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Methylation of the Enolates of Thevinone and some Analogues.

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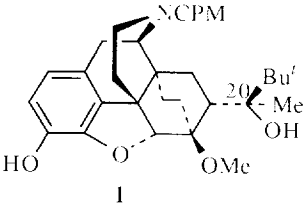
Abstract: Branching has been introduced into various thevinone analogues by utilisation of both kinetic and thermodynamic enolates. No rearrangement was observed in the systems under study.

The potent opioid analgesic buprenorphine (**1**), has been discovered to possess a pharmacological profile useful as a treatment for drug abuse.[1] One of the major aims of our research has been to gain a greater understanding of the significance of the lipophilic group attached to C-20 of buprenorphine and related orvinols and particularly its location with respect to important opioid binding sites. One approach has been to synthesise and evaluate analogues of buprenorphine in which the C-20 lipophilic group has been placed under conformational restraint by being part of an alicyclic system.

Recently we reported the synthesis of the 7,8-ring constrained thevinone* analogues **2**.[2] These can be considered as straight chain thevinones containing an alkyl group fixed below the plane of the ring. In order to access closer analogues of buprenorphine it was necessary to introduce branching into the constrained side chain, particularly dimethyl substitution α to the ketone (e.g. **11**). Since direct Diels-Alder reactions between thebaines **3** and 5,5-dimethyl-2-cyclopenten-1-one were unsuccessful under either pressure or lithium ion catalysed conditions[2], it was decided to attempt two successive methylations of the cyclopentenone adduct **2a**.



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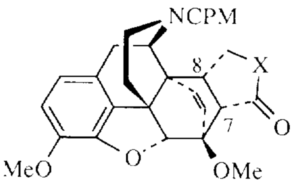
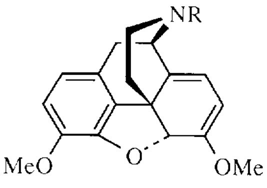
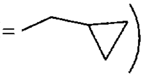


2a: X=CH_2
2b: X=$(CH_2)_2$



3a R=Me, **3b** R=CPM

(CPM=

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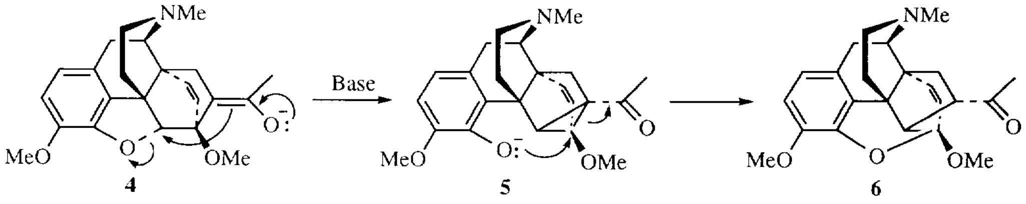
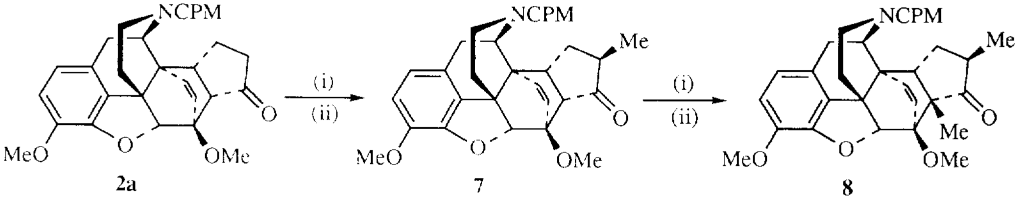
* Bentley *et al*[6] have given the methyl ketone (**33**) the trivial name thevinone and hence close analogues are named as thevinone derivatives, eg. the ethyl ketone (**22**) is called 20-methyl thevinone.

Previously it has been shown that thevinone rearranges in base when the thermodynamic enolate **4** is formed (Scheme 1).[3] The only previous reference to the formation of the kinetic enolate is given by Bentley and Hardy who detected some aldol-type self condensation on treating thevinone with a Grignard reagent.[4] However, the treatment of thevinone with base under kinetic conditions has not previously been studied and we believed that it would allow the desired methylations to be carried out without rearrangement.



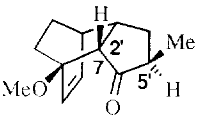
Scheme 1

Treatment of **2a** with lithium diisopropylamide (LDA) at -78 °C failed to form the enolate, but at room temperature treatment with LDA (0.9 equivalents) followed by methyl iodide(MeI) for 3h gave the methylated product **7** in 68% yield. Treatment with any larger proportion of LDA resulted in some dimethylation and made purification difficult (Scheme 2). NOE studies confirmed that the initial methylation had occurred from the less hindered upper face of the enolate. When this methylated ketone was treated with LDA and MeI only a small amount of the desired 5',5'-dimethylated product **11** was observed, the major product being the 2',5' isomer **8** arising from methylation of the alternative enolate. Although this 9:1 mixture of ketones **8** and **11** could not be separated, it was clear that **8** was identical to the impurity formed in the monomethylation. This preferred enolisation reflects the greater accessibility of the 7β proton over the 5'α proton, which is held on the more hindered lower face (partial structure **9**). Although this was not the result desired, it did suggest that the reduced flexibility of the 5-membered ring constrained system prevented any rearrangement of the enolate formed towards C-7.



(i) LDA, THF, 0-25 °C, 1h; (ii) MeI, 25 °C, 3h

Scheme 2



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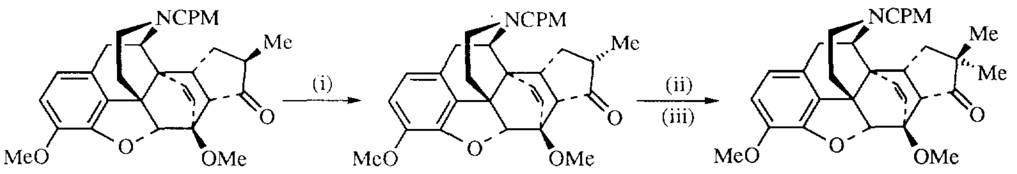
To reach the desired dimethylketone **11** and the epimeric monomethyl ketone **10** a change in conditions was needed to allow the thermodynamic enolate of **7** to be formed. This was achieved by preparing the kinetic enolate using the standard conditions before heating it to reflux in THF for thirty minutes. Quenching with isopropanol yielded a 1:1 mixture of the epimers **7** and **10** which were separated by column chromatography to yield **10** in 35% yield. By subjecting **10** to LDA at room temperature and then treatment with MeI, the desired product **11** was obtained in 84% yield (Scheme 3).

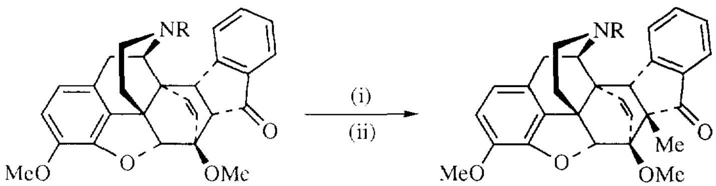


7 **10** **11**

(i) LDA, 25 °C then reflux for 0.5h then Pr^{i}OH; (ii) LDA, THF, 0-25 °C; (ii) MeI, 25 °C, 3h

Scheme 3

To confirm the stability of these 5-membered ring-constrained adducts towards base, the indenone adducts **12a** and **12b**[5] were treated with LDA at 40°C, followed by quenching with MeI. Again the methylated products **13a** and **13b** were isolated in good yield, with no rearrangement taking place (Scheme 4).



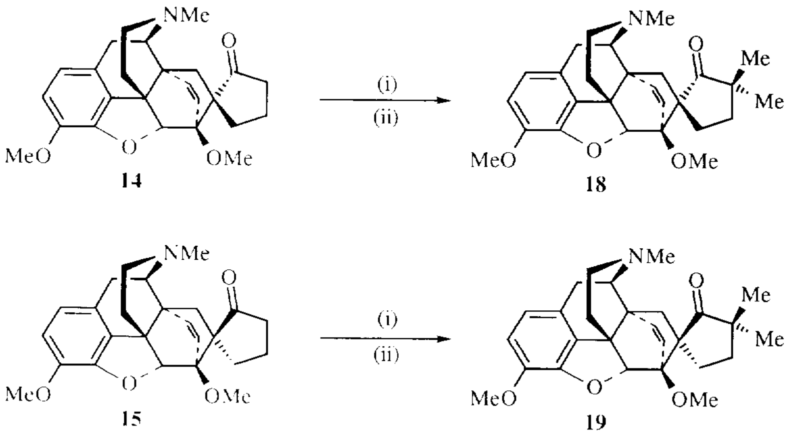
12a R=Me
12b R=CPM

13a (70%)
13b (83%)

(i) LDA, THF, 40 °C for 0.5h; (ii) MeI, 25 °C, 3h

Scheme 4

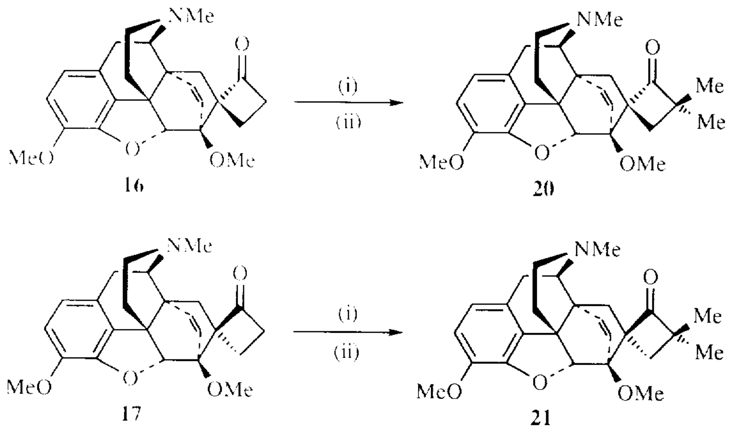
We have reported recently, the synthesis of the spiro adducts **14-17**.[5] Initially it was intended to methylate these following the procedure developed for the 7,8-ring constrained adducts, knowing that rearrangement could not occur due to the lack of any C-7 proton However, even in refluxing THF, no deprotonation could be achieved with LDA. Since the α-protons in **14-17** should be as acidic as those in ketones **2** and **7** it seemed that the problem may not be with the strength of base used, but the steric bulk. Thus the reactions were repeated in the presence of sodium hydride in refluxing THF for 24 hours, followed by quenching with MeI at room temperature for 2 hours. From both the spirocyclopentanone adducts the dimethylated products could be isolated in good yield (β:55%, α:71%) (Scheme 5). The surprising ease of the second methylation (clearly occurring at room temperature) suggested the reaction could be carried out at room temperature and could allow the isolation of the monomethylated ketone. Stirring the ketone, NaH and MeI in THF at room temperature for 2 hours, then quenching the reaction yielded mostly starting material and only small amounts of the mono and dimethylated products, suggesting that the first methylation is the rate-limiting step. In theory the dimethylated ketones could be prepared directly by the Diels-Alder reaction between thebaine and 2,2-dimethyl-5-methylenecyclopentanone. However we found that this reaction proceeded poorly with only a 12% yield (ratio α:β, 1:2) after 7 days reflux in toluene.



