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Preparation of some angularly substituted and highly functionalized quinolizidines as building blocks for the synthesis of various alkaloids and related scaffolds of medicinal interest

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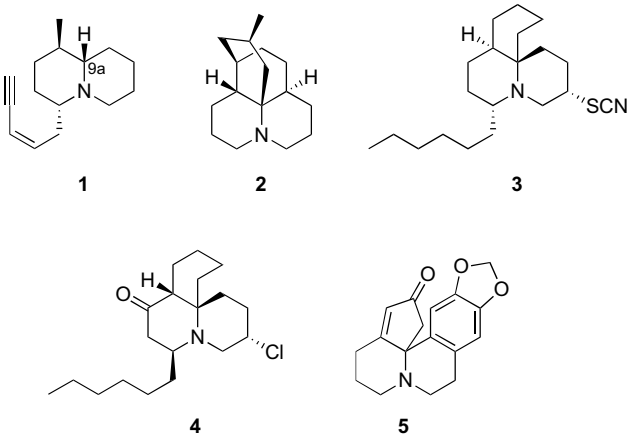
ABSTRACT

The epimeric forms of the angularly substituted quinolizidine **6**, representing potentially useful building blocks for the synthesis of various alkaloids, have been prepared via a pathway involving two consecutive ring-closing metathesis reactions. Variously hydroxy-protected derivatives (**21**, **22**, and **26**–**29**) of these compounds have also been generated.

1. Introduction

Many alkaloids incorporate the quinolizidine framework, and those variants lacking an angular substituent at C9a represent a large and important class of natural product that displays a range of interesting biological properties.[1,2] Such compounds have been isolated from both marine and terrestrial organisms including bacteria, fungi, higher plants, invertebrates, and vertebrates.[1,2] For example, quinolizidine 217A (**1**) is an amphibian alkaloid isolated from skin extracts of the Madagascan frog *Mantella baroni*.[3] Many additional and structurally more complex alkaloids incorporate an embedded quinolizidine unit. Representative examples of this type of system include lycopodine (**2**) (a lycopodium alkaloid that displays a curare-like paralyzing activity),[4] cylindricine B (**3**) (isolated from the ascidian *Clavelina cylindrical* collected off the East Coast of Tasmania),[5] and the structurally related fasicularin (**4**) (isolated from the marine invertebrate *Nephteis fasixcularis* and displaying selective activity against certain DNA repair-deficient organisms).[6] Embedded quinolizidines also represent scaffolds of interest from a medicinal chemistry perspective[7] and/or are encountered as precursors to other natural products.[8] For example, compound **5** has served as a key intermediate in a recently reported synthesis of the intriguing and cytotoxic alkaloid cephalotaxine,[8] derivatives of which have been subjected to clinical trails for the treatment of acute human leukemia.[9]



2. Results and discussion

As part of an ongoing program within our laboratories to establish synthetic routes to various classes of alkaloid,[10] we identified the epimeric forms of the angularly substituted quinolizidine **6** as potentially useful building blocks for the assembly of compounds

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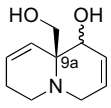
such as **2**–**5** as well as related systems. Thus, for example, manipulation of the angular hydroxymethyl group within compound **6** should provide a system that could engage in 6-*exo*-*trig* radical cyclization processes to give the tricyclic ring systems associated with alkaloids **3** and **4**. On the other hand, the enone generated by oxidation of the allylic alcohol moiety within compound **6** could engage in various cycloaddition reactions to give alternatively annulated systems, while the isomeric enone that would be accessible through the application of Wharton transposition chemistry[11] could engage in related processes to give benzannulated derivatives resembling the ABC-substructure associated with compound **5**. Furthermore, a combination of the radical cyclization and cycloaddition chemistries just mentioned could provide access to the complete tetracyclic framework of the same target.

On the basis of the above-mentioned possibilities we sought to develop syntheses of two epimeric forms of the previously unreported but potentially versatile compound **6**, as well as certain hydroxy-protected precursors. Herein we describe such syntheses, which are capable of delivering the target compounds at useful scale and which should be readily adapted to the preparation of the homologous indolizidines. Furthermore, and as detailed below, the route that has been developed should be amenable to the synthesis of such systems in chiral, non-racemic form.



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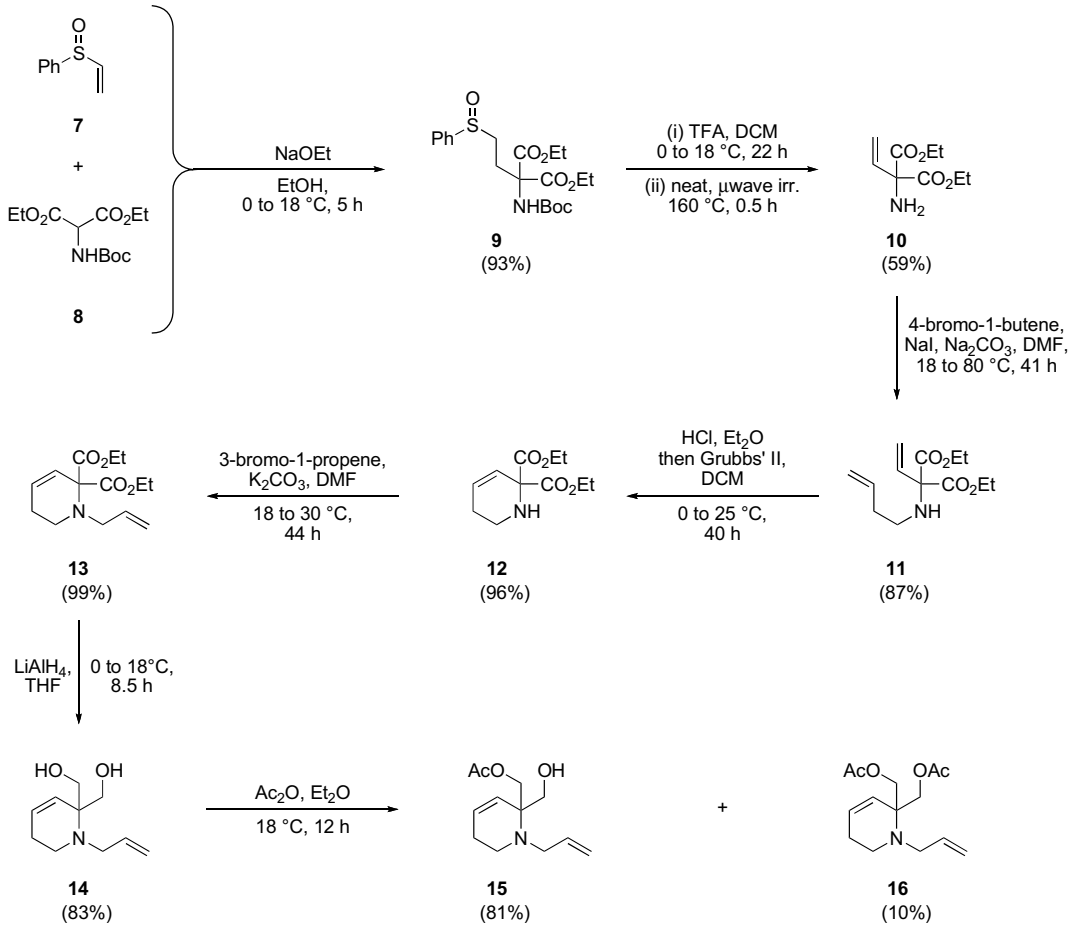
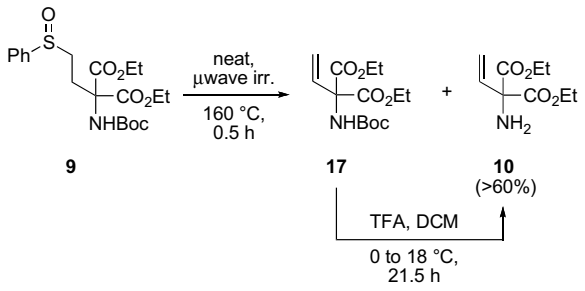
The initial steps of the synthetic route we have established, and that led to the racemic modification of compound **6**, are shown in Scheme 1. Thus, the sequence starts with the conjugate addition of the anion derived from the commercially available α-aminomalonate derivative **8** to the similarly accessible vinyl sulfoxide **7**. The Boc-protecting group within adduct **9**, which was obtained in near quantitative yield, could be removed using trifluoroacetic acid (TFA) and the resulting primary amine (quantitative yield) was subjected to heating at 160 °C in a microwave reactor. This led to the thermal elimination of the elements of phenylsulfenic acid[12] and the production of the α-amino-α-vinylmalonate derivative **10** in 59% yield. Reaction with 4-bromo-1-butene in the presence of base then provided diene **11** (87% yield at 70% conversion). Treatment of the HCl-salt of compound **11** with Grubbs' second generation catalyst[13] gave, after work-up with base, the monounsaturated piperidine **12** (96%) that could be *N*-allylated with allyl bromide to give diene **13** in 99% yield at 81% conversion. Reduction of both ester residues within compound **13** afforded the bis-hydroxymethylated compound **14** (83%) that was acetylated under conventional conditions to give a ca. 8:1 mixture of the chromatographically separable mono- and di-acetates, **15** (81%) and **16** (10%), respectively.

