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Preparation of (+)-nemorensic acid and approaches to nemorensine using the partial reduction of electron deficient furans

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Received (in Cambridge, UK) 12th March 2002, Accepted 15th April 2002
First published as an Advance Article on the web 2nd May 2002

Starting from a commercially available furoic acid, the synthesis of (+)-nemorensic acid is described in nine steps, and in 32% overall yield. Key steps in our sequence are a chiral auxiliary controlled, stereoselective, Birch reduction of 3-methyl-2-furoic acid and the stereoselective reaction of an oxonium ion generated within a tetrahydrofuran ring. Attempts to complete the synthesis of nemorensine did not succeed because of the low nucleophilicity of platynecine, the alkaloid base portion of the natural product.

Introduction

Pyrrolizidine alkaloids are a broad class of natural product, isolated from a variety of different plant sources. In 1994 the existence of some 6000 plants containing a variety of more than 180 known pyrrolizidine alkaloids was noted.[1] These compounds are important because of their biological activity, which ranges from carcinogenicity to hepatotoxicity and pyrrolizidine alkaloids have been reported to be responsible for severe cases of livestock poisoning.[2]

The toxic effect of pyrrolizidine alkaloids is related to P450 mediated oxidation of the 4-azabicyclo[3.3.0] ring system to give a pyrrole unit: this then has the ability to act as a double electrophile and is eminently capable of interstrand cross linking of DNA.[3]

We are interested in synthesising macrocyclic bislactone members of this class of compound and our attention was drawn to one such compound, nemorensine, that has not yet been synthesised.

The isolation of nemorensine was reported in 1973 from three different varieties of *Senecio Nemorensis L.*[4] After some confusion regarding the stereochemistry of the compound, the issue was proven unequovically by X-ray crystal structure in 1995.[5] Hydrolysis of the lactone units of nemorensine gives two components, platynecine (a necine base) and nemorensic acid, Fig. 1.[4]

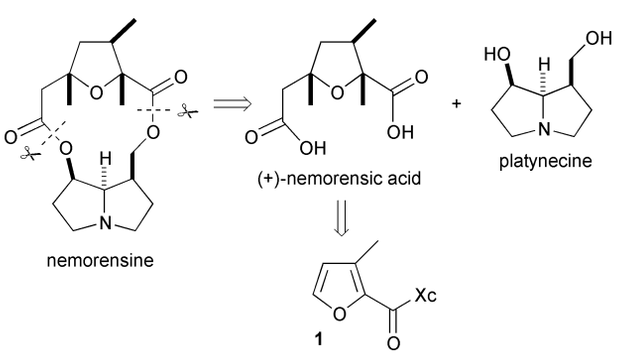

Fig. 1

The first synthesis of nemorensic acid was reported by Klein in 1985[6] and since that time five further syntheses have appeared,[7] including our own.[8]

In this paper we wish to report, in full, our attempts at preparing nemorensic acid using the (stereoselective) partial reduction of substituted furan **1** as a key step.[8] We also wish to disclose our work on the preparation of platynecine and initial efforts at coupling the two halves of nemorensine itself.

Results and discussion

Our synthesis began with the coupling of (commercially available) 3-methyl-2-furoic acid with (*R,R*)-bis(methoxymethyl)-pyrrolidine; this was accomplished by reaction of the corresponding acyl chloride with the amine in a mixture of CH_2Cl_2 and 2 M NaOH and afforded the desired amide **3** in 91% yield, Scheme 1. This amide was then subjected to a Birch reductive alkylation using sodium in liquid ammonia and subsequent addition of methyl iodide quenched the reaction and yielded compound **4** in 87% and as a 30 : 1 mixture of diastereoisomers (this compound was fully characterised and the ratio of diastereoisomers assessed by comparison to an authentic 1 : 1 standard).[9]† The ^{1}H NMR spectrum of **4** showed the appearance of a new methyl peak at 1.4 ppm and an absence of any peaks between 6.0 and 7.0 ppm corresponding to the furan nucleus.

The dihydrofuran obtained was then submitted to an allylic oxidation using Jones' reagent in a mixture of water–acetone to afford the lactone **5** in excellent yield. The IR spectrum of **5** contained two bands at 1764 and 1626 cm^{-1} characteristic of the carbonyl stretches. This lactone was then hydrogenated using palladium hydroxide on carbon to afford the compounds **6** and **7** in 88% yield and with a respective ratio of 92 : 8: these could be easily separated by chromatography on silica gel. The *cis* relationship between the two methyl groups

† We have previously reported methodology for the stereoselective reduction and are confident in both the sense and level of diastereoselectivity. We also know that the auxiliary can be removed without scrambling the stereochemistry at C-2. See ref. 9.

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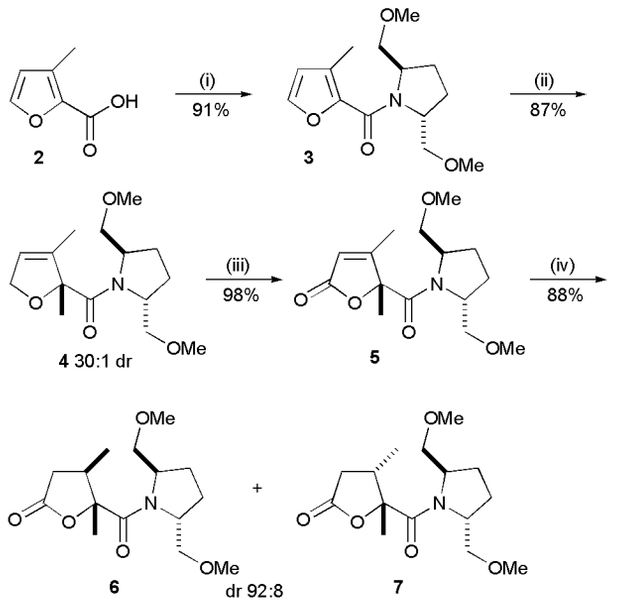
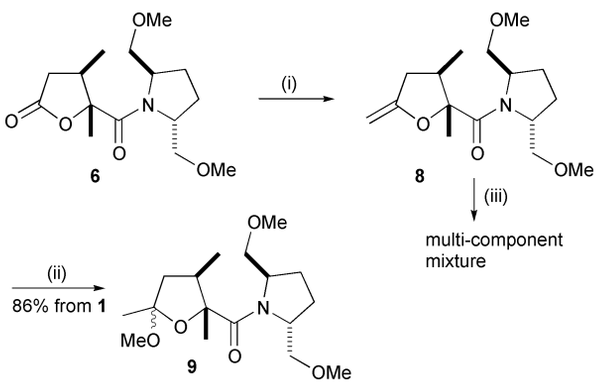