(i) NaH, THF, reflux, 24h; (ii) MeI, 25 °C, 2h

Scheme 5

As expected, the spirocyclobutanone adducts proved more difficult to methylate as the enolate is part of a 4-membered ring. By refluxing for 24 hours, followed by quenching in MeI at room temperature for 72 hours, a mixture containing starting material and dimethylated product was produced. In both cases the dimethylated product could only be isolated in very low yield (α:22%, β:16%) (Scheme 6). In addition to the difficulty in forming the enolate, the low yields may partly be due to quaternisation of the tertiary amine with MeI, leading to increased aqueous solubility and loss of material on work up.

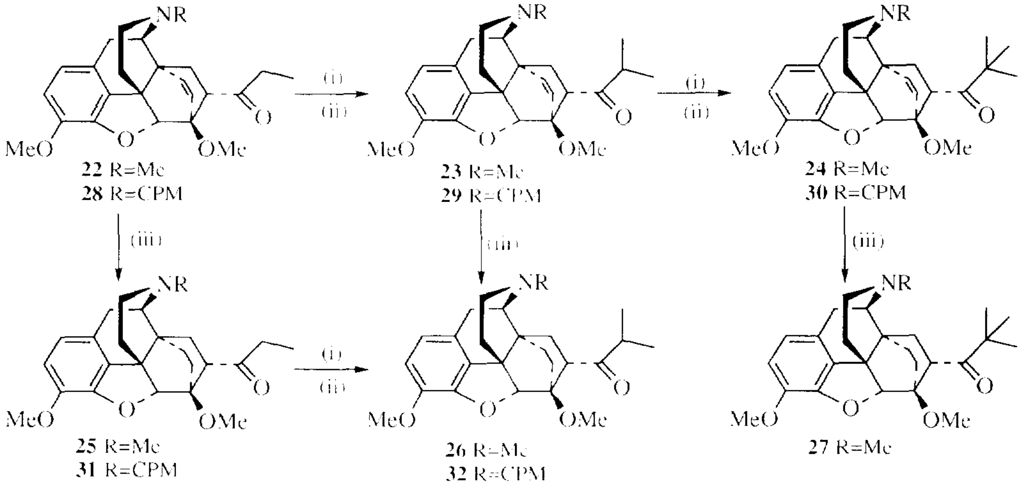


(i) NaH, THF, reflux, 24h, (ii) MeI, 25 °C, 72h

Scheme 6

The success of this work with the constrained thevinones prompted us to extend our studies to the simpler, unconstrained systems that are prone to rearrangement under thermodynamic conditions. The branched chain orvinols, such as buprenorphine (**1**), are prepared by the addition of the appropriate Grignard reagent to the methyl ketone. This occurs with high stereoselectivity, with addition occurring from the upper face.[6] The minor isomer can be isolated, but only in very low yield. To obtain this minor diastereoisomer for evaluation the branched ketone would be required, to which could be added methyl Grignard reagent. Traditional methods of preparing such ketones involved the relatively difficult synthesis of the dienophiles 4-methyl-1-penten-3-one and 4,4-dimethyl-1-penten-3-one.[7] Extension of the methylation procedure of the cyclic thevinones to the ethyl ketone (**22**), prepared from thebaine and 1-penten-3-one,[4] would give the i-propyl and *t*-butyl ketones more conveniently.

Enolisation of 20-methylthevinone (**22**) with LDA at room temperature followed by treatment with MeI gave the i-propyl ketone (**23**) in 76% yield. Similar reaction of the dihydrothevinone (**25**) gave a significantly lower yield of the equivalent i-propyl ketone (**26**) and it proved simpler to access the dihydrothevinones by catalytic reduction of the corresponding etheno bridged thevinones. The lower yield in the dihydro series is likely to be due to the greater steric bulk of the bridge in this series compared to the etheno bridged thevinones. i-Propyl thevinone (**23**) was converted to the *t*-butyl analogue (**24**) by a second enolisation/methylation in 57% yield.

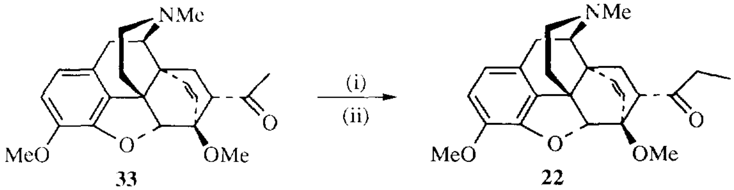


(i) LDA, 0-25 °C, 1h; (ii) MeI, 25 °C, 1h; (iii) H_2, Pd/C (10%), EtOH, 50 °C, 65 psi

Scheme 7

The *N*-cyclopropylmethyl (*N*-CPM) congeners of the branched chain thevinones were prepared by methylating the *N*-CPM ethyl ketone (**28**) and hydrogenation gave the dihydro thevinones. The yields in the methylation reactions were slightly lower than in the *N*-Me series. This is at least partly due to some rearrangement occurring, especially in the i-propyl to *t*-butyl step where 5% of C-4 phenol was isolated. This was not surprising as there is now little difference between the kinetic and thermodynamic enolates.

Surprisingly methylation of thevinone (**33**) in LDA at room temperature gave only a very low yield (13%) of 20-methylthevinone (**22**) after treatment with MeI for 1 hour. This low yield has been shown to be at least partly due to very slow quenching of the enolate by the MeI as extending the quenching time to 18 hours increased the yield to 24%. It has been shown since, that quenching this enolate with more reactive electrophiles gives much better yields of the alkylated ketone and this work will be reported at a later date

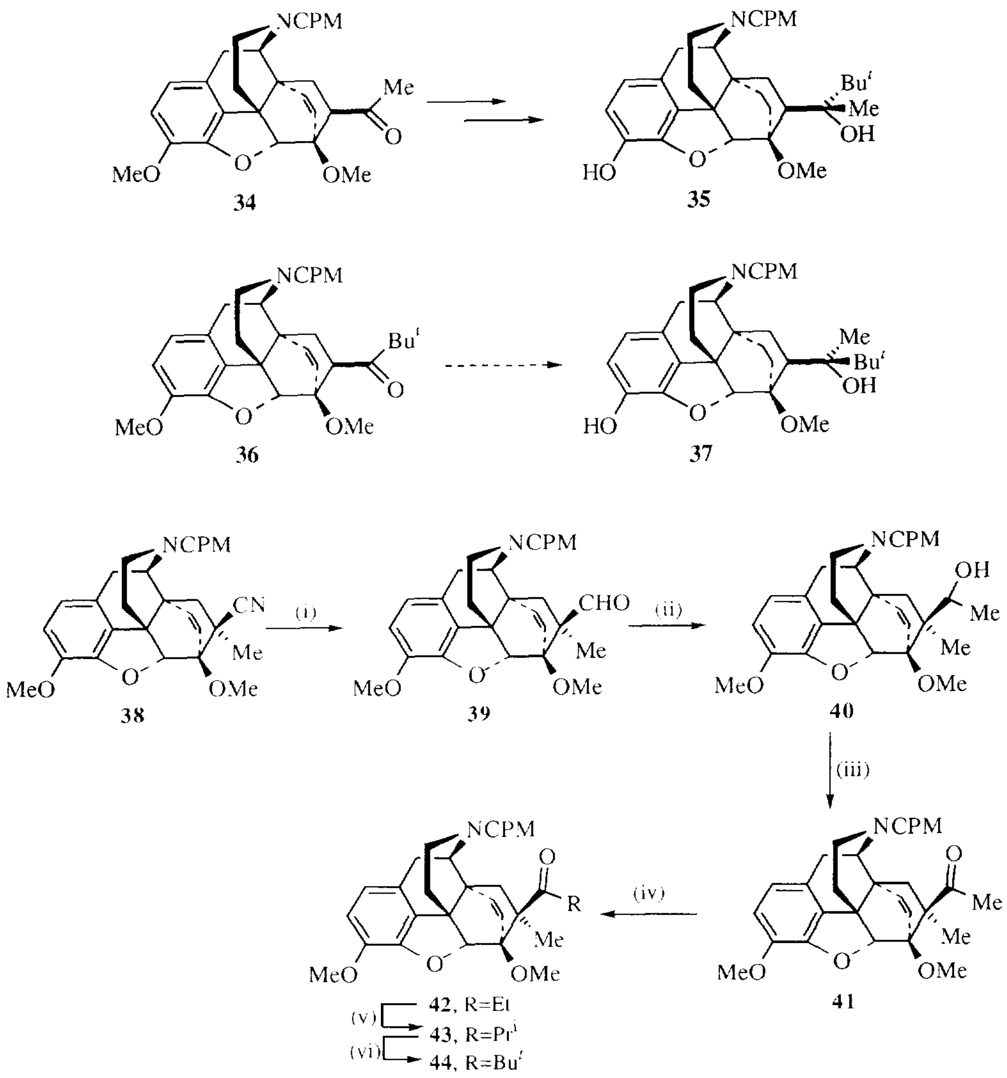


(i) LDA, 0-25 °C, 1h; (ii) MeI, 25 °C, 1h

Scheme 8

Since the Diels-Alder reaction between thebaine (**3a**) and dienophiles typically gives predominantly the 7α thevinones, the corresponding 7β epimers have received little attention. However, they are of interest as the lipophilic group would now not be able to access the region under C-7,C-8, the region occupied by our conformationally restricted analogues. A 7β isomer (**35**) of buprenorphine has been previously prepared by the stereoselective addition of *t*-butyl Grignard reagent to the 7β thevinone (**34**)[8] (obtained in very low yield from the Diels-Alder reaction of thebaine and methyl vinyl ketone). In order to prepare the 7β-epimer of buprenorphine (**37**) it was necessary to prepare the 7β *t*-butyl ketone (**36**). However, treatment of (**34**) with LDA then MeI gave a complex mixture of products, including those due to rearrangement. This could be due to greater hindrance of the methyl group protons leading to less kinetic enolate being formed and/or the 7α proton being more easily removed than the 7β proton (present in the α-adducts) and thus leading to more rearrangement. A simple way around this was to remove the possibility of the thermodynamic (C-7) enolate being formed by utilising the methyl ketone (**41**) which could be accessed using the known adduct (**38**), which is formed from **3a** and methacrylonitrile in good yield (scheme 9).[9] As observed previously in the N-Me series, the *N*-CPM ketone **41** could not be reached directly by reacting methylmagnesium iodide with the nitrile.[9] However, reduction of the nitrile to the aldehyde (**39**) followed by addition of methyl magnesium iodide gave 48% (over two steps) of the secondary alcohol **40** which was oxidised under typical Swern conditions to afford the desired ketone **41** (69%). From this methyl ketone (**41**) the desired *t*-butyl ketone (**44**) can be easily reached by three successive methylations. Treatment of **41** with LDA at room temperature, followed by addition of MeI gave the ethyl ketone **42** in excellent yield (90%), contrasting sharply with the difficulties encountered in methylating the α-methyl ketone (**33**). LDA at room temperature was not sufficient for the next deprotonation, but warming to 40 °C for 15 minutes, followed by MeI quenching at room temperature gave the i-propyl ketone **43** in 76% yield. Again the temperature was raised for the final deprotonation, this time refluxing in THF for 1.5 hours, and the desired *t*-butyl ketone **44** obtained in 78%. For each of the ketones **41**, **42** and **43** the C-5 proton appears at approximately 4.6 ppm in the ^{1}H-nmr. With the bulky *t*-butyl group the signal shifts dramatically downfield to 5.6 ppm, indicating that the *t*-butyl group is fixed in such a position that the carbonyl oxygen is held towards C-5. This could have important consequences in terms of the pharmacology of both this compound and its derivatives and is in accordance with previous work in the α-series of compounds.[10] More direct methods of reaching the *t*-butyl ketone (**44**) have been attempted. However these were unsuccessful with *t*-butyl magnesium bromide failing to give any reaction with the nitrile (**38**) and giving only reduction (40%) to the primary alcohol with the aldehyde (**39**).

