# Exploratory synthetic investigations related to 12a-deoxypillaromycinone

**Lan Wang, Sanath K. Meegalla, Cheng-Lin Fang, Nicholas Taylor, and Russell Rodrigo**

**Abstract**: Furfural is converted to suitably substituted AB synthon **21** for 12a-deoxypillaromycinone in 10 steps by a sequence involving the following key steps: intramolecular Diels-Alder reaction of a furan, *5-endo-trig* cleavage of the oxabicyclo adducts **18**, and catalytic hydrogenation of the double bond of a tetrasubstituted enone to produce **19**. Enones **21a** and **21b** obtained by dehydrogenation of **19a** and **19b**, respectively, are then annulated with ethyl 2-methoxy-6-methylbenzoate in a four-step procedure to generate tetracyclic products **25** in 14 steps from furfural.

*Key words*: antibiotics, furan, intramolecular Diels-Alder, retro Diels-Alder.

**Résumé** : Le furfural peut être transformé par une séquence de synthèse en dix étapes en un synthon AB (**21**) portant des substituants appropriés pour la 12a-désoxypillaromycocinone; les étapes clés sont une réaction de Diels-Alder intramoléculaire sur le furane, un clivage *5-endo-trig* des adduits oxabicycliques (**18**) et une hydrogénation catalytique de la double liaison de l'énone tétrasubstituée conduisant au produit **19**. Les énones **21a** et **21b** été obtenues par déshydrogénation des produits **19a** et **19b** ont été soumises à une annellation en quatre étapes avec le 2-méthoxy-6-méthylbenzoate d'éthyle qui génère les produits tétracycliques **25** en 14 étapes à partir du furfural.

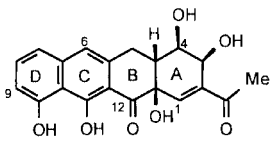
*Mots clés* : antibiotiques, furane, Diels-Alder intramoléculaire, rétro Diels-Alder.

[Traduit par la Rédaction]

## Introduction

Pillaromycin A, isolated from a culture of *Streptomyces flavovirens* in 1970 (1), is an anti-neoplastic antibiotic that is structurally related to the anthracyclines and tetracyclines but with significantly reduced cardiotoxicity. The aglycone pillaromycinone was assigned the linear tetracyclic structure (**1**) characteristic of this group of antibiotics, by a combination of spectroscopic, degradative, and X-ray crystallographic studies (2). More recently, a re-investigation of the biosynthetic pathway to the aureolic acid group of antibiotics resulted in the isolation of premithramycinone **2** from a blocked mutant of *S. argillaceus*. This antibiotic aglycone, structurally similar to pillaromycinone, is the suggested precursor for the aureolic acid group, and is shown to arise by "tetracycline-type" folding of the initial decaketide (3).

All these tetracyclic antibiotic aglycones have been attractive synthetic targets, and although successful routes to the anthracyclinones and the tetracyclines have been developed, no synthesis of pillaromycinone has been reported. The AB *cis*-ring junction of the antibiotic coupled with the *cis* disposition of the A ring hydroxyl groups and the *peri* positioning of the phenolic hydroxyl groups in rings C and D constitute serious stereochemical and regiochemical problems that must be overcome in any synthetic endeavour. Two attempts have been made (4, 5), and both focused on solving the problem of the AB *cis*-ring fusion. In both instances, the C-12a hydroxyl group was omitted from the target and the desired stereochemistry was achieved by Diels-Alder cycloadditions.

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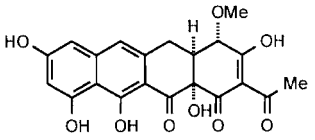


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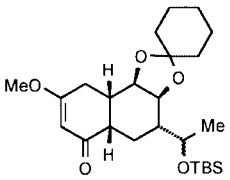


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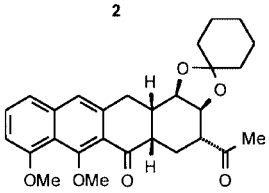


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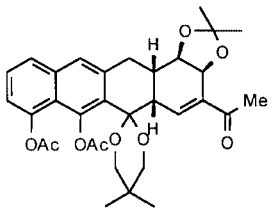


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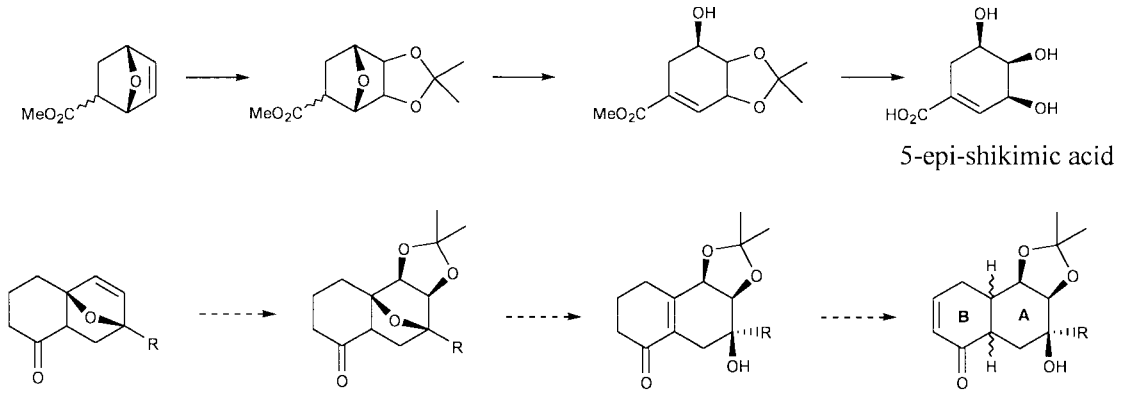
**Scheme 1.**




The latter synthesis (5) commenced with a homochiral diacetate derived from L-rhamnose in three steps. By incorporating a chiral centre from the starting material in the linker of an intramolecular Diels-Alder (IMDA) reaction stereochemical control was achieved in the cycloaddition to eventually obtain the desired *cis*-4a,12a ring fusion with the 4a*R* configuration of natural pillaromycinone. This was an elegant demonstration of fidelity in the transmission of stereochemical information in the IMDA reaction, but the "cost" of this strategy was paid for in separation of isomeric intermediates and in the 17 steps needed to obtain AB synthon **3** from L-rhamnose. The regio-controlled attachment of rings C and D to form the tetracyclic core of 12a-deoxypillaromycinone was effected by the Staunton–Weinreb procedure and the synthesis concluded with the 1,2-dihydro-2,3-cyclohexylidenyl-10,11-dimethyl derivative (**4**) of deoxypillaromycinone in 21 steps from L-rhamnose. The earlier synthetic work (4) also concentrated on the establishment of the *cis* AB-ring fusion, but this time by means of an intermolecular Diels-Alder reaction. Much experience with protection and deprotection sequences for the oxygen functional groups was gained, but this effort also ended short of the target at the tetracyclic intermediate (**5**) after 27 steps.

Our synthetic planning for this project relied on earlier work on the synthesis of the shikimic acids (6) and (±)-daunomycinone (7), and used a similar *5-endo-trig* cleavage of a 7-oxabicyclo[2.2.1]heptane adduct as the key step in the rapid production of a prospective AB synthon from furfural (Scheme 1).

Clearly, the major issues that had to be addressed by this investigation were (*i*) the relative stereochemistry of the AB-ring junction that ensues from saturation of the 4a–8a enone double bond; (*ii*) the exact nature of the acetyl group surrogate R, and its compatibility with the experimental conditions of the individual synthetic steps; and (*iii*) the attachment of rings CD at the 2,3-enone double bond of the AB segment. In this paper we report the outcome of our work and discuss its applicability to the future synthesis of (±)-12a-deoxypillaromycinone.

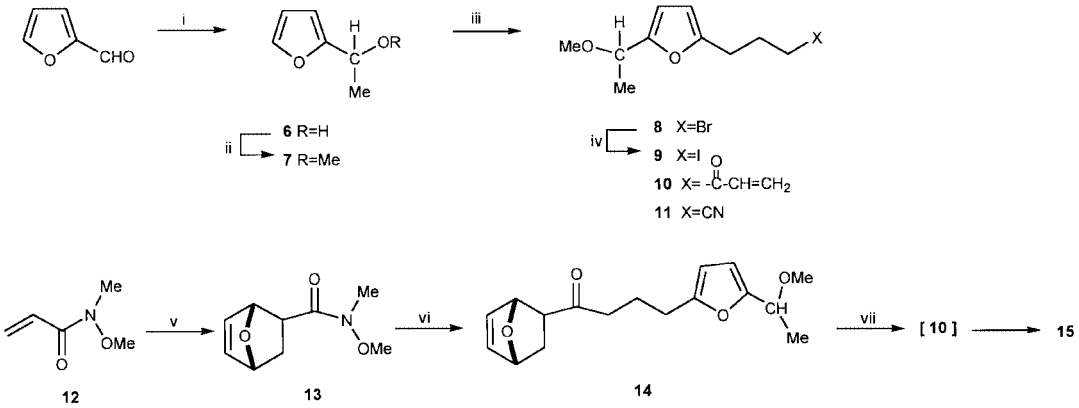
## Results and discussion

### Elaboration of a suitably substituted AB fragment

Furfural was treated with methyllithium, and resulting alcohol **6** was methylated with sodium hydride–iodomethane. 1′-Methoxyethyl furan **7** was deprotonated at the remaining α-position with *n*-butyl lithium, a 10% molar excess of 1,3-dibromopropane was then added rapidly at –78°C, and the solution was allowed to reach room temperature overnight. Chromatography of the resulting products provided 62% yield of desired bromopropylfuran **8**, a smaller amount of the dehydrobrominated allyl furan (5%), and 7% of the symmetrical dimer arising from substitution at both ends of the 1,3-dibromopropane. Inverse addition of the reagents did not significantly improve the yield of **8**. Iodide **9** was obtained in 95% yield from **8** by nucleophilic displacement with potassium iodide in purified (HPLC grade) acetone containing a small amount of sodium bicarbonate. These four routine transformations were conducted on ~20-g scales to furnish **9** in 30% overall yield (Scheme 2).

