A common synthetic route to homochiral tetracycles related to pillaromycinone and premithramycinone

Bryan Hill, Robert Jordan, Yang Qu, Abdeljalil Assoud, and Russell Rodrigo

Abstract: Homochiral AB segments for (+)- and (–)-pillaromycinone were prepared in 11 steps from 2-acetylfuran. The synthesis featured an intramolecular Diels–Alder reaction of a 2,5-disubstituted furan and a hydroxyl-directed homogeneous hydrogenation of the tetrasubstituted alkene double bond of two enones. The CD segment was attached by a modified Staunton–Weinreb annulation to produce the desired homochiral tetracycle **21c** related to (+)-pillaromycinone. An unusual acetonide migration enabled the synthesis of a tetracyclic model for premithramycinone.

Key words: naphthacenone antibiotics, diastereoselective hydrogenation, Stauton–Weinreb annulation, furan Diels–Alder, regioselective dehydrogenation.

Résumé : On a préparé les segments AB homochiraux des (+)- et (–)-pillromycinone en onze étapes à partir du 2-acétylfurane. La synthèse implique une réaction de Diels–Alder intramoléculaire d'un furane 2,5-disubstitué et une hydrogénation homogène orientée par le groupe hydroxyle de la double liaison de l'alcène tétrasubstitué de deux énones. Le segment CD a été fixé par une réaction d'annelation de Staunton–Weinreb modifiée pour conduire au dérivé tétracyclique **21c** désiré, apparenté à la (+)-pillromycinone. Une réaction inusitée de migration d'un acétonide a permis de réaliser la synthèse d'un modèle tétracyclique de la prémithramycinone.

Mots-clés : antibiotiques de la naphtacénone, hydrogénation diastéréosélective, annelation de Stauton–Weinreb, réaction de Diels–Alder avec le furane, déshydrogénation régiosélective.

[Traduit par la Rédaction]

Introduction

Pillaromycin A (**1**) was isolated from a culture of *Streptomyces flavovirens* 40 years ago. Its aglycone, (+)-pillaromycinone **2**, is a linear tetracycle[1] with structural similarities to both the tetracyclines and anthracyclinones. Although it has attracted sporadic attention from the synthetic community,[2–4] no enantioselective route to (+)- or (–)-pillaromycinone has been disclosed as yet. Premithramycinone (**3**), isolated in 1998 from a blocked mutant of *Streptomyces argillaceus* ATCC 12956 is a key intermediate in the biosynthesis of the anticancer aureolic acids.[5] No synthetic work towards this compound has been recorded in the literature.

Some years ago[4a] we tested the viability of a convergent AB + CD plan, designed to provide rapid access to the tetracyclic system of **2**. Accordingly, the structurally appropriate AB intermediates, bicyclic enones (±)-**4a** and (±)-**4b**, were prepared in only 10 steps from furfural and incorporated into tetracycles (±)-**5a** and (±)-**5b** by a Staunton–Weinreb annulation. Two serious problems remained to be solved if the work was to be successfully adapted to a synthesis of any tetracycle related to (+)-pillaromycinone. The configuration at C-4a, established by heterogeneous hydrogenation of a tetrasubstituted double bond, was incorrect and no simple method existed for its correction in (±)-**4a** or (±)-**4b**. The Staunton–Weinreb annulation, although successful, needed four separate steps[4a] to form a tetracycle in an unacceptable yield of only 18% (Fig. 1).

We now report that the stereochemical deficiency has been remedied, the annulation has been profitably modified, overall yields have been improved substantially, and our basic plan[4a] has been adapted into a 14 step route to a homochiral tetracycle closely related to (+)-pillaromycinone from 2-acetylfuran. In addition, a serendipitous migration of an acetonide in one tetracyclic intermediate was discovered. Its possible application to the synthesis of premithramycinone **3** was briefly explored.

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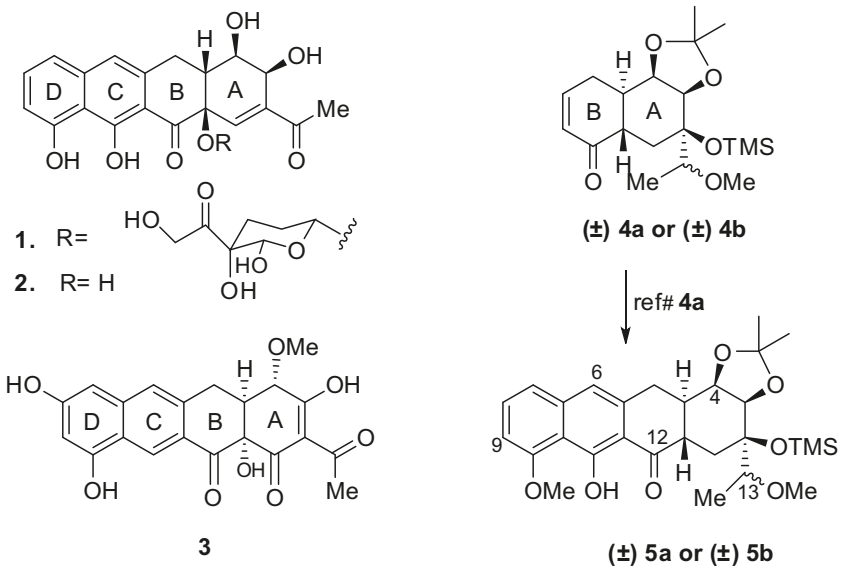
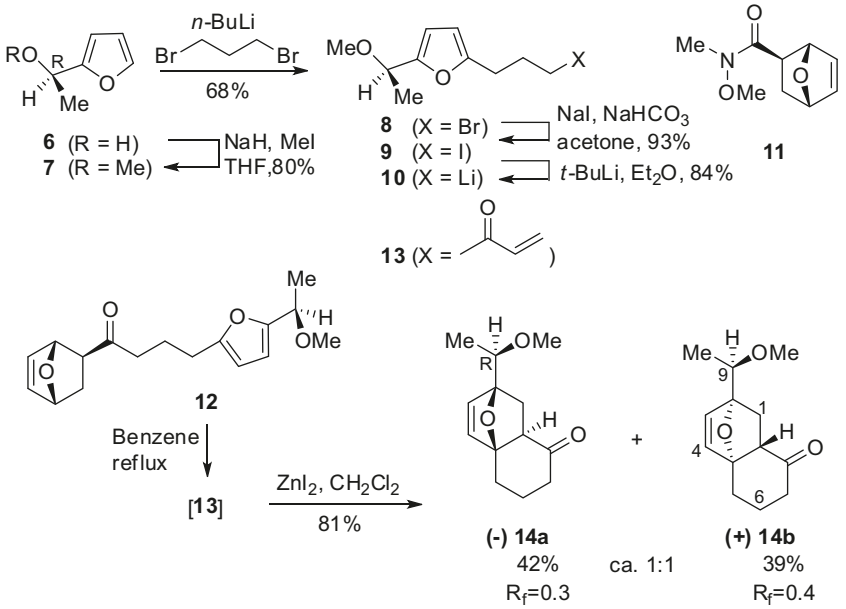
Fig. 1. Summary of previous synthetic work.[4a]



Scheme 1. Preparation of diastereomeric Diels–Alder adducts.

