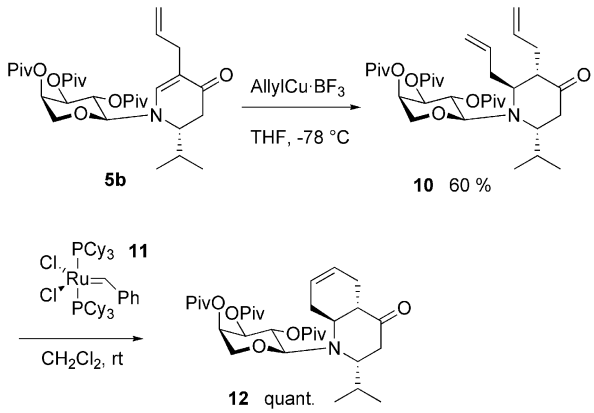
Furthermore, Grignard reagents of type **2** also undergo magnesium–zinc transmetalation leading to organozinc derivatives which are suitable for the application in Negishi cross-coupling[8] reactions.

Thus, conversion of the iododehydropiperidinone **1a** into the corresponding Grignard reagent and transmetalation using $ZnBr_2$ provided organozinc species **8** which was subjected to a palladium catalyzed coupling reaction with 4-iodobenzoic acid methyl ester furnishing 2,5-aryl dehydropiperidinone **9** (Scheme 6).



Scheme 6 Negishi coupling.

The further elaboration of 2,5-disubstituted dehydropiperidinones to provide 2,5,6-trisubstituted piperidinones is illustrated in Scheme 7. Treatment of **5b** with an activated allylcuprate (Yamamoto type cuprate)[9] led to *N*-glycosyl-2,3-diallyl-6-isopropypiperidinone **10** (Scheme 7).



Scheme 7 Cuprate addition and ring closing metathesis.

The relative stereochemistry of the major diastereomer of **10** was determined unequivocally by X-ray analysis. Knowing the absolute stereochemistry of the arabinosyl fragment, this then allowed the absolute configuration of the compound **10** to be deduced (Fig. 1). Interestingly, in this case a 2,6-*trans* configuration was observed, whereas cuprate addition to 2-substituted *N*-arabinosyl dehydropiperidinones, such as **4**, preferentially yielded 2,6-*cis*-configured piperidinones.[1] Probably, sterical hindrance by the 2-isopropyl and the 5-allyl substituents prevents the C1–N-rotamer shown in formula **5b** to convert to the more reactive rotamer exposing the (*Re*)-side at C-6 for nucleophilic attack.[10] The latter rotamer, however, is the one by which compounds like **4** react to preferentially give the 2,6-*cis*-disubstituted piperidinones.[1,11]

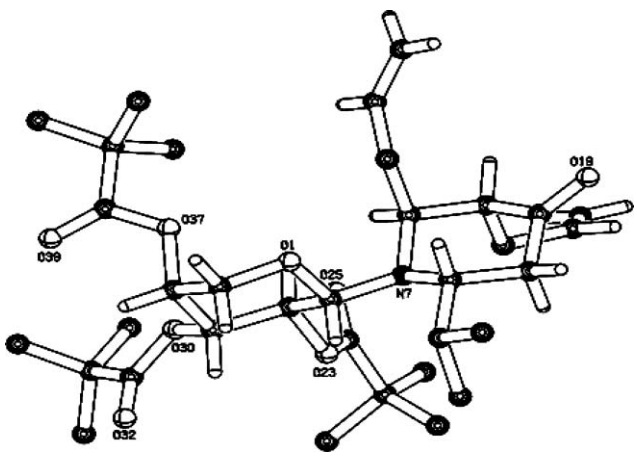


Fig. 1 X-Ray-analysis of piperidinone **10**.

The crystal structure of **10** (Fig. 1) shows that the nitrogen heterocycle adopts a chair conformation with a pyramidally configured nitrogen due to the exoanomeric effect. The allyl substituents are in axial positions. The planes of the carbohydrate and the nitrogen heterocyles are almost perpendicular to each other, enabling overlap of the nitrogen's nonbonding orbital and the σ* orbital of the carbohydrate's C1–O bond.

In the presence of Grubb's catalyst **11**, diallyl piperidinone **10** underwent ring closing metathesis yielding octahydrochinolinone **12** in quantitative yield (Scheme 7). This methodology offers an alternative route to the synthesis of *trans*-hydroquinolines usually achieved by intramolecular aldol condensation.[11]

Conclusions

In conclusion, enantiomerically pure di- and trisubstituted piperidine derivatives are accessible from *N*-glycosyl dehydropiperidinones **4** by regioselective iodination of their enaminone structure, subsequent Knochel iodine–magnesium exchange and organometallic C–C-coupling reactions at the enamine structure of the chiral aliphatic nitrogen heterocycles. Attractive structural elements such as β-arylethylamine (**9**) or hydroquinoline derivatives (**12**) have been synthesized on the basis of this chemistry.

