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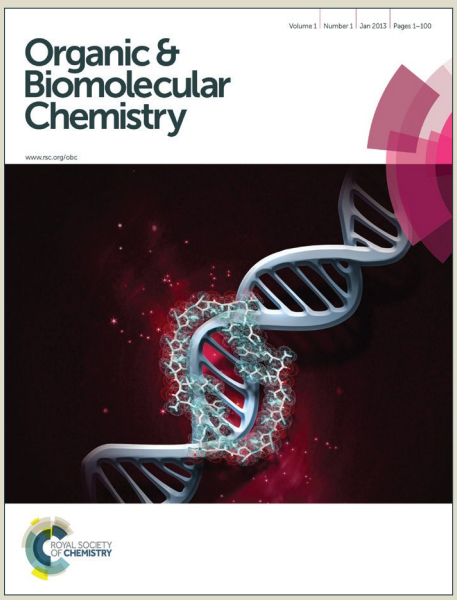

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ARTICLE

Synthesis of the tricyclic core of manzamine A

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An efficient synthetic approach to the core structure of the manzamine alkaloids is reported, particularly in relation to incorporating a one-carbon unit in ring B from which the aldehyde in ircinal A or the beta-carboline unit in manzamine A could potentially be generated. The key steps involve a Johnson–Claisen rearrangement, enolate alkylation, dithiane alkylation and a stereoselective intramolecular dipolar cycloaddition of an azomethine ylide, which provided the desired tricyclic ABC core structure.

Introduction

The alkaloid manzamine A **1** (Fig. 1) was first reported in 1986 and has a complex pentacyclic ABCDE structure.[1] This compound, and related alkaloids,[2] have attracted much attention due to their intricate structures and their reported biological activities.[3] Several syntheses of manzamine A **1** and ircinal **2** have been published to date.[4] In addition, several approaches to the synthesis of the core ring system, especially of the ABC ring system, are known.[5]

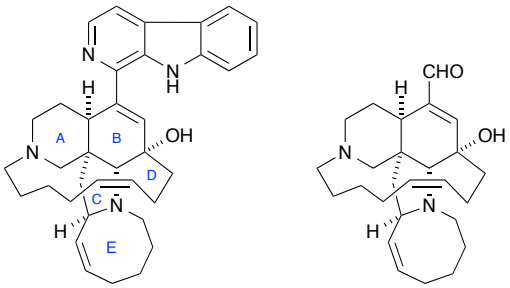
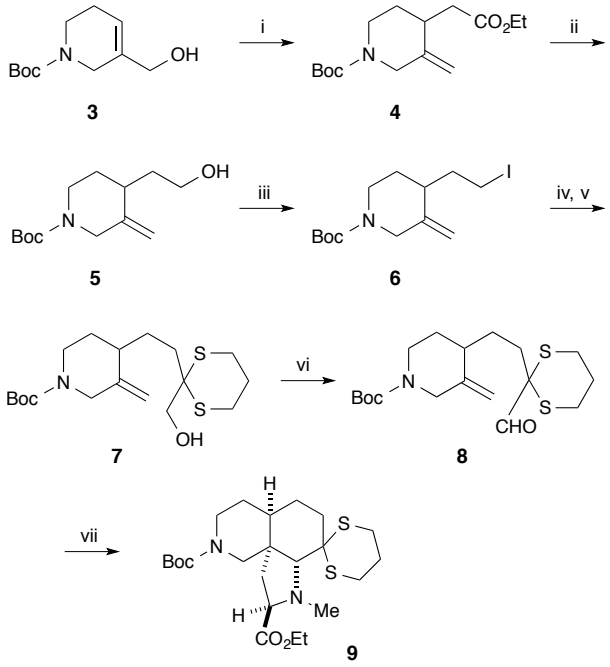
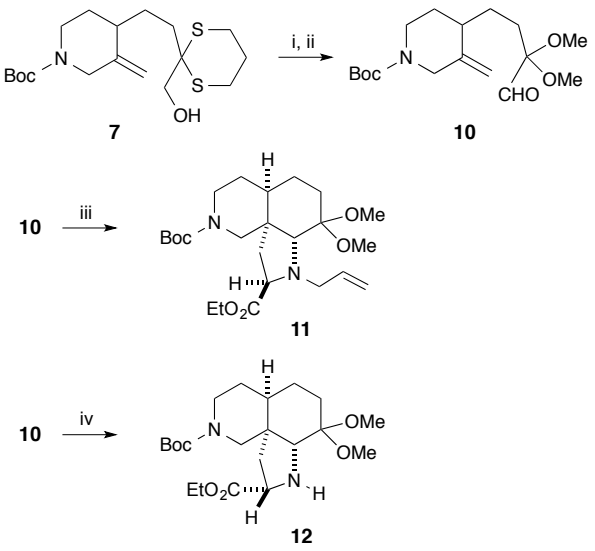


Fig. 1 Structures of some manzamine alkaloids

Our research group has reported the synthesis of the core ring system of manzamine A,[6] and several simpler analogues.[7] Our synthetic approach has focused on the formation of rings B and C of manzamine A by using an intramolecular dipolar cycloaddition reaction of an azomethine ylide.[8] The alcohol **3**[9] was converted to the ester **4** by using a Johnson–Claisen rearrangement (Scheme 1). The ester **4** was converted in 5 steps to the aldehyde **8**. Condensation with *N*-methyl glycine ethyl ester allowed *in situ* dipolar cycloaddition to give the tricyclic compound **9** as a single stereoisomer (stereochemistry verified by single crystal X-ray analysis). However, the aldehyde **8** was found to be a poor substrate for reaction with other secondary amines. Fortunately, the aldehyde **10** (Scheme 2) was amenable to reaction with a variety of secondary amines including *N*-allyl glycine ethyl ester, which gave the desired product **11** as the major diastereomer. Alternatively, reaction with the primary amine glycine ethyl ester gave the tricyclic product **12**, presumably arising from the W-shaped, rather than S-shaped, azomethine ylide.



Scheme 1 Synthetic studies with aldehyde **8**.[6a] i, MeC(OEt)$_3$, xylene, 2,4-dinitrophenol, heat, 63%; ii, LiAlH$_4$, THF, 89%; iii, I$_2$, Ph$_3$P, imidazole, THF, 81%; iv, *n*-BuLi, THF, HMPA, ethyl 1,3-dithiane-2-carboxylate, –40 °C to r.t., 96%; v, LiAlH$_4$, THF, 94%; vi, (COCl)$_2$, DMSO, CH$_2$Cl$_2$, –60 °C then Et$_3$N, 85%; vii, *N*-methyl glycine ethyl ester·HCl, ^{i}Pr$_2$NEt, PhMe, 110 °C, 45%.

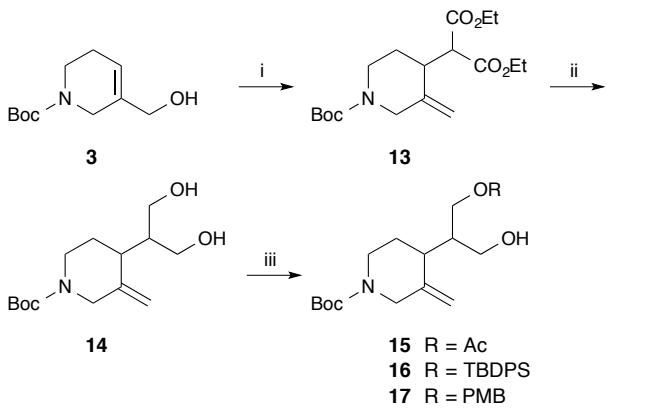


Scheme 2 Synthetic studies with aldehyde **10**.[6b] i, NCS, $AgNO_3$, collidine, THF, MeOH, followed directly by: ii, $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C then Et_3N, 60% over two steps; iii, *N*-allyl glycine ethyl ester, PhMe, 110 °C, 43%; iv, glycine ethyl ester, PhMe, 130 °C, 52%.

The examples in Schemes 1 and 2 demonstrate that an intramolecular dipolar cycloaddition approach to the ABC ring system of the manzamine alkaloids is feasible and can provide the desired relative stereochemistry at four of the five stereocentres. One aspect that we were conscious of relates to the need for a strategy that allows the future incorporation of the β-carboline moiety. Except for the recent approach by Dixon and co-workers, the reported syntheses of manzamine A make use of the alkaloid ircinal A (**2**).[4] We were therefore interested in developing chemistry that would allow the incorporation of a one-carbon unit in ring B that could be suitable for conversion to the aldehyde found in ircinal A (and hence to manzamine A itself). This paper describes our efforts in this area.