Scheme 1 *Reagents*: i. $SOCl_2$, then (*R,R*)-bis(methoxymethyl)pyrrolidine, (aq.) NaOH; ii. Na, NH_3, MeI; iii. CrO_3, H_2SO_4, (aq.) acetone; iv, H_2, $Pd(OH)_2$/C, EtOH.

on the major lactone **6** was proven unambiguously by X-ray crystallography.[10]

The lactone **6** was then treated with the Petasis reagent (Cp_2TiMe_2) to afford the enol ether **8**, Scheme 2. Petasis' reagent

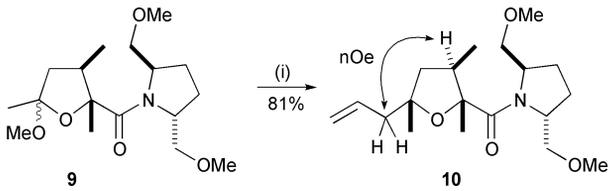


Scheme 2 *Reagents*: i. Cp_2TiMe_2, THF; ii. MeOH, HCl; iii. AcOH.

was prepared by treating bis(cyclopentadienyl)titanium dichloride with 2.2 equivalents of MeLi in ether.[11] The orange needles, obtained after recrystallisation from pentane, could be kept in the freezer in the dark and re-used for up to two weeks. The methylenation reaction was followed by IR (disappearance of the band at 1787 cm^{-1} characteristic of the lactone carbonyl and appearance of a band at 1673 cm^{-1} characteristic of formation of the enol ether). After addition of petrol to the reaction, a solid precipitated and the mixture was filtered through a cotton plug. It was, however, difficult to remove all of the titanium by-products by filtration and the enol ether **8** was not stable to purification by column chromatography. Therefore, we used crude material directly in the next step.

With the aim of making an acetal, the enol ether **8** was treated with acetic acid. However, a multi-component mixture was obtained each time which showed evidence of formation of the corresponding lactol and ring opened isomers. It was decided to replace the acetate by a more stable group and so the reaction of enol ether **8** with methanol was performed under acidic conditions, and this gave acetal **9** in 86% from the lactone **6**. The acetal product obtained was a 1 : 1 mixture of two diastereoisomers separable by column chromatography; this separation was only performed for characterisation. Each of the acetal diastereoisomers, which were not assigned, possessed a methoxy peak in the proton NMR around 3.3 ppm, and both were fully characterised.

The allylation reaction of the methyl acetal mixture **9** proved to be challenging. Different Lewis acids and conditions were used to generate compound **10** Scheme 3. This reaction works in



Scheme 3 *Reagents*: i. $TiCl_4$, allyltrimethylsilane, DCM.

two steps, the first being formation of an oxonium ion and the second being attack on the oxonium by the allyltrimethylsilane nucleophile. Strong Lewis acids worked best and nucleophilic attack was encouraged by using a large excess (20 eq.) of allyltrimethylsilane in dichloromethane at room temperature.[12] Under these conditions, the reaction was reproducible and high yielding for formation of **10**: moreover, examination of the crude NMR spectrum of the reaction showed only a single diastereoisomer of product. In the absence of the other diastereoisomer for comparative purposes, the diastereoselectivity was assigned conservatively as being $\geqslant 10:1$.

The structure of allylated product **10**, could be clearly assigned by examination of its NMR data. A multiplet integrating for one proton at 5.75 ppm, and another, integrating for two protons, at 5.05 ppm confirmed the presence of a terminal double bond in the molecule. The sense of the diastereoselectivity was proved by an NOE experiment which showed strong, and reciprocal, NOE enhancements between the methine at C-3 and the allylic methylene attached to C-5.[8]

This sense of diastereoselectivity (addition of a nucleophile *trans* to the C-3 methyl group) is in accord with the selectivity displayed by the parent 3-methyltetrahydrofuran derived oxonium ion.[12] It may also be the case that geminal substitution at C-2 aids the stereoselectivity, as has been noted by Woerpel[13] in related systems. Assuming that the intermediate oxonium ion reacts in an envelope conformation Fig. 2, the bulky amide

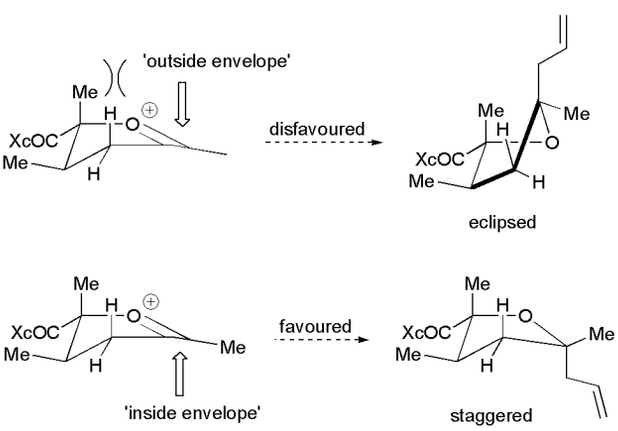


Fig. 2

group at C-2, sits in a pseudo-equatorial position forcing the methyl group to adopt a pseudo-axial orientation where it may block the top face of the oxonium ion as shown.

More recently, Woerpel[14] has proposed a second model based on torsional strain which is also relevant here. In this model, the oxonium ion sits opposite the 'flap' of the envelope and the preferred attack is from inside, rather than outside, the envelope. Nucleophilic attack on an oxonium ion in this conformation from outside the envelope would result in the development of a disfavoured eclipsing interaction between substituents at C-1 and C-2 of the resulting tetrahydrofuran

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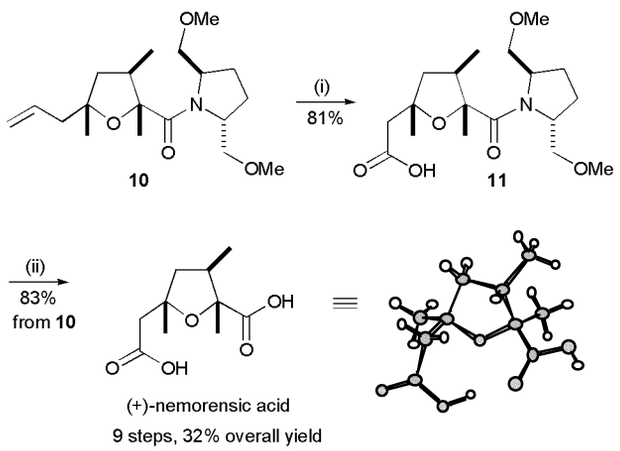
ring, see Fig. 2. Conversely, nucleophilic attack from inside the envelope gives the tetrahydrofuran ring in a staggered conformation and is preferred.