It was now necessary to set the stage for the IMDA reaction with the furan ring as the diene by appending a vinyl ketone residue (the dienophile) at the end of the three-carbon substituent. Various methods are available for accomplishing the transformation of **9** to desired enone **10**; these usually involve the addition of an organolithium or magnesium species to an acrolein (or substituted acrolein) followed by oxidation of the resulting alcohol (8). In our case, the alcohol obtained from **9** in this manner was much more sensitive to the oxidative conditions than alcohols from simple α-methyl furans, and hence the yields were poor and the enone was accompanied by products of decomposition and polymerization. We therefore sought an alternative that did not require oxidative conditions for the conversion of **9** to **10**. Although cyanide **11** could be prepared, it failed to react with vinyl lithium or vinyl magnesium bromide. Amide **12** prepared from acryloyl chloride and *N*,*O*-dimethyl hydroxylamine (9) seemed to be a promising option for this transformation. The conjugated double bond of **12** was "masked" by reacting it with furan (1.1 equiv zinc iodide, 50°C, 10 days) to produce *exo* adduct **13** exclusively. This compound was prepared on a large scale as a crystalline solid after column chromatography. Reaction of iodide **9** with 2.2 equiv of *tert*-butyllithium at –78°C followed by addition of the amide (1.5 equiv in ether) at –78°C provided ketone **14** after work-up in 75% yield. It was heated in dry benzene for 12 h to induce the retro Diels-Alder reaction and the solvent was removed under reduced pressure to leave crude enone **10**. Cyclization of **10** by treatment with a stoichiometric quantity of methyl aluminum dichloride in

**Scheme 2.**




i. MeLi, THF, 85% ii. NaH, MeI, 60% iii.BuLi, -78°C -> -20°C, $C_3H_6Br_2$, 61% iv. KI, $Me_2CO$, 91% v. Furan, $ZnI_2$, reflux, 10 days, 67% vi. **9**, *t*-BuLi, -78°C, 75% vii. PhH, reflux, 12h, PhH removed; $CH_2Cl_2$, $MeAlCl_2$, -78°C, 76%

dry methylene chloride at –78°C to produce a ~1:1 mixture of two IMDA *exo* adducts (8) (diastereomeric at C-9) in an overall yield of 68% (15.3% from furfural in six steps). This was an important but unavoidable consequence of the chirality at C-9 in our surrogate acetyl group; furthermore, the approximately equal amounts of diastereomers produced in the reaction indicated that the configuration at C-9 did not have any influence on the stereochemical outcome of the cycloaddition. The diastereomers were separated by chromatography on silica in 30% ethyl acetate–hexane to provide individual racemic ketones 2*S**,4a*S**,8a*R**,9*S** (**15a**, higher $R_f$), and 2*S**,4a*S**,8a*R**,9*R** (**15b**, lower $R_f$). The chirality at C-9 is immaterial as it must eventually be lost in the conversion of this group to the desired C-2 acetyl substituent, but it was convenient to separate the diastereomers at this stage and process them separately (as the 9*S** series from **15a** and the 9*R** series from **15b**) to accurately monitor the stereochemical integrity of each succeeding intermediate. The 500 MHz $^1$H NMR spectra of the individual diastereomers, though complex in the δ 1.8–2.6 region, displayed the resonance of H-1α as a clear doublet of doublets at ca δ 1.5–1.65 with $J$ = 12.4, 8.9 Hz (9*S** isomer) and 11.7, 8.2 Hz (9*R** isomer). These values of $J_{gem}$ and $J_{vic}$, respectively, imply that the adjacent H-8a proton is in an α configuration; therefore, these signals are diagnostic for *exo* cycloaddition in the IMDA reaction. Similar observations have been recorded (8) for such adducts by other authors.

The alkene double bond of each isomer was hydroxylated with osmium tetroxide in pyridine to install the vicinal dihydroxy function (80%), which was then protected as the acetonide (70%) by treatment with 2,2-dimethoxypropane and *p*-toluene sulfonic acid in methylene chloride (Scheme 3). An X-ray crystallographic structure (Fig. 1) of acetonide **17a** (9*S** series) confirmed the earlier stereochemical assignments as well as the subsequent *exo* hydroxylation common in these oxabicyclo analogues of norbornene (6). Treatment of each of these acetonides with methoxide in methanol resulted in the expected (10) 5-*endo-trig* oxygen-bridge cleavage to produce the respective enones **18a** and **18b** in 72% yield. Many attempts were made to saturate the tetrasubstituted double bond of these enones. Catalytic hydrogenation (Pd, ethylacetate) of each isomer gave complex mixtures of stereoisomeric ketones as well as allylic alcohols of undefined stereochemistry. Use of dissolving metal reductions (sodium amalgam or Birch reduction) gave product mixtures lacking resonances attributable to the acetonide. Complexed tin hydrides and copper hydrides only returned the starting materials. A recent report (11) of the beneficial effects of DBU in the catalytic hydrogenation of the tetrasubstituted double bond of an enone was relevant to this problem. Thus, the hydrogenation of **18a** with hydrogen at atmospheric pressure, 20% palladium hydroxide on carbon, and 0.33 molar proportions of DBU in methanol containing 3% water produced single decalone **19a** in good yield. Furthermore, we were able to combine the reverse Michael oxygen-bridge cleavage with the hydrogenation by treating **17a** with 2 molar proportions of sodium methoxide under the above hydrogenation conditions for four days at room temperature. This resulted in the formation of **19a** in one pot and in 60% yield. Its $^1$H NMR spectrum had a diagnostic signal for H-8a: an apparent triplet of doublets at δ 2.75 with two diaxial coupling constants ($J_{8,8a} \approx J_{4a,8a} \approx 11.8$ Hz) and one axial–equatorial coupling ($J_{8,8a} \approx 2.3$ Hz). This result suggested that hydrogenation of the tetrasubstituted enone double bond occurred from the α-face, which was followed by equilibration of the *cis*-fused decalone to the less crowded *trans*-isomer **19a** by base catalyzed epimerization at C-8a. In the expectation that the haptophilic influence (12) of the neighboring hydroxyl groups would promote hydrogenation from the β-face, we attempted the same reaction with bridged diol **16b**. The major constituent, estimated to be at least 80% of the crude product mixture, from this reaction displayed a similar triplet of doublets in its $^1$H NMR spectrum at δ 2.75 with two diaxial couplings ($J$ = 12.1 Hz) and one equatorial–axial coupling ($J$ = 3.1 Hz) to the neighboring protons at C-8 and C-4a, respectively. The structure and relative stereochemistry of that material was confirmed as **20b** by an X-ray crystallographic determination (Fig. 2). 9*R** acetonide **17b** was treated with DBU, aqueous methanol, methoxide, $Pd(OH)_2$, and $H_2$ as before to produce a mixture of two inseparable isomers, the *trans*-decalone and presumably the α-*cis*-decalone, which were stirred without hydrogen for an additional three days to produce *trans*-decalone **19b** with a similar triplet of doublets ($J$ = 11.9, 2.3 Hz) for