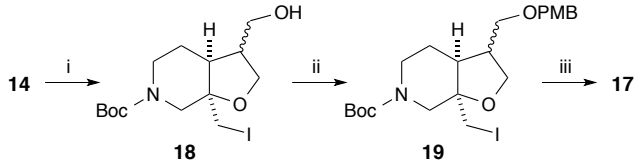
Results and discussion

Several approaches for the synthesis of a suitable precursor compound, with an extra carbon atom in ring B were investigated. Ideally this one-carbon unit would be introduced as part of the sequence of steps for the preparation of the aldehyde used in the key intramolecular dipolar cycloaddition step. One approach studied was to alter the Johnson–Claisen rearrangement using the alcohol **3**. Based on a literature method,[10] the alcohol **3** was heated with 3,3-diethoxyacrylic acid ethyl ester in toluene for just 90 min to give an almost quantitative yield of the diester **13** (Scheme 3). Reduction of the diester **13** gave the diol **14**. Treatment of the diol **14** with acetic anhydride gave the monoester **15** (and 28% diester) as an inseparable mixture of diastereomers. Reaction of the diol **14** with sodium hydride and TBDPSCl or *p*-methoxybenzyl chloride gave the alcohols **16** or **17** respectively, but these also were a 1:1 inseparable mixture of diastereomers.



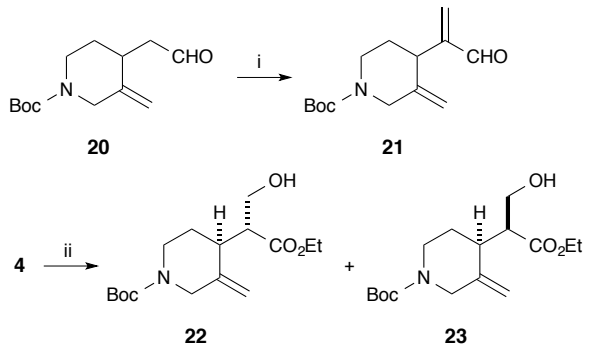
Scheme 3 Studies using diester **13**. i, 3,3-diethoxyacrylic acid ethyl ester, 2,4-dinitrophenol, PhMe, 110 °C, 97%: ii, $LiAlH_4$, THF, 64%; iii, Ac_2O, pyridine, DMAP, CH_2Cl_2, **15** 68%, or NaH, THF, TBDPSCl, **16** 99%, or NaH, THF, PMBCl, **17** 80%.

As a possible way to distinguish the hydroxymethyl groups, we treated the diol **14** with iodine to give the tetrahydrofuran **18** (Scheme 4). This did result in some preference for cyclization of one of the alcohols, although the selectivity was not high (dr 3:1 by ^1H NMR spectroscopy) and the diastereomers were inseparable by column chromatography. Protection of the alcohol gave compound **19**, but these diastereomers were also inseparable. Despite this result, we treated compound **19** with zinc, which promoted ring opening to give the mixture (dr 3:1) of diastereomeric alcohols **17**. Therefore this method is able to provide the desired compound **17** with some selectivity (by ^1H NMR spectroscopy the major isomer was **17a**, see below), although this was insufficient for further studies.



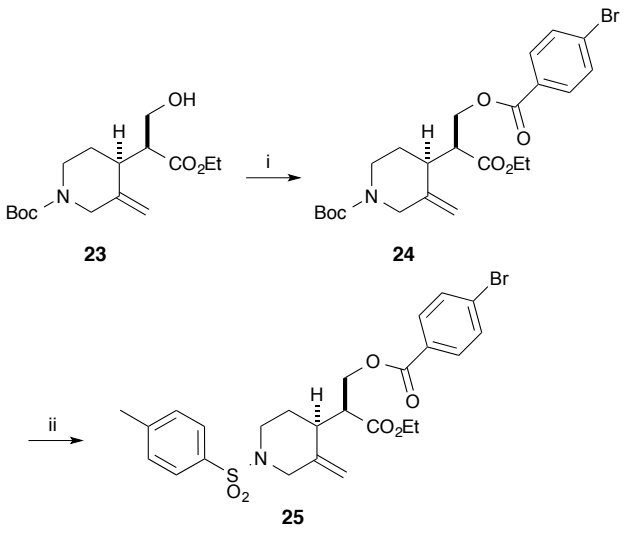
Scheme 4 Studies using diol **14**. i, iodine, $NaHCO_3$, CH_2Cl_2, 0 °C, 75%: ii, NaH, THF, PMBCl, **17** 60%; iii, Zn dust, NH_4Cl, EtOH, 30 °C, 44%.

Two further methods to access a single diastereomer of alcohol **17** were investigated. Following precedent for asymmetric hydroxymethylation of aldehydes,[11] we treated the aldehyde **20**[6b] with proline and aqueous formaldehyde (Scheme 5). However, this gave rise not to the desired α-hydroxymethyl aldehyde product but rather the alkene **21** resulting from elimination. Finally, we performed a simple deprotonation of the ester **4** with LDA followed by addition of formaldehyde (Scheme 5). This gave a mixture of the alcohols **22** and **23** which we were delighted to find were separable by careful column chromatography. Taking a mixture of these isomers through the subsequent chemistry described below gave diastereomeric products that in all cases were inseparable from each other, so it was important to separate alcohols **22** and **23** at this stage.



Scheme 5 Alkylation using **20** or **4**. i, $CH_2O_{(aq)}$, proline, DMF, r.t., 89%: ii, LDA, THF, CH_2O, 63%, **22**:**23** 1:1.

To determine the relative stereochemistry, we took the less polar isomer (which turned out to be compound **23**, see below) and treated it with *p*-bromobenzoyl chloride to obtain the ester **24** (Scheme 6). This compound was not crystalline, so the *N*-Boc group was removed with acid and the crude amine product was protected as the sulfonamide **25**. This compound was amenable to single crystal X-ray analysis, which showed the relative stereochemistry as depicted (Fig. 2).



Scheme 6 Determination of stereochemistry. i, *p*-BrC_6H_4COCl, Et_3N, DMAP, CH_2Cl_2, r.t., 99%: ii, TFA, CH_2Cl_2, r.t., then TsCl, Et_3N, CH_2Cl_2, r.t., 62%.

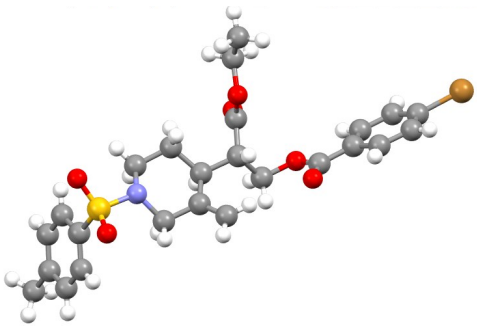
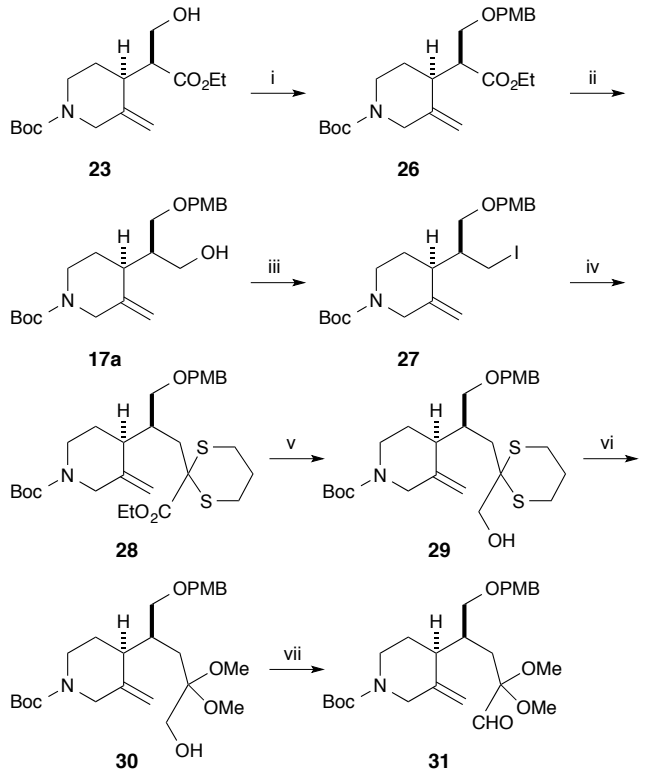


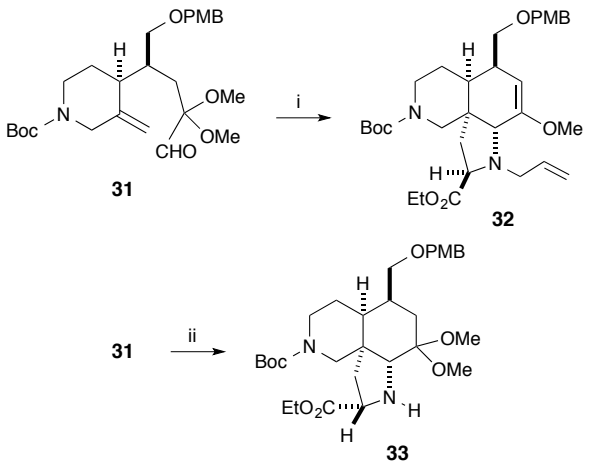
Figure 2 X-ray structure of **25**.