Note that both arguments predict the same outcome (one of only two that are possible) and without further evidence it is difficult to separate the relative contributions that each makes to the stereoselectivity shown.

Ruthenium tetraoxide catalysed oxidation of the terminal double bond within **10** to give the carboxylic acid **11** was realised following Sharpless' methodology,[15] Scheme 4;



Scheme 4 *Reagents*: i. $RuCl_3 \cdot xH_2O$, $NaIO_4$; ii. (6 M) HCl.

compound **11** was used directly in the next step without purification. Cleavage of the chiral auxiliary was achieved by hydrolysis using a 6 M HCl solution heated at reflux and nemorensic acid was obtained as a colourless solid in 83% yield from **10**.

All data (^{1}H, ^{13}C NMR, ms, $[\alpha]_D$) of synthetic (+)-nemorensic acid were in accordance with those reported in the literature.[7] Moreover, the structure of the synthetic material was proved by X-ray crystallography.[8]

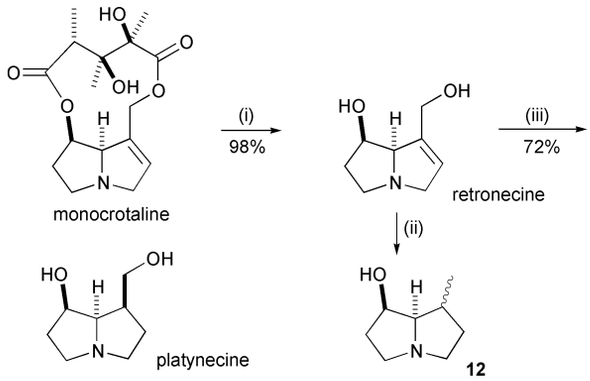
In total, this synthesis was realised in 32% overall yield over nine steps. Moreover, it is amenable to the synthesis of substantial amounts of enantiopure nemorensic acid and, using this route, hundreds of milligrams of this molecule have been synthesised.

Having completed the synthesis of nemorensic acid and made significant quantities of material, it was decided to attempt the first synthesis of nemorensine.

Fig. 1 reveals the main challenge in this coupling, namely that the primary hydroxy group on platynecine has to be coupled to the most hindered carboxylic acid on nemorensic acid, whereas the less reactive alcohol (secondary hydroxy group) has to couple to the most accessible acid. A successful coupling should therefore involve differentiation of either the hydroxys of platynecine and/or the carboxylic acids of nemorensic acid. Without this differentiation between groups, the coupling could conceivably occur in two ways to form either nemorensine or its unnatural regioisomer.

The necine base of nemorensine, platynecine, can be obtained from the naturally occurring pyrrolizidine alkaloid monocrotaline, which is commercially available. Double hydrolysis of this molecule was effected following a literature procedure Scheme 5 which consisted of reacting monocrotaline with 2.2 eq. of barium hydroxide octahydrate in water, followed by heating at reflux.[1] This reaction worked well and 98% yield of retronecine could be isolated. All data (^{1}H, ^{13}C NMR) were in accordance with that reported in the literature.[1]

The next step, stereoselective hydrogenation of retronecine, proved more difficult to accomplish. This reaction has been reported in the literature,[16] when Drewes and co-workers described successful hydrogenation using PtO_2 on carbon under



Scheme 5 *Reagents*: i. $Ba(OH)_2$, H_2O, Δ; ii. PtO_2/C, H_2, MeOH; iii. Rh/C, H_2, THF.

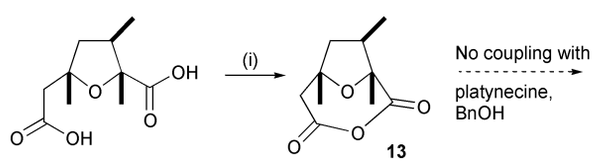
one atmosphere of hydrogen. However, several attempts to repeat this work all met with failure in our hands. The only compound we obtained was the product of hydrogenolysis of the allylic alcohol, followed by hydrogenation of the remaining double bond. A ^{1}H NMR spectrum of the compound **12** so obtained revealed the presence of a (3H) doublet at 1.32 ppm corresponding to a methyl group while the alkene region (5.00–6.00 ppm) was free from any signals.

Changing the catalyst from platinium to palladium and the solvent from methanol to ethanol made little difference and hydrogenolysis was still the principal reaction. Furthermore, reduction under homogeneous conditions, using Wilkinson's catalyst, was attempted but gave only recovered starting material.

Eventually, hydrogenation was achieved by using H_2 and Rh/C (5%) in THF. Under these conditions, and after stirring overnight at room temperature under a balloon of hydrogen, platynecine was isolated in 72% yield Scheme 5. The curved shape of retronecine means that hydrogenation would be expected to occur from the lower face of the molecule, as shown, to furnish platynecine. This was proved by matching of the spectroscopic data (^{1}H, ^{13}C NMR) of the compound so obtained with data from authentic platynecine.[17]

Attempted coupling of nemorensic acid with platynecine

Following encouraging precedent by Niwa,[18] we prepared the cyclic anhydride of nemorensic acid in quantitative yield by coupling with one equivalent of DCC in dichloromethane, Scheme 6. The urea by-product was removed by filtration. The



Scheme 6 *Reagents*: i. DCC, CH_2Cl_2.

anhydride **13** could not be purified by column chromatography and was therefore used straight away in the next step. While ^{1}H and ^{13}C NMR and IR indicated complete formation of **13**, it proved to be extremely sensitive to hydrolysis.

However, we were not able to address the regioselectivity of anhydride coupling with platynecine because of the extreme sensitivity of the anhydride and low nucleophilicity of the diol. Little or no coupling was observed between the two under a variety of conditions (neutral, basic, *etc*.). In fact, opening the anhydride with a range of unhindered alcohols and alkoxides did not give any ester products but always returned nemorensic acid.