**Scheme 3.**

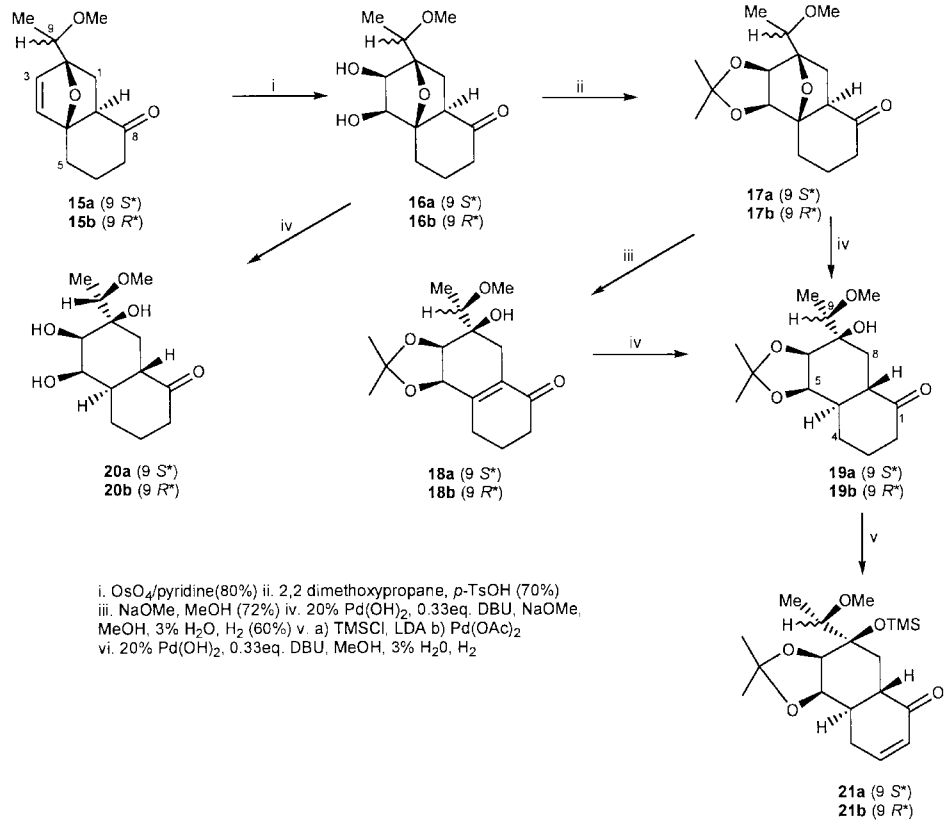



**Fig. 1.** The X-ray crystal structure of **17a**.

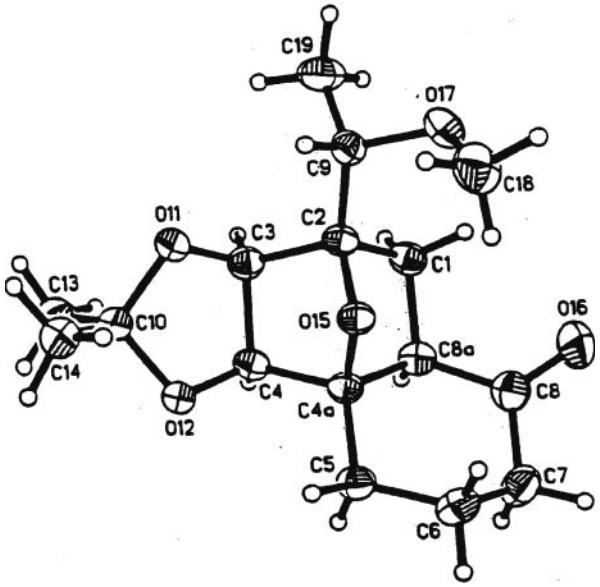
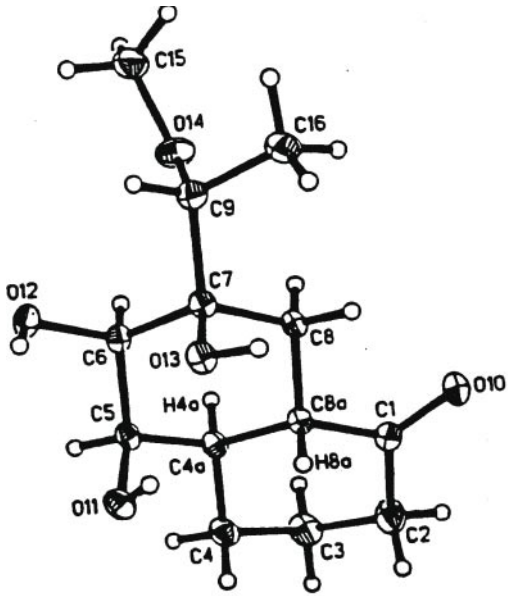


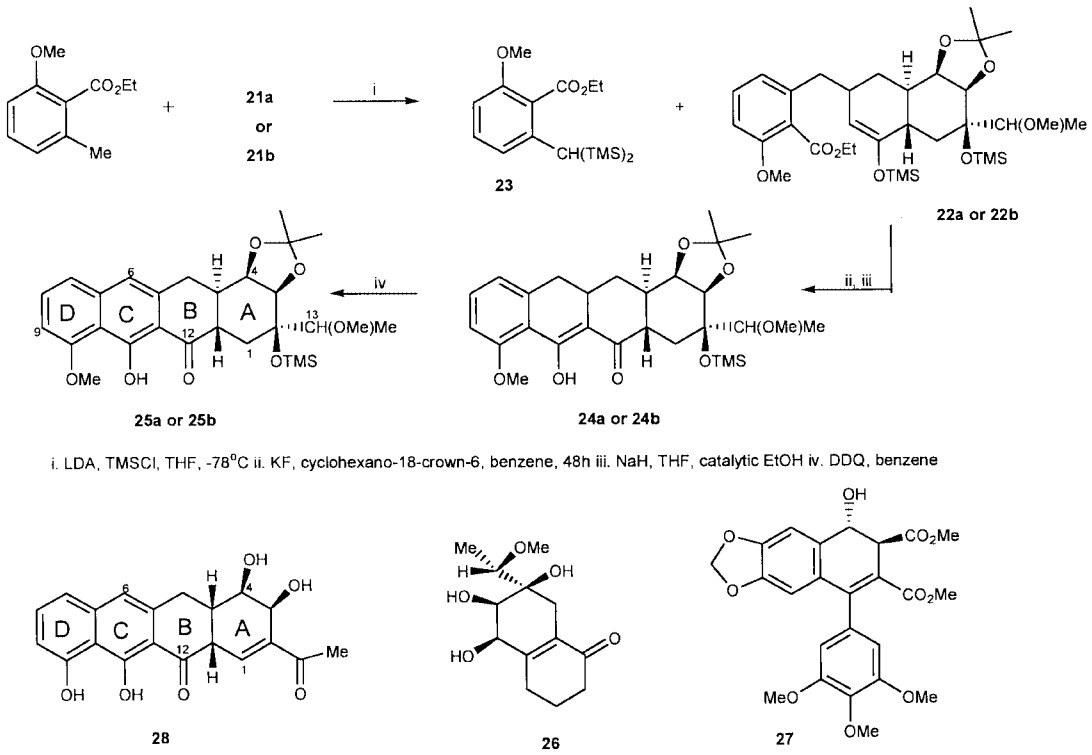

**Fig. 2.** The X-ray crystal structure of **20b**.




the β-oriented C-8a proton. The unfortunate but inescapable conclusion is that heterogeneous hydrogenation of these intermediates takes place predominantly from the α-face of the molecule and the expected haptophilic effect does not operate in these substrates.

In spite of this serious setback, we decided to continue with the final steps of the synthesis to test the viability of the plan for eventual synthesis of a tetracycle with the corrected AB *cis* ring fusion (vide infra). Dehydrogenation (13) of the kinetic enol silanes derived from **19a** and **19b** at $C_2$–$C_3$ was achieved with palladium acetate in 56% yield. Our synthesis of properly functionalized enones **21a** and **21b** was thus completed in ten steps from furfural in an overall yield of ~3%.

**Scheme 4.**




### Attachment of the CD rings

After some experiments with 2-cyclohexenone (serving as a model for bicyclic enones **21**), we settled on a four-step conjugate addition–cyclization procedure to achieve the AB + CD connection with the proper regiochemical outcome. Deprotonation of ethyl 2-methoxy-6-methylbenzoate (14) with excess LDA at –78°C in THF–HMPA and reaction of the ensuing anion with each enone **21a** and **21b** separately at this temperature for 1 h was followed by quenching the reaction mixture with TMS chloride. Standard work-up and flash chromatography gave the crude silyl enol ethers **22** as yellow oils in 48% yield. The optimum ratio of reagents for this step was 4.5:1:0.5 (LDA–benzoate–enone) and the excess benzoate was recovered as its disilylated derivative **23**. The crude enol silanes were desilylated and subjected to a Dieckmann condensation with a catalytic amount of sodium ethoxide to produce the tetracycles **24**, which were dehydrogenated with DDQ in benzene to the desired naphthacenones **25** in 18% overall yield each for the four-step sequence (Scheme 4). These tetracycles are therefore obtainable in 14 steps from furfural. The 500 MHz $^1$H NMR spectra provide conclusive support for the structure and stereochemistry of each compound. Thus **25b** displays an apparent triplet of doublets at δ 3.18 ($J$ ~ 13–14, 3–4 Hz) for H-12a, representing two approximately equal diaxial and one small equatorial coupling (to H-1$_{eq}$). The other AB ring-junction proton, H-4a appears (superficially) as a triplet of triplets at δ 2.21 with two diaxial couplings (13–14 Hz each) and two axial–equatorial couplings (4–5 Hz each) to the neighbouring "equatorial" protons at C-4 and C-5. The 13-*S** isomer **25a** has a very similar spectrum, but the signals for H-12a overlap with the quartet for H-13 so that the approximate coupling constants cannot be measured. The signal for H-4a is, however, a similar triplet of triplets at δ 2.19 with coupling constants of 12.7 and 4.4 Hz.

This investigation has demonstrated that the plan outlined in Scheme 1 delivers a short synthesis (14 steps) of tetracycles **25** with all but one stereocentre (C-4a) correctly established for (±)-12a-deoxypillaromycinone. A method for rectifying the AB stereochemistry still remains to be developed, but now that the structure and stereochemistry of every intermediate has been conclusively established by this work our next goal will be the evaluation of hydroxyl-directed homogeneous hydrogenation methods using cationic Rh and Ir complexes (15). Substrates like **18** and **26** seem to be particularly appropriate for such explorations in view of the recently reported (16) hydrogenation of the tetrasubstituted double bond of α,β-unsaturated ester **27** containing an α-homoallylic hydroxyl group with a Rh(I) cationic complex to produce an 85% yield of hydrogenated products, in which α-hydrogen delivery predominated in a 20:1 ratio. We have already obtained **26** by extended treatment of **16a** with trifluoroacetic acid and confirmed its structure and stereochemistry by X-ray analysis. These investigations will commence shortly, and if successful, the CD annulation procedure developed here will be used to obtain an AB *cis*-fused tetracycle akin to **25**. Subsequent transformations, desilylation, dehydration, demethylation, oxidation at C-13, and acetonide hydrolysis are expected to lead to the first synthesis of (±) 12a-deoxypillaromycinone (**28**).