Scheme 7 Synthesis of the aldehyde **31**. i, PMBOC(=NH)CCl_3, CSA, CH_2Cl_2, 82%; ii, $LiAlH_4$, THF, –5 °C, 69%; iii, I_2, Ph_3P, imidazole, THF, 95%; iv, *n*-BuLi, THF, HMPA, ethyl 1,3-dithiane-2-carboxylate, –78 °C to r.t., 80%; v, $LiAlH_4$, THF, –5 °C, 93%; vi, NCS, $AgNO_3$, collidine, THF, MeOH, 49%; vii, $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C then Et_3N, 80%.

With both single diastereomers **22** and **23** in hand, we selected one of these for further study. The less polar isomer **23** was protected to give the ether **26** and reduction gave the alcohol **17a** (Scheme 7). Conversion of the alcohol to the iodide **27** and displacement with the anion of ethyl 1,3-dithiane-2-carboxylate gave the ester **28**. This was converted in three steps (reduction, transacetalisation, and oxidation) to the aldehyde **31**.

The key step in our synthetic route to the manzamine alkaloids involves an intramolecular dipolar cycloaddition with an aldehyde tethered to the 4-position of a 3-exomethylene-piperidine. We therefore heated aldehyde **31** with *N*-allyl glycine ethyl ester (Scheme 8). This gave the desired tricyclic product **32** as a single stereoisomer, but only in 20–30% yield. The yield did improve (to 38%) by using the hydrochloride salt of *N*-allyl glycine ethyl ester together with $^iPr_2NEt$. Other conditions (such as using excess amine or higher temperature) did not improve the yield. In all cases the product isolated was the enol ether **32**, in which the cycloadduct had lost methanol. It is not clear why this loses methanol in comparison with the formation of cycloadduct **11** but sterics may play a part. As an alternative, the aldehyde **31** was heated with glycine ethyl ester to give the tricyclic product **33**. The stereochemistry of these cycloadducts is assumed to be as shown, based on related chemistry (see Scheme 2).



Scheme 8 Key cycloaddition step. i, *N*-allyl glycine ethyl ester·HCl, $^{i}Pr_2NEt$, PhMe, 110 °C, 38%; ii, glycine ethyl ester·HCl, $^{i}Pr_2NEt$,, PhMe, 110 °C, 60%.

By using the same chemistry as shown in Scheme 7 with a 1:1 unseparated mixture of the diastereomers **22** and **23**, resulted in a 1:1 inseparable mixture of the aldehyde **31** and its diastereomer. Heating this mixture of stereoisomers with *N*-allyl glycine ethyl ester gave the same product **32** in 18% yield as the only product that could be isolated. This indicates that the stereoisomer derived from the ester **22** does not undergo the desired intramolecular dipolar cycloaddition reaction. Analysis of the conformations of the stereoisomers of the azomethine ylides suggests that a favourable conformation exists from the stereoisomer **31** (Fig. 3). The azomethine ylide derived from the other diastereomer of **31** would suffer from greater steric interactions. This may explain the preference for cycloaddition only from diastereomer **31**.

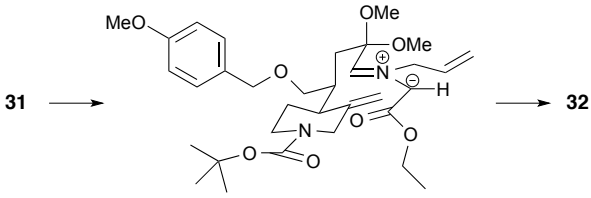
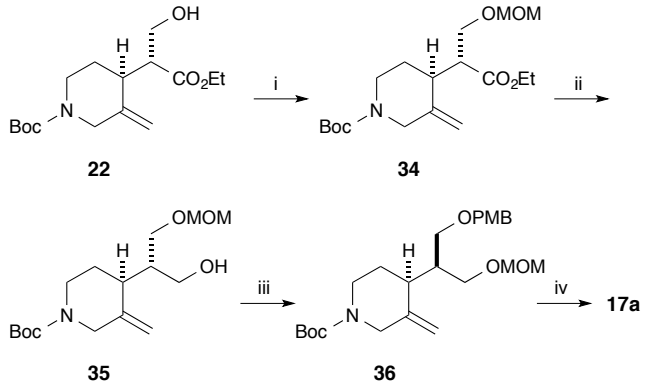


Figure 3 Conformational analysis.

The successful synthesis of the tricyclic product **32** represents a stereoselective approach to the ABC core ring system of the manzamine alkaloids. One of the drawbacks of the chemistry discussed above is that a 1:1 mixture of the stereoisomers **22** and **23** is formed and only one of these is suitable for further elaboration. We have found that the undesired stereoisomer **22** can be converted to the desired compound **17a** by the sequence of reactions shown in Scheme 9. Protection of the alcohol **22** with methoxymethyl chloride followed by reduction of the ester gave the alcohol **35** (Scheme 9). Protection of this alcohol as its PMB ether and removal of the MOM group selectively with mild acid gave the product **17a**. Alternatively, it is possibly to simply treat the undesired isomer **22** with sodium ethoxide to promote epimerization. The resulting 1:1 mixture of esters (quantitative yield) can be separated by column chromatography.



Scheme 9 Inversion of the undesired stereoisomer. i, MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, 86%; ii, $LiAlH_4$, THF, –5 °C, 87%; iii, $PMBOC(=NH)CCl_3$, CSA, CH_2Cl_2, 80%; iv, HCl (2 M), $^{i}PrOH$, 60 °C, 68%.

Conclusions

We have described a short and stereoselective route to prepare the ABC tricyclic ring system found in the manzamine alkaloids. This extends our previous work by demonstrating that a one-carbon unit can be located in ring B. This substituent could potentially be used to later generate the aldehyde functional group found in ircinal A and hence the beta-carboline unit in manzamine A. Although a mixture of stereoisomers was formed when introducing this one-carbon unit, the undesired isomer can be isomerised. The key steps in the chemistry involve a Johnson–Claisen [3,3]-sigmatropic rearrangement, a dithiane alkylation, and an azomethine ylide dipolar cycloaddition. The dipolar cycloaddition was successful with only one diastereomer of the starting material. The yield in this key step was not particularly high, but the chemistry is significant as it demonstrates the importance of the choice of stereochemistry in such intramolecular cycloadditions when used as part of a synthetic endeavour.

Experimental

tert-Butoxycarbonyl-3-methylene-piperidin-4-yl-malonic acid diethyl ester 13

The alcohol **3** (10.0 g, 46.9 mmol), 3,3-diethoxyacrylic acid ethyl ester (17.65 g, 93.8 mmol) and 2,4-dinitrophenol (863 mg, 4.69 mmol) were heated in toluene (250 mL) at 110 °C. After 90 min, the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (9:1), to give the diester **13** (16.1 g, 97%) as an oil; R_f 0.33 [petrol–EtOAc 7:3]; ν_{max} (neat)/cm^{-1} 2965, 2925, 2865, 1725, 1695; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.89 (1H, br s), 4.71 (1H, s), 4.15 (2H, q, *J* 7), 4.12–4.08 (2H, m), 3.94 (1H, br d, *J* 14), 3.76 (1H, d, *J* 14), 3.62 (1H, d, *J* 11), 3.53 (1H, ddd, *J* 13.5, 7.5, 4), 3.36–3.29 (1H, m), 3.02 (1H, ddd, *J* 11, 7.5, 4), 1.75–1.67 (1H, m),

1.54–1.46 (1H, m), 1.39 (9H, s), 1.22 (3H, t, *J* 7), 1.18 (3H, t, *J* 7); ^{13}C NMR (126 MHz, $CDCl_3$) δ =167.9, 154.5, 142.7, 111.2, 79.6, 61.5, 61.4, 53.6, 49.3 (br), 41.9 (br), 40.8, 29.5, 28.3, 14.0; HRMS (ES) Found MNa^+ 378.1882. $C_{18}H_{29}NO_6Na$ requires MNa^+ 378.1893; LRMS *m/z* (ES) 378 (96%), 356 (4%), 256 (100%).