In this reaction *N*-glycosyl dehydropiperidinones proved versatile precursors of highly substituted nitrogen heterocycles which are valuable compounds for medicinal chemistry.

Experimental

All moisture/air sensitive reactions were carried out under a positive pressure of argon in oven dried glassware. Dry THF was distilled from potassium benzophenone ketyl. Dry dichloromethane was distilled from calcium hydride.

Optical rotation values were measured on a Perkin Elmer 241 polarimeter at λ 546 nm and 578 nm and extrapolated to λ 589 nm. The values are quoted in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g per 100 ml. Nuclear magnetic resonance spectra were recorded on a Bruker AC-200, AC-300 or AM-400 NMR spectrometer. ESI mass spectra were recorded on a Navigator 1 instrument from ThermoQuest or a Finnigan MAT 95 spectrometer.

General procedure for the preparation of 1

To a solution of *N*-arabinosyl dehydropiperidinone **4** (1 mmol) in dry THF (20 mL) were added several equivalents (see details for each compound below) of solid *N*-iodosuccinimide at −78 °C and stirred until the starting material was completely consumed. The solution was diluted with diethyl ether (100 mL), washed with 10% aq. $Na_2S_2O_3$ (3 × 20 mL), and the resulting aqueous layers were extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2-(*p*-chlorophenyl)-5-iodo-5,6-dehydropiperidin-4-one (1a). Iododehydropiperidinone **1a** was synthesized according to the general procedure using **4a**[1] (1.18 g, 2 mmol) and *N*-iodosuccinimide (1.35 g, 6 mmol). Purification was carried out by flash chromatography (petroleum ether–ethyl acetate = 6 : 1) to yield **1a** (1.33 g, 1.9 mmol, 93%) as a colourless solid. R_f = 0.65 (petroleum ether–ethyl acetate = 2 : 1); mp: 205 °C under decomposition; $[\alpha]_D^{22}$ +3.77 (*c* 1 in $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 7.70 (s, 1H, H-6), 7.27 (d, 1H, *J* = 4.3 Hz, aryl), 7.17 (d, 1H, *J* = 8.6 Hz, aryl), 5.56 (t, 1H, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.18–5.13 (br s, 1H, H-4′), 5.05 (dd, 1H, $J_{3',2'}$ = 10.0 Hz, $J_{3',4'}$ = 3.3 Hz, H-3′), 4.91 (t, 1H, $J_{2,3a}$ = 6.3 Hz, $J_{2,3b}$ = 6.3 Hz, H-2), 4.37 (d, 1H, $J_{1',2'}$ = 9.0 Hz, H-1′), 3.85 (dd, 1H, $J_{5'a,5'b}$ = 13.3 Hz, $J_{5'a,4'}$ = 2.0 Hz, H-5′a), 3.49 (d, 1H, $J_{5'b,5'a}$ = 12.9 Hz, H-5′b), 3.05 (dd, 1H, $J_{3a,3b}$ = 16.4 Hz, $J_{3a,2}$ = 6.2 Hz, H-3a), 2.83 (dd, 1H, $J_{3b,3a}$ = 16.4 Hz, $J_{3b,2}$ = 6.3 Hz, H-3b), 1.23, 1.16, 1.10 (3s, 9H each, $C(CH_3)_3$); δ_C (75.4 MHz, $CDCl_3$) 184.9 (C-4), 177.2, 177.1, 177.0 (pivC=O), 154.7 (C-6), 136.8 (*ipso*-aryl), 134.2 (*ipso*-aryl), 129.1, 128.0 (aryl), 89.8 (C-1′), 70.8, 67.7, 66.0 (C-2′, C-3′, C-4′), 66.1 (C-5′), 57.9 (C-2), 42.1 (C-3), 39.0, 38.9, 38.8 (piv_{quart}), 27.2, 27.1, 27.0 (piv-CH_3). *m*/*z* (ESI) 718.2 (M(^{35}Cl)+H), 720.2 (M(^{37}Cl)+H), 740.2 (M(^{35}Cl)+Na), 742.2 (M(^{37}Cl)+Na); HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{42}ClINO_8$ (M + H) 718.1638, found 718.1634.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-iodo-2-isopropyl-5,6-dehydropiperidin-4-one (1b). Iododehydropiperidinone **1b** was synthesized according to the general procedure using **4b**[1] (4.0 g, 7.6 mmol) and *N*-iodosuccinimide (5.4 g, 24 mmol). Purification was accomplished by flash chromatography to yield **1b** (4.31 g, 6.6 mmol, 87%) as colourless amorphous solid. R_f = 0.49 (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{22}$ +122.00 (*c* 1 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.45 (s, 1H, H-6), 5.53 (t, 1H, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.26–5.21 (m, 1H, H-4′), 5.12 (dd, 1H, $J_{3',2'}$ = 9.9 Hz, $J_{3',4'}$ = 3.3 Hz, H-3′), 4.51 (d, 1H, $J_{1',2'}$ = 9.2 Hz, H-1′), 4.03 (dd, 1H, $J_{5'a,5'b}$ = 13.2 Hz, $J_{5'a,4'}$ = 2.2 Hz, H-5′a), 3.68 (d, 1H, $J_{5'b,5'a}$ = 13.2 Hz, H-5′b), 3.68–3.60 (m, 1H, H-2), 2.77–2.70 (m, 2H, H-3a, H-3b), 2.34–2.17 (m, 1H, $CH(CH_3)_2$), 1.26, 1.12, 1.11 (3s, 9H each, piv-CH_3), 0.88 (d, 3H, *J* = 7.0 Hz, CH_3), 0.87 (d, 3H, *J* = 6.6 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$) 186.2 (C-4), 177.2, 177.0, 177.0 (pivC=O), 154.8 (C-6), 91.6 (C-1′), 71.1, 67.8, 66.2 (C-2′, C-3′, C-4′), 66.2 (C-5′), 64.2 (C-5), 58.8 (C-2), 39.0, 39.0, 38.8 (piv_{quart}), 34.7 (C-3), 32.3 ($CH(CH_3)_3$), 27.2, 27.1, 27.0 (piv-CH_3), 19.6, 17.6 (CH_3); *m*/*z* (ESI) 650.3 (M + H), 672.2 (M + Na), 688.2 (M + K); HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{45}INO_8$ (M + H) 650.2185, found 650.2186.