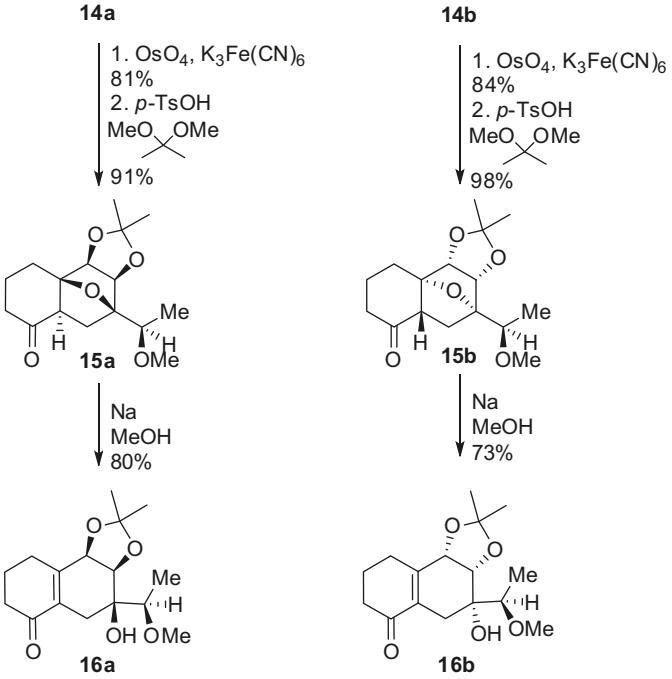


Results and discussion

The synthesis of homochiral AB units 18a–18d

The prochiral ketone 2-acetylfuran was reduced with borane in the presence of 5 mol % of the chiral ligand, diphenyl prolinol.[6] The resulting *R*(+) alcohol **6** (96% yield, >99% enantioselectivity) was methylated (NaH/MeI) to provide methyl ether (+)-**7** (80% yield). Both reactions were routinely conducted on 20 g scales and the product from each step isolated by distillation. The iodopropyl side chain was attached at the remaining furanoid α-carbon atom of **7** as before[4a] in two steps, through the bromide **8** (68%) and the iodide **9** (93%). Lithium–iodine exchange (*t*-BuLi, –78°) produced intermediate **10**, which was quenched in situ with *exo*-amide **11** to form the desired ketone **12** in 84% yield. This circuitous protocol "masks" the double bond of *N*,*O*-dimethyl acrylamide; a necessity because the conjugated amide did not react cleanly with **10**, and the 2,5-disubstituted furanoid core of these compounds was very sensitive to oxidizing agents. The enone **13** was unmasked by a retro-Diels–Alder reaction, effected by refluxing **12** in benzene overnight and removing the solvent under reduced pressure. The residue (**13**) was dissolved in dry methylene chloride and stirred at ambient temperature with 50 mol % zinc iodide for 48 h. The diastereomeric exo adducts[7] **14a** and **14b** resulting thereby were formed in an ~1:1 ratio and a combined yield of 81%. They were separated by flash column chromatography as before[4a] (Scheme 1). The three new chiral centres must have absolute configurations 2*S*,4a*S*,8a*R* and 2*R*,4a*R*,8a*S* with the already established 9*R* centre common to both. In our earlier work with racemates, X-ray crystallography of acetonide (±)-**15b** prepared from the chromatographically

Scheme 2. Synthesis of hydroxy enones **16a** and **16b**.



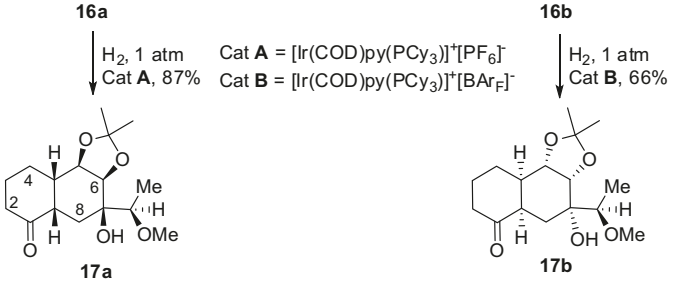
faster adduct (Scheme 2), indicated that its relative configuration was 2*S**,4a*S**,8a*R**,9*S**. It therefore follows that the absolute configuration of the faster adduct (**14b**) is 2*R*,4a*R*,8a*S*,9*R* (R_f = 0.4, $[\alpha]_D$ = +32.2) and the slower (**14a**) is 2*S*,4a*S*,8a*R*,9*R* (R_f = 0.3, $[\alpha]_D$ = –37.5). These assignments are also recorded in Scheme 1.

The 9*R* centre must be destroyed at a subsequent stage to generate the C-2 acetyl group of pillaromycinone, thereby converting the two diastereomers into enantiomers each of which can relate to (+)- or (–)-pillaromycinone. The chiral 9*R* substituent thus serves as a traditional resolving agent, but one that is also an integral part of the target molecule.

Proceeding as before,[4a] the C-3, C-4 double bond of each adduct was dihydroxylated and converted to the respective acetonides **15a** and **15b**. Each acetonide was then subjected to cleavage of the oxygen bridge by brief treatment with sodium in refluxing methanol. The resulting hydroxy enones **16a** and **16b** (higher R_f) were obtained in 10% and 9.3% overall yields, respectively, from 2-acetylfuran after nine steps (Scheme 2). We were able to separate (±)-**16a** on a chiralcell-OD column and show that our sample of **16a** was >99% enantiomerically pure (Fig. 1 of the Supplementary data).

It was now necessary to face the difficult problem of hydrogenation of the tetrasubstituted C-4a, C-8a double bond of each enone with delivery of hydrogen syn to the C-7 hydroxyl group and C_5–C_6 acetonide. Indeed, this was the step that had failed to produce the desired AB ring fusion in our earlier work.[4a] Some promising precedents[8] employing homogeneous hydrogenation techniques are available in the literature. A cationic rhodium catalyst had efficiently hydrogenated a tetrasubstituted double bond syn to a homoallylic hydroxyl group,[9] but our substrates **16a** and **16b** were unaffected by 5 or 10 mol % of $[Rh(nbd)(diphos\text{-}4)]^+BF_4^-$ at pressures of 1–50 atm (1 atm = 101.325 kPa) of hydrogen, at room temperature, after 24 or 36 h. Diimide, used earlier[10]

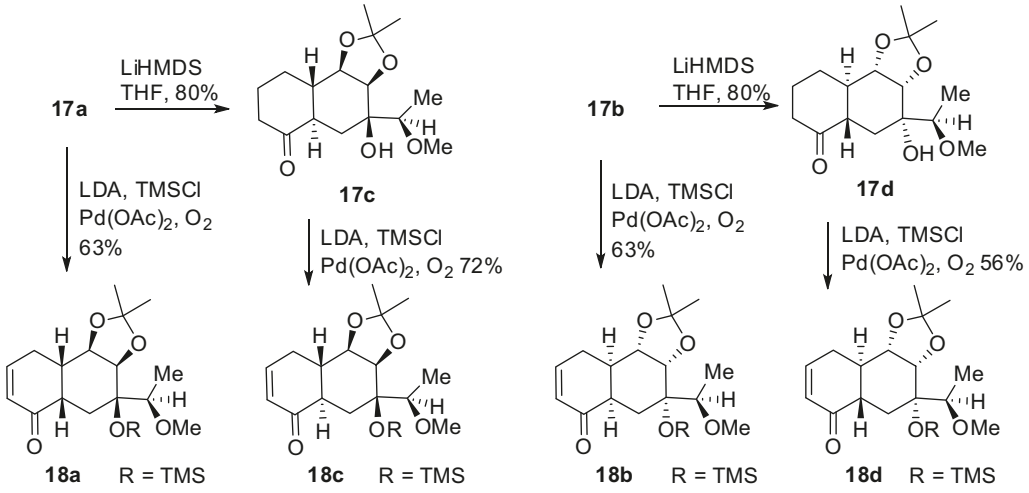
Scheme 3. Synthesis of *cis*-decalones **17a**–**17b**.