4-(2-Hydroxy-1-hydroxymethyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 14

$LiAlH_4$ (18.5 mL, 18.5 mmol, 1.0 solution in THF) was added dropwise to the diester **13** (1.64 g, 4.63 mmol) in THF (15 mL) at 0 °C. After 1 h, water (10.8 mL) and NaOH (2.8 mL, 4 M) were added and the mixture was filtered through celite. The solvent was evaporated and the residue was purified by column chromatography, eluting with EtOAc, to give the diol **14** (0.80 g, 64%) as an oil; R_f 0.44 [EtOAc]; ν_{max} (neat)/cm^{-1} 3395, 2970, 2930, 1670, 1570; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.96 (1H, br s), 4.82 (1H, s), 3.97–3.86 (2H, m), 3.82–3.64 (4H, m), 3.52–3.37 (4H, m), 2.43–2.34 (1H, m), 2.06–1.94 (1H, m), 1.79–1.55 (2H, m), 1.42 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.9, 143.8, 111.6, 79.8, 64.6, 63.2, 41.1 (br), 40.1, 38.6, 28.4, 28.3; HRMS (ES) Found MNa^+ 294.1675. $C_{14}H_{25}NO_4Na$ requires MNa^+, 294.1681; LRMS *m/z* (ES) 294 (100%).

4-(2-Acetoxy-1-hydroxymethyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 15

The diol **14** (0.20 g, 0.73 mmol), Ac_2O (0.10 mL, 0.75 mmol), pyridine (0.05 mL, 0.74 mmol) and 4-dimethylaminopyridine (~10 mg) in CH_2Cl_2 (10 mL) were stirred at room temperature. After 24 h, water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography, eluting with EtOAc, to give the acetate **15** (0.15 g, 68%) as a mixture of diastereomers (1:1) as an oil; R_f 0.64 [EtOAc]; ν_{max} (neat)/cm^{-1} 3445, 2950, 1735, 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.99 (2H, br s), 4.85 (1H, s), 4.83 (1H, s), 4.38 (1H, d, *J* 3.5), 4.35 (1H, d, *J* 3.5), 4.21 (1H, d, *J* 4.5), 4.18 (1H, d, *J* 4.5), 4.12 (1H, d, *J* 6.5), 4.09 (1H, d, *J* 6.5), 3.96 (1H, d, *J* 10), 3.93 (1H, d, *J* 10), 3.80–3.75 (2H, m), 3.74–3.72 (2H, m), 3.66–3.58 (1H, m), 3.54–3.46 (1H, m), 3.43–3.31 (2H, m), 2.46–2.36 (2H, m), 2.19–2.08 (4H, m), 2.08 (6H, s), 1.84–1.72 (2H, m), 1.71–1.62 (2H, m), 1.42 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6, 171.5, 154.7, 154.6, 143.8, 143.5, 111.9, 111.6, 79.7, 79.6, 63.6, 62.3, 61.5, 59.8, 40.8, 39.2, 39.0, 38.9, 38.7, 28.4, 28.3, 28.2, 20.9; HRMS (ES) found: MH^+, 314.1974. $C_{16}H_{28}NO_5$ requires MH^+, 314.1967; LRMS *m/z* (ES) 314 (100%).

4-[1-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-hydroxy-ethyl]-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 16

NaH (220 mg, 5.4 mmol, 60% dispersion in oil) was added to the diol **14** (1.39 g, 5.2 mmol) in THF (30 mL) at 0 °C. After 50 min, *tert*-butyldiphenylsilyl chloride (1.47 mL, 5.6 mmol) was added dropwise. After 1 h, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (4:1), gave the alcohol **16** (2.59 g, 99%) as a mixture of diastereomers (1:1) as an oil; R_f 0.33 [petrol–EtOAc 4:1]; ν_{max} (neat)/cm^{-1} 3450, 3075, 2930, 2855, 1690, 1665, 1590; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68–7.63 (8H, m), 7.46–7.36 (12H, m), 4.92 (1H, s), 4.81 (1H, s), 4.75 (1H, s), 4.64 (1H, s), 3.96–3.87 (5H, m), 3.77–3.68 (7H, m), 3.57 (1H, d, *J* 14), 3.45–3.32 (3H, m), 3.21–3.14 (1H, m), 2.38–2.30 (2H, m), 2.02–1.95 (2H, m), 1.72–1.65 (1H, m), 1.62–1.52 (2H, m), 1.43 (9H, s), 1.43 (9H, s), 1.06 (9H, s), 1.06 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ =154.7, 143.8, 135.6, 132.9, 129.9, 127.8, 111.6, 79.5, 65.9, 64.2, 63.2, 49.0, 41.3, 40.8, 40.3, 38.9, 38.6, 28.4, 28.3, 26.9, 19.2; HRMS (ES) Found MNa^+ 532.2856. $C_{30}H_{43}NO_4NaSi$ requires MNa^+ 532.2859; LRMS *m/z* (ES) 532 (100%), 510 (6%).

4-[2-hydroxy-1-(4-methoxy-benzyloxymethyl)-ethyl]-3-methylene-piperidine-1-carboxylic acid tert-butyl ester 17

NaH (180 mg, 4.48 mmol, 60% dispersion in mineral oil) was added to the diol **14** (1.21 g, 4.48 mmol) in THF (20 mL) at 0 °C. After 50 min, 4-methoxybenzyl chloride (0.67 mL, 4.93 mmol) and tetrabutylammonium iodide (0.165 g, 4.48 mmol) in THF (5 mL) were dropwise. After 3 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (1:1), to give the alcohol **17** (1.39 g, 80%) as a mixture of diastereomers (1:1) as an oil; R_f 0.41 [petrol–EtOAc 1:1]; ν_{max} (neat)/cm^{-1} 3450, 3075, 2970, 2920, 2860, 1680, 1610, 1585; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23–7.18 (4H, m), 6.88–6.84 (4H, m), 4.94 (2H, br s), 4.81 (1H, s), 4.75 (1H, s), 4.46–4.36 (4H, m), 3.89–3.81 (4H, m), 3.78 (3H, s), 3.77 (3H, s), 3.74–3.62 (4H, m), 3.58–3.43 (4H, m), 3.42–3.81 (4H, m), 2.47–2.41 (1H, m), 2.41–2.35 (1H, m), 2.11–2.02 (2H, m), 1.74–1.61 (2H, m), 1.61–1.59 (1H, m), 1.53–1.45 (1H, m), 1.43 (18H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ =163.4, 159.2, 154.7, 143.9, 129.8, 129.7, 129.2, 113.8, 111.4, 79.5, 73.2, 72.4, 70.5, 64.5, 63.5, 55.2, 49.5, 48.0, 40.9, 39.3, 38.9, 38.7, 38.5, 28.3, 28.2; HRMS (ES) Found MNa^+, 414.2257. $C_{22}H_{33}NO_5Na$ requires MNa^+, 414.2256; LRMS *m/z* (ES) 414 (100%).

Alternatively, compound **17a** was prepared from **26** by the following method:

$LiAlH_4$ (96 mg, 2.5 mmol) was added to the ester **26** (1.0 g, 2.3 mmol) in THF (20 mL) at –5 °C. After 40 min, EtOAc (10 mL) was added, followed by addition of Na_2SO_4 until a while salt precipitated. The mixture was filtered through celite. The solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (1:1), to give the alcohol **17a** (0.63 g, 69%) as an oil; data for single stereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (2H, d, *J* 8), 6.90 (2H, d, *J* 8), 4.97 (1H, s), 4.79 (1H, s), 4.46–4.39 (2H, m), 3.97 (1H, d, *J* 14), 3.89 (1H, dd, *J* 11, 2), 3.82 (3H, s), 3.76–3.68 (2H, m), 3.60–3.47 (3H, m), 3.41–3.35 (1H, m), 2.50–2.45 (1H, m), 2.10–2.06 (1H, m), 1.78–1.62 (2H, m), 1.46 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ =159.3, 154.8, 143.8,

129.8, 129.3, 113.9, 111.6, 79.6, 73.3, 72.6, 63.8, 55.3, 48.8 (br), 40.9, 38.7, 38.5, 28.5, 28.3.