A useful modification to the early parts of the sequence just described involved (Scheme 2) taking the crude samples of malonate **9**, which has proven to be a rather intractable compound, and subjecting this to microwave irradiation. In this way varying mixtures of the chromatographically separable amine **10** and its Boc-protected congener **17** could be obtained. The latter product was contaminated with significant quantities of phenylsulfenic acid as well as other impurities but upon deprotection with TFA



Scheme 1.



Scheme 2.

and subjection of the crude reaction mixture to chromatography then additional quantities of pure samples of compound **10** could be obtained. This was found to be a more convenient and practical means for generating preparatively useful quantities of compound **10** than the protocol originally devised and shown in Scheme 1.

The completion of the syntheses of the epimeric forms of target **6** involved (Scheme 3) oxidation of mono-ol **15** under Swern conditions and reaction of the ensuing and rather unstable aldehyde **18** with vinyl magnesium bromide to give a ca. 2:1 mixture of the epimeric forms of the compound **19**. The mixture was immediately acetylated to give the corresponding mixture of triene di-acetates **20** (80% from **15**) that was then subjected to ring-closing metathesis using Grubbs' second generation catalyst.[13] The resulting quinolizidines **21** (62%) and **22** (25%) could be readily separated by flash chromatography and each was subjected to extensive spectroscopic characterization. An equivalent analysis of two related compounds (vide infra) suggests that the major product **21** possesses the illustrated *cis*-relationship between the acetoxy and acetoxymethyl groups. This is consistent with the notion that a chelation-controlled process[14] is preferred in the addition reaction **18**→**19** that establishes the relevant stereogenic center. Independent hydrolysis of each of compounds **21** and **22** using K_2CO_3 in methanol led to the target diols **6a** (98%) and **6b** (97%), respectively. As with all of the precursors to these compounds, except sulfoxide **9**, they were each obtained as oils.

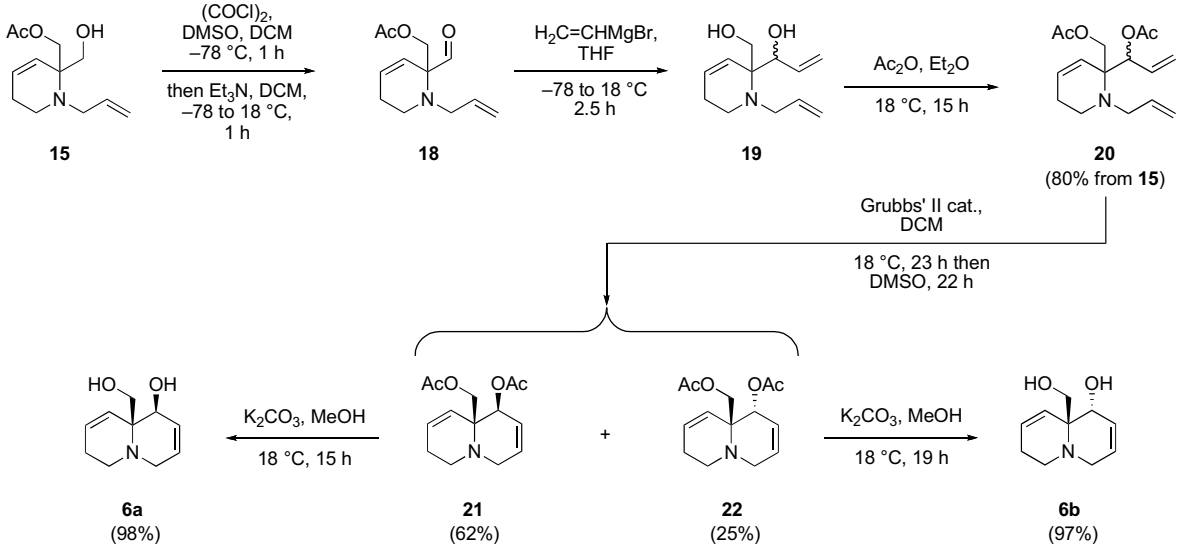
A simple variation on the reaction sequence shown in Scheme 3 has allowed for the preparation of mono-protected derivatives of compounds **6a** and **6b**. Thus, reaction of compound **15** with MOM-chloride in the presence of Hünig's base then treatment of the resulting ether/acetate (83%) with K_2CO_3 in methanol afforded the expected alcohol (99%) that could be oxidized to the corresponding aldehyde **23** under Swern conditions (Scheme 4). Vinylation of this last compound in the same manner as employed earlier gave a ca. 3:1 mixture of the epimeric allylic alcohols **24** that were not separated but committed, as a mixture, to acetylation under conventional conditions. The resulting ca. 3:1 mixture of the epimeric forms of acetate **25** (91% from **23**) was then subjected to ring-closing metathesis[13] and so affording a chromatographically separable mixture of the quinolizidine derivatives **26** (48% at 57% conversion) and **27** (16% at 57% conversion). Each of these was then independently treated with K_2CO_3 in methanol and thereby affording the target mono-ols **28** (99%) and **29** (95%), respectively. The illustrated stereochemistries in compounds **26** and **27** were established using NOESY techniques. In particular, in the former isomer a strong interaction was observed between the proton resonance due to the acetoxymethyl group and that due to the methyl group of the MOM ether. As expected, the equivalent interaction in compound **27** was much less pronounced. These results served to establish the illustrated (relative) configurations for compounds **6a**, **6b**, **21**, **22**, and **26**–**29**.

The reaction sequences shown in Schemes 3 and 4 would be capable of delivering enantiomerically pure forms of the title compounds **6a**, **6b**, **28**, and **29** if the enzymatic desymmetrization of either the diol **14** or diacetate **16** could be achieved. The prospects of achieving this seem rather good given the recent report by Donohoe and co-workers.[15] Accordingly, work directed toward such ends is now underway.

3. Experimental

3.1. General experimental procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ)[multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet or combinations of the above. The residual $CHCl_3$ peak (δ 7.26) was used as a reference for ^{1}H NMR spectra, and



Scheme 3.

the central peak (δ 77.0) of the $CDCl_3$ 'triplet' was used as a reference for proton-decoupled ^{13}C NMR spectra. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in positive ionization mode.

Melting points were measured on an Optimelt automated melting point system and are uncorrected.

Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized with ninhydrin. The retardation factor (R_f) was quoted to the nearest 0.1. Flash column chromatography[16] was performed using silica gel 60 (0.040–0.0063 mm) as the stationary phase and the analytical reagent (AR) or HPLC grade solvents indicated.