(2*S*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-iodo-2-*n*-propyl-5,6-dehydropiperidin-4-one (1c). Iododehydropiperidinone **1c** was synthesized according to the general procedure using **4c**[1] (524 mg, 1 mmol) and *N*-iodosuccinimide (900 mg, 4 mmol). Purification was carried out by flash chromatography (petroleum ether–ethyl acetate = 8 : 1) to yield **1c** (450 mg, 0.7 mmol, 69%) as a colourless amorphous solid. R_f = 0.57 (petroleum ether–ethyl acetate = 2 : 1); $[\alpha]_D^{26}$ 123.19 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.37 (s, 1H, H-6), 5.50 (t, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.27–5.23 (m, 1H, H-4′), 5.12 (dd, 1H, $J_{3',2'}$ = 10.0 Hz, $J_{3',4'}$ = 3.3 Hz, H-3′), 4.47 (d, 1H, $J_{1',2'}$ = 9.0 Hz, H-1′), 4.03 (dd, 1H, $J_{5'a,5'b}$ = 13.3 Hz, $J_{5'a,4'}$ = 2.3 Hz, H-5′a), 3.85–3.76 (m, 1H, H-2), 3.69 (d, 1H, $J_{5'b,5'a}$ = 13.3 Hz, H-5′b), 2.72 (dd, 1H, $J_{3a,3b}$ = 16.6 Hz, $J_{3a,2}$ = 5.7 Hz, H-3a), 2.67 (dd, 1H, $J_{3b,3a}$ = 16.64 Hz, $J_{3b,2}$ = 2.6 Hz, H-3b), 1.90–1.78 (m, 1H, CH_2), 1.67–1.55 (m, 2H, CH_2), 1.40–1.28 (m, 1H, CH_2), 1.25 (s, 9H, piv-CH_3), 1.11 (s, 18H, piv-CH_3), 0.86 (t, 3H, *J* = 7.2 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 185.8 (C-4), 177.2, 177.2, 177.0 (pivC=O), 154.4 (C-6), 91.7 (C-1′), 70.8, 67.8, 66.3 (C-2′, C-3′, C-4′), 66.4 (C-5′), 63.1 (C-5), 53.5 (C-2), 38.9, 38.9, 38.8 (piv_{quart}), 37.9, 32.8 (C-3, CH_2), 27.1, 27.1, 27.0 (piv-CH_3), 18.8 (CH_2), 13.7 (CH_3); *m*/*z* (ESI) 446.04 (M-2 × pivOH + H), 650.21 (M + H), 672.19 (M + Na), 713.08