Summary. It has been shown that branching can be introduced into a range of thevinone analogues without rearrangement occuring. The 7,7 and 7,8 ring constrained thevinones have been demonstrated to be stable to base treatment under both kinetic and thermodynamic conditions. Also, kinetic deprotonation has allowed branching to be introduced into compounds known to be unstable under thermodynamic conditions.



(i) $LiAlH_2(OEt)_2$, THF, 0-25 °C, 16h; (ii) MeMgI, Et_2O, 25 °C, 18h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2;
(iv) LDA, THF, 25 °C, then MeI for 3h; (v) LDA, THF, 40 °C for 15 min, then MeI for 18h;
(vi) LDA, THF, reflux for 1.5h, then MeI for 18h at 25 °C

Scheme 9

Acknowledgements: This work was supported by the National Institute on Drug Abuse (NIDA) Grant DAO-7315

Experimental

General. The infra-red spectra were obtained on a Perkin-Elmer 881 spectrophotometer. The proton and carbon-13 NMR spectra were obtained on a Jeol JNM-GX 270(67.5) FT spectrometer at 20 °C in $CDCl_3$ and referenced to internal tetramethylsilane. All chemical shifts and coupling constants are given in ppm and Hz respectively. Low and high resolution mass spectra were obtained on a Fisons Autosampler instrument with electron impact ionisation (70 eV). Melting points were determined on a Reicher hot-stage microscope and are uncorrected. Elemental analyses were obtained on a Perkin-Elmer 240C analyser. All reactions were monitored by either thin layer chromatography (R_f) on aluminium sheets coated with silica gel 60 F_{254} (Merck), IR spectroscopy, or ^{1}H-NMR spectroscopy in the case of catalytic hydrogenations. All purifications were carried out by either gravity elution chromatography on Fluka silica gel 60, or dry-flash column chromatography on Fluka silica gel H. Butyllithium was standardised using diphenylacetic acid following the method of Kofron and Baclawski.[11] All reagents were used as supplied by commercial sources unless otherwise stated. All solvents used were purified and dried according to literature methods.

General Procedure A: Methylation of Enolates Employing LDA.

Lithium diisopropylamide (LDA) was prepared by the dropwise addition of n-butyl lithium (1 equiv.) to a solution of diisopropylamine (1.5 equiv.) in dry THF at -78 °C under an atmosphere of nitrogen and the solution stirred at -78 °C for 1h. A solution of ketone (1.1 equiv.) in dry THF was added to a stirred solution of LDA and the mixture allowed to warm to room temperature over 1h. Methyl iodide (1.5 equiv.) was added to that solution and allowed to stir for 3h at room temperature before quenching with ammonium chloride. The THF was removed under reduced pressure and the mixture extracted (3x) into ethyl acetate. The organic extracts were washed (H_2O, brine), dried (Na_2SO_4) and evaporated *in vacuo* to yield a foam. The methylated products were purified by gravity elution chromatography.

General Procedure B: Methylation of Enolates Employing NaH.

The ketone in THF (15ml/mmol) was added to a mixture of NaH (15 equiv.) in THF (1ml/2mmol) before refluxing, with stirring, for 24 hours. The mixture was then cooled to room temperature and methyl iodide (5 equiv.) added. Stirring was continued for 2 hours before quenching in ammonium chloride and extracting into ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to yield a foam. Silica gel chromatography (Hexane-EtOAc, 3:2) gave the product as a white powder.

General Procedure C: Catalytic Hydrogenation.

A solution of the ketone in ethanol (3ml/mmol) and 10% palladium on carbon (0.01 equiv.) was hydrogenated at 65psi at 50 °C for 24-48 hours. The mixture was cooled to room temperature, the catalyst was removed by filtration over Celite and the solvent was evaporated under reduced pressure to yield a foam which was used without any further purification.

General Procedure D: Diels-Alder reactions utilising Mannich salts.

A mixture of a thebaine(1 equiv.), the Mannich salt(1.4 equiv. prepared by a standard procedure[5]) and sodium carbonate(1.5 equiv.), was heated to reflux in toluene (100ml/20mmol thebaine). The mixture was diluted with ammonium chloride and extracted in ethyl acetate (x3). The organic layer was dried (Na_2SO_4) and evaprated under reduced pressure to give the α and β spiro adducts which were separated by column chromatography.

***N*-cyclopropylmethyl-[7α,8α,2',3']-1'-oxocyclopentano-6,14-*endo*-ethenotetrahydronorthebaine (2a).**[2] N-cyclopropylmethylnorthebaine (**3**, R=CPM), (1.00g, 2.85mmol), hydroquinone (20mg) and 2-cyclopenten-1-one (0.50ml, 6mmol) were added to degassed toluene (6ml) in a Youngs' tube under an atmosphere of nitrogen. The tube was sealed under vacuum at -198 °C and then heated to 130 °C for 24h. The tube was allowed to cool and the deep red solution and solid were diluted with Et_2O (20ml) and EtOAc (50ml). The basic organic components were extracted into acetic acid (10%, 2x50ml) and washed with CH_2Cl_2 (50ml), $CHCl_3$ (50ml) and EtOAc (50ml). The aqueous solution was basified with ammonia solution, the precipitate extracted into Et_2O (2x30ml) and the organic solution dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a mixture of product and N-cyclopropylmethylnorthebaine The product was purified by gravity elution chromatography (EtOAc, 1%NH_3), (440mg, 36%). R_f (EtOAc) 0.48; IR ν ($CHBr_3$ mull): 1732(CO) cm^{-1}; ^{1}H NMR: δ 0.15-0.23 (2H, m, $NCH_2CH(-CH_2CH_2-)$), 0.46-0.61 (2H, m, $NCH_2CH(-CH_2CH_2-)$), 0.84-0.89 (1H, m, $NCH_2CH(-CH_2CH_2-)$), 2.65 (1H, d *J* 9.7, 2'-H), 3.19 (1H, d *J* 18.5, 10β-H), 3.63 (3H, s, 6-OCH_3), 3.82 (3H, s, 3-OCH_3), 4.61 (1H, d *J* 1.4, 5-H), 5.43 (1H, d *J* 8.2, 19-H), 5.79 (1H, d *J* 8.1, 18-H), 6.56 (1H, d *J* 8.1, 1-H), 6.62 (1H, d *J* 8.1, 2-H); ^{13}C NMR: δ 2.9, 4.6, 9.5, 21.5, 23.1, 33.5, 37.0, 39.4, 44.3, 45.6, 48.6, 49.0, 51.5, 54.1, 56.5, 59.7, 81.0, 91.7, 113.4, 119.4, 127.9, 129.7, 134.1, 134.7, 142.1, 148.0, 216.4; MS m/e (rel. intensity) 433 (M$^+$, 100%), 418 (M$^+$-CH_3, 17); HRMS calc. for $C_{27}H_{31}NO_4$: 433.2253. Found 433.2252.

***N*-cyclopropylmethyl-[7α,8α,2',3']-5'-[*R*]-methyl-1'-oxocyclopentano-6,14-*endo*-ethenotetrahydronorthebaine (7).** Ketone (**2a**) (1.50g, 3.46mmol) was treated as in general procedure A. Column chromatography (CH_2Cl_2-EtOAc, 4:1) yielded desired product (**7**) (1.06g, 68%) and starting ketone (**2a**) (225mg, 15%). R_f (CH_2Cl_2-EtOAc, 4:1) 0.56; IR ($CHBr_3$ mull): ν 1732(CO) cm^{-1}; ^{1}H NMR: δ 0.14-0.21(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.47-0.61(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.86-0.92(1H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.96(3H, d *J* 6.8, 5'β-CH_3), 2.03-2.22(1H, m, 5'α-H, spin saturation enhanced 18-H), 2.43-2.52(1H, m, 10α-H), 2.73 (1H, d *J* 9.3, 2'-H), 3.17(1H, d *J* 18.3, 10β-H), 3.64(3H, s, 6-OCH_3), 3.68-3.77(1H, m, 3'-H), 3.81(3H, s, 3-OCH_3), 4.63(1H, d *J* 1.4, 5β-H), 5.52(1H, d *J* 8.6, 19-H), 5.77(1H, d *J* 8.8, 18-H), 6.54(1H, d *J* 8.1, 1-H), 6.62(1H, d *J* 8.1, 2-H); ^{13}C NMR: δ 2.9, 4.7, 9.5, 14.4, 21.3, 23.1, 30.6, 33.4, 34.3, 44.3, 45.4, 48.8, 50.2, 51.6, 54.0, 56.5, 59.6, 81.2, 91.8, 113.1, 119.4, 127.8, 129.9, 134.2, 134.7, 142.1, 148.1, 217.5; MS m/e (rel. intensity) 447 (M$^+$, 40%); HRMS calcd. for $C_{28}H_{33}NO_4$: 447.2410. Found 447.2408.

***N*-cyclopropylmethyl-[7α,8α,2',3']-2'-methyl-5'-[*R*]-methyl-1'-oxocyclopentano-6,14-*endo*-ethenotetrahydronorthebaine (8).** Ketone (**7**) (690mg, 1.54mmol) was treated as in general procedure A, to yield a mixture of desired product (**11**) and the isomer 2', 5'-dimethyl ketone (**8**) (ratio 1:9). Column chromatography (CH_2Cl_2-EtOAc, 4:1) failed to separate the isomers. R_f (CH_2Cl_2-EtOAc, 4:1) 0.57 (streak); ^{1}H NMR 0.94 (0.3H, s, 5'-CH_3 (**11**)), 0.98 (2.7H, d, *J* 6.8, 5'β-CH_3 (**8**)), 1.05 (0.3H, s, 5'-CH_3 (**11**)), 1.31 (2.7H, s, 2'-CH_3 (**8**)), 4.61 (0.1H, s, 5-H (**11**)), 4.82 (0.9H, d *J* 1.4, 5-H (**8**), m/z 461 (M$^+$, 80%), 446 (M$^+$-CH_3, 14%).

***N*-cyclopropylmethyl-[7α,8α,2',3']-5'-[*S*]-methyl-1'-oxocyclopentano--6,14-*endo*-ethenotetrahydronorthebaine (10).** 5'-[*R*]-methylketone (7) (1.32g, 2.95mmol) was treated with LDA (0.7 equivalents, 2mmol) as in general procedure A to form the corresponding enolate. The solution was then heated at reflux for 0.5h. and then cooled under nitrogen. The reaction was quenched with propan-2-ol (1ml) and stirred at room temperature for 1h. The reaction mixture was diluted with ammonium chloride solution and then the tetrahydrofuran was removed under reduced pressure. The mixture was extracted with dichloromethane (3 x 50ml) and these organic extracts were washed with sodium chloride solution (100ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a mixture of desired (**10**) and starting material (7).