## Experimental

### General

Reactions that were expected to be sensitive to air or moisture were performed under an inert atmosphere of

argon. All glassware and syringes were dried in an oven, and then cooled in a dry box before use. All temperatures are in °C. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled from sodium benzophenone ketyl. Dichloromethane, hexane, diisopropylamine, and HMPA were distilled from $CaH_2$. All reagents were purchased from Aldrich.

Thin layer chromatography was carried out on Merck 5554 precoated silica gel 60 $F_{254}$ aluminum sheets. After development, the sheets were viewed under UV light or with an oxidizing stain solution consisting of ceric ammonium sulfate and hexammonium heptamolybdate in 1.8 M $H_2SO_4$. Flash chromatography was performed using Merck 9385 silica gel 60 (230–400 mesh). Fourier transform infrared spectra (FT-IR) were recorded on a Bomem MB-100 spectrometer as neat films between NaCl plates, or as KBr discs. $^1H$ and $^{13}C$ NMR spectra were obtained on Bruker AM-250, AM-300, and AMX-500 instruments. Samples were prepared in $CDCl_3$ unless otherwise stated. Chemical shifts for NMR were determined relative to the internal standard tetramethylsilane (δ 0.00) or $CHCl_3$ (δ 7.24) for $^1H$ spectra, and $CDCl_3$ (δ 77.0) for $^{13}C$ spectra. All $^1H$ NMR data listed have the following order: chemical shift (ppm), (multiplicity, coupling constants, number of protons, assignment). $^1H$ assignments were confirmed by decoupling. Mass spectra were run at the McMaster Regional Centre for Mass Spectrometry, McMaster University, Hamilton, Ontario. Elemental analysis were performed by MHW Laboratories, Phoenix, Arizona.

**1-Furylethanol (6)**

Methyllithium (300 mL, 1.4 M solution in ether, 4.2 mol) was added dropwise to a solution of 2-furfural (34 mL, 0.4 mol) in dry THF (400 mL) at –78°C under argon over 1.5 h. The solution was allowed to warm to –20°C while stirring for 3 h. Saturated $NH_4Cl$ solution was added and the THF layer was separated and concentrated. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were dried and concentrated in vacuo. Distillation under reduced pressure (water aspirator) gave a clear liquid (bp 70–74°C, 43 g, 85%). IR (neat) ($cm^{-1}$): 3350, 1150, 1009, 738. $^1H$ NMR (250 MHz) δ: 1.53 (d, $J$ = 6.6 Hz, 3H, CHC$H_3$), 2.24 (br s, 1H, OH), 4.86 (q, $J$ = 6.6 Hz, 1H, C$H$CH$_3$), 6.22, 6.31, and 7.36 (m each, 3H, furan-H).

**2-(1′-Methoxy)ethylfuran (7)**

Alcohol **6** (16.1 g, 0.14 mol) in THF (100 mL) was added dropwise to a suspension of NaH (9.0 g, 60% dispersion in mineral oil, 0.22 mol) in THF (50 mL) at 0°C under argon. The solution was stirred for 30 min and iodomethane (18 mL, 0.29 mol) was added dropwise over 15 min. The reaction was stirred overnight. Saturated $NH_4Cl$ solution (100 mL) was added dropwise and the THF layer was separated and concentrated in vacuo. The residue was dissolved in ether (200 mL), dried, and concentrated to give a dark brown oil, which was distilled under reduced pressure (oil pump) to give a colourless liquid (bp 50–55°C, 10.5 g, 60%). $^1H$ NMR (250 MHz) δ: 1.50 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 3.27 (s, 3H, $OCH_3$), 4.36 (q, $J$ = 6.6 Hz, 1H, CH), 6.33 (m, 2H, H-3 and H-4), 7.38 (m, 1H, H-5). HRMS calcd. for $C_7H_{10}O_2$: 126.0681; found: 126.0679. Anal. calcd. for $C_7H_{10}O_2$: C 66.66, H 7.93; found: C 66.61, H 7.91.

**2-(3-Bromopropyl)-5-(1′-methoxy)ethylfuran (8)**

*n*-BuLi (62.5 mL, 0.1 mol) was added dropwise to a solution of methyl ether **7** (12.6 g, 0.1 mol) in THF (100 mL) at –78°C under argon. The solution was allowed to warm to –20°C over 1 h, then stirred for 3 h. The reaction was cooled to –78°C and 1,3-dibromopropane (11.2 mL, 0.11 mol) was added and stirring continued overnight at ambient temperature. The solution was warmed to room temperature and saturated $NH_4Cl$ was added, the organic layer was washed with brine, dried, and concentrated in vacuo. Chromatography using 3–5% EtOAc–hexane gave product **8** as a pale yellow oil (15.1 g, 61%), the dehydrobrominated product (5%), and the dimer (7%). IR (neat) ($cm^{-1}$): 1558, 1445, 1249, 1102, 1013, 790. $^1H$ NMR (250 MHz) δ: 1.48 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 2.18 (m, 2H, $CH_2CH_2CH_2Br$), 2.80 (t, $J$ = 7.2 Hz, 2H, $CH_2CH_2CH_2Br$), 3.27 (s, 3H, $OCH_3$), 3.42 (t, $J$ = 6.6 Hz, 2H, $CH_2Br$), 4.29 (q, $J$ = 6.6 Hz, 1H, CH), 5.98 and 6.15 (d each, $J$ = 3.1 Hz, 2H, H-3 and H-4). EI-MS $m/z$ (%): 248, 246 ($M^+$, 1), 245 (7), 231 (31), 229 (31), 216 (27), 214 (27), 139 (34), 123 (78). HRMS calcd. for $C_{10}H_{15}{}^{79}BrO_2$: 246.0197; found: 246.0198.

**2-(3-Iodopropyl)-5-(1′-methoxy)ethylfuran (9)**

Bromide **8** (15.1 g, 0.061 mol), KI (25 g, 0.153 mol), and $NaHCO_3$ (0.5 g, 6 mmol) were dissolved in HPLC-grade acetone, and heated to reflux for 24 h under argon. The reaction was cooled, and the solvent was removed in vacuo. The residue was dissolved in diethyl ether and water was added. The aqueous layer was extracted with diethyl ether (3 × 200 mL), the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude iodide. Flash chromatography using 10% EtOAc–hexane provided pure iodide **9** as a pale yellow oil (16.3 g, 91%). IR (neat) ($cm^{-1}$): 1557, 1442, 1234, 1114, 1087, 789. $^1H$ NMR (250 MHz) δ: 1.50 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 2.18 (m, 2H, $CH_2CH_2CH_2I$), 2.76 (t, $J$ = 7.2 Hz, 2H, $CH_2CH_2CH_2I$), 3.24 (t, $J$ = 6.6 Hz, 2H, $CH_2I$), 3.30 (s, 3H, $OCH_3$), 4.32 (q, $J$ = 6.6 Hz, 1H, CH), 5.98 and 6.15 (d each, $J$ = 3.1 Hz, 2H, H-3 and H-4). HRMS calcd. for $C_{10}H_{14}O_2$: 166.0990 ($[M - HI]^+$); found: 166.0989 ($[M - HI]^+$).

**2-(3-Cyanopropyl)-5-(1′-methoxy)ethylfuran (11)**

Bromide **8** (2 g, 8.1 mmol) and tetrabutylammonium chloride (0.5 g, 1.8 mmol) were dissolved in $CH_2Cl_2$ and mixed with a saturated KCN solution (2.2 g, 33 mmol); the mixture was stirred at room temperature for 24 h and monitored by TLC while the color of the reaction turned to red-brown. Once the reaction was completed, the organic and aqueous layers were separated, the aqueous layer was extracted with ether (2 × 20 mL), the combined organic layers were dried over $Na_2SO_4$, and concentrated in vacuo to give a dark brown oil. Flash chromatography using 10% EtOAc–hexane provided pure nitrile **11** as a pale yellow oil (1.32 g, 84%). IR (neat) ($cm^{-1}$): 2246, 1114, 1087, 794. $^1H$ NMR (250 MHz) δ: 1.50 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 2.04 (m, 2H, $CH_2CH_2CH_2CN$), 2.39 (t, $J$ = 7.2 Hz, 2H, $CH_2CH_2CH_2CN$), 2.80 (t, $J$ = 6.6 Hz, 2H, $CH_2CH_2CH_2CN$), 3.30 (s, 3H, $OCH_3$), 4.32 (q, $J$ = 6.6 Hz, 1H, CH), 5.98 and 6.15 (d each, $J$ = 3.1 Hz, 2H, H-3 and H-4). HRMS calcd. for $C_{11}H_{15}NO_2$: 193.1103; found: 193.1112.

**2β-(*N*-Methyl-*N*-methoxyamido)-7-oxabicyclo[2.2.1]hept-5-ene (13)**

***N,O-Dimethylhydroxylamine***

*N*,*O*-Dimethylhydroxylamine hydrochloride (80 g) was added to a cooled (0°C) solution of KOH (80 g) in water (120 mL). *N*,*O*-dimethylhydroxylamine was distilled from the mixture to give a clear liquid (47 g); bp 41–43°C.