for a similar hydrogenation, also left these enones intact. The cationic iridium catalysts were evaluated next. A structural requirement for the successful hydrogenation of 3-cyclohexenols was that the hydroxyl group of the substrate be axially disposed. This ensures that both the hydroxyl group and the double bond are within reach of the metal in the putative octahedral Ir^{3+} complex resulting from oxidative addition of hydrogen[8] to the precatalyst. Our substrates did meet this criterion admirably, but they were seriously crowded around the reaction site. The homogenous hydrogenation with the Crabtree catalyst[11] was initially conducted in methylene chloride with the "slower" enone **16a** at various pressures of hydrogen, catalyst loadings, and reaction times. In general, the reaction was slow and incomplete. This was not surprising: tetrasubstituted double bonds are not easily hydrogenated. However, the desired product (the *cis*-decalone **17a**) was obtained in 87% yield after 48 h at a pressure of 1 atm of hydrogen (Scheme 3).

Surprisingly, and for reasons unknown, no conditions could be found that would hydrogenate the double bond of **16b** with the Crabtree catalyst. It has been reported that this catalyst can suffer deactivation over time by the formation of trimeric hydrogen-bridged iridium species, and this would be especially likely in slow reactions such as this. However, it is also known[12] that exchanging the PF_6^- counterion for the more lipophilic tetrakis[3,5-bis(trifluoromethyl)phenyl] borate $(BAr_F)^-$ improved catalyst performance and resistance to deactivation. We decided to prepare this catalyst by reaction of the Crabtree catalyst with $Na^+(BAr_F)^-$ in a two-phase methylene chloride – water system.[13,14] Column chromatography of the product (methylene chloride / silica) followed by crystallization from ethanol/ether gave the desired catalyst $[Ir(cod)py(PCy_3)]^+[BAr_F]^-$, whose structure was confirmed by X-ray crystallography (Supplementary data). Hydrogenation of the other diastereomeric enone (**16b**) with 10 mol % of this catalyst overnight, at a pressure of 1 atm of hydrogen produced the decalone **17b** in 66% yield. These reactions were also performed with the racemates (±)-**16a** and (±)-**16b** and the products (±)-**17a** and (±)-**17b** analysed by X-ray crystallography to establish their structures and relative stereochemistry (Supplementary data). It was gratifying indeed to observe that the difficulty with the configuration at C-4a had finally been resolved and the desired hydroxyl-directed hydrogenation had been achieved. At this stage we decided to also investigate the possibility of epimerising **17a** and **17b** at C-8a to obtain the *trans*-decalones **17c** and **17d** (Scheme 4). This was achieved in 80% yield by treatment with LiHMDS in THF (–78° → 0°), but the reactions could not be taken to completion and the products contained

Scheme 4. Synthesis of *cis*- and *trans*-enones **17a**–**17d**.



~20% of the starting *cis*-decalones **17a** and **17b**, which were separated by column chromatography. In Fig. 2 of the Supplementary data, the ^{1}H NMR spectra (500 MHz) of **17a**–**17d** are displayed. Particularly noteworthy is the small, but measureable W-coupling (found only in **17a**) between H-8α and the C-7 hydroxyl proton. This coupling is greatly reduced upon D_2O exchange. The other diagnostic feature in the figure is the lack of any signals between 2.5 and 3.2 ppm in the spectra of **17c** and **17d**. This region contains the cis-ring junction protons H-4a and H-8a in **17a** and **17b** and their absence reflects the trans-ring fusion in the former compounds.

Unlike the previous reports[2,3] that employed the Diels–Alder reaction to create the AB cis-ring fusion, our hydrogenation/epimerization sequence produces two pairs of AB intermediates cis and trans fused at will, each with a rigorously predetermined absolute configuration. The first pair (**17a** and **17c**) had stereochemistry at C-4a, C-5, and C-6 identical with that of (+)-pillaromycinone, whereas the second (**17b** and **17d**) related to the (–)-enantiomer in a similar manner. With each pair, a choice of configuration at the enolisable C-8a centre was available. We soon found that this versatility was a valuable asset in a subsequent step of the synthesis. Dehydrogenation of each decalone (**17a**–**17d**) at C-2, C-3 was achieved by the two-step Saegusa method.[15] The kinetic enolates were quenched with excess TMSCl and the resulting enol silanes were each oxidized with $Pd(OAc)_2$ in DMSO under an atmosphere of oxygen.[16] The enones (**18a**–**18d**) were isolated in 56%–72% yields. At this stage a final check on structure and stereochemistry of these AB segments was secured by a X-ray crystal structure of one of them, (±)-**18b**. We decided to continue the synthesis with the **18a**, **18c** pair only, because their configurations related to the natural antibiotic and they were produced in the highest overall yields from 2-acetylfuran (5.5% and 4.3%, respectively).

Synthesis of homochiral tetracycles

The next obstacle, the unacceptable yield of the Staunton–Weinreb annulation, was overcome by our "stannane modification" of the process.[4b] No less than seven cyclic enones, with and without[17] enolisable hydrogen atoms, were found to undergo the Michael addition – Dieckmann condensation sequence to afford polycyclic ketones in satisfactory yields. Both diastereomers **18a** and **18c** reacted with the stannane **19** after tin–lithium exchange to form ABCD tetracycles **20a** (62%) and **20c** (71%), respectively.

These homochiral tetracycles were then dehydrogenated with dicyanodichloroquinone (DDQ) in benzene. The AB cis fused heterocycle **20a** was unexpectedly resistant to the aromatisation of ring C and the reactions were difficult to complete, with product (**21a**) yields around 30%. Using other dehydrogenating agents (e.g., Pd/C or chloranil) did not improve matters.

This unfortunate setback was alleviated somewhat by testing the *trans*-enone **18c** instead, in the two-step annulation. As it happened, the AB trans tetracycle **20c** produced (71% yield) in the first step was quantitatively dehydrogenated by DDQ to (+)-**21c** ($[\alpha]_D$ = +32.4). This florescent yellow-green compound bearing the requisite substitution and absolute stereochemistry at C-3, C-4, and C-4a suitable for progressing to (+)-pillaromycinone was obtained in 14 steps and 3.95% overall yield from 2-acetylfuran (Scheme 5).

However, the configuration at the enolisable C-12a centre will have to be inverted in a subsequent hydroxylation step.