Alternatively, compound **17a** was prepared from **36** by the following method:

Aqueous hydrochloric acid (0.07 mL, 2 M) was added to the ether **36** (1.0 g, 2.30 mmol) in dry isopropyl alcohol (10 mL) and the mixture was heated at 60 °C. After 7 h, the mixture was allowed to cool to room temperature and saturated aqueous $NaHCO_3$ solution (20 mL) was added. The mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (1:1), gave the alcohol **17a** (0.61 g, 68%) as an oil; data as above.

tert-Butyl 3-(Hydroxymethyl)-7a-(iodomethyl)-octahydrofuro[2,3-c]pyridine-6-carboxylate 18

Iodine (1.73 g, 6.83 mmol) in CH_2Cl_2 (30 mL) was added to the diol **14** (1.76 g, 6.50 mmol) in saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. After 2 h, aqueous Na_2SO_3 (10 mL) was added dropwise. The aqueous layer was separated and was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), evaporated and purified by column chromatography, eluting with EtOAc, to give iodide **18** (1.94 g, 75%) as mixture of diastereoisomers (3:1) as an oil; R_f 0.41 (EtOAc); ν_{max} (neat)/cm^{-1} 3450, 3310, 2930, 2850, 1695, 1610; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for major diastereomer listed) δ = 4.09 (1H, t, *J* 7), 3.98–3.85 (1H, m), 3.79–3.67 (4H, m), 3.43 (1H, d, *J* 11), 3.35 (1H, d, *J* 11), 3.08–2.98 (2H, m), 2.55–2.50 (1H, m), 2.13–1.92 (2H, m), 1.83–1.70 (2H, m), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ = 154.8, 80.6, 69.5, 63.5, 60.4, 47.6, 45.0, 43.6, 39.3, 28.4, 24.4, 14.3; HRMS (ES) Found MNa^+ 420.0631. $C_{14}H_{24}NO_4INa$ requires MNa^+ 420.0648; LRMS *m/z* (ES) 420 (100%).

tert-Butyl 7a-(Iodomethyl)-3-{[(4-methoxyphenyl)methoxy]methyl}-octahydrofuro[2,3-c]pyridine-6-carboxylate 19

Alcohol **18** (2.14 g, 5.40 mmol) in THF (10 mL) was added via cannula to sodium hydride (0.2 g, 8.6 mmol) in THF (20 mL). After 30 min, the mixture was cooled to 0 °C and 4–methoxybenzyl chloride (0.84 mL, 6.21 mmol) in THF (10 mL) was added. After 30 min the mixture was allowed to warm to room temperature. After 24 h, aqueous sodium chloride solution (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), dried ($MgSO_4$), evaporated and purified by column chromatography, eluting with petrol–EtOAc (9:1), to give the iodide **19** (2.6 g, 60%) as a mixture of diastereomers (3:1) as an oil; R_f 0.51 (petrol–EtOAc 8:2); ν_{max} (neat)/cm^{-1} 2850, 1685, 1615, 1595; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for major diastereomer listed) δ = 7.25 (2H, d, *J* 8.5), 6.90 (2H, d, *J* 8.5), 4.45 (2H, s), 4.08 (1H, t, *J* 7.5), 4.10–4.06 (1H, m), 3.83 (3H, s), 3.69 (1H, t, *J* 7.5), 3.57–3.47 (2H, m), 3.42 (1H, d, *J* 11), 3.32 (1H, d, *J* 11), 3.04–2.93 (2H, m), 2.62–2.57 (1H, m), 2.09–2.06 (1H, m), 1.77–1.71 (2H, m), 1.64–1.56 (1H, m), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ = 159.3, 154.7, 130.0, 129.2, 113.9, 80.5, 73.0, 71.0, 69.9, 69.5, 55.3, 47.3, 44.1, 42.1, 41.6, 28.4, 24.4, 14.4; HRMS (ES) Found MH^+ 518.1392. $C_{22}H_{32}NO_5I$ requires MH^+ 518.1404; LRMS *m/z* (ES) 540 (100%, MNa^+).

***tert*-Butyl 4-[2-(1-Oxo-propenyl)]-3-methylidenepiperidine-1-carboxylate 21**

Aqueous formaldehyde (37%) (0.44 mL, 5.4 mmol) was added to the aldehyde **20**[6b] (1.0 g, 4.2 mmol) and L-proline (48 mg, 0.42 mmol) in DMF (5 mL) at room temperature. After 5 h, brine (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with petrol–EtOAc (4:1), to give the aldehyde **21** (938 mg, 89%) as an oil; R_f 0.40 [petrol–EtOAc 4:1]; ν_{max} (neat)/cm^{-1} 2980, 1685; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.46 (1H, s), 6.21 (1H, s), 6.15 (1H, s), 4.76 (1H, s), 4.34 (1H, s), 4.31 (1H, br s), 3.97 (1H, br s), 3.42 (1H, d, *J* 13), 3.29 (1H, dd, *J* 11, 5), 2.97–2.82 (1H, m), 1.67–1.56 (2H, m), 1.33 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.4, 154.2, 150.0, 143.4, 135.6, 109.9, 79.4, 49.7 (br), 43.2, 39.9, 30.5, 28.1; HRMS (ES) Found MH^+ 252.1589. $C_{14}H_{22}NO_3$ requires MH^+ 252.1600; LRMS *m/z* (ES) 252 (27%), 196 (100%).

4-(1-Ethoxycarbonyl-2-hydroxy-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 22 and 23

n-BuLi (8.12 mL, 16.2 mmol, 2.0 M in hexanes) was added to diisopropylamine (2.45 mL, 17.5 mmol) in THF (50 mL) at 0 °C. After 30 min the mixture was cooled to –78 °C and the ester **4** (3.83 g, 13.5 mmol) was added dropwise. After 3.5 h formaldehyde (1.22 g, 40.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h. Saturated $NH_4Cl_{(aq)}$ (50 mL) was added and the mixture was extracted with Et_2O (4 × 50 mL). The organic layers were washed with water, dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (3:2), gave a 1:1 separable mixture of alcohols **22** and **23** (2.66 g, 63%) as oils;

Data for **22**:

R_f 0.38 [petrol–EtOAc 1:1]; ν_{max} (neat)/cm^{-1} 3455, 2940, 2875, 1730, 1690, 1675; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 4.91 (1H, br s), 4.79 (1H, s), 4.19–4.07 (2H, m), 3.97 (1H, d, *J* 14), 3.80–3.90 (2H, m), 3.59–3.32 (3H, m), 2.91–2.82 (1H, m), 2.80–2.67 (1H, m), 2.30 (1H, br s), 1.84–1.63 (2H, m), 1.43 (9H, s), 1.23 (3H, t, *J* 7); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 174.5, 154.6, 143.1, 111.1, 79.7, 61.0, 60.6, 48.1, 41.4, 40.0, 28.4, 28.3, 14.1; HRMS (ES) Found MH^+ 314.1964. $C_{16}H_{28}NO_5$ requires MH^+ 314.1967; LRMS *m/z* (ES) 336 (43%), 314 (13%), 258 (100%).

Data for **23**:

R_f 0.47 [petrol–EtOAc 1:1]; ν_{max} (neat)/cm^{-1} 3425, 2980, 2935, 1730, 1695; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.91 (1H, br s), 4.80 (1H, s), 4.15–4.06 (2H, m), 4.00–3.86 (1H, m), 3.68–3.56 (3H, m), 3.55–3.45 (1H, m), 3.33–3.23 (1H, m), 3.03–2.74 (2H, m), 2.55–2.50 (1H, m), 1.68–1.57 (1H, m), 1.48–1.35 (1H, m), 1.35 (9H, s), 1.21–1.15 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.2, 154.6, 142.4, 112.5, 79.7, 62.4, 60.7, 48.8 (br), 47.4,

40.5, 40.0, 29.6, 28.3, 14.1; HRMS (ES) Found MNa^+ 336.1785. $C_{16}H_{27}NO_5Na$ requires MNa^+ 336.1787; LRMS *m/z* (ES) 336 (100%).

4-[2-(4-Bromo-benzoyloxy)-1-ethoxycarbonyl-ethyl]-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 24

4-Bromobenzoyl chloride (352 mg, 1.60 mmol), Et_3N (0.27 mL, 1.92 mmol) and DMAP (78 mg, 0.64 mmol) were added to the alcohol **22** (more polar diastereomer) (200 mg, 0.64 mmol) in CH_2Cl_2 (10 mL). After 3 h, saturated aqueous $NaHCO_3$ (10 mL) was added. Extraction with CH_2Cl_2 (3 × 10 mL), drying ($MgSO_4$), and purification by column chromatography, eluting with petrol–EtOAc (4:1), gave the ester **24** (313 mg, 99%) as an oil; R_f 0.18 [petrol–EtOAc 7:3]; ν_{max} (neat)/cm^{-1} 3070, 2965, 2925, 2865, 1725, 1695, 1590; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.82–7.77 (2H, m), 7.54–7.50 (2H, m), 5.01 (1H, br s), 4.92 (1H, br s), 4.48 (1H, dd, *J* 10.5, 4), 4.29 (1H, t, *J* 10.5), 4.15 (2H, q, *J* 7), 3.70 (1H, d, *J* 17), 3.65–3.56 (1H, m), 3.36–3.28 (1H, m), 3.20–3.14 (1H, m), 2.63 (1H, dt, *J* 11, 5), 1.77–1.68 (1H, m), 1.56–1.49 (1H, m), 1.41 (9H, s), 1.18 (3H, t, *J* 7); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.7, 165.3, 154.6, 141.9, 131.7, 131.0, 128.6, 128.3, 113.1, 79.7, 65.1, 60.9, 48.0 (br), 44.7, 40.5, 39.9 (br), 29.7, 28.3, 14.2; HRMS (ES) Found MH^+ 496.1313. $C_{23}H_{31}{}^{79}BrNO_6$ requires MH^+ 496.1335; LRMS *m/z* (ES) 498 (25%), 496 (28%), 442 (92%), 440 (100%), 398 (65%), 396 (68%).