Column chromatography (CH_2Cl_2-EtOAc, 4:1) yielded **(10)** (460mg, 35%). R_f (CH_2Cl_2-EtOAc, 4:1) 0.38; IR ($CHBr_3$ mull): ν 1731(CO) cm^{-1}; ^1H NMR: δ 0.14-0.21(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.47-0.62(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.85-0.94(1H, m, $NCH_2C\mathit{H}(-CH_2-CH_2-)$), 0.9(3H, d *J* 6.7, 5'α-CH_3), 2.64(1H, d *J* 9.2, 2'-H), 3.14(1H, d *J* 18.5, 10β-H), 3.65(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.58(1H, d *J* 1.3, 5β-H), 5.32(1H, d *J* 8.6, 19-H), 5.81(1H, d *J* 8.7, 18-H), 6.53(1H, d *J* 8.1, 1-H), 6.62(1H, d *J* 8.1, 2-H); ^{13}C NMR: δ 2.9, 4.6, 9.4, 12.9, 22.9, 31.4, 33.4, 35.7, 44.1, 44.3, 45.3, 46.7, 48.1, 51.2, 54.0, 56.4, 59.7, 80.7, 91.6, 113.2, 119.3, 127.8, 129.7, 134.2, 134.9, 142.0, 147.9, 215.6; MS m/e (rel. intensity) 447 (M^+, 94%), 432 (M^+-CH_3, 11); HRMS calcd. for $C_{28}H_{33}NO_4$: 447.2410. Found 447.2401.

***N*-cyclopropylmethyl-[7α,8α,2',3']-5',5'-dimethyl-1'-oxocyclopentano-6,14-*endo*-ethenotetrahydronorthebaine (11).** 5'-[*S*]-methylketone **(10)** (460mg, 1.03mmol) was treated as in general procedure A. Column chromatography (CH_2Cl_2-EtOAc, 4:1) yielded **(11)** (400mg, 84%). R_f (CH_2Cl_2-EtOAc, 4:1) 0.55; IR ($CHBr_3$ mull): ν 1732(CO) cm^{-1}; ^1H NMR: δ 0.15-0.22(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.47-0.63(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.81-0.94(1H, m, $NCH_2C\mathit{H}(-CH_2-CH_2-)$), 0.95(3H, s, 5'α-$CH_3$), 1.05(3H, s, 5'β-$CH_3$), 2.80(1H, d *J* 10.2, 2'-H), 3.14(1H, d *J* 18.3, 10β-H), 3.62(3H, s, 6-OCH_3), 3.70-3.77 (1H, m, 3'-H), 3.81(3H, s, 3-OCH_3), 4.59 (1H, d *J* 1.4, 5β-H), 5.30 (1H, d *J* 8.8, 19-H), 5.80(1H, d *J* 8.8, 18-H), 6.52(1H, d *J* 8.2, 1-H), 6.62(1H, d *J* 8.2, 2-H); ^{13}C NMR: δ 2.7, 4.6, 9.4, 12.7, 14.1, 21.9, 23.0, 30.4, 33.3, 34.1, 44.3, 45.1, 48.1, 50.8, 52.7, 54.1, 56.1, 58.5, 81.2, 91.6, 113.2, 119.4, 127.6, 129.6, 134.4, 137.7, 142.1, 148.2, 216.9; MS m/e (rel. intensity) 461 (M^+, 66%), 446 (M^+-CH_3, 9); HRMS calcd. for $C_{29}H_{35}NO_4$: 461.2572. Found 461.2561.

[7α,8α,2',3']-1'-Indanone-6,14-*endo*-ethenotetrahydrothebaine (12a).[5]

A mixture of thebaine (**3a**) (1.20g, 3.85mmol) and 2-(p-chlorophenylsulfinyl)-1-indanone[12] (1.50g, 5.16mmol), was heated at reflux in toluene (60ml) for 9 hours. The solvent was evaporated under reduced pressure to give a black viscous residue which was dissolved in ethyl acetate and then extracted into 2M hydrochloric acid (4x30ml) and basified with concentrated ammonia. The resulting precipitate was extracted with ethyl acetate and then successively washed with water, a saturated solution of sodium chloride and finally dried (K_2CO_3) and evaporated under reduced pressure to dryness to give a black foam. Gravity elution chromatography with EtOAc-Hexane (2:1) gave **12a** (1.59g, 56%). m.p. 200-201 °C (Pr^iOH); R_f (EtOAc-Hexane; 1:1, 0.5%NH_3) 0.20, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.65; IR ($CHBr_3$ mull): ν 1707(CO) cm^{-1}; ^1H NMR: δ 1.95(1H, dd, *J* 13.5, 2.77, 8α-H), 2.56(3H, s, NCH_3), 2.99(1H, d, *J* 6.8, 7β-H), 3.32(1H, d, *J* 18.9, 10β-H), 3.72(1H, d, *J* 6.7, 9α-H), 3.77(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.76(1H, d, *J* 6.1, 8β-H), 4.77(1H, d, *J* 1.3, 5β-H), 4.89(1H, d, *J* 8.9, 19-H), 5.60(1H, d, *J* 8.9, 18-H), 6.54(1H, d, *J* 8.1, 1-H), 6.62(1H, d, *J* 8.1, 2-H), 7.30-7.36(1H, m, aromatics), 7.40-7.43(1H, m, aromatics), 7.53-7.59(1H, m, aromatics), 7.67-7.69(1H, m, aromatics); ^{13}C NMR: δ 22.33, 33.06, 40.92, 43.41, 45.57, 46.84, 47.75, 48.00, 51.64, 56.35, 57.88, 81.88, 91.56, 113.18, 119.43, 123.69, 126.39, 127.32, 127.51, 128.61, 132.13, 133.56, 134.34, 139.77, 142.10, 147.74, 154.67, 202.66(C_{20}); MS m/e (rel. intensity) 441(M^+, 100%); HRMS calcd. for $C_{28}H_{27}NO_4$: 441.19401. Found 441.19366; Found: C, 76.13; H, 6.18; N, 3.05. $C_{28}H_{27}NO_4$ requires C, 76.17; H, 6.16; N, 3.17%.

***N*-Cyclopropylmethyl-[7α,8α,2',3']-1'-indanone-6,14-*endo*-ethenotetrahydronorthebaine (12b).**[5]

A mixture of *N*-cyclopropylmethylnorthebaine (**3b**) (2.00g, 5.70mmol) and 2-(p-chlorophenylsulfinyl)-1-indanone[12] (2.32g, 7.98mmol), was heated at reflux in toluene (120ml) for 10 hours. The solvent was evaporated under reduced pressure to give a black viscous residue which was dissolved in ethyl acetate and then extracted into 2M hydrochloric acid (4x30ml) and basified with concentrated ammonia. The resulting precipitate was extracted with ethyl acetate and then successively washed with water, a saturated solution of sodium chloride and finally dried (K_2CO_3) and evaporated under reduced pressure to dryness to give a black foam. Gravity elution chromatography with EtOAc-Hexane (1:1.5) gave **12b** (880mg, 32%).. (Found: C, ; H, ; N, . $C_{31}H_{31}NO_4$ requires C, 77.30; H, 6.49; N, 2.91%); R_f (Hexane-EtOAc; 1:1, 0.5%NH_3) 0.23, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.44; IR ($CHBr_3$ mull): ν 1704(CO) cm^{-1}; ^{1}H NMR: δ 0.25-0.30(2H, m, NCH_2CH(-CH_2-CH_2-)), 0.63-0.68(2H, m, NCH_2CH(-CH_2-CH_2-)), 1.03-1.10(1H, m, NCH_2CH(-CH_2-CH_2-)), 2.93(1H, d, *J* 5.0, 7β-H), 2.99(1H, d, *J* 7.0, 8β-H), 3.24(1H, d, *J* 18.9, 10β-H), 3.77(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.77(1H, d, *J* 1.5, 5β-H), 4.84(1H, d, *J* 6.8, 9α-H), 4.92(1H, d, *J* 8.9, 19-H), 5.97(1H, d, *J* 8.9, 18-H), 6.51(1H, d, *J* 8.3, 1-H), 6.62(1H, d, *J* 8.3, 2-H), 7.29-7.35(1H, m, aromatics), 7.50-7.56(1H, m, aromatics), 7.61-7.64(1H, m, aromatics), 7.67-7.70(1H, m, aromatics); ^{13}C NMR: δ 3.94, 4.56(, 9.81, 23.21, 33.30(CH_2), 41.08, 44.14, 46.97, 48.02, 48.72, 51.70, 55.95, 56.46, 60.64, 81.92, 91.86, 113.40, 119.32, 123.72, 126.34, 127.42, 127.48, 128.26, 132.53, 133.70, 134.24, 139.86, 142.13, 147.90, 155.00, 202.60(C_{20}); MS m/e (rel. intensity) 481(M^+, 100%); HRMS calcd. for $C_{30}H_{43}NO_4$: 481.22531. Found 481.22476.

[7α,8α,2',3']-1'-Indanone-7β-methyl-6,14-*endo*-ethenotetrahydrothebaine (13a).

Butyllithium (0.34ml (1.6M in hexane), 5.44x10^{-4}mol) was added to a solution of diisopropylamine (1.00ml, 7.15mmol) in tetrahydrofuran (10ml) at -78°C and that mixture was stirred for 1 hour under nitrogen. A solution of **12a** (250mg, 5.49x10^{-4}mol) in tetrahydrofuran (10ml) was added dropwise to that mixture and once the addition had been completed the mixture was heated to 40 °C for 1 hour. The flask was then cooled to -78 °C and iodomethane (0.50ml, 8.05mmol) was added and the mixture was allowed to reach room temperature and stirred for 3.5 hours. A saturated aqueous solution of ammonium chloride and solid sodium thiosulphate was added and then the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3x20ml) and then washed successively with water and with a saturated solution of sodium chloride and then all the extracts were dried (K_2CO_3) and evaporated to dryness under reduced pressure to yield an off-white powder. The product was purified by re-crystallisation with EtOAc-Hexane (2:1), (180mg, 70%). m.p. 270-271 °C; R_f (EtOAc-Hexane; 2:1, 0.5%NH_3) 0.50, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.61; IR ($CHBr_3$ mull): ν 1707(CO) cm^{-1}; ^{1}H NMR: δ 1.39(3H, s, 7β-CH_3), 2.54(3H, s, NCH_3), 3.28(1H, d, *J* 19.0, 10β-H), 3.52(1H, d, *J* 6.7, 9α-H), 3.79(3H, s, 6-OCH_3), 3.84(3H, s, 3-OCH_3), 4.34(1H, d, *J* 8.9, 8β-H), 4.84(1H, d, *J* 8.9, 19-H), 4.92(1H, d, *J* 1.3, 5β-H), 6.01(1H, d, *J* 9.0, 18-H), 6.50(1H, d, *J* 8.3, 1-H), 6.62(1H, d, *J* 8.1, 2-H), 7.34(1H, m, aromatics), 7.40(1H, m, aromatics), 7.57(1H, m, 1.3, aromatics), 7.67(1H, m, aromatics); ^{13}C NMR: δ 16.2, 22.3(CH_2), 31.3(CH_2), 43.3, 45.6(CH_2), 47.2, 49.0, 55.7, 56.2, 57.1, 57.7, 77.2, 81.6, 94.9, 114.5, 119.4, 124.1, 126.8, 127.4, 127.7, 133.0, 134.2, 138.0, 142.2, 147.8, 153.0, 207.1(C_{20}); MS m/e (rel. intensity) 455(M^+, 100%), 440(M^+-CH_3, 9); HRMS calcd. for $C_{29}H_{29}NO_4$: 455.20966. Found 455.2089.