(M + Na + CH_3CN); HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{44}INO_8Na$ (M + Na) 672.2004, found 672.1999.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-allyl-2-(*p*-chlorophenyl)-5,6-dehydropiperidin-4-one (5a). Isopropylmagnesium bromide (4.2 mL, 2.1 mmol, 0.5 M in THF) was added dropwise to a cold (−40 °C) solution of **1a** (3.0 g, 4.2 mmol) in THF (10 mL). The reaction mixture was stirred at −30 °C until complete consumption of the starting material was detected by TLC (1 h). Subsequently, a solution of CuCN·2LiCl in THF (1 M, 4.2 mL, 4.2 mmol) was added, and the reaction mixture was stirred for 30 min at −30 °C. After addition of allylbromide (0.7 mL, 8.4 mmol), the mixture was warmed up to rt, stirred for 5 h and quenched with sat. NH_4Cl–NH_4OH (20 mL, 9 : 1, v/v). The mixture was poured into water (50 mL) and extracted with diethylether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, cyclohexane–ethyl acetate = 6 : 1) yielding **5a** (1.9 g, 3.0 mmol, 71%) as a colourless amorphous solid. R_f = 0.47 (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{22}$ −20.41 (*c* 1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.30 (d, 2H, *J* = 8.6 Hz, aryl), 7.21 (d, 2H, *J* = 8.6 Hz, aryl), 7.14 (s, 1H, H-6), 5.85–5.72 (m, 1H, –CH_2–C*H*=CH_2), 5.60 (t, 1H, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.14–5.10 (m, 1H, H-4′), 5.07–5.03 (m 1H, CH=C*H*$_2$), 5.02–5.00 (m, 1H, =CH_2), 4.96 (dd, 1H, $J_{3',2'}$ = 9.8 Hz, $J_{3',4'}$ = 3.1 Hz, H-3′), 4.75 (dd, 1H, $J_{2,3a}$ = 9.8 Hz, $J_{2,3b}$ = 5.5 Hz, H-2), 4.18 (d, 1H, $J_{1',2'}$ = 9.4 Hz, H-1′), 3.82 (dd, 1H, $J_{5'a,5'b}$ = 13.3 Hz, $J_{5'a,4'}$ = 2.0 Hz, H-5′a), 3.38 (d, 1H, $J_{5'b,5'a}$ = 12.5 Hz, H-5′b), 2.98–2.83 (m, 2H, –C*H*$_2$–CH=CH_2), 2.73 (dd, 1H, $J_{3a,3b}$ = 16.4 Hz, $J_{3a,2}$ = 5.5 Hz, H-3a), 2.64 (dd, 1H, $J_{3a,3b}$ = 16.4 Hz, $J_{3b,2}$ = 9.8 Hz, H-3b), 1.22, 1.14, 1.09 (3s, 9H each, Piv-CH_3); δ_C (50.3 MHz, $CDCl_3$) 190.4 (C-4), 177.2, 177.1, 176.9 (PivC=O), 147.8 (C-6), 137.1 (*ipso*-aryl), 136.1 (CH_2*C*H=CH_2), 134.3 (*ipso*-aryl), 129.1, 128.7 (aryl), 116.2 (CH_2CH=*C*H_2), 113.0 (C-5), 88.7 (C-1′), 71.3, 68.0, 65.5 (C-2′, C-3′, C-4′), 65.9 (C-5′), 59.7 (C-2), 43.8 (C-3), 39.0, 38.9, 38.8 (Piv_{quart}), 30.7 (*C*H_2CH=CH_2), 27.2, 27.2, 27.0 (Piv-CH_3); HRMS (ESI, *m*/*z*) calcd for $C_{34}H_{46}ClNO_8$ (M^+) 632.2985, found 632.2986.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-allyl-2-isopropyl-5,6-dehydropiperidin-4-one (5b). Compound **5b** was prepared according to the above procedure for the synthesis of **5a** using **1b** (1.04 g, 1.6 mmol), dry THF (10 mL), isopropyl magnesium bromide (4.2 mL, 2.1 mmol, 0.5 M in THF), CuCN·2LiCl solution (1.6 mL, 1.6 mmol, 1 M in THF) and allylbromide (0.3 mL, 3.2 mmol). Purification was achieved by flash chromatography on silica gel to afford **5b** (0.71 g, 1.30 mmol, 79%) as a colourless amorphous solid. R_f = 0.40 (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{24}$ +72.65 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.88 (s, 1H, H-6), 5.80–5.67 (m, 1H, −CH_2–C*H*=CH_2), 5.60 (t, 1H, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.25–5.20 (m, 1H, H-4′), 5.11 (dd, 1H, $J_{3',2'}$ = 9.8 Hz, $J_{3',4'}$ = 3.1 Hz, H-3′), 5.03–4.92 (m, 2H, =CH_2), 4.48 (d, 1H, $J_{1',2'}$ = 9.4 Hz, H-1′), 3.98 (dd, 1H, $J_{5'a,5'b}$ = 13.3 Hz, $J_{5'a,4'}$ = 2.0 Hz, H-5′a), 3.65 (d, 1H, $J_{5'b,5'a}$ = 13.3 Hz, H-5′b), 3.54–3.47 (m, 1H, H-2), 2.90 (dd, 1H, J_{gem} = 15.4 Hz, J_{vic} = 6.4 Hz, –C*H*$_2$–CH=CH_2), 2.73 (dd, 1H, J_{gem} = 15.6 Hz, J_{vic} = 7.0 Hz, −C*H*$_2$–CH=CH_2), 2.58 (dd, 1H, $J_{3a,3b}$ = 16.8 Hz, $J_{3,2}$ = 7.4 Hz, H-3a), 2.43 (dd, 1H, $J_{3a,3b}$ = 16.8 Hz, $J_{3,2}$ = 3.5 Hz, H-3), 2.26–2.16 (m, 1H, –CH–(CH_3)$_2$), 1.25, 1.11, 1.09 (3s, 9H each, Piv-CH_3), 0.88 (t, 6H, *J* = 7.2 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$) 191.3 (C=O), 177.3, 177.1, 176.9 (PivC=O), 148.2 (C-6), 136.7 (–CH_2*C*H=CH_2), 115.5 (–CH_2CH=*C*H_2), 109.6 (C-5), 91.3 (C-1′), 71.5, 68.1, 65.8 (C-2′, C-4′, C-3′), 66.0 (C-5′), 59.2 (C-2), 38.9, 38.9, 38.7 (Piv_{quart}), 35.7 (C-3), 31.7 (–*C*H(CH_3)$_2$), 30.7 (–*C*H_2CH=CH_2), 27.1, 27.0 (PivCH_3), 19.6 (CH_3), 17.6 (CH_3); *m*/*z* (ESI) 258.2 (M-3x PivOH + H), 360.4 (M-2 × PivOH + H), 385.4 (arabinosyl), 462.4 (M-PivOH + H), 484.4 (M-PivOH + Na), 564.4 (M + H), 586.4 (M + Na), 602.4 (M + K), 627.5 (M + Na + MeCN), 643.6 (M + K + MeCN); HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{50}NO_8$ (M + H) 564.3531, found 564.3532.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-benzoyl-2-isopropyl-5,6-dehydropiperidin-4-one (6). Isopropylmagnesium bromide (0.52 mL, 0.26 mmol, 0.5 M in THF) was added dropwise to a cold (−40 °C) solution of **1b** (130 mg, 0.2 mmol) in THF (2 mL) and stirred at −30 °C until the starting material was completely consumed. Subsequently, a solution of CuCN·2LiCl in THF (1 M, 0.26 mL, 0.26 mmol) was added, and the mixture was stirred for 30 min at −30 °C. After addition of benzoyl chloride (0.05 mL, 0.40 mmol) the reaction mixture was allowed to warm to rt, stirred for 1 h and then quenched by the addition of sat. NH_4Cl solution (1 mL). The mixture was poured into water (10 mL) and extracted with diethylether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by flash chromatography (silica gel, cyclohexane–ethyl acetate = 4 : 1) to give **6** (79 mg, 0.13 mmol, 63%) as a light yellow solid. R_f = 0.26 (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{22}$ +1.85 (*c* 1 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 8.03 (s, 1H, H-6), 7.56–7.28 (m, 5H, aryl), 5.57 (t, 1H, $J_{2',1'}$ = 9.6 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 5.31–5.24 (m, 1H, H-4′), 5.17 (dd, 1H, $J_{3',2'}$ = 9.9 Hz, $J_{3',4'}$ = 3.3 Hz, H-3′), 4.76 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H-1′), 4.08 (dd, 1H, $J_{5'a,5'b}$ = 13.2 Hz, $J_{5'a,4'}$ = 2.2 Hz, H-5′a), 3.83–3.73 (m, 1H, H-2), 3.74 (d, 1H, $J_{5'b,5'a}$ = 13.6 Hz, H-5′b), 2.72 (dd, 1H, $J_{3a,3b}$ = 16.9 Hz, $J_{3a,2}$ = 8.1 Hz, H-3a), 2.51 (d, 1H, $J_{3b,3a}$ = 16.9 Hz, H-3b), 2.50–2.36 (m, 1H, C*H*(CH_3)$_2$), 1.26, 1.12, 1.10 (3s, 9H each, C(CH_3)$_3$), 0.95 (d, 3H, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$), 0.92 (d, 3H, *J* = 7.4 Hz, CH(C*H*$_3$)$_2$); δ_C (75.4 MHz, $CDCl_3$) 191.8 (C-4), 188.2 (Ph–*C*=O), 177.2, 177.1, 176.9 (PivC=O), 158.0 (C-6), 139.7 (*ipso*-aryl), 131.4, 128.8, 127.6 (phenyl), 111.4 (C-5), 93.5 (C-1′), 70.8, 67.7, 66.0 (C-2′, C-3′, C-4′), 66.5 (C-5′), 58.9 (C-2), 39.0, 38.8 (Piv_{quart}), 35.8 (C-3), 33.2 (*C*H(CH_3)$_2$), 27.2, 27.1, 27.0 (PivCH_3), 19.4, 17.3 (CH_3); *m*/*z* (ESI) 266.1 (dehydropiperidinone$^-$ + H + Na), 307.1 (dehydropiperidinone$^-$ + H + Na + MeCN), 385.2 (arabinosyl), 628.3 (M + H), 650.3 (M + Na), 666.2 (M + K), 691.3 (M + Na + MeCN).