4-Bromobenzoic acid 2-Ethoxycarbonyl-2-[3-methylene-1-(toluene-4-sulfonyl)-piperidin-4-yl]-ethyl ester 25

TFA (0.65, 8.52 mmol) was added to the ester **24** (1.05 g, 2.13 mmol) in CH_2Cl_2 (15 mL). After 16 h, further TFA (4.0 mL, 51.9 mmol) was added. After 2 h, saturated aqueous $NaHCO_3$ was added until the solution became basic and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated to give the secondary amine as an oil. To this, in CH_2Cl_2 (10 mL) with Et_3N (0.33 mL, 2.34 mmol) at room temperature, was added tosyl chloride (446 mg, 2.34 mmol). After 19 h, water (20 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (4:1), followed by recrystallisation from EtOAc, gave the ester **25** (729 mg, 62% over 2 steps) as needles; m.p. 153–154 °C; R_f 0.35 [petrol–EtOAc 4:1]; ν_{max} (neat)/cm^{-1} 2955, 2915, 2855, 1725, 1715, 1650, 1585, 1340, 1155; ^1H NMR (250 MHz, $CDCl_3$) δ = 7.77 (2H, d, *J* 8), 7.63 (2H, d, *J* 8), 7.52 (2H, d, *J* 8), 7.30 (2H, d, *J* 8), 5.12 (1H, br s), 5.02 (1H, br s), 4.40 (1H, dd, *J* 10.5, 3.5), 4.28–4.07 (3H, m), 3.73 (1H, d, *J* 12.5), 3.45–3.23 (2H, m), 3.07–2.85 (2H, m), 2.64–2.49 (1H, m), 2.42 (3H, s), 1.96–1.74 (1H, m), 1.72–1.51 (1H, m), 1.18 (3H, t, *J* 7); ^{13}C NMR (63 MHz, $CDCl_3$, one C not observed) δ = 172.3, 165.2, 143.7, 139.8, 133.2, 131.8, 131.0, 129.8, 128.4, 127.7, 114.8, 64.7, 61.1, 50.3, 44.5, 42.7, 39.8, 28.9, 21.5, 14.2; HRMS (ES) Found MNa^+ 572.0706. $C_{25}H_{28}{}^{79}BrNNaO_6S$ requires MNa^+ 572.0718; LRMS *m/z* (ES) 574 (96%), 572 (100%); Found C, 54.65; H, 4.91; N, 2.40; Br, 14.62; S, 5.88, $C_{25}H_{28}BrNO_6S$ requires C, 54.55; H, 5.13; N, 2.54; Br, 14.52; S, 5.82. For X-ray data, see CCDC 1025236 [Monoclinic, Unit cell dimensions: a 19.1472(17), b 5.7177(5), c 22.9157(19), Volume 2484.3(4) $Å^3$, *T* = 150 K, P21/n, *Z* = 4].

tert-Butyl 4-{1-Hydroxy-3-[(4-methoxyphenyl)methoxy]propan-2-yl}-3-methylidenepiperidine-1-carboxylate 26

p-Methoxybenzyl alcohol (5.57 mL, 20 mmol) was added to a suspension of NaH (0.62 g, 20 mmol) in Et_2O (15 mL) at room temperature. After 30 min, the mixture was cooled to 0 °C and Cl_3CCN (4.30 mL, 20 mmol) was added. The mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Petrol (30 mL) and MeOH (0.5 mL) were added, the mixture was filtered through celite and the solvent was evaporated to give the crude trichloroacetimidate. To this was added CH_2Cl_2 (35 mL), the alcohol **23** (3.1 g, 10 mmol) and CSA (0.3 g, 1.0 mmol) at room temperature. After 18 h, the saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The organic layers were washed with water and purified by column chromatography on silica, eluting with petrol–EtOAc (9:1), to give the ester **26** (3.51 g, 82%) as an oil; R_f 0.50 [petrol–EtOAc 9:1]; ν_{max} (neat)/cm^{-1} 2990, 2935, 1725, 1695, 1610; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21 (2H, d, *J* 8), 6.89 (2H, d, *J* 8), 4.96 (1H, s), 4.83 (1H, s), 4.44 (1H, d, *J* 11.5), 4.39 (1H, d, *J* 11.5), 4.20 (2H, q, *J* 7), 3.81 (3H, s), 3.70–3.66 (1H, m), 3.64–3.59 (2H, m), 3.50 (1H, dd, *J* 9, 4.5), 3.40–3.33 (1H, m), 3.09–3.01 (1H, m), 2.59–2.51 (1H, m), 1.76–1.65 (1H, m), 1.57–1.46 (2H, m), 1.45 (9H, s), 1.27 (3H, t, *J* 7); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks could not be observed) δ = 159.3, 154.8, 144.0, 129.9, 129.3, 113.9, 111.6, 79.6, 73.3, 72.5, 65.8, 63.7, 55.3, 38.8, 38.6, 28.4, 28.3, 15.3; HRMS (ES) Found MH^+ 434.2538. $C_{24}H_{36}NO_6$ requires MH^+ 434.2543; LRMS *m/z* (ES) 456 (100%, MNa^+).

***tert*-Butyl 4-{1-Iodo-3-[(4-methoxyphenyl)methoxy]propan-2-yl}-3-methylidenepiperidine-1-carboxylate 27**

Imidazole (0.18 g, 2.8 mmol) and iodine (0.67 g, 2.8 mmol) were added to PPh_3 (0.74 g, 2.8 mmol) in CH_2Cl_2 (15 mL). After 10 min, the alcohol **17a** (1.0 g, 2.55 mmol) in CH_2Cl_2 (5 mL) was added. After 5 min, the mixture was filtered through celite, washed with EtOAc (3 × 15 mL) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the iodide **27** (1.24 g, 95%) as an oil; R_f 0.40 (petrol–EtOAc 9:1); ν_{max} (neat)/cm^{-1} 2970, 2925, 2855, 1695, 1650, 1610, 1585; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27 (2H, d, *J* 8.5), 6.90 (2H, d, *J* 8.5), 4.99 (1H, m), 4.81 (1H, s), 4.44 (2H, s), 3.97 (1H, d, *J* 14), 3.83 (3H, s), 3.82–3.76 (1H, m), 3.67 (1H, dd, *J* 10, 2.5), 3.52–3.47 (2H, m), 3.41–3.31 (2H, m), 3.22 (1H, dd, *J* 10, 5.5), 2.33–2.28 (1H, m), 1.78–1.71 (2H, m), 1.62–1.55 (1H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 154.7, 143.5, 130.3, 129.3, 113.8, 111.9, 79.7, 73.0, 70.6, 55.3, 42.0, 40.8 (br), 37.8, 28.4, 27.7, 10.4; HRMS (ES)

Found MNa^+ 524.1262. $C_{22}H_{32}NO_4INa$ requires MNa^+ 524.1274; LRMS *m/z* (ES) 524 (100%).