***N*-Cyclopropylmethyl-[7α,8α,2',3']-1'-indanone-7β-methyl-6,14-*endo*-ethenotetrahydronor-thebaine (13b).** Butyllithium (0.37ml (1.6M), 5.92x10^{-4}mol) was added to a solution of diisopropylamine (1.00ml, 7.15mmol) in tetrahydrofuran (10ml) at -78 °C and that mixture was stirred for 1 hour under nitrogen. A solution of **12b** (290mg, 6.03x10^{-4}mol) in tetrahydrofuran (10ml) was added dropwise to that mixture and once the addition had been completed the mixture was heated to 40 °C for 1 hour. The flask was then cooled to -78 °C and iodomethane (0.50ml, 8.05mmol) was added and the mixture was allowed to reach room temperature and stirred for 3.5 hours. A saturated aqueous solution of ammonium chloride and solid sodium thiosulphate was added and then the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3x20ml) and then washed successively with water and with a saturated solution of sodium chloride and then all the extracts were dried (K_2CO_3) and evaporated to dryness under reduced pressure to yield an off-white foam. Chromatography with EtOAc-Hexane (1:1) as the eluent gave **13b**, (120mg, 83%); R_f (Hexane-EtOAc; 1:1, 0.5%NH_3) 0.48, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.64; IR ($CHBr_3$ mull): ν 1707(CO) cm^{-1}; ^{1}H NMR: δ 0.27-0.28(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.64-0.69(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.88(1H, m, $NCH_2C\mathit{H}(-CH_2-CH_2-)$), 1.41(3H, s, 7β-$CH_3$), 3.20(1H, d, *J* 18.9, 10β-H), 3.63(1H, d, *J* 4.6, 9α-H), 3.78(3H, s, 6-OCH_3), 3.83(3H, s, 3-OCH_3), 4.40(1H, s, 8β-H), 4.86(1H, d, *J* 8.9, 19-H), 4.93(1H, d, *J* 1.4, 5β-H), 5.98(1H, dd, *J* 8.9, 1.4, 18-H), 6.47(1H, d, *J* 7.9, 1-H), 6.61(1H, d, *J* 7.9, 2-H), 7.33(1H, m, aromatics), 7.56(1H, m, aromatics), 7.63(1H, m, aromatics), 7.66(1H, m, aromatics); ^{13}C NMR: δ 3.3, 5.3, 9.8, 16.2, 23.2, 29.7, 31.34, 43.7, 47.3, 47.8, 48.9, 60.9, 61.8, 72.4, 81.5, 94.8, 114.3, 119.2, 124.0, 126.8, 127.0, 127.5, 127.8, 133.4, 134.1, 134.8, 138.00, 142.1, 147.7, 153.3, 207.1(C_{20}); MS m/e (rel. intensity) 495(M$^+$, 100%), 480(M$^+$-CH_3, 10); HRMS calcd. for $C_{32}H_{33}NO_4$: 495.24096. Found 495.23883.

6,14-*Endo*-etheno-[7,7,2',2']-1'α-oxospirocyclopentanotetrahydrothebaine (14) and 6,14-*Endo*-etheno-[7,7,2',2']-1'β-oxospirocyclopentanotetrahydrothebaine (15).[5]

Use of general procedure D gave the two adducts **14** and **15**.

14: Yield 23%; R_f (EtOAc) 0.32; IR ($CHBr_3$ mull): ν 1731(CO) cm^{-1}; ^{1}H NMR: δ 2.36(3H, s, NCH_3), 3.21(1H, d, 10β–H), 3.61(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.75(1H, s, 5β-H), 5.46(1H, d, 19-H), 6.18(1H, d, 18-H), 6.51(1H, d, 1-H), 6.63(1H, d, 2-H); ^{13}C NMR: δ 15.2, 19.6, 22.4, 31.6, 33.2, 38.4, 44.0, 44.1, 45.4, 46.9, 55.3, 56.7, 60.3, 65.7, 77.5, 95.4, 113.7, 119.1, 126.6, 128.2, 134.3, 134.4, 141.8, 147.8, 220.3; MS m/e (rel. intensity) 407(M$^+$, 83%), 392(M$^+$-CH_3, 22); HRMS calcd. for $C_{25}H_{29}NO_4$: 407.20966. Found 407.20859.

15: Yield 31%; R_f (EtOAc) 0.36; IR ($CHBr_3$ mull): ν 1724(CO) cm^{-1}; ^{1}H NMR: δ 2.35(3H, s, NCH_3), 3.23(1H, d, 10β-H), 3.57(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 5.40(1H, d, 19-H), 5.68(1H, s, 5β-H), 5.94(1H, d, 18-H), 6.50(1H, d, 1-H), 6.62(1H, d, 2-H); ^{13}C NMR: δ 18.6, 22.3, 29.5, 36.8, 39.3, 40.2, 43.5, 44.3, 45.4, 46.9, 54.4, 56.7, 60.6, 83.0, 91.5, 113.6, 118.9, 127.8, 128.4, 128.8, 135.8, 135.9, 141.9, 147.9, 222.9; MS m/e (rel. intensity) 407(M$^+$, 97%), 392(M$^+$-CH_3, 24); HRMS calcd. for $C_{25}H_{29}NO_4$: 407.20966. Found 407.21037

6,14-*Endo*-etheno-[7,7,2',2']-1'α-oxospirocyclobutanotetrahydrothebaine (16) and 6,14-*Endo*-etheno-[7,7,2',2']-1'β-oxospirocyclobutanotetrahydrothebaine (17).[5]

Use of general procedure D gave the two adducts **16** and **17**.

16: Yield 30%; R_f (EtOAc-CH_2Cl_2, 1:1) 0.43, IR ($CHBr_3$ mull): ν 1773(CO) cm^{-1}; ^{1}H NMR: δ 2.35(3H, s, NCH_3), 3.20(1H, d, 10β-H), 3.63(3H, s, 6-OCH_3), 3.83(3H, s, 3-OCH_3), 4.69(1H, s, 5β-H), 5.59(1H, d, 19-H), 6.05(1H, d, 18-H), 6.52(1H, d, 1-H), 6.63(1H, d, 2-H); ^{13}C NMR: δ 22.3, 22.7, 32.2, 37.7, 43.9, 44.0, 44.9, 45.0, 47.0, 55.4, 56.7, 60.0, 69.4, 81.6, 95.0, 113.8, 119.3, 125.3, 128.1, 134.2, 137.1, 141.9, 147.8, 213.5; MS m/e (rel. intensity) 393(M$^+$, 100%), 378(M$^+$-CH_3, 15%0; HRMS calcd. for $C_{24}H_{27}NO_4$: 393.19401. Found 393.19424.

17: Yield 30%; R_f (EtOAc-CH_2Cl_2, 1:1) 0.48, IR ($CHBr_3$ mull): ν 1760(CO) cm^{-1}; ^{1}H NMR: δ 2.35(3H, s, NCH_3), 3.19(1H, d, 10β–H), 3.64(3H, s, 6-OCH_3), 3.83(3H, s, 3-OCH_3), 5.02(1H, s, 5β-H), 5.51(1H, d, 19-H), 5.93(1H, d, 18-H), 6.52(1H, d, 1-H), 6.61(1H, d, 2-H); ^{13}C NMR: δ 22.2, 22.3, 24.8, 30.1, 38.6, 43.5, 43.8, 44.0, 45.4, 46.8, 55.3, 56.7, 56.8, 69.7, 82.0, 93.5, 113.8, 119.0, 126.1, 128.0, 135.2, 137.7, 141.9, 147.7, 215.0; MS m/e (rel. intensity) 393(M$^+$, 100%), 378(M$^+$-CH_3, 19); HRMS calcd. for $C_{24}H_{72}NO_4$: 393.19401. Found 393.19456.

6,14-*Endo*-etheno-[7,7,2',2']-5',5'-dimethyl-1'α-oxocyclopentanotetrahydrothebaine (18) and 6,14-*Endo*-etheno-[7,7,2',2']-5',5'-dimethyl-1'β-oxocyclopentanotetrahydrothebaine (19). The Mannich quaternary salt was prepared by a standard procedure.[6] A mixture of thebaine (**3a**) (540mg, 1.73mmol), Mannich salt (500mg, 1.61mmol) and sodium carbonate (350mg) in toluene (30ml) was heated to reflux for 8 days. After cooling, the mixture was diluted with water (50ml) and extracted into dichloromethane (3 x 50ml). The organic extracts were washed with water (50ml) and dried (Na$_2$SO$_4$). After removal of the solvent under reduced pressure, column chromatography (CH$_2$Cl$_2$-EtOAc, 1:1) gave a mixture of **18** and **19** (90mg, 12%) in the ratio 1:2 (^{1}H nmr). Data as shown below.

6,14-*Endo*-etheno-[7,7,2',2']-5',5'-dimethyl-1'α-oxospirocyclopentanotetrahydrothebaine (18). Use of general method B on compound **14**. Yield 71%, R$_f$ (Hexane-EtOAc, 3:2) 0.5, IR (CHBr$_3$ mull): ν 1732(CO) cm^{-1}; ^{1}H NMR: δ 0.99(3H, s, CH$_3$), 1.00(3H, s, CH$_3$), 2.33(3H, s, NCH$_3$), 3.15(1H, d, 10β–H), 3.60(3H, s, 6-OCH$_3$), 3.80(3H, s, 3-OCH$_3$), 4.72(1H, s, 5β-H), 5.28(1H, d, 19-H), 6.25(1H, d, 18-H), 6.50(1H, d, 1-H), 6.62(1H, d, 2-H); ^{13}C NMR: δ 22.5, 23.1, 25.5, 29.7, 31.6, 35.4, 39.4, 43.6, 44.2, 44.4, 45.6, 46.9, 55.4, 56.8, 57.3, 60.5, 85.2, 95.5, 113.7, 119.2, 127.3, 128.2, 133.7, 134.8, 141.9, 148.0, 224.1; MS m/e (rel. intensity) 435(M$^+$, 97%), 420(M$^+$-CH$_3$, 23); HRMS calcd. for C$_{27}$H$_{33}$NO$_4$: 435.24096. Found 435.24017.