We began our effort to approach (+)-pillaromycinone by examining the possibility of O-desilylation and subsequent elimination of the tertiary hydroxyl group at C-2. Initially, treatment with TBAF in wet THF resulted in a complex mixture of products (see later), but PPTS in methanol at 0° did accomplish the desired desilylation in excellent yield. Many attempts were made to dehydrate the resulting C-2 tertiary hydroxyl group of **22**. With milder reagents like DCC, thiocarbonyl diimidazole, and mesyl chloride / DMAP, the starting material was recovered. Other reagents like thionyl chloride or triphenyl phosphine / iodine caused extensive decomposition. Acid-catalyzed dehydration with *p*-TsOH in moist THF was examined at temperatures between 0° and 25° with regular monitoring by TLC. After reaction under such conditions overnight at room temperature, the starting material **22** was consumed and two products were detected. One was the deprotected acetonide, a tetrahydroxy compound that could be eluted from a column only with neat ethyl acetate. The other, slightly slower on TLC than the starting

Scheme 5. Synthesis of homochiral tetracycles.

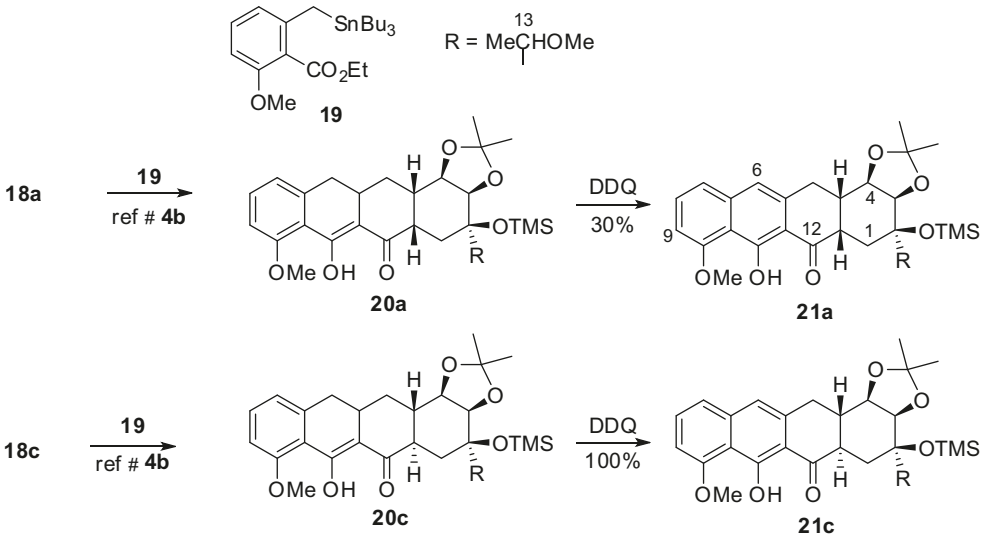
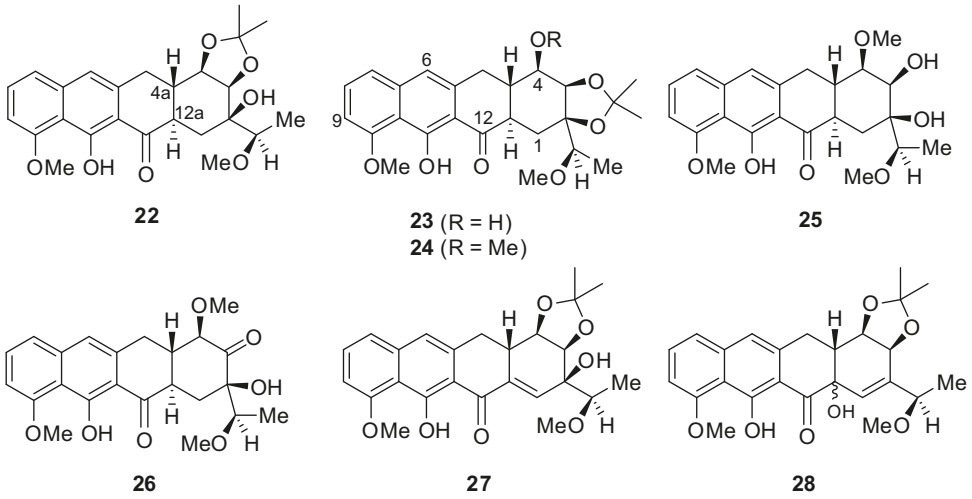


Fig. 2. Progress made towards pillaromycinone and premithramycinone.

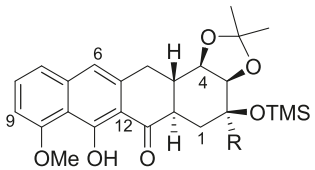
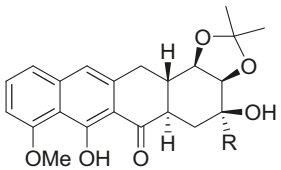
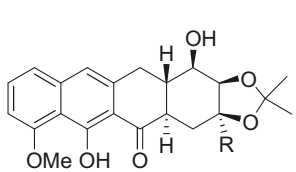
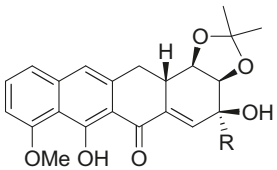
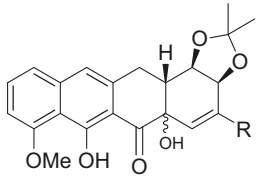
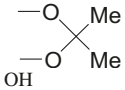


material **22**, had the same molecular formula (HRMS), but a different ^{1}H NMR spectrum, particularly in the signals of the protons on ring A (H-1, H-3, H-4, and H-4a, Table 1).[18] We were able to crystallize this product and establish its structure as **23** by X-ray crystallography. This isomeric acetonide was also formed from the silyl ether **21c** under identical conditions. Although these results were frustrating, we did not lose sight of the fact that the formation of **23** from **21c** or **22** represents the selective deprotection of the C-3, C-4 acetonide at C-4. This finding could be of much significance for a future attempt to synthesize premithramycinone **3**. To illustrate, methylation (NaH/MeI) of the now unprotected C-4 hydroxyl group afforded methyl ether **24** quantitatively. Hydrolysis of the acetonide (THF / aq HCl) left the C-2, C-3 diol **25**, which was oxidized (IBX, acetonitrile, 80°)[19] to provide the C-3 ketone **26**. These simple transformations produced a tetracycle with structure and stereochemistry not far removed from the A ring of **3** (Fig. 2).

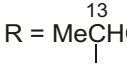
Even though these were interesting and potentially useful reactions, they represented no advance towards pillaromycinone. In particular, we had no success in dehydrating the C-2 alcohol to generate the C-1, C-2 double bond as we had intended to do in our synthetic planning. Therefore, we decided to examine the complex mixture produced by the TBAF treatment of **21c** more carefully. Purification by chromatography provided a crystalline reddish yellow compound in an optimized yield of 60%. It had a molecular formula of $C_{25}H_{28}O_7$ (HRMS) in contrast to the starting material **21c** ($C_{28}H_{38}O_7Si$). Therefore, it must have been desilylated ($-C_3H_8Si$), but in addition had a deficiency of two hydrogen atoms. These features were confirmed by comparison of its ^{1}H and ^{13}C NMR spectra with those of **21c**.