***Reaction with acryloyl chloride (12)***

*N*,*O*-Dimethylhydroxylamine (14.0 g, 0.24 mol) and pyridine (18.9 mL, 0.24 mol) in ether (100 mL) was added dropwise to a cooled (–78°C) solution of acryloyl chloride (19 mL, 0.24 mol) in ether (400 mL) under argon over a period of 1 h. The mixture was allowed to warm to 0°C while stirring for 3 h. The ether was decanted from the solid and the solid was washed with dry ether. The combined ether solutions were concentrated in vacuo to give a pale yellow liquid, which was distilled under reduced pressure (oil pump) to give a clear liquid (10.3 g); bp 45°C (0.05 mm Hg). IR (neat) ($cm^{-1}$): 1664, 1619. $^1H$ NMR (250 MHz) δ: 3.26 (s, 3H), 3.71 (s, 3H), 5.74 (dd, *J* = 10.35, 2.1 Hz, 1H), 6.41 (dd, *J* = 17.1, 2.1 Hz, 1H), 6.72 (dd, *J* = 17.1, 10.35 Hz, 1H). Anal. calcd. for $C_5H_9NO_2$: C 52.17, H 7.88, N 12.17; found: C 51.90, H 8.00, N 12.28 (17).

***Diels-Alder addition to furan (13)***

*N*,*O*-Dimethylacryloylamide **12** (10.33 g, 89 mmol) and zinc iodide (28.7 g, 90 mmol) were heated at reflux in distilled furan (90 mL) for 10 days. The reaction mixture was diluted with EtOAc (400 mL) and washed with $H_2O$ (200 mL). The organic layer was separated, washed with brine, dried, and concentrated in vacuo (bath < 35°C) to give a yellow oil. Chromatography over silica using 80% EtOAc–hexane gave a colourless oil (**13**), which crystallized on refrigeration (mp 46–47°C; yield 67%). IR (neat) ($cm^{-1}$): 1660, 1440, 1381, 1317, 1032, 908, 704. $^1H$ NMR (250 MHz) δ: 1.57 (dd, *J* = 11.3, 8.4 Hz, 1H, H-6α), 2.12 (dt, *J* = 11.3, 4.5 Hz, 1H, H-6β), 2.67 (dd, *J* = 8.4, 4.1 Hz, 1H, H-5α), 3.22 and 3.68 (s each, 6H, $NCH_3$ and $OCH_3$), 5.07 (d, *J* = 4.5 Hz, 1H, H-1), 5.13 (s, 1H, H-4), 6.39 (ABq, *J* = 4.5 Hz, 2H, H-5 and H-6). HRMS calcd. for $C_9H_{13}NO_3$: 183.0896; found: 183.1074. Anal. calcd. for $C_{19}H_{13}NO_3$: C 59.03, H 7.15; found: C 59.13, H 7.13.

**4-[5-(1-Methoxyethyl)furan-2-yl]-1-(7-oxabicyclo-[2.2.1]hept-5-en-2-yl)butan-1-one (14)**

Iodide **9** (11.2 g, 38 mmol) was dissolved in anhydrous $Et_2O$ (200 mL), and the solution was cooled to –78°C in a dry ice – acetone bath. *tert*-Butyllithium (52 mL, 1.7 M in pentane, 88.4 mmol) was added dropwise to the cooled solution, and the reaction was stirred for 1 h at –78°C. Amide **13** (10.5 g, 57 mmol) in $Et_2O$ was purged with argon for 15 min and added to the reaction by cannulation at –78°C. The reaction was continued for a further 4 h, and was then quenched at low temperature with saturated $NH_4Cl$ (100 mL). After warming to room temperature, the aqueous layer was extracted with $Et_2O$ (3 × 50 mL) and $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash chromatography of the crude ketone using 30% EtOAc–hexane provided pure product **14** as a yellow oil (8.2 g, 75%). IR (neat) ($cm^{-1}$): 1707, 1557, 1100, 793. $^1H$ NMR (250 MHz) δ: 1.48 (d, *J* = 6.6 Hz, 3H, $CH_3$), 1.95 (m, 3H, $CH_2CH_2CH_2CO$ and H-3β), 2.65 (m, 6H, $CH_2CH_2CH_2CO$, H-3α, and H-2α), 3.26 (s, 3H, $OCH_3$), 4.29 (q, *J* = 6.6 Hz, 1H, CHOMe), 5.08 (m, 2H, H-1 and H-4), 5.95 and 6.15 (d each, *J* = 3.0 Hz, 2H, furan-H), 6.38 (ABq, *J* = 5.7, 1.3 Hz, 2H, H-5 and H-6). HRMS calcd. for $C_{17}H_{22}O_4$: 290.1512; found: 290.1510.

**2*H*-2-(1′-Methoxyethyl)-2,4a-epoxy-8aβ,4aα-1,8a,5,6,7,8-hexahydro-naphthalen-8-one (15a and 15b)**

Ketone **14** (8.2 g, 37 mmol) was dissolved in dry benzene (50 mL) and heated to reflux for 12 h. Benzene was removed by distillation under reduced pressure (water aspirator, bath temperature 40°C). Enone **10** generated in situ was dissolved in dry $CH_2Cl_2$ (50 mL), and the solution was cooled to –78°C. Methylaluminum dichloride (41 mmol, 1.0 M in hexane) was added to the cooled enone solution, and the reaction was stirred for a further 1 h at –78°C. The reaction was quenched with 10% $NaHCO_3$, and warmed until no frozen material remained. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were washed with $H_2O$, dried over $Na_2SO_4$, filtered, and concentrated in vacuo without external heat to provide a mixture of two stereoisomers. Flash chromatography using 30% EtOAc–hexane gave the C9-*S** isomer **15a** and C9-*R** isomer **15b** as pale yellow oils (total yield: 76%).[2]

***C9-S* isomer 15a ($R_f$ = 0.41)***

IR (neat) ($cm^{-1}$): 1701, 1446, 1375, 1062, 715. $^1H$ NMR (500 MHz) δ: 1.23 (d, *J* = 6.4 Hz, 3H, Me), 1.61 (dd, *J* = 12.4, 8.9 Hz, 1H, H-1α), 1.8–2.31 (m, 2H), 2.22 (ddd, *J* = 14.8, 12.6, 5.0 Hz, 1H, H-5α), 2.37 (dd, *J* = 12.4, 3.2 Hz, 1H, H-1β), 2.39–2.44 (m, 2H), 2.45 (dd, *J* = 8.9, 3.1 Hz, 1H, H-8a), 2.52 (dtd, *J* = 14.0, 3.5, 1.6 Hz, 1H, H-7β), 3.42 (s, 3H, OMe), 3.66 (q, *J* = 6.4 Hz, 1H, H-9), 6.16 and 6.40 (d each, *J* = 5.8 Hz, 2H, H-3 and H-4). $^{13}C$ NMR (63 MHz) δ: 15.2, 21.8, 28.4, 31.4, 41.6, 53.0, 57.4, 76.8, 90.7, 91.8, 137.5, 138.5, 209.5. EI-MS *m*/*z* (%): 190 ($[M - CH_3OH]^+$, 41), 152 (20), 137 (80), 121 (100), 108 (69), 59 ($[Me - O{=}CHMe]^+$, 80). CI-MS *m*/*z* (%): 240 ($[M + NH_4]^+$, <2), 191 (100). HRMS calcd. for $C_{12}H_{15}O_3$: 207.1021; found: 207.1040 ($[M - Me]^+$). Anal. calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11; found: C 70.12, H 8.02.

***C9-R* isomer 15b ($R_f$ = 0.31)***

IR (neat) ($cm^{-1}$): 1710, 1449, 1322, 1102, 714. $^1H$ NMR (500 MHz) δ: 1.28 (d, *J* = 6.5 Hz, 3H, Me), 1.51 (dd, *J* = 11.7, 8.2 Hz, 1H, H-1α), 1.90–2.02 (m, 2H), 2.18–2.25 (m,

[2] Supplementary material ($^1H$ NMR spectra of compounds **15a**, **b**, **19a**, **b**, **21a**, **b** and **25a**, **b**; and X-ray crystallographic data for **17a** and **20b**) may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. For information on obtaining material electronically go to http://www.nrc.ca/cisti/irm/unpub_e.shtml. Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

1H), 2.28 (dd, *J* = 11.7, 3.0 Hz, 1H, H-1β), 2.36 (dd, *J* = 8.0, 3.0 Hz, 1H, H-8a), 2.38–2.53 (m, 3H), 3.41 (s, 3H, OMe), 3.66 (q, *J* = 6.4 Hz, 1H, H-9), 6.19 and 6.46 (d each, *J* = 5.8 Hz, 2H, H-3 and H-4). $^{13}$C NMR (63 MHz) δ: 15.0, 21.5, 28.2, 31.1, 41.3, 52.5, 56.95, 76.5, 90.6, 92.0, 137.0, 137.5, 209.1. EI-MS *m*/*z* (%): 191 ([M – $OCH_3$]$^+$, 38), 190 (52), 152 (24), 137 (76), 121 (100), 108 (71), 59 (80). CI-MS *m*/*z* (%): 240 ([M + $NH_4$]$^+$, <2), 191 (100). HRMS calcd. for $C_{12}H_{15}O_3$: 207.1021; found: 207.1061 ([M – Me]$^+$). Anal. calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11; found: C 70.12, H 8.36.