6,14-*Endo*-etheno-[7,7,2',2']-5',5'-dimethyl-1'β-oxospirocyclopentanotetrahydrothebaine (19). Use of general method B on compound **15**. Yield 55%, R$_f$ (Hexane-EtOAc, 3:2) 0.6; IR (CHBr$_3$ mull): ν 1720(CO) cm^{-1}; ^{1}H NMR: δ 1.05(6H, s, 2xCH$_3$), 2.35(3H, s, NCH$_3$), 3.21(1H, d, 10β–H), 3.59(3H, s, 6-OCH$_3$), 3.83(3H, s, 3-OCH$_3$), 5.21(1H, d, 19-H), 5.72(1H, s, 5β-H), 5.97(1H, d, 18-H), 6.50((1H, d, 1-H), 6.61(1H, d, 2-H); ^{13}C NMR: δ 22.9, 23.8, 25.7, 29.9, 34.1, 35.0, 41.1, 44.2, 45.1, 46.0, 47.2, 47.3, 55.3, 57.4, 58.3, 61.3, 83.7, 92.8, 114.3, 119.4, 128.4, 129.3, 135.9, 136.4, 142.4, 147.9, 227.8; MS m/e (rel. intensity) 435(M$^+$, 84%), 420(M$^+$-CH$_3$, 17); HRMS calcd. for C$_{27}$H$_{33}$NO$_4$: 435.24096. Found 435.24000.

6,14-*Endo*-etheno-[7,7,2',2']-4',4'-dimethyl-1'α-oxospirocyclobutanotetrahydrothebaine (20). General Method B on compound **16** but quenching with methyl iodide continued for 72 hours. Yield 22%, R$_f$ (Hexane-EtOAc, 3:2) 0.3; IR (CHBr$_3$ mull): ν 1770(CO) cm^{-1}; ^{1}H NMR: δ 1.18(3H, s, CH$_3$), 1.19(3H, s, CH$_3$), 2.35(3H, s, NCH$_3$), 3.18(1H, d, 10β–H), 3.67(3H, s, 6-OCH$_3$), 3.83(3H, s, 3-OCH$_3$), 4.62(1H, s, 5β-H), 5.60(1H, d, 19-H), 6.18(1H, d, 18-H), 6.55(1H, d, 1-H), 6.64(1H, d, 2-H); ^{13}C NMR: δ 20.2, 22.4, 23.7, 31.9, 37.9, 39.3, 43.5, 44.0, 45.5, 46.9, 55.3, 56.7, 60.1, 60.3, 64.9, 81.3, 95.0, 113.8, 119.2, 125.7, 128.2, 134.3, 136.7, 141.9, 147.9, 220.0; MS m/e (rel. intensity) 421(M$^+$, 100%), 406(M$^+$-CH$_3$, 13); HRMS calcd. for C$_{26}$H$_{31}$NO$_4$: 421.22531. Found 421.22475.

6,14-*Endo*-etheno-[7,7,2',2']-4',4'-dimethyl-1'β-oxospirocyclobutanotetrahydrothebaine (21). General Method B on compound **17** but quenching with methyl iodide continued for 72 hours. Yield 16%, R$_f$ (Hexane-EtOAc, 3:2) 0.35; IR (CHBr$_3$ mull): ν 1762(CO) cm^{-1}; ^{1}H NMR: δ 1.17(3H, s, CH$_3$), 1.19(3H, s, CH$_3$), 2.32(3H, s, NCH$_3$), 3.20(1H, d, 10β–H), 3.66(3H, s, 6-OCH$_3$), 3.82(3H, s, 3-OCH$_3$), 5.22(1H, s, 5β-H), 5.48(1H, d, 19-H), 5.89(1H, d, 18-H), 6.48(1H, d, 1-H), 6.60(1H, d, 2-H); ^{13}C NMR: δ 20.3, 22.3, 24.2, 30.2, 40.1, 40.8, 43.6, 44.1, 45.5, 46.7, 54.7, 55.0, 56.9, 60.4, 64.7, 81.9, 93.7, 114.0, 119.1, 126.4, 128.0, 135.3, 137.1, 141.9, 147.9, 222.1; MS m/e (rel. intensity) 421(M$^+$, 100%), 406(M$^+$-CH$_3$, 15); HRMS calcd. for C$_{26}$H$_{31}$NO$_4$: 421.22531. Found 421.22457.

20-Methylthevinone (22). A mixture of thebaine (**3a**), (7.00g, 22.5mmol) and 1-penten-3-one (3.00ml, 30mmol) were heated at reflux in toluene (150ml) for 36h. The solvent and excess dienophile were removed *in vacuo* to yield a viscous residue which was purified by dry-flash chromatography. with EtOAc-Hexane (1:1), (8.63g, 97%); R_f (EtOAc, 0.5%NH_3) 0.53, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.; IR ($CHBr_3$ mull): ν 1712(CO) cm^{-1}; ^{1}H NMR: δ 0.98(3H, t, *J* 7.4, 20-CH_2CH_3), 2.36(3H, s, NCH_3), 2.90(2H, q, *J* 7.6, 20-CH_2CH_3), 3.19(1H, d, *J* 6.5, 9α-H), 3.22(1H, d, *J* 18.5, 10β-H), 3.59(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.56(1H, d, *J* 1.5, 5β-H), 5.56(1H, d, *J* 9.1, 19-H), 5.92(1H, d, *J* 8.9, 18-H), 6.53(1H, d, *J* 8.3, 1-H), 6.63(1H, d, *J* 8.1, 2-H); ^{13}C NMR: δ 7.6, 22.4, 30.3, 33.4, 36.8, 43.3, 43.5, 45.5, 47.4, 49.9, 53.8, 56.6, 60.0, 81.4, 95.8, 113.6, 119.3, 125.8, 128.2, 134.1, 135.6, 141.8, 148.0, 211.5(C_{20}); MS m/e (rel. intensity) 395(M^+, 100%), 380(M^+-CH_3, 19), 338(M^+-$COCH_2CH_3$, 37); HRMS calcd. for $C_{24}H_{29}NO_4$: 395. 20966. Found 395.20879.

22 was also prepared by treating thevinone (**34**) as in general procedure A. Treatment with MeI for 1 hour gave a 13% yield while treatment for 18 hours gave 24%. Analysis as above.

20, 20-Dimethylthevinone (23). The ketone (**22**) (1.00g, 2.53mmol) was treated as in general procedure A. Gravity elution chromatography with EtOAc-Hexane (1:1, 0.5%NH_3), (790mg, 76%); R_f (EtOAc-Hexane; 1:1, 0.5%NH_3) 0.40, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.59; IR ($CHBr_3$ mull): ν 1709(CO) cm^{-1}; ^{1}H NMR: δ 1.01(1H, d, *J* 3.9, 20-$CH(CH_3)_2$), 1.04(1H, d, *J* 4.2, 20-$CH(CH_3)_2$), 1.34(1H, dd, *J* 12.4, 6.5, 8α-H), 2.37(3H, s, NCH_3), 3.03(1H, dd, *J* 9.0, 7.2, 8β-H), 3.18(1H, d, *J* 6.5, 9α-H), 3.21(1H, d, *J* 18.7, 10β-H), 3.59(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.54(1H, d, *J* 1.5, 5β-H), 5.54(1H, d, *J* 8.9, 19-H), 5.94(1H, d, *J* 9.0, 18-H), 6.52(1H, d, *J* 8.1, 1-H),6.61(1H, d, *J* 8.3, 2-H); ^{13}C NMR: δ 17.3, 18.2, 22.4, 30.7, 33.4, 42.1, 43.4, 43.5, 45.5, 47.4, 48.5, 54.2, 56.7, 60.0, 82.1, 96.8, 113.8, 119.3, 125.3, 128.3, 134.2, 135.4, 141.8, 148.1, 215.0(C_{20}); MS m/e (rel. intensity) 409(M^+, 100%), 394(M^+-CH_3, 18), 338(M^+-$COCH(CH_3)_2$, 46) ; HRMS calcd. for $C_{25}H_{31}NO_4$: 409.22531. Found 409.22470.

20, 20, 20-Trimethylthevinone (24). The ketone (**23**) (800mg, 1.95mmol) was treated as in general procedure A. Gravity elution chromatography with EtOAc-Hexane (1:1, 0.5%NH_3), (490g, 59%). m.p.157-159 °C (aq. EtOH) (lit.,[10] 159-160 °C); R_f (EtOAc-Hexane; 1:1, 0.5%NH_3) 0.43, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.54; IR ($CHBr_3$ mull): ν 1706(CO) cm^{-1}; ^{1}H NMR: δ 1.13(9H, s, 20-$C(CH_3)_3$), 2.35(3H, s, NCH_3), 2.94(1H, dd, *J* 12.4, 9.6, 8β-H), 3.58(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.47(1H, s, *J* 1.3, 5β-H), 5.48(1H, d, *J* 9.0, H-19), 6.14(1H, d, *J* 8.9, H-18), 6.52(1H, d, *J* 8.3, 1-H), 6.62(1H, d, *J* 8.1, 2-H); ^{13}C NMR: δ 22.5, 26.1, 33.5, 33.5, 43.5, 43.7, 44.7, 44.9, 45.6, 47.5, 54.6, 56.8, 60.0, 81.8, 97.5, 113.8, 119.2, 126.3, 128.4, 133.8, 134.8, 141.7, 216.0(C_{20}); MS m/e (rel. intensity) 423(M^+, 100%), 408(M^+-CH_3, 16), 338(M^+-$COC(CH_3)_3$, 53); HRMS calcd. for $C_{25}H_{31}NO_4$: 423.24096. Found 423.24136; Anal. calcd. for $C_{25}H_{31}NO_4$: C, 73.73; H, 7.85; N, 3.31 %. Found: C, 73.60; H, 8.11; N, 3.22%.

6, 14-Dihydro-20-methylthevinone (25). Ketone (**22**) (2.40g, 6.07mmol) was treated as in general procedure C (reaction time: 24h; 2.3g, 96%); R_f (EtOAc, 0.5%NH_3) 0.65, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.55; ν_{max}($CHBr_3$ mull) 1711(CO) cm^{-1}; ^{1}H NMR: δ 1.01(3H, t, *J* 7.21, 20-CH_2CH_3), 2.67(2H, q, *J* 7.2, 20-CH_2CH_3), 2.91(3H, s, NCH_3), 3.41(3H, s, 6-OCH_3), 3.89(3H, s, 3-OCH_3), 4.56(1H, s, 5β–H), 6.67(1H, d, *J* 8.1, 1-H), 6.80(1H, d, *J* 8.1, 2-H); ^{13}C NMR: δ 7.5, 17.2, 25.0, 28.8, 30.2, 32.0, 36.0, 39.6, 43.0, 44.2, 46.5, 47.8, 52.3, 56.8, 63.4, 93.3, 115.4, 119.8, 123.7, 130.3, 142.9, 147.0, 212.3(C_{20}); MS m/e (rel. intensity) 397(M^+, 100%), 382(M^+-CH_3, 26), 340(M^+-$COCH_2CH_3$, 58); HRMS calcd. for $C_{24}H_{29}NO_4$: 397.22531. Found 397.22442; Anal. calcd. for $C_{24}H_{29}NO_4.0.5H_2O$: C, 70.89; H, 7.94; N, 3.45%. Found: C, 71.04; H, 7.95; N, 3.11.