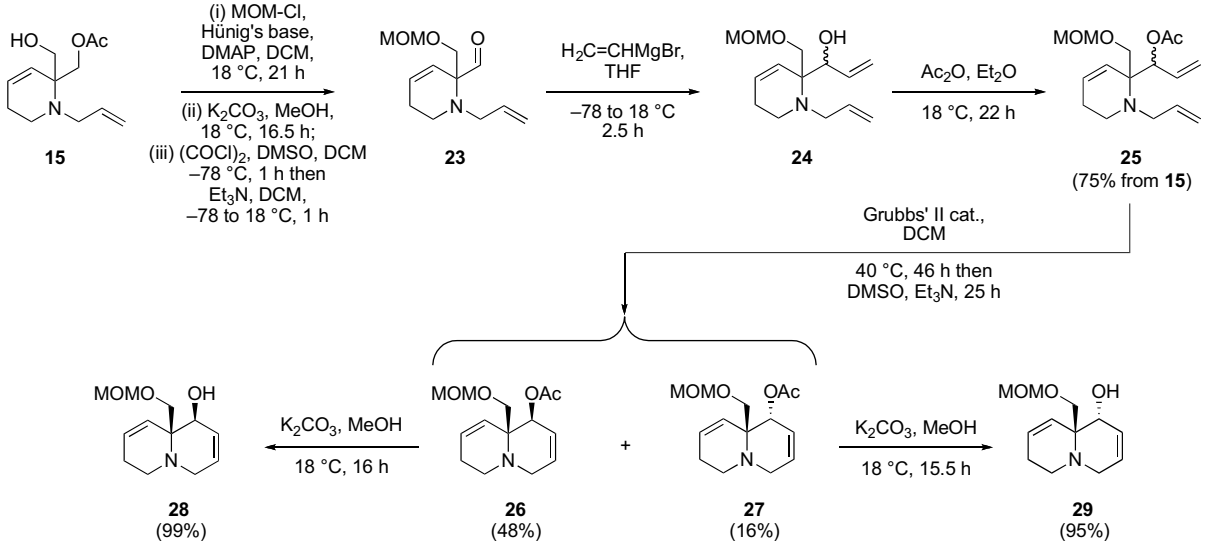
Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF) and diethyl ether (ether) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Methanol was distilled from its magnesium alkoxide salt. CH_2Cl_2 was distilled from calcium hydride. Triethylamine was distilled from and stored over potassium hydroxide pellets.

3.2. Specific chemical conversions

3.2.1. Compound ***9****.* Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred ethanol (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of sodium ethoxide in ethanol was cooled to 0 °C and 2-[*N*-(*tert*-butoxycarbonyl)amino]malonate (**8**) (4.79 mL, 17.8 mmol, ex. Aldrich) was added. The resulting mixture was maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**7**) (2.61 mL, 19.5 mmol, ex. Aldrich) was added dropwise. The reaction mixture so-formed was maintained at this temperature for 2 h then warmed to 18 °C and maintained at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in ethyl acetate (50 mL) and the resulting solution was washed with sodium bicarbonate (3×15 mL of a saturated solution). The combined aqueous washings were extracted with ethyl acetate (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 97:2:1 v/v/v dichloromethane/methanol/triethylamine elution). Concentration of the appropriate fractions (R_f=0.2) afforded *title compound* ***9*** (7.08 g, 93%) as a white, crystalline solid, mp=72–75 °C [Found: $(M+H)^+$, 428.1751. $C_{20}H_{29}NO_7S$ requires $(M+H)^+$, 428.1743]. ^1H NMR (300 MHz) δ 7.62–7.56 (m, 2H), 7.55–7.42 (m, 3H), 5.91 (br s, 1H), 4.19 (m, 4H), 2.85–2.44 (m, 4H), 1.40 (s, 9H), 1.20 (td, J=7.2 and 0.9 Hz, 6H); ^{13}C NMR (75 MHz) δ 167.6, 167.5, 154.0, 143.4, 131.2, 129.3, 124.1, 80.7, 65.5, 62.9, 62.8, 52.0, 28.2, 26.2, 14.0(0), 13.9(8) (additional signals attributed to carbamate rotamers); ν_{max} (NaCl) 3424, 2979, 1739, 1718, 1479, 1367, 1257, 1203, 1159, 1088, 1026, 749 cm^{-1}; MS (ESI) *m*/*z* 450 [$(M+Na)^+$, 48%], 428 [$(M+H)^+$, 8], 372 (9), 328 (100), 202 (20), 174 (48).

3.2.2. Compound ***10****. Step i.* Trifluoroacetic acid (0.13 mL, 1.64 mmol) was added to a magnetically stirred solution of compound **9** (140 mg, 0.33 mmol) in dichloromethane (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was kept at this temperature for 0.5 h, then warmed to 18 °C and maintained at this temperature for a further 21 h. After this time sodium bicarbonate (3 mL of a saturated aqueous solution) was added, the phases separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *diethyl 2-amino-2-[2-(phenylsulfinyl)ethyl]malonate* (1.70 g, 100%) as a clear, light-yellow oil [Found: $(M+H)^+$, 328.1205. $C_{15}H_{21}NO_5S$ requires $(M+H)^+$, 328.1219]. ^1H NMR (300 MHz) δ 7.64–7.56 (m, 2H), 7.54–7.44 (m, 3H), 4.18 (dq, J=7.2, 3.3 Hz, 4H), 3.12–2.96 (m, 1H), 2.90–2.80 (m, 1H), 2.40–2.28 (m, 1H), 2.20–2.08 (m, 1H), 1.92 (br s, 2H), 1.23(3) (t, J=7.2 Hz, 3H), 1.22(7) (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 170.6, 143.2, 130.9, 129.2, 129.1, 123.9, 64.7, 62.1, 51.1, 27.8, 13.9; ν_{max} 3385, 2982, 1736, 1477, 1444, 1369, 1250, 1206, 1188, 1086, 1037, 750, 693 cm^{-1}; MS (ESI) *m*/*z* 350 [$(M+Na)^+$, 100%], 328 [$(M+H)^+$, 84], 256 (16), 202 (18), 174 (62).

Step ii. A neat sample of diethyl 2-amino-2-[2-(phenylsulfinyl)ethyl]malonate (107 mg, 0.33 mmol), obtained as described immediately above, was heated at 160 °C for 0.5 h in a microwave reactor and, after cooling, the ensuing brown oil was



Scheme 4.

subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution). Concentration of the appropriate fractions (R_f=0.3 in 97:3 v/v dichloromethane/methanol) afforded *title compound* **10** (39 mg, 59%) as a clear, light-yellow oil [Found: $(M+H)^+$, 202.1070. $C_9H_{15}NO_4$ requires $(M+H)^+$, 202.1079]. ^{1}H NMR (300 MHz) δ 6.31 (dd, J=17.4, 10.5 Hz, 1H), 5.49 (dd, J=17.4, 0.6 Hz, 1H), 5.33 (dd, J=10.5, 0.6 Hz, 1H), 4.28–4.18 (m, 4H), 2.11 (br s, 2H), 1.27 (td, J=7.2, 0.3 Hz, 6H); ^{13}C NMR (75 MHz) δ 170.5, 134.8, 116.5, 67.1, 62.3, 14.1; ν_{max} (NaCl) 3392, 2984, 1738, 1368, 1299, 1257, 1197, 1038 cm^{-1}; MS (ESI) m/z 224 [$(M+Na)^+$, 100%], 202 [$(M+H)^+$, 20], 128 (80), 102 (84), 100 (88).

3.2.3. Compound ***11***. Sodium carbonate (6.07 g, 57.3 mmol), sodium iodide (5.14 mg, 34.3 mmol), and 4-bromo-1-butene (5.81 mL, 57.3 mmol) were added to a magnetically stirred solution of compound **10** (5.76 mg, 28.6 mmol) in *N*,*N*-dimethylformamide (70 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 80 °C for 41 h in a reaction flask fitted with a Liebig condenser. After this time, the reaction mixture was cooled to 18 °C then diluted with dichloromethane (150 mL) and water (30 mL). The separated aqueous layer was extracted with dichloromethane (3×50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) and so affording two major fractions, A and B.