Being unable to open the anhydride successfully, we decided to mono-protect nemorensic acid and attempt more conventional ester coupling reactions. Several conditions were

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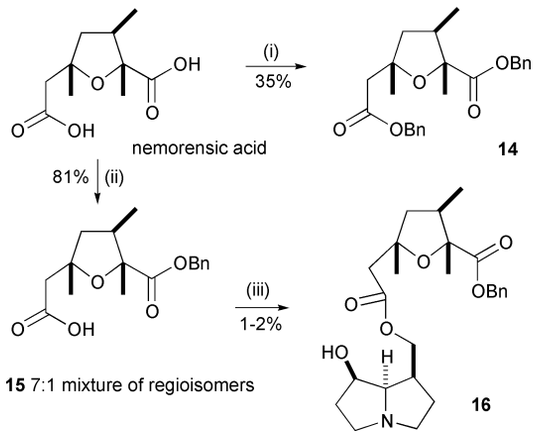
investigated for placement of a single benzyl group on nemorensic acid. Firstly, we showed that the diacid could indeed be activated and then coupled with a nucleophile by preparing the dibenzylester **14** in 35% yield, Scheme 7. Attempts to



Scheme 7 *Reagents*: i. DCC, DMAP, BnOH (excess); ii. Et_3N (1.2 eq.), BnBr, CH_2Cl_2; iii. $(EtO)_2POCl$, Et_3N; then platynecine, NaH, THF.

mono-protect by reducing the amount of coupling reagent and benzyl alcohol gave inseparable mixtures of the two possible regioisomers, together with doubly protected nemorensic acid.

Eventually, the best conditions found for this mono-protection were those involving benzyl bromide in CH_2Cl_2 with 1.2 eq. of Et_3N. Under these conditions, 81% of a 7 : 1 ratio of regio-isomers **15** was obtained. The ratio was measured by proton NMR by comparison of the integration of the methylene benzyl peak and compared to the mixtures obtained earlier.

The connectivity (major compound) within compound **15** was shown by a HMBC experiment which revealed that the benzyl singlet at δ 5.23 was coupled to the carbonyl at δ 177.1 and that the AB signals at δ 2.32 and 2.65 were both coupled to a different carbonyl at δ 171.4. This two and three bond coupling array can arise after benzylation at the most hindered acid group, which is presumably favoured because of the enhanced acidity of the α-oxy carboxylic acid relative to the other one.

Having successfully selectively protected one of the carboxylic acid groups, we now decided to probe the reactivity of the other towards platynecine.

Coupling of acid **15** was attempted under a variety of different conditions and was successful with non-hindered alcohols using diethylchlorophosphate and a sodium alkoxide[19] (details not shown). However, the poor nucleophilicity of platynecine thwarted its coupling under conditions that we knew to work with simpler alcohols. In fact, we were only ever able to isolate just 1–2% of a coupled product **16** which was incompletely characterised (and therefore its structure only tentatively assigned) because of the small amount available. The ^{1}H NMR spectrum of **16** shows an ABX system at 4.35 and 4.54 ppm, which corresponds to the methylene group attached to oxygen of the newly formed ester linkage. In contrast, the methylene attached to the primary alcohol in platynecine resonates at 3.8 ppm which points to coupling at the primary alcohol end (C8) of platynecine. If nemorensine were ever to be made *via* this route, then the acid **15** would have to be coupled to the more hindered secondary alcohol of platynecine, which is clearly a formidable proposition.

So, our attempts to complete the synthesis of nemorensine were thwarted by the low nucleophilicity of platynecine; the concave nature of this compound means that both primary and secondary hydroxy groups are placed in the cleft and are poor nucleophiles. A successful approach to nemorensine will probably involve coupling of acid **15** with a protected form of retronecine followed by stereoselective hydrogenation.

In total, we have developed an extremely efficient route to nemorensic acid and protected derivatives thereof; coupling strategies which involve platynecine as a nucleophile were not successful in our hands and other ways of completing the synthesis must be pursued.

Experimental

General experimental

All reactions, except aqueous reactions, were carried out under an atmosphere of argon.

Proton nuclear magnetic resonance spectra (NMR) were recorded on a Gemini 200 at 200 MHz, a Varian Unity Inova 300 at 300 MHz, a Varian Unity Inova 400 at 400 MHz and a Varian Unity Inova 500 at 500 MHz. ^{13}C nuclear magnetic resonance spectra were recorded on a Varian Unity Inova 300 at 75 MHz, a Varian Unity Inova 400 at 100 MHz and a Varian Unity Inova 500 at 125 MHz. Chemical shifts (δ) are quoted in parts per million (ppm), downfield from tetramethylsilane. Coupling constants (J) are quoted in Hz. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FTIR as evaporated films (EF). Optical rotation were recorded on an Optical Activity Ltd. AA-100 polarimeter and $[\alpha]_D$ values (all reported at 21 °C) are given in units of 10^{-1} deg cm^2 g^{-1}; concentration c in units of g 100 ml^{-1}. Mass spectra were recorded on a Kratos Concept or a Fisson VG Trio 2000. Melting points were obtained on a Kofler block and are uncorrected.

Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as indicator, under an atmosphere of argon. Dichloromethane (DCM) was distilled over calcium hydride. Petroleum ether (boiling range 40–60 °C) was distilled prior to use and ammonia was distilled from sodium metal and ferric chloride.

[(2′*R*,5′*R*)-2′,5′-Bis(methoxymethyl)tetrahydro-1′*H*-pyrrol-1′-yl](3-methyl-2-furyl)methanone 3

Thionyl chloride (12 ml, 0.16 mol) was added to 3-methyl-2-furoic acid (2.39 g, 19.0 mmol). The resulting dark mixture was heated at reflux for 3–4 h and the excess thionyl chloride was then removed under pressure (azeotroped with toluene). The brown liquid obtained was mixed with dichloromethane (10 ml) and was then added dropwise to a stirring mixture of (*R,R*)-bis(methoxymethyl)pyrrolidine (3.32 g, 21.0 mmol), 2.0 M aq. sodium hydroxide (40 ml, 80 mmol) and dichloromethane (40 ml) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The dichloromethane was removed *in vacuo* and the residue extracted with ethyl acetate (3 × 20 ml). The combined organics were then dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield a brown oil. The crude product was purified by column chromatography (25 : 75 ethyl acetate–petrol) to give the title compound as a pale oil (4.6 g, 17 mmol, 91%). (Found M + H$^+$ 268.1557, $C_{14}H_{21}NO_4$ requires 268.1549, deviation 2.98 ppm), $[\alpha]_D$ +130.1 (*c* 2.17 in $CHCl_3$); ν_{max}/cm^{-1} 2927, 1615; δ_H (300 MHz, $CDCl_3$) 1.79–2.20 (4H, m), 2.25 (3H, s), 2.88–3.04 (2H, m), 3.12 (3H, s), 3.26 (3H, s), 3.23–3.36 (1H, m), 3.48 (1H, dd, *J* 9.0 and 3.0), 4.37–4.48 (1H, m), 4.64–4.74 (1H, m), 6.25 (1H, d, *J* 1.5), 7.25 (1H, d, *J* 1.5); δ_C (75 MHz, $CDCl_3$) 11.60, 23.98, 27.30, 57.10, 57.50, 58.90, 59.00, 71.86, 73.77, 114.9, 128.6, 141.6, 143.0, 159.6 (C=O); *m*/*z* (CI) 268 (M + 1, 100%).