6, 14-Dihydro-20, 20-dimethylthevinone (26). Ketone (**23**) (500mg, 1.22mmol) was treated as in general procedure C (reaction time: 24h; 490mg, 98%); R_f (EtOAc-Hexane; 1:1, 0.5%NH_3) 0.47, (MeOH-

$CHCl_3$; 1:50, 0.5%NH_3) 0.55; IR ($CHBr_3$ mull): ν 1708(CO) cm^{-1}; ^1H NMR: δ 1.03(3H, d, J 6.7, 20-$CH(CH_3)_2$), 1.06(3H, d, J 7.4, 20-$CH(CH_3)_2$), 2.30(3H, s, NCH_3), 3.11(1H, d, J 18.7, 10β-H), 3.12(1H, d, J 6.8, 9α-H), 3.38(3H, s, 6-OCH_3), 3.87(3H, s, 3-OCH_3), 4.46(1H, d, J 2.0, 5β-H), 6.59(1H, d, J 8.3, 1-H), 6.71(1H, d, J 8.1, 2-H); ^{13}C NMR: δ 16.7, 17.0, 18.3, 22.0, 28.7, 31.4, 35.2, 35.8, 43.3, 43.5, 45.3, 45.9, 47.8, 52.4, 56.8, 61.4, 77.9, 95.4, 114.0, 119.1, 128.7, 132.5, 141.8, 146.8, 216.8(C_{20}); MS m/e (rel. intensity) 411(M^+, 100), 396(M^+-CH_3, 21), 340(M^+-$COCH(CH_3)_2$, 49); HRMS calcd. for $C_{25}H_{33}NO_4$: 411.24096. Found: M^+, 411.23978; Anal. calcd. for $C_{25}H_{33}NO_4$: C, 76.17; H, 6.16; N, 3.17%. Found: C, 75.91; H, 6.23; N, 2.95%.

6, 14-Dihydro-20, 20, 20-trimethylthevinone (27). Ketone (**24**) (1.00g, 2.36mmol) was treated as in general procedure C (reaction time: 48h; 980mg, 98%). m.p. 185-187 °C (EtOH) (lit.,[10] 185.5-187.5 °C); R_f (Hexane-EtOAc; 1:1, 0.5%NH_3) 0.81, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.65; IR ($CHBr_3$ mull): ν 1702(CO) cm^{-1}; ^1H NMR: δ 1.13(9H, s, 20-$C(CH_3)_3$), 2.26(3H, s, NCH_3), 2.67(1H, d, J 6.5, 9α-H), 3.08(3H, d, J 18.7, 10β-H), 3.30(3H, s, 6-OCH_3), 3.84(3H, s, 3-OCH_3), 4.35(1H, d, J 2.2, 5β-H), 6.58(1H, d, J 8.2, 1-H), 6.71(1H, d, J 8.1, 2-H); ^{13}C NMR: δ 17.3, 22.3, 26.3, 29.5, 34.4, 35.7, 36.8, 43.6, 45.6, 45.6, 46.4, 52.5, 57.2, 61.7, 78.2, 96.0, 114.7, 119.5, 129.4, 133.0, 142.1, 147.4, 218.0(C_{20}); MS m/e (rel. intensity) 425(M^+, 100%), 368(M^+-$C(CH_3)_3$, 31), 340(M^+-$COC(CH_3)_3$, 48); HRMS calcd. for $C_{26}H_{35}NO_4$: 425.25661. Found 425.25449; Anal. calcd. for $C_{26}H_{35}NO_4$: C, 73.38; H 8.29; N 3.29%. Found: C, 73.46; H 8.55; N 3.28%.

***N*-Cyclopropylmethyl-20,20-dimethylnorthevinone (29).**

Ketone (**28**) (6.80g, 15mmol) was treated as in general procedure A. Gravity elution chromatography with EtOAc-Hexane (1:3), (4.63g, 66%). R_f (Hexane-EtOAc; 1:3, 0.5%NH_3) 0.50, (MeOH-$CHCl_3$; 1:50, 0.5%NH_3) 0.72; IR ($CHBr_3$ mull): ν 1708(CO) cm^{-1}; ^1H NMR: δ 0.12-0.16(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.47-0.54(2H, m, $NCH_2CH(-CH_2-CH_2-)$), 0.80-0.82(1H, m, $NCH_2CH(-CH_2-CH_2-)$), 1.03(3H, d, J 6.7, 20-$CH(CH_3)_2$), 1.06(3H, d, J 7.4, 20-$CH(CH_3)_2$), 1.34(1H, dd, J 12.3, 6.4, 8α-H), 3.09(1H, d, J 18.5, 10β-H), 3.60(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.55(1H, s, J 1.5, 5β-H), 5.56(1H, d, J 8.9, 19-H), 5.94(1H, d, J 9.0, 18-H), 6.50(1H, d, J 8.3, 1-H), 6.61(1H, d, J 8.1, 2-H); ^{13}C NMR: δ 3.3, 4.2, 9.4, 17.4, 18.3, 23.1, 30.6, 33.6, 42.1, 43.3, 44.1, 48.5, 54.3, 56.9, 59.8, 82.2, 96.9, 113.6, 119.3, 125.1, 128.4, 134.4, 135.8, 141.8, 148.0, 215.3(C_{20}); MS m/e (rel. intensity) 449(M^+, 100%), 434(M^+-CH_3, 16), 378(M^+-$COCH(CH_3)_2$, 68); HRMS calcd. for $C_{28}H_{35}NO_4$: 449.25661. Found 449.25642.

***N*-Cyclopropylmethyl-20, 20, 20-trimethylnorthevinone (30).**

Ketone (**29**) (200mg, 0.45mmol) was treated as in general procedure A. Column chromatography (CH_2Cl_2-EtOAc, 5:1) yielded **30** (95mg, 42%). R_f (CH_2Cl_2-EtOAc, 4:1) 0.66; IR ($CHBr_3$ mull): ν 1705(CO) cm^{-1}; ^1H NMR: δ 0.13-0.21(2H, m, $NCH_2CH(CH_2CH_2)$), 0.47-0.51(2H, m, $NCH_2CH(CH_2CH_2)$), 0.82-0.91(1H, m, $NCH_2CH(CH_2CH_2)$), 1.14(9H, s, $COC(CH_3)_3$), 3.09(1H, d J 18.6, 10β-H), 3.59(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.48(1H, d J 1.3, 5β-H), 5.50(1H, d J 8.8, 19-H), 6.14(1H, d J 8.9, 18-H), 6.49(1H, d J 8.1, 1-H), 6.61(1H, d J 8.1, 2-H); ^{13}C NMR: δ 3.2, 4.3, 9.4, 23.1, 26.2, 33.5, 33.6, 41.3, 43.6, 44.1, 44.7, 45.0, 48.2, 54.7, 56.9, 59.8, 81.9, 97.6, 113.7, 119.2, 126.1, 128.5, 134.1, 134.4, 141.7, 148.2, 216.2; MS m/e (rel. intensity) 463 (M^+, 100%), 448 (M^+-CH_3, 23), 378 (M^+-$COC(CH_3)_3$, 89). HRMS calcd. for $C_{29}H_{37}NO_4$: 463.27226. Found 463.2722.

A slower running material was also isolated (10mg, 5%) and was shown to possess a 4-phenolic group. R_f = 0.05 (CH_2Cl_2-EtOAc, 5:1); Positive Gibbs test.[13]

N-Cyclopropylmethyl-20-methylnorthevinone (31).

Adduct **31** (15.0g, 34.5mmol) was treated as in general procedure B (reaction time 12h; 50 °C, 65 psi, 14.8g, 98%). ; R$_f$ (EtOAc, 0.5%NH$_3$) 0.67; IR (CHBr$_3$ mull): ν 1708(CO) cm^{-1}; ^{1}H NMR: δ 0.07-0.10(2H, m, NCH$_2$CH(-CH$_2$-CH$_2$-)), 0.46-0.49(2H, m, NCH$_2$CH(-CH$_2$-CH$_2$-)), 0.68-0.76(1H, m, NCH$_2$C*H*(-CH$_2$-CH$_2$-)), 1.03(3H, t, *J* 7.4, 20-CH$_2$C*H*$_3$), 2.47(3H, q, *J* 7.4, 20-C*H*$_2$CH$_3$), 2.98(1H, d, *J* 18.7, 10β-H), 3.41(3H, s, 6-OCH$_3$), 3.87(3H, s, 3-OCH$_3$), 4.47(1H, d, *J* 1.8, 5β-H), 6.56(1H, d, *J* 8.1, 1-H), 6.70(1H, d, *J* 8.1, 2-H) ^{13}C NMR: 3.33, 4.14, 7.68, 9.44, 17.37, 22.78, 28.79, 30.78, 35.30, 35.54, 39.57, 43.81, 46.51, 49.07, 52.32, 56.76, 58.37, 59.8, 77.65, 95.05, 113.93, 119.13, 128.82, 132.72, 141.75, 146.82, 213.58; m/z 437(M$^+$, 100%), 422(M$^+$-CH$_3$, 16), 380(M$^+$-COCH$_2$CH$_3$, 5); HRMS calc. for C$_{27}$H$_{35}$NO$_4$: 437.256609. Found: 437.255920.

N-Cyclopropylmethyl-20, 20-dimethylnorthevinone (32).

Ketone **29** (2.00g, 4.45mmol) was treated as in general procedure B (reaction time: 1 day; 1.83g, 91%). R$_f$ (EtOAc-Hexane; 1:1, 0.5%NH$_3$) 0.66, (MeOH-CHCl$_3$; 1:50, 0.5%NH$_3$) 0.74; IR (CHBr$_3$ mull): ν 1707(CO) cm^{-1}; ^{1}H NMR: δ 0.07-0.12(2H, m, NCH$_2$CH(-CH$_2$-CH$_2$-)), 0.50-0.52(2H, m, NCH$_2$CH(-CH$_2$-CH$_2$-)), 1.03(3H, d, *J* 6.7, 20-CH(C*H*$_3$)$_2$), 1.08(3H, d, *J* 7.4, 20-CH(C*H*$_3$)$_2$), 2.98(1H, d, *J* 18.5, 10β-H), 3.39(3H, s, 6-OCH$_3$), 3.87(3H, s, 3-OCH$_3$), 4.47(1H, s, *J* 1.8, 5β-H), 6.56(1H, d, *J* 8.3, 1-H), 6.71(1H, d, *J* 8.1, 2-H); ^{13}C NMR: 3.11, 4.27, 8.96, 16.60, 16.87, 18.22, 22.66, 28.70, 31.03, 33.47, 43.09, 43.84, 46.28, 47.65, 52.22, 56.57, 57.95, 59.55, 65.68, 77.78, 95.17, 113.89, 119.00, 132.34, 141.64, 146.65, 216.67; MS m/e(rel. intensity) 451(M$^+$, 100%), 436(M$^+$-CH$_3$, 15), 380(M$^+$-COCH(CH$_3$)$_2$, 55); HRMS calc. for C$_{28}$H$_{37}$NO$_4$: 451.272259. Found: 451.272385.

N-Cyclopropylmethyl-7β-formyl-6,14-*endo*-etheno-7α-methyltetrahydronorthebaine (39).