### 2*H*-2-(1′-Methoxyethyl)-3β,4β-dihydroxy-2,4a-epoxy-8aβ,4aα-octahydro-naphthalen-8-one (16a and 16b)

$OsO_4$ (4.0 g, 15.6 mmol) and bicyclic ketone **15a** or **15b** (3.46 g, 15.6 mmol) were dissloved in pyridine (40 mL) and stirred at room temperature under argon for 48 h. The resulting dark solution was stirred with a mixture of $NaHSO_3$ (8.4 g), pyridine (88 mL), and water (140 mL) for a further 4 h. The reaction was continuously extracted with EtOAc (600 mL) for 48 h. The organic layer was dried over $Na_2SO_4$, and EtOAc and pyridine were removed under reduced pressure. Flash chromatography using 70% EtOAc–hexane gave each diol as a white solid (3.2 g, 80%).

#### *C9-S* isomer 16a*

mp 132–134°C. IR (KBr) (cm$^{-1}$): 3380, 1714, 1383, 1110, 946, 826. $^1$H NMR (250 MHz) δ: 1.29 (d, *J* = 6.3 Hz, 3H, $CH_3$), 1.30 (dd, *J* = 13.2, 8.9 Hz, 1H, H-1α), 2.29 (dd, *J* = 8.9, 3.2 Hz, 1H, H-1β), 2.00 and 2.46 (m each, 6H, H-5, H-6, and H-7), 2.51 (dd, *J* = 13.2, 3.3 Hz, 1H, H-8a), 3.43 (s, 3H, OMe), 3.60 (d, *J* = 6.8 Hz, 1H, OH), 3.82 (dd, *J* = 6.6, 5.9 Hz, 1H, OHC*H*CHOH), 3.96 (q, *J* = 6.3 Hz, 1H, H-9), 4.01 (dd, *J* = 5.9, 3.2 Hz, 1H, HOCHC*H*OH), 5.14 (d, *J* = 3.5 Hz, 1H, OH). $^{13}$C NMR (63 MHz) δ: 14.1, 22.2, 25.2, 28.7, 41.2, 51.7, 56.9, 75.7, 76.7, 77.3, 86.9, 91.1, 208.6. CI-MS *m*/*z* (%): 257 ([M + 1]$^+$, 67), 207 (30), 197 (36), 195 (44), 179 (27), 165 (24), 59 (100). Anal. calcd. for $C_{13}H_{20}O_5$: C 60.94, H 7.81; found: C 60.72, H 7.68.

#### *C9-R* isomer 16b*

mp 114–116°C. IR (KBr) (cm$^{-1}$): 3377, 1710, 1458, 1106, 942, 835. $^1$H NMR (250 MHz) δ: 1.37 (d, *J* = 6.6 Hz, 3H, $CH_3$), 1.42 (dd, *J* = 13.1, 8.8 Hz, 1H, H-1α), 2.16 (dd, *J* = 13.1, 3.7 Hz, 1H, H-8a), 2.01 and 2.45 (m each, 6H, H-5, H-6, and H-7), 2.28 (dd, *J* = 8.9, 3.7 Hz, 1H, H-1β), 3.44 (s, 3H, OMe), 3.80 (m, 3H, OH, H-9, and OHCHC*H*OH), 4.11 (dd, *J* = 5.7, 3.8 Hz, 1H, OHC*H*CHOH), 5.17 (d, *J* = 3.7 Hz, 1H, OH). $^{13}$C NMR (75 MHz) δ: 15.2, 21.2, 24.4, 31.4, 40.6, 51.8, 57.9, 74.1, 75.6, 79.4, 87.9, 91.8, 208.9. HRMS calcd. for $C_{13}H_{21}O_5$: 257.1388; found: 257.1376 ([M + 1]$^+$, 10). Anal. calcd. for $C_{13}H_{20}O_5$: C 60.94, H 7.81; found: C 61.05, H 7.63.

### 2*H*-2-(1′-Methoxyethyl)-3β,4β-di-*O*-isopropylidene-2,4a-epoxy-8aβ,4aα-octahydro-naphthalen-8-one (17a and 17b)

A mixture of each diol **16** (0.6 g, 2.34 mmol), 2,2-dimethoxypropane (6 mL, 49 mmol), and TsOH (6 mg) was stirred in $CH_2Cl_2$ for 12 h under argon. Anhydrous $K_2CO_3$ (1.5 g) was added to the reaction and stirred for a further 3 h. The solution was filtered and concentrated in vacuo. Flash chromatography using 20% EtOAc–hexane gave the pure acetonide as a white solid (0.478 g, 69%).

#### *C9-S* isomer 17a*

mp 109–110°C. IR (KBr) (cm$^{-1}$): 1714, 1458, 1380, 1207, 1101, 873, 606. $^1$H NMR (250 MHz) δ: 1.23 (d, *J* = 6.6 Hz, 3H, $CH_3$), 1.31 (dd, *J* = 13.0, 9.2 Hz, 1H, H-1α), 1.30 and 1.48 (s each, 6H, C$H_3$CC$H_3$), 1.96, 2.38, and 2.50 (m each, 6H, H-5, H-6, and H-7), 2.18 (dd, *J* = 9.1, 4.1 Hz, 1H, H-1β), 2.57 (dd, *J* = 13.1, 4.1 Hz, 1H, H-8a), 3.36 (s, 3H, OMe), 3.79 (q, *J* = 6.6 Hz, 1H, H-9), 4.20, 4.24 (ABq, *J* = 5.56 Hz, 2H, H-3 and H-4). $^{13}$C NMR (75 MHz) δ: 16.5, 21.7, 25.3, 25.5, 25.9, 26.1, 41.3, 50.4, 58.1, 74.3, 84.3, 84.4, 88.8, 90.0, 112.4, 208.6. CI-MS *m*/*z* (%): 297 ([M + 1]$^+$, 14), 239 (10), 206 (13), 59 (100). Anal. calcd. for $C_{16}H_{24}O_5$: C 64.86, H 8.11; found: C 64.77, H 7.97. Crystal data: Colourless bicapped prism, 0.30{100} × 0.66{101} mm, $C_{16}H_{24}O_5$, *M* = 296.4, tetragonal, *a* = 25.901(2), *c* = 9.458(1) Å, *U* = 6344.9(11) Å$^3$, space group $I4_1/a$ (No. 88), *Z* = 16, μ(Mo Kα) = 0.091 mm$^{-1}$, 2945 reflections measured, 2804 unique ($R_{int}$ = 1.33%), 1915 observed ($F > 6.0\sigma(F)$). Final *R* and $R_w$ values were 3.18 and 3.19%, respectively (based on *F*).

#### *C9-R* isomer 17b*

mp 98–101°C. IR (KBr) (cm$^{-1}$): 1718, 1456, 1374, 1164, 1096, 870, 669. $^1$H NMR (250 MHz) δ: 1.16 (d, *J* = 6.3 Hz, 3H, $CH_3$), 1.30 (dd, *J* = 13.5, 9.0 Hz, 1H, H-1α), 1.32 and 1.46 (s each, 6H, C$H_3$CC$H_3$), 2.22 (dd, *J* = 9, 3.7 Hz, 1H, H-1β), 1.95 and 2.40 (m each, 6H, H-5, H-6, and H-7), 2.46 (dd, *J* = 13.5, 3.7 Hz, 1H, H-8a), 3.39 (s, 3H, OMe), 3.88 (q, *J* = 6.3 Hz, 1H, H-9), 4.24, 4.35 (AXq, *J* = 5.55 Hz, 2H, H-3 and H-4). $^{13}$C NMR (75 MHz) δ: 13.5, 22.0, 25.2, 25.5, 25.8, 26.1, 41.3, 50.6, 57.0, 73.2, 83.0, 84.5, 87.7, 89.0, 112.2, 208.6. HRMS calcd. for $C_{16}H_{25}O_5$: 297.1702 ([M + 1]$^+$); found: 297.1684. Anal. calcd. for $C_{16}H_{24}O_5$: C 64.86, H 8.11; found: C 65.12, H 8.03.

### 7-(1′-Methoxyethyl)-5β,6β,7β-trihydroxy-8aβ,4aα-octahydro-naphthalen-1-one (20b)

Palladium hydroxide on carbon (17.4 mg, 20% palladium by dry weight) was added to the argon-flushed solution of the diol **16b** (100 mg, 0.39 mmol), DBU (15 mg), $CH_3OH$ (16 mL), and $H_2O$ (0.5 mL). The flask was evacuated and backfilled with $H_2$ three times and then maintained at 1 atm $H_2$ for 2 days. TLC analysis indicated formation of two isomers. The resulting solution was then filtered through a thin layer of celite and concentrated. The residue was diluted with $CH_2Cl_2$ (50 mL), washed with 1N HCl; the organic layer was dried with $Na_2SO_4$ and concentrated in vacuo to give a pale yellow oil. Flash chromatography of the crude material using 7:3 EtOAc–hexane gave (*a*) a single isomer as colourless crystals **20b** and (*b*) mixture of two isomers (total yield 72%). $^1$H NMR (250 MHz) δ: 1.22 (d, *J* = 6.4 Hz, 3H, $CH_3$), 1.41 (dd, *J* = 14.4, 12.1, 1H, H-8α), 1.5–1.8 (m, 3H), 1.85 (dd, *J* = 14.4, 3.4 Hz, 1H, H-8β), 1.9–2.24 (m, 2H), 2.38 (m, 2H, H-2), 2.75 (td, *J* = 12.1, 3.1 Hz, 1H, H-8a), 3.37 (q, *J* = 6.5 Hz, 1H, H-9), 3.42 (s, 3H, $OCH_3$), 3.65 and 3.90 (d and br m, 4H, H-5, H-6, and two OH). $^{13}$C NMR (63 MHz) δ: 13.4, 26.2, 27.6, 31.4, 41.6, 43.2, 46.8, 57.9, 70.2, 74.6, 76.9, 83.3, 212.4. Crystal data:

Colourless prism fragment, 0.38{100} × 0.66{010} × 0.42{001} mm, $C_{13}H_{22}O_5$, $M$ = 258.3, monoclinic, $a$ = 24.4438(17), $b$ = 5.8361(4), $c$ = 17.8409(13) Å, β = 101.287(4)°, $U$ = 2495.9(4) Å$^3$, $T$ = 180 K, space group $C2/c$ (No. 15), $Z$ = 8, μ(Mo Kα) = 0.104 mm$^{-1}$, 3712 reflections measured, 3636 unique ($R_{int}$ = 1.35%), 2974 observed ($F > 6.0\sigma(F)$). The final $R$ and $R_w$ values were 3.08 and 3.87%, respectively (based on $F$).