Concentration of fraction A (R_f=0.5, 97:3 v/v dichloromethane/methanol) afforded the *title compound* ***11*** (4.45 g, 87% at 70% conversion) as a clear, light-yellow oil [Found: $(M+H)^+$, 256.1541. $C_{13}H_{21}NO_4$ requires $(M+H)^+$, 256.1549]. ^{1}H NMR (300 MHz) δ 6.23 (dd, J=17.4, 10.5 Hz, 1H), 5.82–5.70 (m, 1H), 5.55 (dd, J=17.4, 1.2 Hz, 1H), 5.40 (dd, J=10.5, 1.2 Hz, 1H), 5.18–5.00 (m, 2H), 4.23 (q, J=7.2 Hz, 4H), 2.50 (t, J=6.6 Hz, 2H), 2.28 (q, J=6.6 Hz, 2H), 1.25 (t, J=7.2 Hz, 6H) (signal due to NH proton not observed); ^{13}C NMR (75 MHz) δ 169.2, 135.8, 132.5, 118.1, 116.6, 71.0, 61.8, 42.3, 34.3, 13.9; ν_{max} (NaCl) 3352, 3078, 2981, 1738, 1640, 1465, 1447, 1391, 1367, 1255, 1198, 1047, 991, 936, 918, 860 cm^{-1}. MS (ESI) m/z 278 [$(M+Na)^+$, 51%], 256 [$(M+H)^+$, 30], 182 (80), 108 (100).

Concentration of fraction B (R_f=0.3, 97:3 v/v dichloromethane/methanol) afforded the starting amine **10** (1.75 g, 30% recovery) as a clear, light-yellow oil.

3.2.4. Compound ***12***. Hydrochloric acid (0.03 mL of a 10 M aqueous solution) was added to a magnetically stirred solution of compound **11** (108 mg, 0.42 mmol) in diethyl ether (1.5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was warmed to 18 °C and after 0.5 h at this temperature it was concentrated under reduced pressure. A magnetically stirred solution of the ensuing yellow oil in dichloromethane (7 mL) was treated with Grubbs' second generation catalyst (18 mg, 21.2 μmol) then warmed to 25 °C and maintained at this temperature for 40 h. After this time sodium bicarbonate (3 mL of a saturated solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a brown oil. This material was subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) and concentration of the appropriate fractions (R_f=0.2 in 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***12*** (92 mg, 96%) as a clear, colorless oil [Found: $(M+H)^+$, 228.1225. $C_{11}H_{17}NO_4$ requires $(M+H)^+$, 228.1236]. ^{1}H NMR (300 MHz) δ 6.14 (dt, J=10.2, 3.6 Hz, 1H), 5.97 (td, J=10.2, 1.8 Hz, 1H), 4.22 (q, J=7.2 Hz, 4H), 3.00 (t, J=5.7 Hz, 2H), 2.84 (br s, 1H), 2.13–2.05 (m, 2H), 1.26 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz) δ 169.6, 129.7, 122.9, 66.4, 61.9, 39.8, 24.5, 13.9; ν_{max} (NaCl) 3353, 2981, 1738, 1453, 1274, 1230, 1199, 1133, 1107, 1078, 1027 cm^{-1}; MS (ESI) m/z 250 [$(M+Na)^+$, 14%], 228 [$(M+H)^+$, 58], 154 (100), 126 (89).

3.2.5. Compound ***13***. 3-Bromo-1-propene (1.36 mL, 15.8 mmol) and potassium carbonate (2.28 g, 16.5 mmol) were added to a magnetically stirred solution of compound **12** (3.41 g, 15.0 mmol) in *N*,*N*-dimethylformamide (20 mL) maintained under nitrogen at 18 °C. The ensuing mixture was warmed to 30 °C and maintained at this temperature for 44 h then cooled and diluted with dichloromethane (40 mL) and water (10 mL). The separated aqueous layer was extracted with dichloromethane (3×20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f=0.3, 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***13*** (3.25 g, 99% at 81% conversion) as a clear, yellow oil [Found: $(M+H)^+$, 268.1560. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.93–5.75 (m, 2H), 5.19 (d, J=17.1 Hz, 1H), 5.10 (d, J=10.2 Hz, 1H), 4.28–4.16 (m, 4H), 3.30 (d, J=6.0 Hz, 2H), 2.83–2.76 (m, 2H), 2.24–2.10 (m, 2H), 1.32–1.23 (m, 6H); ^{13}C NMR (75 MHz) δ 168.8, 136.1, 128.7, 124.1, 116.1, 71.6, 61.0, 55.2, 42.6, 25.0, 13.8; ν_{max} 2980, 2924, 1729, 1641, 1395, 1366, 1251, 1204, 1158, 1142, 1111, 1064, 1037 cm^{-1}; MS (ESI) m/z 290 [$(M+Na)^+$, 70%], 268 [$(M+H)^+$, 23], 194 (100).

Concentration of fraction B (R_f=0.2, 9:1 v/v dichloromethane/ethyl acetate) afforded the starting piperidine **12** (658 mg, 19% recovery) as a clear, colorless oil.

3.2.6. Compound ***14***. Lithium aluminum hydride (19.5 mL of a 1.0 M solution in THF, 19.5 mmol) was added to a magnetically stirred solution of compound **13** (1.49 g, 5.54 mmol) in THF (53 mL) maintained under nitrogen at 0 °C. After 2 h the reaction mixture was warmed to 18 °C and maintained at this temperature for a further 6.5 h then THF (50 mL) was added. The ensuing mixture was cooled to 0 °C then water (0.75 mL), sodium hydroxide (0.75 mL of a 15% aqueous solution), and water (2.25 mL) were added dropwise and in the specified order. The resulting mixture was warmed to 18 °C, maintained at this temperature for 0.25 h then dried ($MgSO_4$). After 0.25 h the reaction mixture was filtered and the solids thus retained were washed with THF (250 mL). The combined filtrates were concentrated under reduced pressure to afford the *title diol* ***14*** (850 mg, 83%) as a clear, yellow oil [$(M+H)^+$, 184.1339. $C_{10}H_{17}NO_2$ requires $(M+H)^+$, 184.1338]. ^{1}H NMR (300 MHz) δ 6.15 (dt, J=6.0, 3.9 Hz, 1H), 5.86–5.70 (m, 1H), 5.44 (d, J=10.2 Hz, 1H), 5.26–5.10 (m, 2H), 3.65 (d, J=11.1 Hz, 2H), 3.43 (d, J=11.1 Hz, 2H), 3.28 (d, J=6.0 Hz, 2H), 2.91 (t, J=5.7 Hz, 2H), 2.42 (s, 2H), 2.14–2.05 (m, 2H); ^{13}C NMR (75 MHz) δ 136.4, 130.2, 129.2, 116.8, 63.0, 62.2, 51.2, 43.0, 25.0; ν_{max} (NaCl) 3400, 2918, 1641, 1417, 1392, 1279, 1077, 1043, 992, 918, 830, 732 cm^{-1}; MS (ESI) m/z 206 [$(M+Na)^+$, 7%], 184 [$(M+H)^+$, 44], 70 (100).

3.2.7. Compounds ***15*** *and* ***16***. Acetic anhydride (0.46 mL, 4.91 mmol) was added to a magnetically stirred solution of compound **14** (900 mg, 4.91 mmol) in diethyl ether (20 mL) maintained under nitrogen at 18 °C. After 12 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1→4:1 v/v hexane/ethyl acetate gradient elution) affording two major fractions, A and B.

Concentration of fraction A (R_f=0.7 in 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***16*** (130 mg, 10%) as a clear, colorless oil [Found: $(M+H)^+$, 268.1549. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 5.97 (dt, J=9.9, 3.9 Hz, 1H), 5.80–5.64 (m, 1H), 5.54 (dt, J=10.2, 2.1 Hz, 1H), 5.18 (dq, J=17.1,

1.5 Hz, 1H), 5.08 (dq, *J*=9.9, 1.5 Hz, 1H), 4.24 (d, *J*=11.4 Hz, 2H), 4.08 (d, *J*=11.4 Hz, 2H), 3.26 (dd, *J*=5.7, 1.2 Hz, 2H), 2.71 (t, *J*=5.7 Hz, 2H), 2.10–2.00 (m, 2H), 2.05 (s, 6H); ^{13}C NMR (75 MHz) δ 170.6, 137.1, 129.0, 127.5, 116.3, 64.6, 58.7, 52.9, 43.1, 25.5, 20.9; ν_{max} (NaCl) 2961, 2917, 2832, 1745, 1641, 1381, 1231, 1044, 916 cm^{-1}; MS (ESI) *m*/*z* 268 [(M+H)$^+$, 37%], 226 (6), 208 (5), 166 (7), 148 (71), 69 (100).