In particular, the ^{1}H NMR signals assigned to the C-1 protons (δ 1.68, 2.67) and the C-12a proton (δ 2.95) of the starting material were absent in the spectrum of the product, but a new signal was evident as a singlet at 7.13 ppm. The ^{13}C spectrum confirmed the presence of a trisubstituted alkene with the appearance of two new signals at 135.3 and 136.5 ppm (protonated and nonprotonated, respectively). Based on these and other NMR comparisons (Table 1) we assigned the structure **27** to this compound and confirmed it by single-crystal X-ray analysis. We found that **27** was also

Table 1. ^{1}H NMR data (500 MHz, δ (in ppm), *J* (in Hz)) for tetracycles **21c**, **22**, **23**, **27**, and **28** in $CDCl_3$.

	Compound				
	21c	**22**	**23**	**27**	**28**
Proton					
H-1	ax. 1.68(t), *J*=12.8, 12.8 eq. 2.68 overlapped by H-5	ax. 2.07(dd), *J*=15, 8.7 eq. 2.33(dd), *J*=15, 7.5	ax. 1.43(t), *J*=13.5, 13.5 eq. 2.85(dd), *J*=14.3, 3.6	7.13(d), *J*=2.9	6.9(s)
H-3	4.02(d), *J*=4.8	4.33(d), *J*=7.0	4.19(d), *J*=3.8	4.30(d), *J*=6.6	4.72(d), *J*=6.3
H-4	4.15(dd), *J*=8.6, 4.7	4.11(dd), *J*=9.0, 7.0	3.86(td), *J*=10.5, 10.5, 3.8	4.19(t), *J*=6.2, 6.2	4.49(dd), *J*=10.2, 6.3
H-4a	1.98(m), *J*=12.5, 12.5, 8.6, 3.6	2.5(m), overlapped by C-2 OH	2.2 (complex m)	3.0 (complex m)	2.16(m)
H-5	ax. 2.68 overlapped by H-leq eq. 3.3 overlapped by H-13 and C_{13}–OMe	ax. 2.68, partially overlapped by H-4a, and H-12a eq. 3.3 overlapped by H-13 and C_{13}–OMe	ax. 2.7(m) overlapped with H-12a eq. 3.49(dd), *J*=16, 3.6	ax. 2.79(t), *J*=14, 14 eq. 3.30(dd), *J*=14.8, 5.4	ax. and eq. 3.2–3.25 complex multiplet
H-12a	2.95(td), *J*=12.6, 12.6, 2.9	2.63(dt), *J*=13, 8.2, 8.0 partially overlapped by H-5_{ax}	2.7 (complex m) overlapped with H-5ax	—	—
H-13	3.3, overlapped by H-5_{eq} and C_{13}–OMe	3.32(q), *J*=6.3	3.45(q), *J*=6.2	3.34(q), *J*=6.3	4.02–4.06 overlapped by C_{10}–OMe
C_{13}-Me	1.29(d), *J*=6.3	1.29(d), *J*=6.3	1.34(d), *J*=6.2	1.29(d). *J*=6.3	1.44(d), *J*=6.4
OMe	C_{10} 4.03, C_{13} 3.31	C_{10} 4.03, C_{13} 3.37	C_{10} 4.04, C_{13} 3.33	C_{10} 4.01, C_{13} 3.36	C_{10} 4.05, C_{13} 3.4
	1.5, 1.43	1.53, 1.45	1.47, 1.37	1.50, 1.43	1.49, 1.38
OH	C_{11}–OH, 15.2	C_2 2.46, C_{11} 15.1	C_4 2.13(d), *J*=10.3, C_{11} 15.56	C_2 2.9, C_{11} 15.45	C_{12a} 2.21, C_{11} 14.66

Note: Aromatic H signals appeared in a narrow range in all compounds as follows: H-8(t) 7.47–7.53, H-7(d) 7.20–7.25, H-6(s) 6.90–7.01, and H-9(d) 6.80–6.84, with coupling constants *J* = 7.80–8.0 Hz.



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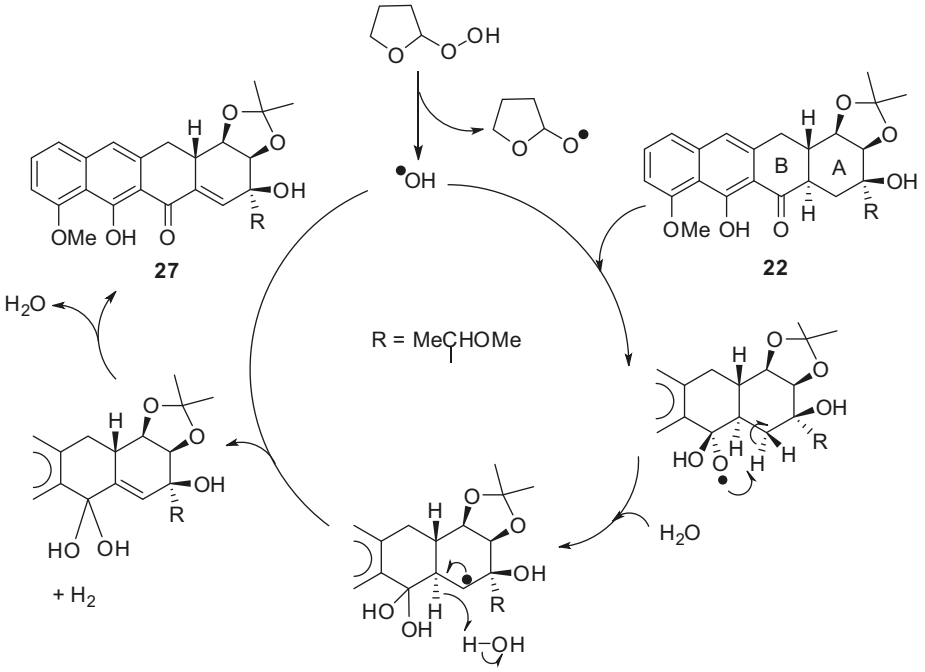
Scheme 6. Proposed mechanism for the formation of **27** from **21c** or **22**.



produced from the desilylated tetracycle **22** in similar yield under identical conditions. This remarkably selective dehydrogenation probably occurs by means of a radical chain process initiated by THF peroxide[20] and propagated by hydroxyl radicals. We propose a mechanism (Scheme 6) that accounts for the regioselectivity by assigning a crucial role to the carbonyl group at C-12 and avoids the intermediacy of an enolate radical at C-12a. The collapse of such a radical would result in the aromatization of ring B. The absolute configurations at every other chiral centre besides C-12a were unaffected in the transformation, and we had recognized earlier that the existing configuration at that centre would have to be corrected eventually. Consequently, we saw this γ-hydroxy enone **27** as an opportune substrate either for introducing the required hydroxyl group at C-12a in the correct orientation or for generating the desired C-2 acetyl group by dehydration at C-2, C-13.