### 7-(1′-Methoxyethyl)-7β-hydroxy-5β,6β-di-*O*-isopropylidene-8aβ,4aα-octahydro-naphthalen-1-one (19a and 19b)

#### *Synthesis of C9-S* isomer 19a*

Palladium hydroxide on carbon (100 mg, 20% palladium by dry weight) was added to the argon-flushed solution of the acetonide **17a** (500 mg, 1.69 mmol), DBU (50 mg, 0.33 mol), $CH_3ONa$ (183 mg, 3.4 mmol), $CH_3OH$ (128 mL), and $H_2O$ (4 mL). The flask was evacuated and backfilled by $H_2$ three times and then maintained at 1 atm $H_2$ for 4 days. The resulting solution was then filtered, and the filtrate was neutralized by adding dry ice, then concentrated. The residue was dissolved in EtOAc and the precipitate was filtered. EtOAc solution was concentrated in vacuo to give a dark oil which was chromatographed using EtOAc–hexane–methanol (1:4:0.5) to give colourless crystals (304 mg, 60%); mp 110–112°C. IR (KBr) (cm$^{-1}$): 3527, 2948, 1703, 1435, 1379, 1100, 1030, 881. $^1$H NMR (500 MHz) δ: 1.11 (d, $J$ = 6.3 Hz, 3H, $CH_3$), 1.36 and 1.52 (s each, 6H, C$H_3$CC$H_3$), 1.47 (dd, $J$ = 14.9, 12.2 Hz, 1H, H-8α), 1.61(m, 1H, H-3α), 1.68 (tt, $J$ = 12.4, 3.6 Hz, 1H, H-4a), 1.78 (m, 1H, H-4β), 1.91 (qt, $J \approx$ 13.3, 3.8 Hz, 1H, H-4α), 2.01 (dd, $J$ = 14.5, 2.4 Hz, 1H, H-8β), 2.14 (m, 1H, H-3β), 2.38 (m, 2H, H-2), 2.76 (td, $J$ = 11.9, 2.3 Hz, 1H, H-8a), 2.90 (br s, 1H, OH), 3.02 (q, $J$ = 6.3 Hz, 1H, H-9), 3.34 (s, 3H, OMe), 4.11 (d, $J$ = 6.3 Hz, 1H, H-6), 4.30 (dd, $J$ = 6.3, 3.9 Hz, 1H, H-5). $^{13}$C NMR (75 MHz) δ: 12.5, 25.1, 26.1, 26.4, 27.7, 31.9, 41.7, 42.9, 44.1, 57.2, 71.5, 73.9, 83.4 (2 × C), 108.7, 212.8. CI-MS $m/z$ (%): 299 ([M + 1]$^+$, 15), 241 (25), 239 (30), 191 (10), 181 (41), 135 (14), 91 (11), 81 (14), 59 (100). Anal. calcd. for $C_{16}H_{26}O_5$: C 64.43, H 8.72; found: C 64.20, H 8.53.

#### *Synthesis of C9-R* isomer 19b*

Palladium hydroxide on carbon (120 mg, 20% palladium by dry weight) was added to the argon flushed solution of the acetonide 1**7b** (600 mg, 2.03 mmol), DBU (60 mg, 0.4 mmol), $CH_3ONa$ (219 mg, 4.1 mmol), $CH_3OH$ (128 mL), and $H_2O$ (4 mL). The flask was evacuated and backfilled with $H_2$ three times and then maintained at 1 atm for 24 h. The hydrogen source was then turned off and the reaction was stirred at room temperature for further 3 days. The resulting solution was then filtered, and the filtrate was neutralized by adding dry ice, then concentrated. The residue was dissolved in EtOAc (250 mL) and the precipitate was filtered. EtOAc solution was concentrated in vacuo to give a dark oil which was chromatographed using EtOAc–hexane (1:4) to give colourless crystals (420 mg, 70%); mp 140–142°C. IR (KBr): 3516, 2955, 1763, 1443, 1373, 1158, 1041, 873. $^1$H NMR (250 MHz) δ: 1.10 (d, $J$ = 6.3 Hz, 3H, $CH_3$), 1.18 (dd, $J$ = 14.6, 11.7 Hz, 1H, H-8α), 1.35 and 1.48 (s each, 6H, C$H_3$CC$H_3$), 1.53 (m, 1H, H-3α), 1.64 (m, 1H, H-4a), 1.68–1.97 (m, 2H, H-4), 2.07 (dd and m, $J$ = 14.4, 2.2 Hz, 1H, H-8β and H-3β), 2.32 (m, 2H, H-2), 2.55 (br s, 1H, OH), 2.70 (td, $J$ = 11.8, 2.3 Hz, 1H, H-8a), 3.03 (q, $J$ = 6.3 Hz, 1H, H-9), 3.24 (s, 3H, OMe), 4.15 (d, $J$ = 6.24 Hz, 1H, H-6), 4.29 (dd, $J$ = 6.23, 4.04 Hz, 1H, H-5). $^{13}$C NMR (75 MHz) δ: 11.7, 25.2, 26.3, 26.4, 27.2, 27.7, 41.6, 42.8, 43.9, 57.0, 71.5, 74.1, 81.1 (2 × C), 108.7, 212.2. CI-MS $m/z$ (%): 299 ([M + 1]$^+$, 28), 241 (20), 239 (31), 209 (12), 181 (33), 163 (12), 135 (11), 59 (100). Anal. calcd. for $C_{16}H_{26}O_5$: C 64.43, H 8.72; found: C 64.49, H 8.64.

### 7-(1′-Methoxyethyl)-7β-trimethylsiloxy-5β,6β-di-*O*-isopropylidene-8aβ,4aα-hexahydro-naphthalen-1-one (21a and 21b)

A fresh LDA solution was prepared from *n*-BuLi (6.6 mL, 1.36 M in hexane, 9.0 mmol) and diisopropylamine (1.25 mL, 8.9 mmol) at 0°C in dry THF.

A solution of hydroxy ketone **19** (210 mg, 0.71 mmol) in dry THF was slowly added to the LDA solution at –78°C under argon. The mixture was stirred for 1 h at –78°C. TMSCl (1.8 mL, 14.2 mmol) was then added. The reaction was stirred for 30 min at –78°C and then allowed to warm to room temperature. The THF was evaporated under reduced pressure and the residue was diluted with dry hexane, white precipitates were filtered, and the hexane solution was concentrated in vacuo to give the crude silyl enol ether. The silyl enol ether was heated at reflux with $Pd(OAc)_2$ (177 mg, 0.78 mmol) in $CH_3CN$ (20 mL) for 1 h under argon. The reaction mixture was filtered through a thin pad of Celite and the solvent was concentrated in vacuo to give a dark brown oil. Flash chromatography using 20% EtOAc–hexane of the crude mixture gave colourless crystals (116 mg, 56%) in each case.

#### *C9-S* isomer 21a*

$^1$H NMR (500 MHz) δ: 0.12 (s, 9H, $OSiMe_3$), 1.21 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 1.31 and 1.51 (s each, 6H, C$H_3$CC$H_3$), 1.52 (dd, $J$ = 14.7, 11.8 Hz, 1H, H-8α), 2.09 (m, 1H, H-4a), 2.27 (dd, $J$ = 14.8, 3.1 Hz, 1H, H-8β), 2.33 (dt, $J$ = 19.1, 5.1 Hz, 1H, H-4α), 2.66 (td, $J$ = 11.8, 2.9 Hz, 1H, H-8a), 2.7 (m, 1H, H-4β), 3.16 (q, $J$ = 6.4 Hz, 1H, H-9), 3.28 (s, 3H, OMe), 4.07 (d, $J$ = 5.7 Hz, 1H, H-6), 4.19 (t, $J$ = 5.4 Hz, 1H, H-5), 5.78 (dd, $J$ = 10, 2.2 Hz, 1H, H-2), 6.97 (ddd, $J$ = 10, 6, 2.2, 1H, H-3). $^{13}$C NMR (75 MHz) δ: 2.9 (3 × C), 13.8, 26.0, 26.2, 28.4, 32.0, 39.5, 40.6, 56.7, 74.5, 75.6, 76.6, 104.9, 108.6, 129.1, 149.3, 201.1. EI-MS $m/z$ (%): 309, 251 (17), 161 (12), 131 (19), 89 ([$Me_3SiO$]$^+$, 15), 73 ([$Me_3Si$]$^+$, 100), 59 ([Me-CH=OMe]$^+$, 96). HRMS calcd. for $C_{16}H_{25}O_4Si$: 309.1522; found: 309.1525 ([M – MeCHOMe]$^+$, 7).