(2*R*,2′*R*,5′*R*)-[2′,5′-Bis(methoxymethyl)tetrahydro-1′*H*-pyrrol-1′-yl][2,3-dimethyl-2,5-dihydrofuran-2-yl]methanone 4

To a blue solution of sodium (0.44 g, 19 mmol) in liquid ammonia (75 ml) at −78 °C was added the substrate **3** (1.25 g, 4.67 mmol) in 1 ml of THF. After 10 min, isoprene was added (until the blue colour dispersed) followed by iodomethane (1 ml, 16 mmol) to give a yellow solution. After 15 min, the

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solution was quenched with a solution of saturated aq. ammonium chloride (10 ml). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 ml). The combined organics were dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (20 : 80 diethyl ether–petrol) to afford the title compound as a colourless oil (1.15 g, 4.06 mmol, 87%). (Found M + H^+ 284.1861, $C_{15}H_{25}NO_4$ requires 284.1862, deviation 0.35 ppm), $[\alpha]_D$ +130.9 (*c* 1.28 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2924, 1621; δ_H (300 MHz, $CDCl_3$) 1.44 (3H, s), 1.74–2.04 (7H, m), 2.97 (1H, t, *J* 9.0), 3.10–3.30 (2H, m), 3.21 (3H, s), 3.27 (3H, s), 3.46 (1H, dd, *J* 9.0 and 3.0), 4.19–4.27 (1H, m), 4.56 (2H, br s), 4.64–4.72 (1H, m), 5.46 (1H, dd, *J* 3.5 and 1.5); δ_C (75 MHz, $CDCl_3$) 12.83, 23.30, 27.30, 27.95, 57.63, 57.92, 58.71, 58.78, 71.39, 73.07, 74.01, 93.42, 120.4, 141.0, 172.2; *m*/*z* (CI) 284 (M + 1, 100%), 97 (25).

(5*R*,2′*R*,5′*R*)-5-[2′,5′-Bis(methoxymethyl)tetrahydro-1′*H*-pyrrol-1′-ylcarbonyl]-4,5-dimethyl-2,5-dihydrofuran-2-one 5

To a solution of substrate **4** (1.15 g, 4.06 mmol) in acetone (15 ml), was added at 0 °C a solution of chromium trioxide (2.7 g, 27 mmol) in water (6.5 ml) and 5 drops of conc. sulfuric acid. The reaction was stirred at 50 °C for 7 hours before being quenched by addition of brine. The solution was then extracted with dichloromethane (7 × 20 ml). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. Flash chromatography (50 : 50 diethyl ether–hexane) afforded the title compound as a colourless oil (1.20 g, 4.04 mmol, 98%). (Found M + H^+ 298.1652, $C_{15}H_{23}NO_5$ requires 298.1654, deviation 0.67 ppm), $[\alpha]_D$ +169.8 (*c* 1.63 in $CHCl_3$); ν_{max}/cm^{-1} 2926, 1764, 1626; δ_H (300 MHz, $CDCl_3$) 1.64 (3H, s), 1.70–2.08 (4H, m), 2.20 (3H, d, *J* 1.5), 2.90 (1H, dd, *J* 9.0 and 6.0), 3.04–3.37 (2H, m), 3.14 (3H, s), 3.27 (3H, s), 3.42 (1H, dd, *J* 9.0 and 2.5), 4.09–4.14 (1H, m), 4.73 (1H, q, *J* 6.0), 5.84 (1H, d, *J* 1.5); δ_C (75 MHz, $CDCl_3$) 14.78, 24.06, 26.65, 27.26, 57.66, 58.46 (× 2), 58.92, 71.42, 73.94, 90.03, 116.15, 168.4, 171.3, 171.6; *m*/*z* (CI) 298 (M + 1, 100%).

(5*R*,4*R*,2′*R*,5′*R*) and (5*R*,4*S*,2′*R*,5′*R*)-5-[2′,5′-Bis(methoxymethyl)tetrahydro-1′*H*pyrrol-1′-ylcarbonyl]-4,5-dimethyltetrahydrofuran-2-one (6 and 7)

To a solution of compound **5** (1.20 g, 1.68 mmol) in ethanol (15 ml), was added acetic acid (2.0 ml) and palladium (10% on carbon, 50 mg). The solution was stirred under 1 atm of hydrogen overnight. The catalyst was removed by filtration through Celite®, washed with ethanol, and the filtrate evaporated *in vacuo*. The two diastereoisomers were then separated by column chromatography (55 : 45 diethyl ether–hexane) to afford **6** and **7** as colourless oils (1.05 g, 3.51 mmol, 88%).

6: (850 mg, 71%) (Found M + H^+ 300.1808 $C_{15}H_{25}NO_5$ requires 308.1811, deviation 0.97 ppm), $[\alpha]_D$ +22.9 (*c* 0.21 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2977, 1787, 1623; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0), 1.48 (3H, s), 1.78–2.10 (4H, m), 2.19 (1H, dd, *J* 17.5 and 10.0), 2.61 (1H, dd, *J* 17.5 and 9.0), 2.95–3.10 (1H, m), 3.16 (1H, dd, *J* 9.0 and 6.5), 3.24–3.40 (2H, m), 3.30 and 3.32 (6H, 2s), 3.50 (1H, dd, *J* 9.0 and 3.0), 4.24–4.32 (1H, m), 4.72 (1H, q, *J* 7.0); δ_C (75 MHz, $CDCl_3$) 15.67, 21.43, 24.17, 27.45, 35.63, 36.63, 57.44, 58.25, 58.67, 58.83, 71.31, 74.56, 88.39, 172.3, 174.7; *m*/*z* (CI) 300 (M + 1, 100%).

Dimethyldicyclopentadienyltitanium [11]

To a solution of dichlorodicyclopentadienyltitanium (1.52 g, 6.13 mmol) in diethyl ether (15 ml) was added, at 10–15 °C, a 1.6 M solution of methyllithium (8.4 ml, 13.40 mmol) in diethyl ether. The solution was stirred for one hour at room temperature before being quenched with ice water. The aqueous layer was extracted with diethyl ether (3 × 20 ml). The resulting organics were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the product as an orange solid (1.12 g, 5.39 mmol, 88%). δ_H (200 MHz, $CDCl_3$) −0.18 (6H, s, C*H*$_3$), 6.05 (10H, s, C*H*).