We attempted the dehydration first by applying a simple procedure recommended specifically[21] for tertiary alcohols and illustrated with many examples of success with sensitive substrates. Under the conditions cited (mesyl chloride, triethylamine, DMAP in dry dichloromethane 0° → rt, 30 min) we obtained a green fluorescent compound that was separated from the reaction mixture by column chromatography on silica gel, first in ethyl acetate / hexane and then in dichloromethane/ether (85:15). However, even after careful chromatography, this material (a single spot on the TLC analysis) could not be obtained pure. The base peak at *m*/*z* 440 in its mass spectrum corresponded to a molecular formula $C_{25}H_{28}O_7$ (by HRMS) making it isomeric with the starting enone. In addition, the spectrum did not display an ion of significant intensity at *m*/*z* 422, thereby implying that the projected dehydration had not occurred. The ^{1}H and ^{13}C NMR spectra indicated the presence of about 10% of an impurity that appeared to be structurally similar to the major component. The ^{1}H spectrum of the green fluorescent product, when compared with the starting enone, showed many changes in the chemical shifts of protons associated with ring A. The alkene proton remained as a singlet, now at 6.9 ppm, and the signals assigned to H-3, H-4, and H-13 showed significant downfield shifts, whereas H-4a, no longer allylic, was shifted upfield considerably (Table 1). These changes taken together suggested that an allylic rearrangement[22] had occurred in ring A. The structure **28** is proposed for the fluorescent product with the double bond now at C-1, C-2 and the hydroxyl group at C-12a. The evident lack of a C-12a proton and the presence of a broad OH signal at 2.21 ppm supported the structural assignment. The configuration of the hydroxyl substituent at C-12a is still uncertain, however, and the difficulties experienced with purification of the product implies that it is an epimeric mixture of two C-12a alcohols. We have tried very hard to obtain suitable crystals of **28** for X-ray analysis without success so far, but these attempts are continuing.

Conclusion

If the configuration of **28** can be conclusively settled it would mean that we have succeeded in developing a synthesis of a very advanced intermediate for (+)-pillaromycinone requiring only minor structural adjustments for completion. It incorporates the correct absolute configuration at C-3, C-4, and C-4a and the double bond at C-1, C-2. Its synthesis required only 16 steps from 2-acetylfuran and features novel protocols for (*i*) stereochemical control at C-4a, C-4, and C-3; (*ii*) the Staunton–Weinreb annulation; (*iii*) regioselective dehydrogenation of a tetracyclic ketone at C-1, C-12a; and (*iv*) introduction of the hydroxyl group at C-12a. In addition, an interesting possibility of modifying ring A for the synthesis of premithramycinone has been created.

Experimental

Experimental procedures and spectroscopic data for racemic compounds **6**–**15**, stannane **19**, and chiral tetracycles **20a** and **20c** have been published previously.[4] Experimental protocols have been modified in some instances and yields improved. In such cases, the new conditions and yields are provided. See the Supplementary data for notes on general experimental methods.

R-(+)-1-Furylethanol (6)

To a stirred solution of *S*-diphenylprolinol (2.3 g, 9.08 mmol) in THF (650 mL) was added 2.0 mol/L BH_3–SMe_2 (64 mL, 128 mmol). The mixture was stirred overnight at room temperature (rt). A solution of 2-acetylfuran (20 g, 181.6 mmol) in THF (30 mL) was added slowly via a syringe pump and the mixture was stirred overnight at rt. The reaction was quenched with methanol and the solvents removed in vacuo at rt. Distillation (water aspirator) gave **6** (19.5 g, 96%) as a clear colourless liquid, bp 64°–70°. $[\alpha]_D$ = +21.1 (*c* 1.06, $CHCl_3$). Optical rotation suggests >99% enantioselectivity for the reduction.[23]

R(+)-2-(1′-Methoxy)ethylfuran (7)[4a]

$[\alpha]_D$ = +109.9 (*c* 1.006, $CHCl_3$), 80% yield.

R(+)-2-(3-Bromopropyl)-5-(1′-methoxy)ethylfuran (8)[4a]

$[\alpha]_D$ = +67.0 (*c* 1.216, $CHCl_3$), 68% yield.

R(+)-2-(3-Iodopropyl)-5-(1′-methoxy)ethylfuran (9)[4a]

$[\alpha]_D$ = +59.1 (*c* 1.482, $CHCl_3$), 93% yield.

2β-(*N*-Methyl-*N*-methoxyamido)-7-oxabicyclo[2.2.1]hept-5-ene (11)[4a] and *R*(+)4-[5-(1-methoxyethyl)furan-2-yl]-1-(7-oxabicyclo[2.2.1]hept-5-ene-2-yl)butan-1-one (12)[4a]

$[\alpha]_D$ = +61.0 (*c* 1.184, $CHCl_3$), 84% yield.

2*H*-2-(1′-Methoxyethyl)-2,4a-epoxy-1,8a,5,6,7,8-hexahydronaphthalen-8-one (14a and 14b)

A solution of ketone **12** (10.98 g, 37.8 mmol) in benzene (100 mL) was heated at reflux for 48 h. The liquids were evaporated and the residue dissolved in dichloromethane (100 mL) and zinc iodide (4.82 g, 15.1 mmol) was added. The suspension was stirred for 48 h at rt and quenched with aqueous sodium bicarbonate. The mixture was extracted with dichloromethane (3 × 50 mL), the organic extracts combined and washed with brine, then dried ($MgSO_4$) and concentrated. Flash chromatography (30% ethyl acetate – hexanes) gave 6.7 g (81%) of a mixture of **14a** and **14b** and 0.23 g of unchanged starting material. The diastereomeric adducts **14a** and **14b** were separated as before[4a] by chromatography. **14b** $R_f \approx 0.4$; $[\alpha]_D$ = +32.2 (*c* 1.006, $CHCl_3$); 39% yield. **14a**: $R_f \approx 0.3$; $[\alpha]_D$ = –37.5 (*c* 1.004, $CHCl_3$); 42% yield.

Dihydroxylation of 14a and 14b: 2*H*-2-(1′-methoxyethyl)-3β,4β-dihydroxy-2,4a-epoxy-octahydronaphthalen-8-one[4a]

Modified procedure

A mixture of **14a** or **14b** (1 equiv), OsO_4 (0.2 equiv), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), H_2O, and *tert*-butyl alcohol were stirred at rt for 48 h. The reaction was quenched with solid $NaHSO_3$ and stirred for a further 0.5 h. It was extracted with ethyl acetate (3×) and the remaining aqueous layer continuously extracted with ethyl acetate for a further 48 h. The ethyl acetate extracts were combined, dried ($MgSO_4$), and then evaporated. The residue was purified by chromatography to obtain a white solid in each case.

Dihydroxylation of 14a

13a (2.87 g, 12.9 mmol), OsO_4 (0.0714 mol/L) in water (36 mL), $K_3Fe(CN)_6$ (12.73 g, 38.7 mmol), K_2CO_3 (5.35 g, 38.7 mmol), *t*-BuOH (50 mL), and water (14 mL). Yield: 2.63 g (81%). $[\alpha]_D$ = –4.73 (*c* 0.676, $CHCl_3$).

Dihydroxylation of 14b

13b (2.0 g, 9.0 mmol), OsO_4 (0.098 mol/L) in water (18 mL), $K_3Fe(CN)_6$ (8.89 g, 27 mmol), K_2CO_3 (3.73 g, 27 mmol), *t*-BuOH (35 mL), and water (17 mL). Yield: 1.934 g (84%). $[\alpha]_D$ = +4.44 (*c* 0.608, $CHCl_3$).