(2*S*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-5-formyl-2-*n*-propyl-5,6-dehydropiperidin-4-one (7). Isopropylmagnesium bromide (0.65 mL, 0.33 mmol, 0.5 M in THF) was added dropwise to a solution of **1c** (162 mg, 0.25 mmol) in dry THF (5 mL) at −35 °C. The solution was stirred at −30 °C until complete consumption of the starting material was detected by TLC (1 h). After addition of *N*,*N*-dimethylformamide (0.04 mL, 0.50 mmol), the solution was slowly warmed up to rt overnight and the reaction was quenched by the addition of sat. NH_4Cl (5 mL). The mixture was extracted with diethyl ether (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the product was purified by flash

chromatography on silica gel (cyclohexane–ethyl acetate = 4 : 1) to afford **7** (66 mg, 0.12 mmol, 48%) as colourless amorphous solid. $R_f = 0.22$ (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{22}$ +21.02 (*c* 1 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 9.80 (s, 1H, CHO), 7.87 (s, 1H, H-6), 5.52 (t, 1H, $J_{2',1'} = 9.4$ Hz, $J_{2',3'} = 9.4$ Hz, H-2′), 5.32–5.26 (m, 1H, H-4′), 5.16 (dd, 1H, $J_{3',2'} = 9.9$ Hz, $J_{3',4'} = 3.3$ Hz, H-3′), 4.66 (d, 1H, $J_{1',2'} = 8.8$ Hz, H-1′), 4.10 (dd, 1H, $J_{5'a,5'b} = 13.2$ Hz, $J_{5'a,4'} = 1.8$ Hz, H-5′a), 3.94–3.82 (m, 1H, H-2), 3.76 (d, 1H, $J_{5'b,5'a} = 13.2$ Hz, H-5′b), 2.67 (dd, 1H, $J_{3a,3b} = 16.5$ Hz, $J_{3a,2} = 5.9$ Hz, H-3a), 2.43 (d, 1H, $J_{3b,3a} = 16.5$ Hz, H-3b), 1.86–1.58 (m, 2H, CH_2), 1.45–1.15 (m, 2H, CH_2), 1.26, 1.11, 1.05 (3s, je 9H, $C(CH_3)_3$), 0.87 (t, 3H, $J = 7.4$ Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$) 190.0 (C-4), 186.1 (CHO), 177.2, 177.0, 176.9 (PivC=O), 153.8 (C-6), 110.5 (C-5), 93.3 (C-1′), 70.4, 67.5, 66.0 (C-2′, C-3′, C-4′), 66.7 (C-5′), 53.8 (C-2), 38.9, 38.9, 38.8 (Piv_{quart}), 38.2 (C-3), 33.5 (CH_2), 27.1, 27.1, 27.0 ($PivCH_3$), 18.8 (CH_2), 13.6 (CH_3); *m/z* (ESI) 552.3 (M + H), 574.3 (M + Na), 590.3 (M + K), 1103.6 (2M + H), 1125.6 (2M + Na), 1141.6 (2M + K); HRMS (ESI, *m/z*) calcd for $C_{29}H_{46}NO_9$ (M + H) 552.3167, found 552.3165.

(2*R*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2-(*p*-chlorphenyl)-5-*p*-(methoxycarbonyl)phenyl-5,6-dehydropiperidin-4-one (9). To a solution of **1a** (180 mg, 0.25 mmol) in dry THF (5 mL) was added dropwise isopropylmagnesium bromide (0.6 mL, 0.3 mmol, 0.5 M in THF) at −30 °C. After complete conversion of the starting material (2 h), $ZnBr_2$ (0.5 mL, 0.5 mmol, 1 M in THF) was added and the mixture was warmed up to room temperature. In a second flask, bis(dibenzylidenacetone)palladium (14.4 mg, 0.025 mmol) and triphenylarsine (31 mg, 0.10 mmol) in dry THF (2 mL) were stirred for 5 min for the formation of the active catalyst. 4-Iodobenzoic acid methylester (131 mg, 0.5 mmol) in dry THF (1 mL), and subsequently the solution prepared from **1a** were added stirred at 40 °C. The reaction was terminated by the addition of sat. NH_4Cl (2 mL). The mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The product was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 5 : 1) to afford **9** (93 mg, 0.13 mmol, 51%) as pale yellow amorphous solid. $R_f = 0.35$ (cyclohexane–ethyl acetate = 2 : 1); $[\alpha]_D^{26}$ −7.41 ($c = 1$, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.97 (d, 2H, $J = 8.4$ Hz, C_6H_4–COOMe), 7.57 (s, 1H, H-6), 7.47 (d, 2H, $J = 8.5$ Hz, C_6H_4–COOMe), 7.31 (d, 2H, $J = 8.5$ Hz, C_6H_5–Cl), 7.24 (d, 2H, $J = 8.4$ Hz, C_6H_5–Cl), 5.68 (t, $J_{2',1'} = 9.6$ Hz, $J_{2',3'} = 9.6$ Hz, H-2′), 5.20–5.14 (m, 1H, H-4′), 5.04 (dd, 1H, $J_{3',2'} = 9.9$ Hz, $J_{3',4'} = 3.3$ Hz, H-3′), 4.94–4.85 (m, 1H, H-2), 4.41 (d, 1H, $J_{1',2'} = 9.2$ Hz, H-1′), 3.59 (s, 3H, OCH_3), 3.92–3.83 (m, 1H, $J_{5'a,4'} = 2.2$ Hz, H-5′a), 3.49 (d, 1H, $J_{5'b,5'a} = 13.2$ Hz, H-5′b), 2.98 (dd, 1H, $J_{3a,3b} = 16.2$ Hz, $J_{3a,2} = 5.9$ Hz, H-3a), 2.76 (dd, 1H, $J_{3b,3a} = 16.2$ Hz, $J_{3b,2} = 7.7$ Hz, H-3b), 1.21, 1.12, 1.11 (3s, 9H each, Piv-CH_3); δ_C (75.4 MHz, $CDCl_3$) 188.4 (C-4), 177.2, 177.1, 177.0 (PivC=O), 167.1 (*C*–OCH_3), 149.3 (C-6), 139.9, 136.9, 134.4 (*ipso*-aryl), 129.6, 129.2, 128.3 (aryl), 127.8 (*ipso*-aryl), 127.3 (aryl), 114.1 (C-5), 89.7 (C-1′), 71.0 (C-3′), 67.8 (C-4′), 66.1 (C-5′), 65.7 (C-2′), 58.6, 52.0 (C-2, OCH_3), 43.9 (C-3), 38.9, 38.9, 38.8 (Piv_{quart}), 27.2, 27.1, 27.0 (Piv-CH_3); *m/z* (ESI) 726.5 (M(^{35}Cl)+H), 728.5 (M(^{37}Cl)+H), 748.4 (M(^{35}Cl)+Na), 750.4 (M(^{37}Cl)+Na), 789.6 (M(^{35}Cl)+Na + CH_3CN), 791.6 (M(^{37}Cl)+Na + CH_3CN); HRMS (ESI, *m/z*) calcd for $C_{39}H_{48}ClNO_{10}Na$ (M + Na) 748.2859, found 748.2858.