[(2*R*,5*R*)-2,5-Bis(methoxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-[(2*R*,3*R*)-2,3-dimethyl-5-methylenetetrahydrofuran-2-yl]-methanone 8

To a solution of compound **6** (315 mg, 1.05 mmol) in THF (15 ml) was added dimethyldicyclopentadienyltitanium (877 mg, 4.20 mmol) in the dark at room temperature. The reaction was then stirred for 4 hours at 70 °C. The reaction was followed by IR (disappearance of the band at 1783 cm^{-1} and formation of a band at 1673 cm^{-1}). Petrol was added and the yellow precipitate removed by filtration over Celite®. The filtrate was then evaporated to dryness to give the crude product as a red oil. This compound was not particularly stable and therefore was used immediately in the next step. ν_{max}/cm^{-1} 2952, 1673, 1622; δ_H (200 MHz, $CDCl_3$), 1.14 (3H, d, *J* 7.5), 1.35 (3H, s), 1.80–2.30 (5H, m), 2.50–2.80 (2H, m), 3.10 (1H, t, *J* 9.0), 3.15–3.55 (2H, m), 3.30 (6H, br s), 3.50 (1H, dd, *J* 9.0 and 3.0), 3.82 (1H, br s), 4.15–4.30 (2H, m), 4.50–4.65 (1H, m).

[(2*R*,5*R*)-2,5-Bis(methoxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-[(2*R*,3*R*)-5-(methoxymethyl)-2,3,5-trimethyltetrahydrofuran-2-yl]methanone 9

To a solution of crude compound **8** in 2,2′-dimethoxypropane (2 ml) stirred at room temperature under argon was added 4 ml of methanol followed by a few drops of concentrated hydrochloric acid. After 2 hours, the reaction was quenched by addition of a 2.0 M sodium hydroxide solution and extracted with diethyl ether (3 × 15 ml). The combined organics were then dried over magnesium sulfate and evaporated *in vacuo* to give the crude product as a red oil. Purification by flash chromatography (60 : 40 diethyl ether–petrol) afforded the title compound as a yellow oil (299 mg, 0.91 mmol, 86% over two steps).

For the mixture of diastereoisomers: (Found M + H^+ 330.2276, $C_{17}H_{31}NO_3$ requires 330.2280, deviation 1.12 ppm); ν_{max}/cm^{-1} 2934, 2826, 1630; *m*/*z* (CI) 330 (M + 1, 95), 298 (M − 31, 100%).

Diastereoisomer 1. δ_H (300 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5), 1.35 (3H, s), 1.42 (3H, s), 1.78 (1H, dd, *J* 13.0 and 11.0), 1.84–2.05 (4H, m), 2.16 (1H, dd, *J* 13.0 and 9.0), 2.62 (1H, qdd, *J* 7.0, 2.5 and 2.0), 3.04–3.12 (1H, dd, *J* 9.0 and 8.0), 3.21–3.30 (1H, m), 3.28 (3H, s), 3.33 (6H, s), 3.51–3.58 (2H, m), 4.16–4.24 (1H, m), 4.47–4.55 (1H, m); δ_C (75 MHz, $CDCl_3$) 15.7, 20.8, 23.2, 23.8, 26.8, 40.5, 45.6 (× 2), 49.3, 57.4, 58.0, 58.7, 71.0, 75.0, 87.9, 107.2, 174.1.

Diastereoisomer 2. δ_H (300 MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.0), 1.21 (3H, s), 1.44 (3H, s), 1.79 (1H, t, *J* 13.0), 1.88–2.03 (4H, m), 2.20 (1H, dd, *J* 13.0 and 7.0), 2.85–2.99 (1H, m), 3.15 (1H, t, *J* 9.0), 3.19–3.26 (1H, m), 3.22 (3H, s), 3.32 and 3.35 (6H, s), 3.56 (1H, dd, *J* 9.0 and 3.0), 3.81 (1H, dd, *J* 9.0 and 4.0), 4.15–4.24 (1H, m), 4.43–4.46 (1H, m); δ_C (75 MHz, $CDCl_3$) 15.4, 21.3, 23.9, 25.7, 26.5, 30.2, 38.9, 42.3, 50.3, 57.6, 58.5, 58.7, 70.9, 73.6, 87.7, 107.3, 173.8.

[(2*R*,3*R*,5*R*)-5-Allyl-2,3,5-trimethyltetrahydrofuran-2-yl]-[(2*R*,5*R*)-2,5-bis(methoxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-methanone 10

Allyltrimethylsilane (2.18 g, 19.1 mmol) was added to a solution of compound **9** (315 mg, 0.96 mmol) in CH_2Cl_2 (5 ml) at room temperature, followed by the addition of a 1 M solution of titanium(IV) chloride (2.9 ml, 2.87 mmol). The red–brown

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solution was stirred for one hour and quenched by addition of sodium hydroxide (2 M). The solution was then extracted with diethyl ether (3 × 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the crude product as a yellow oil. Purification by flash chromatography (20 : 80 diethyl ether–petrol) afforded the title compound as a colourless oil (265 mg, 0.78 mmol, 81%). (Found M + H^+ 340.2492, $C_{19}H_{33}NO_4$ requires 340.2488, deviation 1.17 ppm), $[\alpha]_D$ +46.06 (*c* 6.0, CH_2Cl_2); ν_{max}/cm^{-1} 2974, 1632; δ_H (300 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5), 1.22 (3H, s), 1.28 (3H, s), 1.41 (1H, t, *J* 13.0), 1.86–2.00 (4H, m), 2.04 (1H, dd, *J* 13.0 and 7.0), 2.25 (2H, 2 dd, *J* 13.0 and 8.0), 2.68–2.82 (1H, m), 3.09–3.16 (1H, t, *J* 7.0), 3.27 (1H, t, *J* 7.0), 3.32 (3H, s), 3.34 (3H, s), 3.55 (1H, dd, *J* 9.0 and 3.0), 3.69 (1H, dd, *J* 9.0 and 3.0), 4.12–4.20 (1H, m), 4.40–4.51 (1H, m), 5.05 (2H, m), 5.68–5.82 (1H, m); δ_C (75 MHz, $CDCl_3$) 15.46, 21.84, 24.00, 26.34, 29.35, 40.18, 42.49, 46.69, 57.20, 57.45, 58.53, 58.71, 70.90, 74.03, 82.16, 86.92, 117.7, 134.7, 174.2; *m*/*z* (CI) 340 (M + 1, 100%).