2*H*-2-(1′-Methoxyethyl)-3β,4β-di-*O*-isopropylidene-2,4a-epoxy-octahydronaphthalen-8-one (15a and 15b)[4a]

To a refluxing solution of the diol (1.0 equiv) in 2,2-dimethoxypropane and dichloromethane was added a few crystals of TsOH. Refluxing was continued for a further 0.5 h, the mixture cooled, neutralized with solid K_2CO_3, and the solvents removed in vacuo. Flash column chromatography (3:1, hexanes / ethyl acetate) gave the pure acetonides. **15a**: Diol (5.817 g, 22.7 mmol), 2,2-dimethoxy propane (66.2 g, 636 mmol), CH_2Cl_2 (360 mL), TsOH (a few crystals). Yield: 6.09 g (91%). $[\alpha]_D$ = –26.8 (*c* 0.954, $CHCl_3$). **15b**: Diol (1.774 g, 6.92 mmol), 2,2-dimethoxypropane (20 g, 194 mmol), CH_2Cl_2 (150 mL), TsOH (a few crystals). Yield: 2.0 g (98%). $[\alpha]_D$ = +33.2 (*c* 1.05, $CHCl_3$).

7-(1′-Methoxyethyl)-7β-hydroxy-5β,6β-di-*O*-isopropylidene-4a,8a-dehydro-1-decalone (16a and 16b)

To a solution of sodium (5 equiv) in methanol was added the ketone **15a** or **15b** (1 equiv) in methanol. After 20–30 min the solution was cooled and poured onto dry ice. It was diluted with ether and filtered. The filtrate was evaporated to dryness and purified by flash chromatography (hexanes / ethyl acetate, 2:1). **16a**: ketone **15a** (2.0 g, 6.75 mmol), MeOH (55 mL), sodium (0.775 g, 33.7 mmol) in MeOH (55 mL), refluxed for 20 min. Yield: 1.595 g (79.8%). $[\alpha]_D$ = –102.7 (*c* = 0.736, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (3H, d, *J* = 6.3 Hz), 1.42, 1.46 (3H each, s), 1.99 (2H, m), 2.2, 2.42 (4H, m), 2.68 (2H, m), 3.25 (1H, qt), 3.31 (3H, s), 4.42 (1H, d, *J* = 7.2 Hz), 4.53 (1H, d, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.2, 22.1, 24.7, 24.8, 26.6, 26.9, 37.7, 57.1, 71.3, 74.6, 75.2, 78.6, 109.0, 130.1, 150.6, 198.6. EI HRMS $(M - CH_3)^+$ found: 281.1387; $C_{15}H_{21}O_5$ calcd: 281.1367. **16b**: ketone **15b** (0.485 g, 1.63 mmol) in MeOH (11 mL), sodium (0.188 g, 8.18 mmol) in MeOH (11 mL) refluxed for 30 min. Yield: 0.353 g (73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (3H, d, *J* = 6.3 Hz), 1.35, 1.36 (3H each, s), 1.99 (2H, m), 2.2, 2.42, 2.64 (6H, m), 3.09 (1H, qt), 3.29 (3H, s), 4.42 (1H, d, *J* = 7.2 Hz), 4.48 (1H, d, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.7, 22.2, 25.3, 26.6, 27.1, 27.4, 37.6, 57.1, 72.8, 75.4, 76.1, 79.9,

109.3, 129.8, 151.4, 198.6. EI HRMS $(M - Me)^+$ found: 281.1386; $C_{15}H_{21}O_5$ calcd: 281.1356.

7-(1′-Methoxyethyl)-7-hydroxy-5,6-di-*O*-isopropylidene-decal-1-ones (**17a** and **17b**)

A solution of the enone **16a** or **16b** (1 equiv) with iridium catalyst (0.1 equiv) in dichloromethane was flushed with hydrogen (3×) and stirred under an atmosphere of hydrogen for 24–48 h at rt. Brine was added and the layers separated. The aqueous layer was extracted with dichloromethane (3×) and the organic layers were combined, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexanes / ethyl acetate, 2:1) yielded pure products as white solids. **17a**: enone **16a** (0.332 g, 1.12 mmol), $[Ir(COD)py(PCy_3)]^+[PF_6]^-$ (0.09 g, 0.112 mmol) in CH_2Cl_2 (80 mL), stirred under H_2 for 48 h. Yield: 0.291 g (87%). $[\alpha]_D$ = +9.63 (*c* 0.114, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.10 (3H, d, *J* = 6.3 Hz), 1.28 (3H, s), 1.62 (1H, dd, *J* = 15.0, 8.0 Hz), 1.8–1.9 (4H, m), 2.08 (1H, ddd, *J* = 15.0, 6.5, 2.1 Hz), 2.31 (2H, m), 2.45 (1H, d, *J* = 2.1 Hz), 2.81 (2H, m), 3.08 (1H, q, *J* = 6.3 Hz), 3.28 (3H, s), 3.89 (1H, dd, *J* = 8.0, 7.6 Hz), 4.16 (1H, d, *J* = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.1, 22.5, 23.0, 24.6, 25.6, 26.7, 39.0, 40.7, 44.4, 57.3, 73.1, 73.3, 74.4, 80.4, 108.0, 212.7. Anal calcd for $C_{16}H_{26}O_5$: C 64.41, H 8.78; found: C 64.60, H 8.87. **17b**: enone **16b** (0.125 g, 0.421 mmol), $[Ir(COD)py(PCy_3)]^+[BAr_F]^-$ (0.064 g, 0.042 mmol) in CH_2Cl_2 (30 mL) under H_2 for 24 h. Yield: 0.0835 g (66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J* = 6.3 Hz), 1.36 (3H, s), 1.51 (3H, s), 1.63 (1H, dd, *J* = 15.0, 8.0 Hz), 1.89 (4H, m), 2.27 (1H, ddd, *J* = 15.0, 9.4, 1.5 Hz), 2.40 (2H, m), 2.84 (1H, m), 2.91–2.93 (2H, m), 3.09 (1H, q, *J* = 6.3 Hz), 3.34 (3H, s), 3.86 (1H, dd, *J* = 9.2, 7.5 Hz), 4.11 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.0, 22.5, 25.0, 25.3, 26.3, 27.0, 38.5, 40.7, 44.2, 57.5, 73.2, 73.5, 75.1, 83.0, 108.4, 213.0. EI HRMS $(M - Me)^+$ found: 283.1548; $C_{15}H_{23}O_5$ calcd: 283.1546.