(2*R*,5*R*,6*S*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabino-pyranosyl)-5,6-diallyl-2-isopropylpiperidin-4-one (10). A solution of allylmagnesium bromide (2 mL, 2 mmol, 1 M in diethyl ether) was added to a suspension of copper cyanide (179 mg, 2 mmol) in dry THF (10 mL) at −40 °C and stirred for 30 min. Subsequently, the mixture was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added. After 15 min, **5b** (225 mg, 0.4 mmol) in dry THF (10 mL) was added to the cuprate and the mixture was stirred for 3 h at −78 °C. The reaction was terminated by the addition of conc. NH_4OH–sat. NH_4Cl (1 : 1 v/v, 20 mL). The mixture was allowed to warm to room temperature, diluted with diethyl ether (50 mL), and the layers were separated. The organic phase was washed with conc. NH_4OH–sat. NH_4Cl (1 : 1, v/v). The aqueous layers were extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification was achieved by flash chromatography on silica gel to afford 145 mg (0.24 mmol, 60%) of **10** as colourless solid. Mp: 129 °C; $R_f = 0.44$ (cyclohexane–ethyl acetate = 5 : 1); $[\alpha]_D^{22}$ −10.79 (*c* 1 in $CHCl_3$); diastereomeric ratio 90 : 10 (determined by HPLC); HPLC: gradient: 85% CH_3CH, 15% H_2O → 95% CH_3CN, 5% H_2O (20 min); R_t (min) = 21.35 (main diastereomer), 23.52 (second diastereomer); δ_H (400 MHz, $CDCl_3$) 5.75–5.50 (m, 2H, 2 × –CH_2–C*H*=CH_2), 5.68 (t, 1H, $J_{2',1'} = 9.2$ Hz, $J_{2',3'} = 9.2$ Hz, H-2′), 5.22–5.17 (m, 1H, H-4′), 5.09 (dd, 1H, $J_{3',2'} = 9.4$ Hz, $J_{3',4'} = 3.5$ Hz, H-3′), 5.06–4.88 (m, 4H, 2 × =CH_2), 4.53 (d, 1H, $J_{1',2'} = 9.4$ Hz, H-1′), 3.85 (dd, 1H, $J_{5'a,5'b} = 13.1$ Hz, $J_{5'a,4'} = 2.2$ Hz, H-5′a), 3.55–3.43 (m 1H, H-2), 3.48 (d, 1H, $J_{5'b,5'a} = 12.9$ Hz, H-5′b), 3.39–3.30 (m, 1H, H-6), 2.94–2.83 (m, 1H, H-3a), 2.54–2.34 (m, 2H, H-5, 1 × –C*H*$_2$–CH=CH_2), 2.27–2.04 (m, 5H, H-3b, 3 × –C*H*$_2$–CH=CH_2, *C*H$(CH_3)_2$), 1.23, 1.14, 1.12 (3s, 9H each, Piv-CH_3), 0.93 (d, 3H, $J = 6.7$ Hz, CH_3), 0.89 (d, 3H, $J = 6.6$ Hz); δ_C (100.6 MHz, $CDCl_3$) 212.5 (C-4), 177.5, 177.3, 176.7 (PivC=O), 134.9 (CH_2=*C*HCH_2–), 134.6 (CH_2=*C*HCH_2–), 117.6 (*C*H_2=CHCH_2–), 116.3 (*C*H_2=CHCH_2-), 87.9 (C-1′), 73.3, 68.2, 65.3 (C-2′, C-3′, C-4′), 65.0 (C-5′), 58.0 (C-2), 56.4 (C-6), 53.0 (C-5), 38.9, 38.8, 38.8 (Piv_{quart}), 37.0, 36.5 (CH_2=CH*C*H$_2$–), 36.1 (C-3), 27.2, 27.1, 27.1 (Piv-CH_3), 26.6 (–C*H*$(CH_3)_2$), 19.8 (CH_3), 14.1 (CH_3); *m/z* (ESI) 300.3 (M-3 × PivOH + H), 402.3 (M-2 × PivOH + H), 504.4 (M-PivOH + H), 526.3 (M-PivOH + Na), 606.4 (M + H), 628.4 (M + Na), 644.4 (M + K), 669.5 (M + Na + MeCN); HRMS (ESI, m/z) calcd for $C_{34}H_{56}NO_8$ (M + H) 606.4000, found 606.3999.