***tert*-Butyl 4-{1-[2-(Ethoxycarbonyl)-1,3-dithian-2-yl]-3-[(4-methoxyphenyl)methoxy]propan-2-yl}-3-methylidenepiperidine-1-carboxylate 28**

To a solution of ethyl 1,3-dithiane-2-carboxylate (0.80 mL, 5.08 mmol) in THF (20 mL) at –78 °C was added *n*BuLi (2.0 mL, 5.08 mmol, 2.5 M in hexane) and HMPA (CAUTION, toxic) (3.1 mL, 17.6 mmol). After 10 min, the mixture was warmed to –40 °C, and the iodide **27** (2.0 g, 4.0 mmol) in THF (10 ml) was added. The mixture was allowed to warm to room temperature. After 24 h, water (40 mL) was added and the mixture was extracted with EtOAc (4 × 40 mL), dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with petrol–EtOAc (9:1), to give ester **28** (1.8 g, 80%) as an oil; R_f 0.38 (petrol–EtOAc, 8:2); ν_{max} (neat)/cm^{-1} 3065, 2970, 2865, 1720, 1695, 1610, 1585; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 (2H, d, *J* 8), 6.88 (2H, d, *J* 8), 4.97 (1H, s), 4.92 (1H, s), 4.34 (2H, s), 4.21 (2H, q, *J* 7), 3.95 (1H, d, *J* 14), 3.82 (3H, s), 3.79–3.75 (2H, m), 3.57–3.50 (1H, m), 3.46–3.41 (2H, m), 3.37–3.30 (1H, m), 3.19–3.12 (1H, m), 2.72–2.67 (2H, m), 2.53–2.32 (3H, m), 2.15–2.02 (2H, m), 1.93–1.83 (1H, m), 1.71–1.63 (2H, m), 1.47 (9H, s), 1.31 (3H, t, *J* 7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1, 159.1, 154.8, 144.0, 130.6, 129.2, 113.6, 111.7, 79.4, 72.6, 70.7, 69.5, 62.0, 55.3, 53.8, 42.3, 41.3 (br), 37.0, 34.4, 28.5, 28.2, 27.3, 24.4, 14.1; HRMS (ES) Found MH^+ 566.2604. $C_{29}H_{44}NO_6S_2$ requires MH^+ 566.2610; LRMS *m/z* (ES) 588 (100%), 566 (92%).

***tert*-Butyl 4-{1-[2-(Hydroxymethyl)-1,3-dithian-2-yl]-3-[(4-methoxyphenyl)methoxy]propan-2-yl}-3-methylidenepiperidine-1-carboxylate 29**

$LiAlH_4$ (1.40 mL, 2.78 mmol, 2.0 M in THF) was added to the ester **28** (1.45 g, 2.57 mmol) in THF (40 mL) at –5 °C. After 40 min, the EtOAc (20 mL) and then saturated aqueous Na_2SO_4 were added until a white salt precipitated. After 15 min, the mixture was filtered through celite, evaporated and purified by column chromatography, eluting with petrol–EtOAc (1:1), to give the alcohol **29** (1.15 g, 85%); alternatively, using $LiAlH_4$ (37.5 mg, 0.95 mmol) with the ester **28** (500 mg, 0.88 mmol) gave the alcohol **29** (440 mg, 93%) as an oil; R_f 0.39 (petrol–EtOAc, 1:1); υ_{max} (neat)/cm^{-1} 3450, 3075, 2930, 2855, 1685, 1610, 1580; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 (2H, d, *J* 8), 6.88 (2H, d, *J* 8), 4.95 (1H, br s), 4.86 (1H, s), 4.38 (2H, s), 4.10–3.90 (1H, m), 3.83 (3H, s), 3.79 (2H, s), 3.74–3.64 (1H, m), 3.54–3.47 (4H, m), 3.00–2.91 (2H, m), 2.77–2.69 (1H, br s), 2.63–2.59 (2H, m), 2.40–2.36 (1H, m), 2.29–2.23 (1H, m), 2.13–2.07 (1H, m), 2.03–1.98 (1H, m), 1.88–1.75 (3H, m), 1.72–1.63 (1H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 154.8, 144.4, 130.2, 129.4, 113.7, 111.8, 79.4, 72.8, 72.0, 63.4, 55.3, 54.7, 43.8, 37.2, 33.7, 28.5, 26.0, 25.9, 24.8; HRMS (ES) Found MH^+ 524.2484. $C_{27}H_{41}NO_5S_2$ requires MH^+ 524.2504; LRMS *m/z* (ES) 546 (38%), 524 (100%).

***tert*-Butyl 4-{5-Hydroxy-4,4-dimethoxy-1-[(4-methoxyphenyl)methoxy]pentan-2-yl}-3-methylidenepiperidine-1-carboxylate 30**

The alcohol **29** (1.15 g, 2.20 mmol) in THF (10 mL) was added to $AgNO_3$ (1.70 g, 5.17 mmol), 2,4,6-collidine (2.33 mL, 17.6 mmol) and *N*-chlorosuccinimide (1.15 g, 8.80 mmol) in THF (20 mL) and MeOH (30 mL) at 0 °C. After 1 h, saturated aqueous Na_2CO_3 (15 mL) and brine (15 mL) were added and the mixture was filtered through celite, washed with CH_2Cl_2, dried ($MgSO_4$), evaporated and purified by column chromatography, eluting with petrol–EtOAc (6:4), to give alcohol **30** (0.52 g, 49%) as an oil; R_f 0.64 (petrol–EtOAc, 1:1); υ_{max} (neat)/cm^{-1} 3450, 2970, 2930, 2860, 1690, 1610, 1590; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26–7.24 (2H, m), 6.91–6.88 (2H, m), 4.94 (1H, s), 4.86 (1H, s), 4.44–4.38 (2H, m), 4.00–3.98 (1H, m), 3.82 (3H, s), 3.73–3.70 (1H, m), 3.65–3.55 (2H, m), 3.49–3.45 (2H, m), 3.40–3.34 (1H, m), 3.22 (6H, s), 3.04 (1H, s), 2.55 (1H, s), 2.35–2.31 (2H, m), 2.20 (1H, br s), 1.80–1.76 (2H, m), 1.67–1.63 (1H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0, 154.8, 143.4, 129.6, 129.3, 113.8, 111.5, 102.4, 79.5, 73.1, 71.9, 70.3, 58.6, 54.3, 48.3, 48.1, 43.9, 32.7, 31.9, 31.5, 28.4, 27.2; HRMS (ES) Found MNa^+ 502.2749, $C_{26}H_{41}NO_7Na$ requires MNa^+ 502.2724; LRMS *m/z* (ES) 502 (100%).

***tert*-Butyl 4-{4,4-Dimethoxy-1-[(4-methoxyphenyl)methoxy]-5-oxopentan-2-yl}-3-methylidenepiperidine-1-carboxylate 31**

DMSO (0.14 mL, 1.99 mmol) in CH_2Cl_2 (1 mL) was added to oxalyl chloride (0.084 mL, 0.99 mmol) in CH_2Cl_2 (4 mL) at –60 °C. After 10 min, alcohol **30** (0.40 g, 0.83 mmol) in CH_2Cl_2 (1.5 mL) was added. After 10 min, Et_3N (0.52 mL, 3.73 mmol) was added and the mixture was allowed to warm to room temperature. After 1 h, CH_2Cl_2 (5 mL) and water (5 mL) were added and the mixture was filtered through celite, washed with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), evaporated and purified by column chromatography, eluting with petrol–EtOAc (7:3), to give aldehyde **31** (0.32 g, 80%) as an oil; R_f 0.79 (petrol–EtOAc 1:1); υ_{max} (neat)/cm^{-1} 2975, 2930, 2860, 2835, 1745, 1690, 1645, 1610, 1585; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.33 (1H, s), 7.24 (2H, d, *J* 8), 6.88 (2H, d, *J* 8), 4.96 (1H, br s), 4.78 (1H, s), 4.26 (2H, s), 4.00–3.92 (1H, m), 3.82 (3H, s), 3.70 (1H, d, *J* 14), 3.44–3.39 (2H, m), 3.31 (3H, s), 3.25 (3H, s), 2.46–2.42 (1H, m), 1.99–1.87 (3H, m), 1.71–1.59 (4H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.7, 160.4, 154.6, 143.3, 129.6, 129.3, 113.9, 111.2, 102.2, 79.4, 72.8, 71.3, 55.5, 54.3, 49.7, 49.6, 43.6, 41.3, 32.7, 30.5, 28.5, 27.8; HRMS (ES) Found MNa^+ 500.2649. $C_{26}H_{39}NO_7Na$ requires MNa^+ 500.2624; LRMS *m/z* (ES) 500 (100%) 478 (10%).