#### *C9-R* isomer 21b*

$^1$H NMR (500 MHz) δ: 0.11 (s, 9H, $OSiMe_3$), 1.1 (dd, $J$ = 14.8, 11.4 Hz, 1H, H-8α), 1.16 (d, $J$ = 6.3 Hz, 3H, $CH_3$), 1.33 and 1.52 (s each, 6H, C$H_3$CC$H_3$), 2.11 (m, 1H, H-4a), 2.32 (dt, $J$ = 19.1, 5.2 Hz, 1H, H-4α), 2.61 (td, $J$ = 11.4, 3.4 Hz, 1H, H-8a), 2.65 (m, 1H, H-4β), 2.68 (dd, $J$ = 14.6, 3.4 Hz, 1H, H-8β), 3.0 (q, $J$ = 6.3 Hz, 1H, H-9), 3.29 (s, 3H, OMe), 3.78 (d, $J$ = 5.8 Hz, 1H, H-6), 4.20 (t, $J$ = 5.3 Hz, 1H, H-5), 5.99 (dd, $J$ = 10, 2.3 Hz, 1H, H-2), 6.97 (ddd, $J$ = 10, 6, 2.1, 1H, H-3). $^{13}$C NMR (75 MHz) δ: 3.0 (3 × C), 13.1, 25.5, 26.4, 28.1, 32.0, 39.3, 41.1, 56.3, 75.8, 77.5, 77.8, 78.5, 109.9, 128.3, 148.1, 199.8. EI-MS $m/z$ (%): 353 ([M –

Me]$^+$, 8), 309 ([M – MeCHOMe]$^+$, 63), 279 ([M – $OSiMe_3$]$^+$, 41), 251 (72), 73 ([$Me_3Si$]$^+$, 51), 59 ([MeCH=OMe]$^+$, 100). HRMS calcd. for $C_{19}H_{33}O_5Si$: 369.2097 ([M + 1]); found: 369.2084.

**11-Hydroxy-10-methoxy-2-trimethylsilyloxy-2-[1′-(1′-methoxyethyl)]-3β,4β-di-*O*-isopropylidene-1,2,3,4,4a,5,12,12a-octahydronaphthacene-12-one (25a and 25b) from 21a and 21b, separately**

The LDA solution was prepared by adding *n*-BuLi (6.1 mL, 4.75 mmol) to freshly distilled diisopropylamine (0.66 mL, 4.75 mmol) in THF at 0°C under argon.

Ethyl 2-methoxy-6-methylbenzoate (0.208 mg, 1.08 mmol) in THF was added to the LDA solution under argon at –78°. The resulting dark red solution was stirred for 15 min and HMPA (0.169 mL, 0.978 mmol) was added. After 5 min, enone **21** (180 mg, 0.489 mmol) was slowly added and the solution was stirred for 1 h. TMSCl (0.5 mL, 3.91 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was slowly added to a solution of saturated $NaHCO_3$ (20 mL) and stirred for 15 min. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was dried over $Na_2SO_4$, and concentrated in vacuo. Flash chromatography of the crude product using 20% EtOAc–hexane gave silyl enol ether **22** as a yellow oil (150 mg, 48%).

The silyl enol ether **22** (150 mg, 0.237 mmol) was dissolved in benzene (20 mL) and stirred with KF (30 mg, 0.52 mmol) and dicyclohexano-18-crown-6 (194 mg, 0.52 mmol) under argon for 48 h. The reaction was quenched by $H_2O$ (15 mL), the aqueous layer was extracted with $Et_2O$ (3 × 20 mL). The combined organic layer was dried over $Na_2SO_4$, and concentrated in vacuo. Flash chromatography of the crude product using 20% EtOAc–hexane gave a pale yellow oil (96 mg, 72%).

NaH (13.6 mg in 60% mineral oil, 0.34 mmol) was washed with dry hexane, which was then removed by Pasteur pipette. A solution of the above product (96 mg, 0.17 mmol) in THF was slowly added to a stirring suspension of NaH and a drop of ethanol in THF (10 mL). The reaction mixture was stirred at room temperature for 3 h, and then water (15 mL) was added. The resulting solution was neutralized with dry ice, and extracted with $Et_2O$ (3 × 10 mL) and EtOAc (2 × 15 mL). The combined organic layer was dried over $Na_2SO_4$, and concentrated in vacuo. Flash chromatography of the crude product using 20% EtOAc–hexane gave yellow crystals of **24** (48 mg, 55%).

DDQ (21 mg, 0.093 mmol) was slowly added to a solution of **24** (48 mg, 0.093 mmol) in benzene (10 mL) under argon at room temperature. The reaction was stirred for 1 h, $H_2O$ (10 mL) and ether (10 mL) were added to the solution, and the aqueous layer was separated and extracted with ether (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to give a dark oil. Flash chromatography of the crude product using 20% EtOAc–hexane gave naphthacenone **25** as a yellow solid (46 mg, 96%).

***C9-S* isomer 25a (18% overall)***

mp 182–184°C (dec.). IR (KBr) (cm$^{-1}$): 2935, 1624, 1575, 1370, 1259, 1103, 840, 757. $^1$H NMR (500 MHz) δ: 0.16 (s, 9H, $OSiMe_3$), 1.24 (d, $J$ = 6.32 Hz, 3H, $CH_3$), 1.37 and 1.55 (s each, 3H each, $CH_3CCH_3$), 1.66 (dd, $J$ = 14.6, 11.6 Hz, 1H, H-1α), 2.19 (tt, $J$ = 12.7, 4.4 Hz, 1H, H-4a), 2.49 (dd, $J$ = 14.6, 3 Hz, 1H, H-1β), 2.96 (m, 2H, H-5), 3.22 (m, 2H, H-13 and H-12a overlapping), 3.30 (s, 3H, CH-$OCH_3$), 3.99 (s, 3H, Ar-$OCH_3$), 4.15 (d, $J$ = 5.77 Hz, 1H, H-3), 4.33 (t, $J$ = 5.36 Hz, 1H, H-4), 6.77 (d, $J$ = 7.84 Hz, 1H, H-9), 6.95 (s, 1H, H-6), 7.19 (d, $J$ = 7.97 Hz, 1H, H-7), 7.45 (t, $J$ = 7.98 Hz, 1H, H-8) 8.23 (s, 1H, Ar-OH). $^{13}$C NMR (125 MHz) δ: 2.9 (3 × C), 13.7, 25.9, 26.2, 32.1, 32.4, 38.9, 41.5, 56.1, 56.6, 74.6, 75.9, 82.1, 77.4, 105.4, 108.6, 111.1, 115.1, 116.4, 119.7, 130.8, 138.1, 140.1, 159.8, 165.7, 205.9. CI-MS *m*/*z* (%): 515 ([M + 1]$^+$, 11), 397 (19), 281 (11), 253 (10), 239 (12), 74 (15), 59 (100). Anal. calcd. for $C_{28}H_{38}O_7Si$: C 65.36, H 7.39; found, C 65.32, H 7.44.

***C9-R* isomer 25b: (18% overall)***

mp 176–178°C (dec.). IR (KBr) (cm$^{-1}$): 2939, 1622, 1573, 1099, 841, 761. $^1$H NMR (500 MHz) δ: 0.15 (s, 9H, $OSiMe_3$), 1.19 (d, $J$ = 6.22 Hz, 3H, $CH_3$), 1.28 (m, 2H, H-1), 1.38 and 1.55 (s each, 3H each, $CH_3CCH_3$), 2.21 (tt, $J$ = 12.2, 5.28 Hz, 1H, H-4a), 2.87 (m, 2H, H-5), 3.07 (q, $J$ = 6.14 Hz, 1H, H-13), 3.18 (td, 1H, H-12a), 3.29 (s, 3H, CH-$OCH_3$), 3.88 (d, $J$ = 5.82 Hz, 1H, H-3), 4.00 (s, 3H, Ar-$OCH_3$), 4.33 (t, $J$ = 5.28 Hz, 1H, H-4), 6.77 (d, $J$ = 8.02 Hz, 1H, H-9), 6.95 (s, 1H, H-6), 7.19 (d, $J$ = 7.85 Hz, 1H, H-7), 7.45 (t, $J$ = 8 Hz, 1H, H-8), 8.23 (s, 1H, Ar-OH). $^{13}$C NMR (125 MHz) δ: 2.9 (3 × C), 12.8, 25.5, 26.3, 29.6, 31.5, 38.9, 41.7, 56.1, 56.2, 75.9, 77.1, 78.2, 82.9, 105.4, 108.1, 111.1, 115.1, 116.4, 119.6, 130.8, 138.5, 140.1, 159.8, 165.7, 205.9. CI-MS *m*/*z* (%): 515 ([M + 1]$^+$, 16), 397 (26), 253 (11), 89 ([$Me_3SiO$]$^+$, 18), 73 ([$Me_3Si$]$^+$, 93), 59 ([MeO=CHMe]$^+$, 100).

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