Concentration of fraction B (R_f=0.1 in 4:1 v/v hexane/ethyl acetate) gave the *title compound* ***15*** (896 mg, 81%) as a clear, colorless oil [Found: (M+H)$^+$, 226.1432. $C_{12}H_{19}NO_3$ requires (M+H)$^+$, 226.1443]. ^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.82–5.65 (m, 1H), 5.48–5.38 (m, 1H), 5.24–5.08 (m, 2H), 4.15 (d, *J*=11.7 Hz, 1H), 4.08 (d, *J*=11.7 Hz, 1H), 3.63–3.47 (m, 2H), 3.33 (d, *J*=10.2 Hz, 2H), 2.99 (s, 1H), 2.94–2.82 (m, 1H), 2.68 (td, *J*=11.1, 3.9 Hz, 1H), 2.28–2.10 (m, 1H), 2.06 (s, 3H), 1.96 (d, *J*=17.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 170.6, 136.2, 129.6, 128.9, 117.0, 64.0, 62.3, 60.8, 51.4, 42.8, 25.4, 20.9; ν_{max} (NaCl) 3444, 2918, 2833, 1742, 1641, 1381, 1236, 1043, 918 cm^{-1}; MS (ESI) *m*/*z* 226 [(M+H)$^+$, 85%], 166 (77), 148 (52), 136 (46), 70 (100).

3.2.8. Improved procedure for the preparation of compound ***10****. Step i.* Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred ethanol (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of sodium ethoxide in ethanol was cooled to 0 °C and 2-[*N*-(*tert*-butoxycarbonyl)-amino]malonate (**8**) (4.79 mL, 17.8 mmol, ex. Aldrich) was added and maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**7**) (2.61 mL, 19.5 mmol, ex. Aldrich) was added dropwise. The ensuing reaction mixture was maintained at this temperature for 2 h, then warmed to 18 °C and held at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in ethyl acetate (30 mL) and washed with sodium bicarbonate (3×20 mL of a saturated aqueous solution). The aqueous washings were extracted with ethyl acetate (3×10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material, which was presumed to contain compound **9**, was evenly divided between ten 10 mL Pyrex™ microwave reaction vials and these were then subjected (neat) to simultaneous microwave irradiation under the same conditions as described earlier. The cooled reaction mixtures were then combined and subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) affording two major fractions, A and B.

Concentration of fraction A (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) afforded a ca. 2:3 mixture (as determined by ^{1}H NMR spectroscopic analysis) of the compound **17** and phenylsulfenic acid.

Concentration of fraction B (R_f=0.3, 97:3 v/v dichloromethane/methanol) afforded the *title compound* ***10*** as a light-yellow oil. This material was identical, in all respects, with an authentic sample obtained as described above.

Subjection of a portion of fraction A to flash chromatography (9:90:1 v/v/v ethyl acetate/hexane/triethylamine elution) and concentration of the appropriate fractions (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) gave a spectroscopically pure sample of *compound* ***17*** as a clear, colorless oil [Found: (M+Na)$^+$, 324.1426. $C_{14}H_{23}NO_6$ requires (M+Na)$^+$, 324.1423]. ^{1}H NMR (300 MHz) δ 6.50 (dd, *J*=17.4, 10.8 Hz, 1H), 6.09 (br s, 1H), 5.42–5.26 (m, 2H), 4.40–4.14 (m, 4H), 1.43 (s, 9H), 1.26 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (75 MHz) δ 167.0, 153.6, 132.7, 116.3, 80.3, 67.1, 62.7, 28.1, 13.9; ν_{max} (NaCl) 3435, 2981, 2937, 1743, 1724, 1484, 1368, 1271, 1254, 1205, 1166, 1059, 1022, 986 cm^{-1}; MS (ESI) *m*/*z* 324 [(M+Na)$^+$, 46%], 246 (40), 202 (100), 128 (95).

Step ii. A magnetically solution of the 2:3 mixture of the compound **17** and phenylsulfenic acid (obtained as described immediately above) in dichloromethane (50 mL) maintained at 0 °C was treated with trifluoroacetic acid (7.5 mL, 97.4 mmol). After 0.5 h the reaction mixture was warmed to 18 °C, stirred at this temperature for 16 h then treated with sodium bicarbonate (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×30 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (9:90:1 v/v/v ethyl acetate/hexane/triethylamine elution) and concentration of the relevant fractions (R_f=0.3 in 97:3 v/v dichloromethane/methanol) gave compound **10** in sufficient quantities to sustain the synthetic procedures defined below. This material was identical, in all respects, with an authentic sample obtained as described above.

3.2.9. Compound ***18****.* A solution of dimethyl sulfoxide (0.24 mL, 3.33 mmol) in dichloromethane (10 mL) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (0.19 mL, 2.22 mmol) in dichloromethane (6 mL) maintained under nitrogen at −78 °C. After 0.25 h a solution of compound **15** (250 mg, 1.11 mmol) in dichloromethane (10 mL) was added dropwise over 0.25 h. After 1 h a solution of triethylamine (0.62 mL, 4.44 mmol) in dichloromethane (10 mL) was added and the ensuing mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. Sodium bicarbonate (10 mL of a saturated aqueous solution) was then added and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *compound* ***18*** as a light-yellow oil, R_f=0.7 (in 9:1 v/v dichloromethane/ethyl acetate) [Found: (M+H)$^+$, 224.1285. $C_{12}H_{17}NO_3$ requires (M+H)$^+$, 224.1287]. ^{1}H NMR (300 MHz) δ 9.20 (s, 1H), 6.24–6.16 (m, 1H), 5.82–5.68 (m, 1H), 5.32–5.23 (m, 1H), 5.22–5.08 (m, 2H), 4.45 (d, *J*=11.7 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 3.32–3.20 (m, 1H), 3.18–3.06 (m, 1H), 2.97–2.88 (m, 1H), 2.74–2.62 (m, 1H), 2.35–2.20 (m, 1H), 2.14–2.07 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz) δ 199.9, 170.5, 136.0, 133.1, 122.3, 117.4, 68.8, 63.0, 54.3, 42.1, 26.1, 21.0; ν_{max} (NaCl) 2921, 2817, 1746, 1377, 1234, 1078, 1045, 924, 711 cm^{-1}; MS (ESI) *m*/*z* 246 [(M+Na)$^+$, 20%], 224 [(M+H)$^+$, 12], 178 (62), 164 (51), 109 (100).

This somewhat unstable aldehyde was immediately subjected to the vinylation reaction described directly below.

3.2.10. Compound ***19****.* Vinyl magnesium bromide (5.55 mL of a 1.0 M solution in THF, 5.55 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **18** (obtained as described immediately above) in THF (20 mL) maintained under nitrogen at −78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After 1 h the reaction mixture was cooled to 0 °C then water (4 mL) and ammonium chloride (2 mL of a saturated aqueous solution) were added. The separated aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 2:1 mixture of the two diastereoisomeric forms of *compound* ***19*** as a light-yellow oil [Found: (M+H)$^+$, 210.1492. $C_{12}H_{19}NO_2$ requires (M+H)$^+$, 210.1494]. ^{1}H NMR (300 MHz) δ 6.30–5.65 (m, 3H), 5.50–4.90 (m, 5H), 4.26 (dd, *J*=27.0, 6.0 Hz, 1H), 3.85–3.10 (m, 4H), 3.20–2.50 (m, 2H), 2.25–1.80 (m, 4H); ^{13}C NMR (75 MHz) δ 137.6, 136.8, 136.5, 136.4, 132.3, 129.4, 127.4, 126.0, 117.5, 117.3, 116.7, 116.6, 75.2, 73.0, 64.7, 63.8, 63.4, 63.3, 51.3, 51.2, 43.8, 41.7, 25.4, 23.3; ν_{max} (NaCl) 3400, 2919, 1641, 1417, 1279, 1066, 994, 918 cm^{-1}; MS (ESI) *m*/*z* 232 [(M+Na)$^+$, 6%], 210 [(M+H)$^+$, 18], 192 (6), 70 (100).