2-*tert*-Butyl 9-Ethyl 7-Methoxy-5-{[(4-methoxyphenyl)methoxy]methyl}-8-(prop-2-en-1-yl)-1H,2H,3H,4H,5H,7aH,8H,9H,10H,10bH-pyrrolo[2,3-j]isoquinoline-2,9-dicarboxylate 32

N-Allylglycine ethyl ester hydrochloride salt (0.23 g, 1.26 mmol), the aldehyde **31** (300 mg, 0.63 mmol) and $^iPr_2NEt$ (0.22

mL, 1.26 mmol) in toluene (5 mL) were heated under reflux with a Dean–Stark trap. After 2 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (4:1), to give the cycloadduct **32** (140 mg, 38%) as an oil; R_f 0.14 (petrol–EtOAc, 4:1); υ_{max} (neat)/cm^{-1} 2930, 2860, 1730, 1690, 1610, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (2H, d, *J* 8), 6.90 (2H, d, *J* 8), 5.86–5.73 (1H, m), 5.08 (1H, br d, *J* 17), 4.96 (1H, br d, *J* 10), 4.83 (1H, br s, vinyl ether CH), 4.52–4.44 (2H, ABq), 4.14 (2H, q, *J* 7), 3.95–3.87 (1H, br m), 3.82 (3H, s), 3.71 (1H, dd, *J* 9, 4), 3.67–3.52 (2H, m), 3.52 (3H, s), 3.38–3.25 (3H, m), 2.90–2.73 (2H, m), 2.62–2.58 (1H, m), 2.19–2.11 (1H, m), 1.90–1.45 (5H, m), 1.43 (9H, s), 1.27 (3H, t, *J* 7); ^{13}C NMR (100 MHz, $CDCl_3$, data from JMOD and HSQC) δ = 174.4 (C=O), 159.2 (C), 155.0 (C=O), 153.2 ($C_{vinyl\ ether}$), 136.7 (CH), 130.4 (C), 129.1 (CH), 115.9 (CH_2), 113.8 (CH), 97.4 ($CH_{vinyl\ ether}$), 79.3 (C), 74.7 (CH_2), 72.8 (CH_2), 64.2 (CH), 61.6 (CH), 60.1 (CH_2), 55.2 (CH_3), 54.0 (CH_3), 52.6 (CH_2), ~49.0 (sometimes could discern very broad, possible NCH_2), 45.0 (C), ~39.0 (sometimes could discern very broad, possible NCH_2), 38.6 (CH_2), 35.7 (CH), 35.5 (CH), 28.4 (CH_3), 23.7 (CH_2), 14.3 (CH_3); HRMS (ES) Found MH^+ 571.3374. $C_{32}H_{47}N_2O_7$ requires MH^+ 571.3383; LRMS *m/z* (ES) 571 (100%).

2-*tert*-Butyl 9-Ethyl 7,7-Dimethoxy-5-{[(4-methoxyphenyl)methoxy]methyl}-dodecahydropyrrolo[2,3-j]isoquinoline-2,9-dicarboxylate 33

The aldehyde **31** (0.25 g, 0.52 mmol), glycine ethyl ester hydrochloride salt (0.15 g, 1.05 mmol) and ^{i}Pr$_2$NEt (0.18 mL, 1.05 mmol) were heated in toluene (5 mL) were heated under reflux with a Dean–Stark trap. After 3 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (3:2), to give the cycloadduct **33** (0.17 g, 60%) as an oil; R_f 0.10 (petrol–EtOAc 3:2); υ_{max} (neat)/cm^{-1} 3285, 2930, 1690, 1615; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (2H, d, *J* 8.5), 6.88 (2H, d, *J* 8.5), 4.41 (2H, q, *J* 7), 4.26–4.10 (2H, m), 4.05–3.78 (2H, m), 3.82 (3H, s), 3.58–3.30 (4H, m), 3.27 (3H, s), 3.21 (3H, s), 3.12–2.87 (1H, m), 2.83–2.61 (1H, m), 2.41–1.95 (4H, m), 1.94–1.51 (4H, m), 1.46 (9H, s), 1.24 (3H, t, *J* 7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.5, 159.1, 154.8, 130.5, 129.0, 113.7, 100.4, 79.5, 72.7, 72.5, 71.1, 61.3, 56.9, 55.3, 48.0, 47.6, 45.7, 40.9, 36.9, 32.0, 31.7, 28.5, 23.9, 22.5, 20.8, 14.1; HRMS (ES) Found MH^+ 563.3304. $C_{30}H_{47}N_2O_8$ requires MH^+ 563.3332; LRMS *m/z* (ES) 563 (100%).

***tert*-Butyl 4-[1-Ethoxy-3-(methoxymethoxy)-1-oxopropan-2-yl]-3-methylidenepiperidine-1-carboxylate 34**

Chloromethyl methyl ether (0.44 mL, 5.76 mmol) was added to the alcohol **22** (1.50 g, 4.80 mmol) and diisopropyl ethylamine (6.33 mL, 6.24 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After 1 h, H_2O (20 mL) was added and the mixture was extracted with Et_2O (2 × 30 mL). The organic layers were washed with aqeuous HCl (10 mL, 1 M) and brine (10 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (7:3), gave the ester **34** (1.47 g, 86%) as an oil; R_f 0.69 (petrol–EtOAc, 3:2); ν_{max} (neat)/cm^{-1} 2930, 2860, 1735, 1695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.92 (1H, s), 4.79 (1H, s), 4.59 (2H, s), 4.17–4.08 (2H, m), 3.99 (1H, d, *J* 14), 3.85–3.76 (2H, m), 3.73–3.68 (1H, m), 3.60–3.53 (1H, m), 3.42–3.34 (1H, m), 3.33 (3H, s), 2.99 (1H, td, *J* 7, 4), 2.65–2.57 (1H, m), 1.81–1.73 (1H, m), 1.55–1.46 (1H, m), 1.44 (9H, s), 1.23 (3H, t, *J* 7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 154.6, 143.4, 111.2, 96.5, 79.6, 66.7, 60.5, 55.3, 46.7, 41.5 (br), 40.7, 28.6, 28.4, 14.2; HRMS (ES) Found MH^+ 358.2247. $C_{18}H_{32}NO_6$ requires MH^+ 358.2230; LRMS *m/z* (ES) 358 (50%), 302 (100%).

***tert*-Butyl 4-[1-Hydroxy-3-(methoxymethoxy)propan-2-yl]-3-methylidenepiperidine-1-carboxylate 35**

$LiAlH_4$ (2.03 mL, 2.78 mmol, 2.0 M in THF) was added to the ester **34** (1.45 g, 4.06 mmol) in THF (40 mL) at –5 °C. After 40 min, the EtOAc (20 mL) and then saturated aqueous Na_2SO_4 were added until a white salt precipitated. After 15 min, the mixture was filtered through celite, evaporated and purified by column chromatography, eluting with petrol–EtOAc (3:2), to give the alcohol **35** (1.11 g, 87%) as an oil; R_f 0.23 (petrol–EtOAc, 3:2); υ_{max} (neat)/cm^{-1} 3430, 2925, 2860, 1690, 1670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.02 (1H, s), 4.88 (1H, s), 4.64 (2H, ABq), 3.95 (1H, d, *J* 14), 3.86 (1H, d, *J* 14), 3.82 (1H, dd, *J* 10, 4), 3.75 (1H, dd, *J* 10, 4), 3.70 (1H, dd, *J* 10, 7), 3.65 (1H, dd, *J* 10, 7), 3.47 (2H, t, *J* 6), 3.39 (3H, s), 2.46–2.41 (1H, m), 2.17–2.10 (2H, m), 1.79–1.70 (1H, m), 1.66–1.57 (1H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 144.1, 111.4, 96.8, 79.6, 67.8, 64.1, 55.5, 49.3, 41.3, 39.4, 39.1, 28.4, 28.3; HRMS (ES) Found MH^+ 316.2112. $C_{16}H_{30}NO_5$ requires MH^+ 316.2124; LRMS *m/z* (ES) 316 (25%), 260 (100%).

***tert*-Butyl 4-[1-(Methoxymethoxy)-3-[(4-methoxyphenyl)methoxy]propan-2-yl]-3-methylidenepiperidine-1-carboxylate 36**

To a solution of alcohol **35** (450 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was added 4-methoxybenzyl 2,2,2-trichloroacetimidate (722 mg, 2.55 mmol) and CSA (33 mg, 0.14 mmol) at room temperature. After 24 h, saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with water, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (3:2), gave the ether **36** (490 mg, 80%) as an oil; R_f 0.60 (petrol–EtOAc, 3:2); υ_{max} (neat)/cm^{-1} 2930, 2835, 1615, 1515; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (2H, d, *J* 8.5), 6.89 (2H, d, *J* 8.5), 4.96 (1H, s), 4.82 (1H, s), 4.61 (2H, s), 4.41 (2H, s), 3.88 (2H, s), 3.82 (3H, s), 3.72 (1H, dd, *J* 10, 3.5), 3.55 (1H, dd, *J* 10, 6), 3.45–3.52 (2H, m), 3.37–3.45 (2H, m), 3.35 (3H, s), 2.40–2.49 (1H, m), 2.15–2.24 (1H, m), 1.68–1.79 (1H, m), 1.55–1.66 (1H, m), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1, 154.8, 144.3, 130.6, 129.2, 113.7, 111.0, 96.7, 79.6, 72.8, 69.1, 65.6, 55.3, 48.8, 41.4, 39.4, 38.2, 28.5, 28.1; HRMS (ES) Found MH^+ 436.2692. $C_{24}H_{38}NO_6$ requires MH^+ 436.2699; LRMS *m/z* (ES) 436 (100%).

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