2-((2*R*,4*R*,5*R*)-5-[(2*R*,5*R*)-2,5-Bis(methoxymethyl)tetrahydro-1*H*-pyrrol-1-ylcarbonyl]-2,4,5-trimethyltetrahydrofuran-2-yl)-acetic acid 11

To a solution of compound **10** (410 mg, 1.20 mmol) in a 2 : 2 : 3 mixture of carbon tetrachloride (3 ml), acetonitrile (3 ml) and water (4.5 ml) was added sodium periodate (1.19 g, 5.60 mmol). Ruthenium trichloride hydrate (catalytic) was then added to this biphasic solution. The reaction was allowed to stir for 2 hours and quenched with a 2 M solution of sodium hydroxide. The solution was extracted with dichloromethane (1 × 20 ml) and the aqueous layer acidified with conc. hydrochloric acid to pH < 1. The aqueous layer was then extracted again with dichloromethane (5 × 20 ml). The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford the crude compound as a colourless oil. This compound was used in the next step without further purification. (Found M + H^+ 358.2232, $C_{18}H_{31}NO_6$ requires 358.2229, deviation 0.84 ppm), ν_{max}/cm^{-1} 3167, 2976, 1730, 1629; δ_H (300 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.5), 1.22 (3H, s), 1.36 (3H, s), 1.51 (1H, t, *J* 12.5), 1.76–1.98 (4H, m), 2.25 (1H, dd, *J* 13.0 and 7.5), 2.48 (2H, s), 2.60–2.72 (1H, m), 3.04–3.36 (2H, m), 3.26 (6H, s), 3.38–3.50 (2H, m), 4.04–4.16 (1H, m), 4.22–4.36 (1H, m); δ_C (75 MHz, $CDCl_3$) 15.29, 21.79, 24.29, 26.73, 29.02, 40.47, 43.80, 46.12, 57.69 (× 2), 58.79 (× 2), 70.98, 74.29, 80.67, 87.44, 174.3, 174.7; *m*/*z* (CI) 358 (M + 1, 100%).

(2*R*,3*R*,5*S*)-5-Carboxymethyl-2,3,5-trimethyltetrahydrofuran-2-carboxylic acid ((+)-nemorensic acid)

A 6 M solution of hydrochloric acid (10 ml) was added to the crude compound **11**. The reaction was heated at reflux for 5 hours and then quenched by addition of a 2 M solution of NaOH until pH = 14. The solution was extracted with dichloromethane (1 × 20 ml). The aqueous layer acidified until pH < 1 by addition of HCl concentrated and extracted with dichloromethane (5 × 20 ml). The remaining organic layer was then dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as a colourless solid (217 mg, 1.00 mmol, 83% over two steps from **10**). (Found M + H^+ 217.1073, $C_{10}H_{16}O_5$ requires 217.1076, deviation 1.38 ppm), mp 171–173 °C (lit.[5] 174–175 °C); $[\alpha]_D$ +84.4 (*c* 0.18, EtOH) (lit.[5] +87.2 (*c* 0.24 EtOH)); ν_{max}(film)/cm^{-1} 3451, 3120, 2974, 2934, 1712; δ_H (400 MHz, CD_3OD) 1.12 (3H, d, *J* 6.8), 1.28 (3H, s), 1.39 (3H, s), 1.68 (1H, t, *J* 12.4), 2.25 (1H, dd, *J* 12.4 and 6.8), 2.47 (1H, d, *J* 13.6), 2.56–2.69 (1H, m), 2.60 (1H, d, *J* 13.6); δ_C (100 MHz, CD_3OD) 14.22, 20.62, 27.73, 41.66, 46.03, 46.31, 82.48, 86.81, 175.1, 179.7; *m*/*z* (CI) 234 (M + 18, 100%), 217 (10), 171 (20).

Retronecine[1]

Water (7 ml) was added to a mixture of monocrotaline (229 mg, 0.70 mmol) and barium hydroxide octahydrate (457 mg, 1.45 mmol). The resulting mixture was stirred at 60 °C for 45 min and heated at reflux for a further 3 hours. The solution was allowed to cool to room temperature and three pieces of CO_2 solid were carefully added. The reaction was stirred for 30 min, filtered and washed with water and chloroform. The solvents and aqueous were evaporated *in vacuo*. The resulting oil was purified by flash column chromatography (13 : 5 : 2 $CHCl_3$–MeOH–Et_3N) to afford the title compound as a pale beige solid. After recrystallisation from hot acetone, the compound was obtained as a colourless crystalline solid (93 mg, 0.60 mmol, 86%). δ_H (300 MHz, D_2O) 1.76–1.88 (2H, m), 2.52–2.64 (1H, m), 3.06–3.14 (1H, m), 3.30 (1H, ddd, *J* 15.5, 5.0 and 2.0), 3.70 (1H, dt, *J* 15 and 2.0), 4.04–4.12 (3H, m), 4.26–4.28 (1H, m), 5.60 (1H, d, *J* 1.5); δ_C (75 MHz, D_2O) 35.26, 52.61, 58.33, 61.18, 70.44, 76.32, 124.9, 137.2. All data were in accordance with that reported in the literature.[1]

Platynecine[17]

A solution of retronecine (50 mg, 0.32 mmol) in THF (10 ml) containing a catalytic amount of rhodium on carbon (5%) was stirred under an atmospheric pressure of hydrogen for 12 hours. The solution was then filtered through Celite®, washed with methanol and the solvents evaporated *in vacuo*. Purification by column chromatography (10 : 5 : 1 $CHCl_3$–MeOH–NH_4OH_{sol}) afforded the title compound as a pale yellow oil, which crystallised at room temperature (38 mg, 0.24 mmol, 75%). (M^+ 157.1104, $C_8H_{15}NO_2$ requires 157.1103, deviation 0.64 ppm), δ_H (300 MHz, CD_3OD) 1.54–2.00 (4H, m), 2.26–2.40 (1H, m), 2.62–2.82 (2H, m), 2.95–3.24 (3H, m), 3.84 (2H, d, *J* 5.5), 4.13–4.17 (1H, m); δ_C (75 MHz, CD_3OD) 27.40, 35.84, 43.55, 53.36, 55.09, 60.17, 71.25, 71.58; *m*/*z* (CI) 158 (M + 1, 100%). All data were in accordance with that reported in the literature.[17]

(1*R*,6*S*,8*R*)-1,6,8-Trimethyl-3,9-dioxabicyclo[4.2.1]nonane-2,4-dione 13

To a solution of nemorensic acid (20 mg, 0.09 mmol) in dichloroethane (1 ml) was added a solution of 1,3-dicyclocarbodiimide (19 mg, 0.09 mmol) in dichloroethane (1 ml). The reaction was stirred at 80 °C for 7 hours. The solvents were then evaporated *in vacuo*. The residue was taken up in acetone and filtered through a cotton plug. The acetone was evaporated to afford the title compound as a clear oil (18 mg, 0.09 mmol, 99%). ν_{max}(film)/cm^{-1} 1805, 1758; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.0), 1.45 (1H, dd, *J* 12.5 and 8.0), 1.49 (3H, s), 1.52 (3H, s), 2.24 (1H, dd, *J* 12.5 and 8.0), 2.78–2.88 (1H, m), 2.86 (1H, d, *J* 13.5), 2.92 (1H, d, *J* 13.5); δ_C (100 MHz, $CDCl_3$) 16.23, 20.64, 26.44, 40.18, 47.66, 47.75, 79.23, 86.18, 162.7, 174.6. This compound was not stable enough to obtain any mass spectrometry measurements.