3.2.11. Compound ***20****.* Acetic anhydride (0.31 mL, 3.33 mmol) was added to a magnetically stirred solution of compound **19** in diethyl ether (10 mL) maintained under nitrogen at 18 °C. After 15 h the

reaction mixture was concentrated was under reduced pressure and the ensuing yellow oil subjected to flash chromatography (silica, 19:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.7 in 9:1 v/v dichloromethane/ethyl acetate) afforded a ca. 2:1 mixture of the two diastereoisomeric forms of the *title compound* ***20*** (260 mg, 80% over 3 steps) as a clear, light-yellow oil [Found: $(M+H)^+$, 294.1707. $C_{16}H_{23}NO_4$ requires $(M+H)^+$, 294.1705]. ^{1}H NMR (300 MHz) δ 6.10–5.40 (complex m, 5H), 5.30–5.00 (m, 3H), 4.40–3.95 (m, 2H), 3.67 (dm, J=14.7 Hz, 1H), 3.10–2.75 (m, 2H), 2.63–2.48 (m, 1H), 2.08 (s, 3H—minor diastereoisomer), 2.06 (s, 3H—major diastereoisomer), 2.04 (s, 3H—minor diastereoisomer), 2.03 (s, 3H—major diastereoisomer), 2.10–1.80 (m, 3H); ^{13}C NMR (75 MHz) δ 170.8, 170.6, 169.9, 137.4, 136.9, 133.7, 133.0, 130.1, 130.0, 127.0, 125.7, 117.4, 117.3, 116.2, 115.9, 75.8, 72.8, 64.1 62.5, 61.8, 61.7, 52.9, 52.6, 43.3, 42.8, 25.8, 25.7, 21.2, 21.1, 21.0, 20.9 (one signal obscured or overlapping); ν_{max} (NaCl) 2958, 2919, 2833, 1746, 1642, 1375, 1239, 1104, 1028, 918 cm^{-1}; MS (ESI) m/z 316 [$(M+Na)^+$, 1%], 294 [$(M+H)^+$, 15], 234 (23), 174 (52), 104 (51), 70 (100).

3.2.12. Compounds ***21*** *and* ***22****.* Grubbs' second generation catalyst (87 mg, 0.10 mmol) was added to a magnetically stirred solution of a ca. 2:1 mixture of the epimeric forms of compound **20** (300 mg, 1.02 mmol) in dichloromethane (50 mL) kept under nitrogen at 18 °C. The ensuing mixture was maintained at this temperature for 23 h then dimethyl sulfoxide (0.36 mL, 5.12 mmol) was added. After a further 22 h the reaction mixture was concentrated under reduced pressure and the ensuing brown residue was subjected to flash chromatography (silica, 9:1→4:1 v/v hexane/ethyl acetate gradient elution) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f=0.1, 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***22*** (69 mg, 25%) as a clear, light-yellow oil [Found: $(M+H)^+$, 266.1393. $C_{14}H_{19}NO_4$ requires $(M+H)^+$, 266.1392]. ^{1}H NMR (300 MHz) δ 5.94–5.82 (m, 2H), 5.62–5.48 (m, 2H), 5.27 (br s, 1H), 4.40 (dd, J=12.0, 2.1 Hz, 1H), 4.33 (dd, J=12.0, 2.1 Hz, 1H), 3.38–3.13 (m, 3H), 2.76–2.64 (m, 1H), 2.42–2.40 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.05–1.94 (m, 1H); ^{13}C NMR (75 MHz) δ 170.3, 128.1, 127.5, 126.8, 125.2, 73.8, 61.9, 56.5, 50.0, 46.2, 25.2, 21.2 (two signals obscured or overlapping); ν_{max} (NaCl) 2921, 2853, 1742, 1371, 1229, 1043 cm^{-1}; MS (ESI) m/z 288 [$(M+Na)^+$, 5%], 266 [$(M+H)^+$, 41], 206 (24), 146 (100).

Concentration of fraction B (R_f=0.1 in 4:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***21*** (169 mg, 62%) as a clear, light-yellow oil [Found: $(M+H)^+$, 266.1388. $C_{14}H_{19}NO_4$ requires $(M+H)^+$, 266.1392]. ^{1}H NMR (300 MHz) δ 6.14–6.05 (m, 1H), 5.96–5.88 (m, 1H), 5.87–5.80 (m, 1H), 5.19 (d, J=10.2, 1H), 5.10 (d, J=4.5 Hz, 1H), 4.30 (d, J=10.8 Hz, 1H), 4.16 (d, J=10.8 Hz, 1H), 3.43–3.26 (m, 2H), 3.07–2.96 (m, 1H), 2.84–2.75 (m, 1H), 2.53–2.38 (m, 1H), 2.06 (s, 6H), 2.04–1.96 (m, 1H); ^{13}C NMR (75 MHz) δ 171.1, 170.8, 131.7, 127.5, 126.9, 122.2, 67.7, 62.7, 58.0, 49.7, 45.5, 25.0, 21.2, 21.0; ν_{max} (NaCl) 2920, 2852, 1732, 1372, 1236, 1022, 974 cm^{-1}; MS (ESI) m/z 288 [$(M+Na)^+$, 1%], 266 [$(M+H)^+$, 12], 206 (13), 146 (100).

3.2.13. Compound ***6a****.* Potassium carbonate (94 mg, 0.68 mmol) was added to a magnetically stirred solution of compound **21** (180 mg, 0.68 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 19 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title compound* ***6a*** (119 mg, 98%) as a clear, light-yellow oil [Found: $(M+H)^+$, 182.1182. $C_{10}H_{15}NO_2$ requires $(M+H)^+$, 182.1181]. ^{1}H NMR (300 MHz) δ 6.21–6.05 (m, 1H), 5.97–5.83 (m, 2H), 5.59 (dd, J=10.2, 0.9 Hz, 1H), 3.89 (d, J=11.4 Hz, 1H), 3.42 (d, J=11.4 Hz, 1H), 3.67 (br s, 1H), 3.36 (m, J=16.5 Hz, 1H), 3.26–3.14 (m, 2H), 2.82–2.70 (m, 1H), 2.42–2.28 (m, 1H), 2.12–1.98 (m, 1H), 1.85 (br s, 2H); ^{13}C NMR (75 MHz) δ 130.1, 128.6, 128.1, 127.2, 66.0, 62.4, 61.5, 50.2, 46.2, 25.1; ν_{max} (NaCl) 3386, 2922, 2852, 1467, 1341, 1286, 1140, 1109, 1075, 1050, 1028, 970, 730 cm^{-1}; MS (ESI) m/z 204 [$(M+Na)^+$, 4%], 182 [$(M+H)^+$, 58], 164 (55), 146 (34), 134 (44), 112 (100).

3.2.14. Compound ***6b****.* Potassium carbonate (36 mg, 0.26 mmol) was added to a magnetically stirred solution of compound **22** (69 mg, 0.26 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 15 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *compound* ***6b*** (46 mg, 97%) as a clear, light-yellow oil [Found: $(M+H)^+$, 182.1180. $C_{10}H_{15}NO_2$ requires $(M+H)^+$, 182.1181]. ^{1}H NMR (300 MHz) δ 6.13–6.07 (m, 1H), 6.00–5.90 (m, 1H), 5.70–6.84 (m, 2H), 4.29 (s, 1H), 3.97 (d, J=10.8 Hz, 1H), 3.76 (d, J=10.8 Hz, 1H), 3.42–3.28 (m, 1H), 3.18–3.08 (m, 1H), 3.05–2.93 (m, 1H), 2.80–2.70 (m, 1H), 2.40–2.20 (m, 1H), 2.18–2.00 (m, 1H) (signals due to OH protons not observed); ^{13}C NMR (75 MHz) δ 129.0, 128.8, 126.6, 126.0, 72.2, 60.7, 57.4, 49.9, 45.9, 25.3; ν_{max} (NaCl) 3356, 2923, 2853, 1466, 1384, 1287, 1180, 1142, 1075, 1042, 990 cm^{-1}; MS (ESI) m/z 182 [$(M+H)^+$, 100], 164 (33), 146 (12), 134 (23).