Crystal data: $C_{34}H_{55}NO_8$, $M = 605.80$, space group: $P2_1$ (monoklin), lattice parameters: $a = 9.576(2)(7)$ Å, $b = 20.504(5)$ Å, $c = 10.143(2)$ Å, $V = 1840.9(8)$ Å^3, $z = 2$, $F(000) = 660$, diffractometer: CAD4, irridation: Cu Kα graphite monochromator, 6691 reflections measured, 6285 unique ($R_{int} = 0.0243$), $wR2 = 0.1696$ ($R_1 = 0.0562$ for observed reflexes, 0.604 for all reflexes).†

(2*R*,4a*S*,8a*S*)-*N*-(2′,3′,4′-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2-isopropyl-*trans*-6,7-dehydrochinolin-4-one (12). A solution of **10** (48 mg, 0.08 mmol) and Grubb's catalyst [bis-(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (8 mg, 0.01 mmol) in dichloromethane was stirred for 2 h. The solvent was removed in vacuum and the residue was purified by flash chromatography (silica gel, cyclohexane–ethyl acetate = 20 : 1)

† CCDC reference numbers 624381. For crystallographic data in CIF format see DOI: 10.1039/b615113b

to give **12** (46 mg, 0.08 mmol, quant.) as a colourless amorphous solid. $R_f = 0.25$ (cyclohexane–ethyl acetate = 5 : 1); $[\alpha]_D^{24}$ −8.99 (*c* 1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.69–5.52 (m, 3H, H-2′, H-6, H-7), 5.24–5.20 (m 1H, H-4), 5.05 (dd, 1H, $J_{3',2'} = 9.4$ Hz, $J_{3',4'} =$ 2.7 Hz, H-3′), 4.38 (m, 1H, H-1′), 3.90 (dd, 1H, $J_{5'a,5'b} = 13.3$ Hz, $H_{5'a,4'} = 1.6$ Hz, H-5′a), 3.56 (d, 1H, $J_{5'b,5'a} = 12.9$ Hz, H-5′b), 3.46–3.18 (m, 1H, H-2), 2.80–1.98 (m, 8H, $H\text{-}3_I$, $H\text{-}3_{II}$, H-4a, $H\text{-}5_I$, $H\text{-}5_{II}$, $H\text{-}8_I$, $H\text{-}8_{II}$, H-8a), 1.72–1.46 (m, 1H, $-CH(CH_3)_2$), 1.23, 1.13, 1.11 (3s, 9H each, $PivCH_3$), 0.90 (d, 3H, $J = 7.0$ Hz, CH_3), 0.83 (d, 3H, $J = 6.6$ Hz, CH_3). δ_C (75.4 MHz, $CDCl_3$) 210.8 (C-4), 177.4, 177.4, 177.0 (PivC=O), 125.6, 124.4 (C-6, C-7), 68.5 (C-3′), 68.4 (C-4′), 65.3 (C-5′), 51.3 (C-2), 42.5 (CH_2), 38.9, 38.8, 38.7 (Piv_{quart}), 30.7, 29.7 (C-4a, C-8a), 27.3, 27.1, 27.1 ($PivCH_3$), 25.4 (CH_2), 20.2 (CH_3); *m*/*z* (ESI) 194.2 (dehydropiperidinone$^-$ + H + H), 272.2 (M-3 × PivOH + H), 374.3 (M-2 × PivOH + H), 476.4 (M-PivOH + H), 498.3 (M-PivOH + Na), 578.5 (M + H), 600.4 (M + Na), 616.3 (M + K), 641.5 (M + Na + MeCN); HRMS (ESI, *m*/*z*) calcd for $C_{32}H_{51}NO_8Na$ (M + Na) 600.3507, found 600.3500.

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