Ethanol (1.04ml, 17.7mmol) was added dropwise to a suspension of fresh LiAlH$_4$ (348mg, 9.17mmol) in dry THF (35ml) at -70 °C. The mixture was stirred at this temperature for 45 minutes before allowing to warm to 0 °C. At this point the nitrile **38** (3.80g, 9.09mmol) in THF(20ml) was added and the solution allowed to warm to room temperature. After stirring for 16 hours the reaction was quenched with a Rochelles salt solution, most of the THF removed *in vacuo* and the organics extracted into dichloromethane. The organic layer was washed with water (2x), dried (CaCl$_2$) and evaporated to give a foam. Silica gel chromatography gave the desired aldehyde in 50% yield. R$_f$ (MeOH-CH$_2$Cl$_2$, 1:50) 0.1; IR (CHBr$_3$ mull): ν 1715(CO) cm^{-1}; ^{1}H NMR: δ 1.05(3H, s, 7-CH$_3$), 3.45(3H, s, 6-OCH$_3$), 3.82(3H, s, 3-OCH$_3$), 4.55(1H, s, 5β-H), 5.51(1H, d, 19-H), 6.01(1H, d, 18-H), 6.49(1H, d, 1-H), 6.60(1H, d, 2-H), 9.95(1H, s, CHO); ^{13}C NMR: δ ; MS m/e (rel. intensity) 421(M$^+$, 100%), 406(M$^+$-CH$_3$, 19); HRMS calcd. for C$_{26}$H$_{31}$NO$_4$:421.22531. Found 421.22588.

N-Cyclopropylmethyl-6,14-*endo*-etheno-7β-(21-hydroxy)ethyl-7α-methyltetrahydronorthebaine (40).

Methyl iodide (0.30ml, 4.73mmol) was added dropwise to a vigorously stirred mixture of magnesium metal turnings (115mg, 4.8mmol) in dry ether (5ml). Once the reaction was complete the aldehyde **39** (1.00g, 2.4mmol) in ether (35ml) was added and the resulting suspension stirred at room temperature overnight. The reaction was quenched with aqueous ammonium chloride and the product extracted into ethyl acetate. Drying (Na$_2$SO$_4$) and evaporation yielded the product (1.01g, 96%) as a white powder that needed no further purification. R$_f$ (MeOH-CH$_2$Cl$_2$, 3:100) 0.2; IR (CHBr$_3$ mull): ν 3432(OH) cm^{-1}; ^{1}H NMR: δ 0.93(3H, s, 7-CH$_3$), 1.23(3H, d, 20-CH$_3$), 3.73(3H, s, 6-OCH$_3$), 3.85(3H, s, 3-OCH$_3$), 5.13(1H, s, 5β-H), 5.44(1H, d, 19-H), 6.01(1H, d, 18-H), 6.48(1H, d, 1-H), 6.63(1H, d, 2-H); ^{13}C NMR: δ 3.7, 4.7, 9.9, 18.0, 19.8, 23.6, 31.7, 38.3, 43.3, 44.5, 47.6, 48.3, 56.2, 57.4, 57.8, 60.3, 72.2, 87.0, 95.9, 114.4, 119.7, 127.5, 128.6, 135.8, 136.3, 142.5, 148.2; MS m/e (rel. intensity) 437(M$^+$, 58%), 392(M$^+$ -CH(OH)Me, 25); HRMS calcd. for $C_{27}H_{35}NO_4$: 437.25661. Found 437.25658

7β-Acetyl-*N*-cyclopropylmethyl-6,14-*endo*-etheno-7α-methyltetrahydronorthebaine (41).

Oxalyl chloride (0.28ml, 3.21mmol) in dry CH_2Cl_2 (9ml) was cooled to -78 °C before adding DMSO (0.48ml, 6.76mmol) in CH_2Cl_2 (9ml) over 5 minutes, followed by stirring for 5 minutes. The alcohol **40** (1.30g, 2.97 mmol) in CH_2Cl_2 (30ml) was then added over 10 minutes and the solution stirred for 15 minutes before adding triethylamine (2.1ml, 15.1mmol) and allowing to warm to room temperature. Stirring was continued for 2 hours before quenching in a brine solution. The organic layer was then washed succesively with NH_4Cl, H_2O, $NaHCO_3$ and H_2O, before drying ($CaCl_2$) and evaporation in vacuo to give an off-white foam. Silica gel chromatography gave the desired ketone as a white powder (0.89g:69%). R_f (MeOH-CH_2Cl_2, 3:100) 0.45; IR ($CHBr_3$ mull): ν 1693(CO) cm^{-1}; ^{1}H NMR: δ 1.11(3H, s, 7-CH_3), 2.92(3H, s, $COCH_3$), 3.71(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.60(1H, s, 5β-H), 5.40(1H, d, 19-H), 5.99(1H, d, 18-H), 6.48(1H, d, 1-H), 6.61(1H, d, 2-H); ^{13}C NMR: δ 4.0, 4.5, 9.3, 22.4, 23.6, 30.8, 31.7, 35.2, 37.0, 43.4, 45.2, 47.3, 56.2, 57.9, 59.2, 60.0, 85.0, 95.7, 113.5, 119.3, 126.6, 129.3, 137.3, 138.0, 142.5, 149.2, 216.6; MS m/e (rel. intensity) 435(M$^+$, 100%), 420(M$^+$-CH_3, 14); HRMS calcd. for $C_{27}H_{33}NO_4$: 435.24096. Found 435.24132.

***N*-Cyclopropylmethyl-6,14-*endo*-etheno-7α-methyl-7β-propionyltetrahydronorthebaine (42).**

Diisopropylamine (0.17ml, 1.21mmol) in THF (10ml) was cooled to -70 °C before adding BuLi (0.69ml, 1.6M, 1.10mmol) dropwise. After 15 minutes the ketone **41** (430mg, 0.98 mmol) was added in THF (10ml) and the solution allowed to warm to room temperature. MeI (0.23ml, 3.65mmol) was then added and the solution stirred for 3 hours before quenching with NH_4Cl(aq). The product was extracted into ether and washed with water before drying (Na_2SO_4) and removal of the solvent to give a yellow foam. Silica gel chromatography gave the product as a white foam (400mg, 90%), R_f (MeOH-CH_2Cl_2, 3:100) 0.31; IR ($CHBr_3$ mull): ν 1691(CO) cm^{-1}; ^{1}H NMR: δ 1.07(3H, t, 20-CH_2CH_3), 1.19(3H, s, 7β-CH_3), 2.70(2H, q, 20-CH_2CH_3), 3.71(3H, s, 6-OCH_3), 3.82(3H, s, 3-OCH_3), 4.61(1H, s, 5β-H), 5.43(1H, d, 19-H), 5.99(1H, d, 18-H), 6.47(1H, d, 1-H), 6.61(1H, d, 2-H); ^{13}C NMR: δ 3.9, 4.6, 9.0, 10.0, 23.6, 23.9, 30.5, 31.4, 34.8, 37.2, 44.0, 44.4, 48.4, 55.9, 57.9, 58.2, 60.5, 83.9, 95.9, 114.5, 119.6, 126.6, 128.7, 136.8, 137.2, 142.4, 148.1, 216.3; MS m/e (rel. intensity) 449(M$^+$, 100%) 434(M$^+$-CH_3, 17); HRMS calcd. for $C_{28}H_{35}NO_4$: 449.25661. Found 449.25584.

***N*-Cyclopropylmethyl-6,14-*endo*-etheno-7β-isobutyryl-7α-methyltetrahydronorthebaine (43).**

BuLi (0.69ml, 1.7M, 1.10mmol) was added dropwise to diisopropylamine (0.17ml, 1.21mmol) in THF(10ml) at -70 °C. After 15 minutes the ketone **42** (0.40g, 0.89 mmol) was added in THF (10ml) and the solution warmed to 40 °C for 15 minutes. After allowing to cool to room temperature MeI (0.23ml, 3.65mmol) was added and stirring continued for 18 hours. Quenching in NH_4Cl(aq) and extraction into ether was followed by washing with water, drying (Na_2SO_4), and evaporation to give an orange foam. Silica gel chromatography yielded the product as a white foam (315mg:76%) R_f (Hexane-EtOAc, 7:3) 0.4; IR ($CHBr_3$ mull): ν 1689(CO) cm^{-1}; ^{1}H NMR: δ 1.06(3H, d, 20-CH(CH_3)$_2$), 1.11(3H, d, 20-CH(CH_3)$_2$), 1.28(3H, s, 7β-CH_3), 2.70(1H, m, 20-CH(CH_3)$_2$), 3.72(3H, s, 6-OCH_3), 3.81(3H, s, 3-OCH_3), 4.61(1H, s, 5β-H), 5.49(1H, d, 19-H), 5.98(1H, d, 18-H), 6.46(1H, d, 1-H), 6.60(1H, d, 2-H); ^{13}C NMR: δ 3.4, 4.0, 9.5, 19.9, 21.3, 22.9, 23.2, 30.1, 36.2, 37.2, 43.2, 43.9, 47.9, 55.5, 56.9, 57.7, 60.0, 83.8, 95.8, 113.7, 119.1, 126.2, 128.2, 136.2, 136.8, 141.9, 147.5, 220.1; MS m/e (rel. intensity) 463(M^+, 96%) 448(M^+-CH_3, 17); HRMS calcd. for $C_{29}H_{37}NO_4$: 463.27226. Found 463.27086.

N-Cyclopropylmethyl-6,14-*endo*-etheno-7α-methyl-7β-trimethylacetyltetrahydronorthebaine (44). BuLi (0.69ml, 1.7M, 1.10mmol) was added dropwise to a solution of diisopropylamine (0.17ml, 1.21mmol) in THF (10ml) at -70 °C. After 15 minutes the ketone **43** (315mg, 0.68 mmol) in THF (10ml) was added and the solution warmed to reflux for 90 minutes. After cooling to room temperature MeI (0.23ml, 3.65mmol) was added and stirring continued for 18 hours. Quenching in NH_4Cl(aq) and extraction into ether was followed by washing with water, drying (Na_2SO_4) and evaporation to leave an orange foam. Silica gel chromatography yielded the product as a white foam (240mg, 74%); R_f (Hexane-EtOAc, 7:3) 0.38; IR ($CHBr_3$ mull): ν 1687(CO) cm^{-1}; ^1H NMR: δ 1.31(9H, s, 20-(CH_3)$_3$), 1.35(3H, s, 7β-CH_3), 3.69(3H, s, 6-OCH_3), 3.83(3H, s, 3-OCH_3), 5.39(1H, d, 19-H), 5.62(1H, s, 5β-H), 5.89(1H, d, 18-H), 6.43(1H, d, 1-H), 6.60(1H, d, 2-H); ^{13}C NMR: δ 3.4, 4.0, 9.6, 22.9, 30.9, 31.1, 38.2, 43.1, 43.9, 46.2, 47.5, 52.2, 57.0, 58.4, 59.7, 84.8, 93.3, 114.1, 118.8, 128.1, 129.4, 134.8, 136.1, 141.9, 148.3, 216.5; MS m/e (rel. intensity) 477(M^+, 100%) 462(M^+-CH_3, 29); HRMS calcd. for $C_{30}H_{39}NO_4$: 477.28791. Found 477.28832.

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