3.2.15. Compound ***23****. Step i.* Chloromethyl methyl ether (0.35 mL, 4.66 mmol) was added in three equal portions over 2 h to a magnetically stirred solution of compound **15** (420 mg, 1.86 mmol), *N*,*N*-diisopropylethylamine (1.62 mL, 9.30 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (11 mg, 0.09 mmol) in dichloromethane (20 mL) maintained under nitrogen at 18 °C. After 21 h sodium bicarbonate (5 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was further extracted with dichloromethane (3×15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.3, 9:1 v/v dichloromethane/ethyl acetate) afforded the expected *{1–allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}-methyl acetate* (418 mg, 83%) as a clear, light-yellow oil [Found: $(M+H)^+$, 270.1701. $C_{14}H_{23}NO_4$ requires $(M+H)^+$, 270.1705]. ^{1}H NMR (300 MHz) δ 5.94 (dt, J=10.2, 3.9 Hz, 1H), 5.82–5.68 (m, 1H), 5.58 (dt, J=10.2, 2.1 Hz, 1H), 5.18 (dq, J=17.1, 1.5 Hz, 1H), 5.07 (dq, J=9.9, 1.5 Hz, 1H), 4.59 (s, 2H), 3.68 (d, J=11.4 Hz, 1H), 3.50 (d, J=11.4 Hz, 1H), 3.68 (d, J=9.9 Hz, 1H), 3.49 (d, J=9.9 Hz, 1H), 3.38–3.20 (m, 3H), 3.34 (s, 3H), 2.93 (td, J=6.0, 1.2 Hz, 1H), 2.08–2.02 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz) δ 170.4, 137.3, 128.3, 127.9, 115.8, 96.4, 69.1, 64.6, 58.9, 55.0, 52.9, 43.0, 25.3, 20.8; ν_{max} (NaCl) 2924, 2822, 1744, 1380, 1237, 1150, 1109, 1044, 918 cm^{-1}; MS (ESI) m/z 270 [$(M+H)^+$, 24%], 210 (62), 166 (4), 148 (80), 70 (100).

Step ii. Potassium carbonate (254 mg, 1.84 mmol) was added to a magnetically stirred solution of the {1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl acetate (495 mg, 1.84 mmol) in methanol (15 mL) maintained under nitrogen at 18 °C. After 16.5 h the reaction mixture was concentrated under reduced pressure then dichloromethane (15 mL) and water (3 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the expected *{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol*

(410 mg, 99%) as a clear, yellow oil [Found: $(M+H)^+$, 228.1592. $C_{12}H_{21}NO_3$ requires $(M+H)^+$, 228.1600]. ^{1}H NMR (300 MHz) δ 6.05–5.95 (m, 1H), 5.83–5.65 (m, 1H), 5.52 (dd, J=9.9, 1.5 Hz, 1H), 5.23–5.08 (m, 2H), 4.58 (s, 2H), 3.67–3.50 (m, 3H), 3.40–3.33 (m, 2H), 3.35 (s, 3H), 3.10–3.04 (m, 1H), 2.95–2.84 (m, 2H), 2.72 (td, J=10.5, 3.9 Hz, 1H), 2.26–2.10 (m, 1H), 2.04–1.90 (m, 1H); ^{13}C NMR (75 MHz) δ 136.7, 130.0, 128.7, 116.6, 96.5, 68.2, 62.7, 61.3, 55.3, 51.5, 42.8, 25.4; ν_{max} (NaCl) 3423, 2921, 1149, 1107, 1038, 917 cm^{-1}; MS (ESI) m/z 250 [$(M+Na)^+$, 19%], 228 [$(M+H)^+$, 39], 196 (7), 166 (22), 148 (30), 70 (100).

Step iii. A solution of dimethyl sulfoxide (1.51 mL, 21.3 mmol) in dichloromethane (5 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (1.24 mL, 14.2 mmol) in dichloromethane (40 mL) maintained under nitrogen at −78 °C. After 0.25 h a solution of the {1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol (1.60 g, 7.10 mmol) in dichloromethane (30 mL) was added dropwise over 0.25 h. After 1 h a solution of triethylamine (3.95 mL, 28.4 mmol) in dichloromethane (15 mL) was added and the reaction mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. Sodium bicarbonate (20 mL of a saturated solution) was added and the phases separated. The aqueous layer was extracted with dichloromethane (3×30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *aldehyde* ***23*** as a clear, colorless oil [Found: $(M+H)^+$, 226.1438. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^{1}H NMR (300 MHz) δ 9.28 (s, 1H), 6.24–6.13 (m, 1H), 5.86–5.72 (m, 1H), 5.40–5.32 (m, 1H), 5.28–5.08 (m, 2H), 4.61 (s, 2H), 3.86 (d, J=10.5 Hz, 1H), 3.80 (d, J=10.5 Hz, 1H), 3.36 (s, 3H), 3.32–3.16 (m, 2H), 2.98–2.88 (m, 1H), 2.82–2.72 (m, 1H), 2.32–2.18 (m, 1H), 2.14–2.02 (m, 1H); ^{13}C NMR (75 MHz) δ 201.0, 136.4, 132.0, 127.9, 123.3, 117.0, 96.7, 69.3, 67.3, 55.4, 54.3, 42.3, 25.9; ν_{max} (NaCl) 3421, 2924, 1722, 1440, 1262, 1212, 1150, 1110, 1045, 919 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 2%], 240 (100), 226 [$(M+H)^+$, 43], 210 (28), 194 (28), 178 (40), 164 (52), 146 (24), 109 (82).

This somewhat unstable aldehyde was immediately subjected to the vinylation reaction described directly below.

3.2.16. Compound ***25****. Step i*. Vinyl magnesium bromide (21.3 mL of a 1.0 M solution in THF, 21.3 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **23** (obtained as described immediately above) in THF (60 mL) maintained under nitrogen at −78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After a further 1 h the reaction mixture was cooled to 0 °C and water (12 mL) followed by ammonium chloride (8 mL of a saturated aqueous solution) were added then the phases separated. The aqueous layer was extracted with dichloromethane (3×30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 3:1 mixture of the epimers of the *alcohol* ***24*** as a light-yellow oil [Found: $(M+H)^+$, 254.1755. $C_{14}H_{23}NO_3$ requires $(M+H)^+$, 254.1756]. ^{1}H NMR (300 MHz) δ 6.10–5.90 (m, 1H), 5.75 (br s, 1H), 5.60 (dm, J=10.2 Hz, 1H), 5.34 (dm, J=17.4 Hz, 1H), 5.22–5.04 (m, 3H), 4.61 (ABq, J=6.6 Hz, 2H), 4.26 (s, 1H), 3.72 (s, 3H), 3.67 (s, 1H), 3.38 (s, 3H), 3.00–2.80 (m, 3H), 2.65 (m, 1H), 2.20–1.85 (m, 2H); ^{13}C NMR (75 MHz) δ 138.2, 136.9, 136.7, 136.1, 130.1, 129.2, 128.0, 126.6, 117.4, 116.7, 116.2, 115.4, 96.9, 96.8, 73.4, 71.1, 68.7, 67.8, 63.1, 55.6, 53.2, 51.7, 43.7, 43.4, 25.5, 24.9 (two signals obscured or overlapping); ν_{max} (NaCl) 3436, 2918, 1641, 1440, 1417, 1384, 1275, 1211, 1150, 1107, 1041, 916 cm^{-1}; MS (ESI) m/z 254 [$(M+H)^+$, 100%], 228 (14), 210 (5).

This material was immediately subjected to an acetylation reaction described directly below.