(2*R*,3*R*,5*S*)-5-Benzyloxycarbonylmethyl-2,3,5-trimethyltetrahydrofuran-2-carboxylic acid benzyl ester 14

To a solution of nemorensic acid (20 mg, 0.09 mmol) in dichloromethane (2 ml) at −20 °C were successively added benzyl alcohol (10 mg, 0.09 mmol) followed by 1,3-dicyclohexylcarbodiimide (28 mg, 0.14 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (2 mg, 0.02 mmol). The reaction was slowly allowed to warm to room temperature and was stirred for 12 hours before addition of a saturated solution of ammonium chloride. The solution was extracted with dichloromethane (3 × 20 ml), dried over magnesium sulfate and evaporated *in vacuo*. The oil obtained was purified by column chromatography (40 : 60 diethyl ether–petrol) to give the title compound **14** (12 mg, 0.030 mmol, 35%). (Found M + H^+ 397.2016, $C_{24}H_{28}O_5$ requires 397.2015, deviation 0.25 ppm), $[\alpha]_D$ +12.6 (*c* 0.70, $CHCl_3$); ν_{max}(film)/cm^{-1} 1728; δ_H (300 MHz,

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$CDCl_3$) 0.98 (3H, d, *J* 7.0), 1.22 (3H, s), 1.34 (3H, s), 1.46 (1H, t, *J* 13.0), 2.32 (1H, dd, *J* 13.0 and 7.0), 2.53 (1H, d, *J* 13.5), 2.53–2.65 (1H, m), 2.62 (1H, d, *J* 13.5), 5.00 (2H, s), 5.60 (2H, d, *J* 7.0), 7.22–7.30 (10H, m); δ_C (75 MHz, $CDCl_3$) 14.13, 20.45, 28.04, 40.02, 43.90, 45.23, 66.06, 66.57, 81.47, 85.30, 127.9, 128.1, 128.1, 128.1, 128.4, 135.8, 170.7, 174.6; *m*/*z* (CI) 397 (M + 1, 90), 94 (M − 302, 100%).

(2*R*,3*R*,5*S*)-5-Carboxymethyl-2,3,5-trimethyltetrahydrofuran-2-carboxylic acid benzyl ester 15

To a solution of nemorensic acid (33 mg, 0.15 mmol) in dichloromethane (1 ml) at room temperature were successively added triethylamine (18.5 mg, 0.18 mmol) followed by benzyl bromide (27 mg, 0.16 mmol). The reaction was stirred at room temperature for 12 hours. The solvents were then evaporated and the residue dry loaded on silica to allow purification by flash column chromatography (EtOAc). The title compound was isolated as a colourless oil (7 : 1 mixture of regioisomers, 38 mg, 0.12 mmol, 81%). (Found M + H^+ 307.1540, $C_{17}H_{22}O_5$ requires 307.1545, deviation 1.63 ppm), ν_{max}(film)/cm^{-1} 3257, 1735, 1720; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.0), 1.36 (3H, s), 1.43 (3H, s), 1.71 (1H, t, *J* 12.5), 2.02 (1H, dd, *J* 12.5 and 7.0), 2.32 (1H, d, *J* 13.5), 2.46–2.58 (1H, m), 2.65 (1H, d, *J* 13.5), 5.23 (2H, s), 7.32–7.41 (5H, m); δ_C (125 MHz, $CDCl_3$) 14.28, 20.46, 26.99, 40.93, 46.29, 46.52, 68.15, 81.41, 86.39, 128.6, 128.9, 129.0, 135.2, 171.4, 177.1; *m*/*z* (CI) 324 (M + 18, 100%), 307 (35).

(2*R*,3*R*,5*S*)-5-(8-Platynecinylcarboxymethyl)-2,3,5-trimethyltetrahydrofuran-2-carboxylic acid benzyl ester 16

To a cold (0 °C) solution of compound **15** (19 mg, 0.062 mmol) in THF (1 ml) was added triethylamine (22 mg, 0.22 mmol) followed by diethylchlorophosphate (16 mg, 0.093 mmol). The solution was stirred at 0 °C for 1 hour and at room temperature for a further 30 min. The mixture was then filtered through a cotton plug and added to a cold (0 °C) solution of platynecine-alkoxide in THF [this solution was previously prepared by stirring, at 0 °C, a mixture of NaH (60% in mineral oil) (8 mg, 0.20 mmol) and platynecine (24 mg, 0.155 mmol) in THF (1 ml) for 20 min]. The resulting solution was stirred at room temperature for 12 hours before addition of a saturated solution of ammonium chloride. After extraction with dichloromethane (3 × 5 ml), the organics were dried using magnesium sulfate, filtered and evaporated *in vacuo*. Purification by flash chromatography (1 : 20 : 79 NH_4OH_{sol}–MeOH–$CHCl_3$) afforded the title compound as a colourless oil (*ca.* 1 mg, 0.002 mmol, 1%). δ_H (300 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.0), 1.34 (3H, s), 1.49 (5H, s), 1.96–2.25 (3H, m), 2.34 (1H, dd, *J* 13.0 and 7.0), 2.58–2.62 (2H, m), 2.66–2.73 (1H, m), 2.78–2.84 (1H, m), 3.00–3.15 (2H, m), 3.55–3.65 (1H, m), 3.84–3.92 (1H, m), 4.03 (1H, br d, *J* 8.0), 4.35 (1H, dd, *J* 11 and 6.2), 4.54 (1H, dd, *J* 11 and 10), 4.80–4.90 (1H, m), 5.08 (2H, s), 7.23–7.38 (5H, m); *m*/*z* (ES) $C_{25}H_{36}NO_6$ requires 446, obtained 446 (100%). It was not possible to obtain further characterisation on this compound because of the small mass available.

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