Step ii. Acetic anhydride (1.34 mL, 14.2 mmol) was added to a magnetically stirred solution of the above-mentioned mixture of the epimeric forms of alcohol **24** (obtained as described immediately above) and 4-(*N*,*N*-dimethylamino)pyridine (43 mg, 0.36 mmol) in diethyl ether (30 mL) maintained under nitrogen at 18 °C. After 22 h the reaction mixture was concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.5, 9:1 v/v dichloromethane/ethyl acetate) afforded an indeterminable mixture of the epimers of the *title compound* ***25*** (1.99 g, 91% over 3 steps) as a clear, light-yellow oil [Found: $(M+H)^+$, 296.1863. $C_{16}H_{25}NO_4$ requires $(M+H)^+$, 296.1862]. ^{1}H NMR (300 MHz) δ 6.05–5.90 (m, 2H), 5.75–5.60 (m, 2H), 5.60–5.45 (m, 1H), 5.20–5.00 (m, 3H), 4.60–4.50 (m, 2H), 3.75–3.60 (m, 2H), 3.51 (d, J=10.5 Hz, 1H), 3.34 (s, 3H), 3.12–2.92 (m, 1H), 2.84–2.74 (m, 1H), 2.64–2.53 (m, 1H), 2.09 (s, 3H), 2.00–1.84 (m, 3H); ^{13}C NMR (75 MHz) δ 169.8, 137.3, 134.1, 129.2, 127.9, 126.7, 117.0, 115.7, 96.8, 95.4, 73.5, 68.7, 67.8, 62.0, 55.3, 52.8, 42.9, 25.7, 21.1 (thirteen signals obscured or overlapping); ν_{max} (NaCl) 2925, 2825, 1743, 1641, 1370, 1238, 1149, 1109, 1039, 918 cm^{-1}; MS (ESI) m/z 318 [$(M+Na)^+$, 5%], 296 [$(M+H)^+$, 29], 236 (66), 206 (14), 174 (51), 105 (63), 70 (100).

3.2.17. Compounds ***26*** *and* ***27***. Grubbs' second generation catalyst (572 mg, 0.67 mmol) was added to a magnetically stirred solution of the epimeric forms of compound **25** (1.99 g, 6.74 mmol) in dichloromethane (335 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 46 h then cooled and treated with dimethyl sulfoxide (2.38 mL, 33.5 mmol) and triethylamine (4.66 mL, 33.5 mmol). After a further 23 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1 → 4:1 v/v hexane/ethyl acetate elution) affording three major fractions, A, B, and C.

Concentration of fraction A (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) afforded the starting triene **25** (847 mg, 43% recovery) as a clear, light-yellow oil.

Concentration of fraction B (R_f=0.2, 1:1 v/v hexane/ethyl acetate) afforded *title compound* ***27*** (169 mg, 16% at 57% conversion) as a clear, light-yellow oil (Found: $(M+H)^+$, 268.1549. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 5.97–5.90 (m, 1H), 5.90–5.80 (m, 1H), 5.64 (d, J=9.6 Hz, 1H), 5.50 (d, J=10.2 Hz, 1H), 5.30 (s, 1H), 4.63 (d, J=6.3 Hz, 1H), 4.58 (d, J=6.3 Hz, 1H), 3.98 (d, J=10.8 Hz, 1H), 3.62 (d, J=10.8 Hz, 1H), 3.50–3.15 (m, 3H), 3.36 (s, 3H), 2.76–2.65 (m, 1H), 2.42–2.26 (m, 1H), 2.08 (s, 3H), 2.04–1.97 (m, 1H); ^{13}C NMR (75 MHz) δ 170.3, 128.3, 128.1, 127.0, 125.0, 96.7, 73.9, 66.0, 57.0, 55.3, 50.0, 46.4, 25.2, 21.2; ν_{max} (NaCl) 2924, 1746, 1370, 1231, 1150, 1109, 1041 cm^{-1}; MS (ESI) m/z 268 [$M+H)^+$, 51%], 208 (12), 176 (21), 148 (51), 146 (100).

Concentration of fraction C (R_f=0.1 in 1:1 v/v hexane/ethyl acetate) afforded the *title compound* ***26*** (49 mg, 48% at 57% conversion) as a clear, light-yellow oil [Found: $(M+H)^+$, 268.1548. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 6.03–5.95 (m, 1H), 5.86–5.74 (m, 2H), 5.53 (d, J=10.2 Hz, 1H), 5.30 (d, J=5.1 Hz, 1H), 4.53 (d, J=6.6 Hz, 1H), 4.49 (d, J=6.6 Hz, 1H), 3.68 (d, J=9.0 Hz, 1H), 3.54 (d, J=9.0 Hz, 1H), 3.32–3.18 (m, 2H), 3.26 (s, 3H), 2.97 (td, J=11.1, 4.5 Hz, 1H), 2.76–2.66 (m, 1H), 2.46–2.30 (m, 1H), 2.06–1.91 (m, 1H), 1.99 (s, 3H); ^{13}C NMR (75 MHz) δ 170.9, 131.5, 128.2, 126.3, 122.3, 96.4, 67.8, 66.0, 58.4, 55.1, 49.6, 45.4, 24.9, 21.1; ν_{max} (NaCl) 2922, 1731, 1370, 1241, 1140, 1109, 1041, 1022 cm^{-1}; MS (ESI) m/z 290 [$(M+Na)^+$, 38%], 268 [$(M+H)^+$, 17], 236 (4), 208 (12), 148 (40), 146 (100).

3.2.18. Compound ***28***. Potassium carbonate (54 mg, 0.39 mmol) was added to a magnetically stirred solution of compound **26** (105 mg, 0.39 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 15.5 h the reaction mixture was concentrated under reduced pressure then dichloromethane (10 mL) and water

(2 mL) were added to the residue and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title compound* ***28*** (88 mg, 99%) as a clear, yellow oil [Found: $(M+H)^+$, 226.1432. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^1H NMR (300 MHz) δ 6.01–5.94 (m, 2H), 5.90–5.82 (m, 1H), 5.72 (d, J=10.2 Hz, 1H), 4.59 (d, J=6.6 Hz, 1H), 4.54 (d, J=6.6 Hz, 1H), 3.90–3.82 (m, 1H), 3.76 (d, J=9.3 Hz, 1H), 3.53 (d, J=9.3 Hz, 1H), 3.32 (s, 3H), 3.28 (s, 2H), 3.09 (td, J=11.1, 4.2 Hz, 1H), 2.72–2.62 (m, 1H), 2.48–2.22 (m, 2H), 2.07–1.94 (m, 1H); ^{13}C NMR (75 MHz) δ 129.7, 128.6, 127.2, 126.5, 96.4, 66.4, 65.8, 59.5, 55.1, 50.2, 45.6, 25.1; ν_{max} 3401, 2922, 1140, 1109, 1031, 732 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 12%], 226 [$(M+H)^+$, 29], 208 (5), 176 (10), 156 (35), 148 (37), 146 (100).

3.2.19. Compound ***29***. Potassium carbonate (21 mg, 0.15 mmol) was added to a magnetically stirred solution of compound **27** (40 mg, 0.15 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 16 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added to the residue and the phases separated. The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *compound* ***29*** (32 mg, 95%) as a clear, yellow oil [Found: $(M+H)^+$, 226.1437. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^1H NMR (300 MHz) δ 6.16–6.08 (m, 1H), 5.92–5.84 (m, 1H), 5.72 (s, 2H), 4.57 (s, 2H), 4.16–4.08 (m, 1H), 3.89 (d, J=9.6 Hz, 1H), 3.72 (d, J=9.6 Hz, 1H), 3.33 (s, 3H), 3.18 (d, J=11.1 Hz, 2H), 3.02 (td, J=11.1, 4.2 Hz, 1H), 2.70–2.58 (m, 1H), 2.44–2.28 (m, 1H), 2.06–1.96 (m, 1H) (signal due to OH proton not observed); ^{13}C NMR (75 MHz) δ 130.1, 128.7, 125.7, 125.4, 96.7, 73.2, 65.7, 56.7, 55.5, 50.2, 45.7, 25.3; ν_{max} (NaCl) 3422, 3032, 2918, 2883, 1150, 1108, 1091, 1041, 761 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 18%], 226 [$(M+H)^+$, 31], 208 (10), 176 (12), 148 (55), 146 (100).

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