4aβ,8aα-Decal-1-one (**17c**)

cis-Decalone **17a** prepared above was dissolved in dry THF (0.25 mol/L solution) and cooled to –78°. LiHMDS (1.5 equiv) was added and the mixture stirred at –78° for 10 min. It was allowed to warm to 0° and stirred at that temperature for a further 30 min. The reaction was quenched at 0° with methanol and allowed to reach rt. The solvents were removed and the crude product purified by chromatography to leave a thick oil. Yield: 80%. $[\alpha]_D$ = –10.6 (*c* 0.46, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (3H, d, *J* = 6.3 Hz), 1.29–1.34 (1H, m), 1.36 (3H, s), 1.45 (3H, s), 1.63 (1H, qt, *J* = 13.6, 4.0 Hz), 1.77 (1H, dd, *J* = 15.0, 7.1 Hz), 1.96–2.06 (3H, m), 2.38–2.41 (1H, m), 3.21 (1H, m), 3.21 (1H, q, *J* = 6.3 Hz), 3.29 (3H, s), 3.99 (1H, dd, *J* = 9.0, 7.1 Hz), 4.18 (1H, d, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.1, 24.2, 24.9, 25.8, 27.2, 30.3, 41.6, 43.5, 46.3, 57.0, 73.4, 76.2, 80.3, 80.7, 108.3, 210.1. EI HRMS M^+ found: 298.1780; $C_{16}H_{26}O_5$ calcd: 298.1779.

4aβ,8aα-Decal-1-one (**17d**)

Prepared from **17b** as above. The product was obtained in a similar yield as a 7:1 mixture of **17d**:**17b** and purified by column chromatography as before. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.15 (3H, d, *J* = 6.3 Hz), 1.23–1.30 (1H, m), 1.35 (3H, s), 1.46 (3H, s), 1.66 (1H, br.q, *J* = 14.0 Hz), 1.81 (1H, q, *J* = 9.1 Hz), 1.98 (1H, br.q, *J* = 11.0 Hz), 2.06–2.12 (3H, m), 2.21–2.31 (2H, m), 2.42 (1H, br.d, *J* = 14.0 Hz), 2.5–2.7 (1H, br), 3.14 (1H, q, *J* = 6.0 Hz), 3.33 (3H, s), 3.90 (1H, dd, *J* = 8.4, 6.5 Hz), 4.24 (1H, d, *J* = 6.5 Hz). ^{13}C NMR (125 MHz) δ: 12.5, 25.2, 25.9, 27.5, 27.9, 29.8, 41.5, 43.6, 47.0, 57.3, 73.4, 74.8, 80.2, 81.8, 108.7, 209.7. EI HRMS (M^+) found: 298.1788; $C_{16}H_{26}O_5$ calcd: 298.1780

The ^{1}H NMR (500 MHz) spectra of **17a**–**17d** are displayed in Fig. 2 of the Supplementary data.

7-(1′-Methoxyethyl)-7-trimethylsilyloxy-5,6-di-*O*-isopropylidene-2,3-dehydrodecal-1-ones (**18a**–**18d**)

Diisopropylamine (12 equiv) in THF at 0° was stirred with *n*-BuLi (12 equiv) for 15 min. The solution was cooled to –78° and the ketone **17** (1 equiv) in THF was added slowly by a syringe. After stirring for a further 1 h at –78°, TMSCl (20 equiv) was added and the stirring was continued for a further 1.25 h. The solution was allowed to warm to 0° and was stirred for a further 15 min and then quenched with aq NH_4Cl, extracted with ether (3×), washed with brine, dried ($MgSO_4$), and concentrated. The crude bis-silylether was taken up in DMSO and $Pd(OAc)_2$ (0.5 equiv) was added and flushed with O_2 (3×). It was then stirred under an atmosphere of oxygen for 48 h at rt. The reaction was quenched with brine and extracted with EtOAc (5×) and the extracts washed with water and then brine, and then dried ($MgSO_4$). The solvents were removed and the residue purified by flash chromatography (hexanes / ethyl acetate, 8:1). **18a**: **17a** (0.336 g, 1.13 mmol in THF 12 mL), 2.0 mol/L *n*-BuLi (6.75 mL, 13.5 mmol), *i*-Pr_2NH (2.0 mL, 14.0 mmol), THF (12 mL); TMSCl (2.9 mL, 22.5 mmol), $Pd(OAc)_2$ (0.126 g, 0.563 mmol), DMSO (12 mL) yielded **18a** as an oil. Yield: 0.264 g, (63%). $[\alpha]_D$ = +13.4 (*c* 0.298, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.13 (9H, s) 1.16 (3H, d, *J* = 6.3 Hz), 1.30 (3H, s), 1.48 (3H, s), 1.89 (1H, dd, *J* = 14.7, 7.1 Hz), 2.08 (1H, dd, *J* = 14.7, 6.0 Hz), 2.42–2.48 (2H, m), 2.59–2.69 (2H, m), 3.12 (1H, q, *J* = 6.3 Hz), 3.16 (3H, s), 3.87 (1H, d, *J* = 6.0 Hz), 4.01 (1H, dd, *J* = 7.5, 6.2 Hz), 5.99 (1H, dt, *J* = 10.0, 1.9 Hz), 6.76 (1H, dd, *J* = 10.0, 4.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 2.8 (3C), 12.0, 25.6, 26.5, 27.2, 27.5, 35.3, 41.9, 55.7, 76.1, 76.9, 77.5, 82.5, 107.6, 130.1, 146.3, 199.0. EI HRMS $[M - Me]^+$ found: 353.1785; $C_{18}H_{29}O_5Si$ calcd: 353.1785. **18b**: **17b** (0.171 g, 0.572 mmol in THF (6 mL)), 2.0 mol/L BuLi (3.43 mL, 6.86 mmol), *i*-Pr_2NH (1.0 mL, 7.16 mmol) in THF (6 mL), TMSCl (1.5 mL, 11.44 mmol); $Pd(OAc)_2$ (64 mg, 0.286 mmol) in DMSO (6 mL). Yield: 0.133 g (63%) of **18b** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.12 (9H, s), 1.16 (3H, d, *J* = 6.3 Hz), 1.25 (3H, s), 1.45 (3H, s), 1.65 (1H, dd, *J* = 14.9, 6.8 Hz), 2.22 (1H, dd, *J* = 14.9, 7.0 Hz), 2.41–2.46, (2H, m), 2.76–2.85 (2H, m), 3.19 (3H, s), 3.15–3.21 (1H, m), 3.91 (1H, d, *J* = 6.6 Hz), 4.0 (1H, t, *J* = 6.3 Hz), 5.99 (1H, d, *J* = 10.0 Hz), 6.80 (1H, dt, *J* = 10.0, 4.0, 4.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 2.6 (3C), 13.6, 25.8, 26.7, 27.2, 28.2, 35.1, 40.8, 56.0, 74.3, 75.7, 77.1, 81.7, 108.3, 129.7, 147.3, 199.8. **18c**: ketone **17c** (0.463 g, 1.56 mmol)

in THF (17 mL), 1.6 mol/L BuLi (12.5 mL, 20 mmol), *i*-Pr_2NH (2.8 mL, 20 mmol) in THF (17 mL), TMSCl (4 mL, 30 mmol), $Pd(OAc)_2$ (0.179 g, 0.79 mmol) in DMSO (17 mL) yielded **18c** (0.415 g, 1.13 mmol, 72%). A small amount (0.03 g) of the cis fused enone **18a** was also isolated. $[\alpha]_D$ = +45.5 (*c* 1.156, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.08 (9H, s), 1.16 (3H, d), 1.34 (3H, s), 1.45 (3H, s), 1.50 (1H, t, *J* = 13.4 Hz), 1.79–1.85 (1H, m), 1.98–2.08 (1H, m), 2.38 (1H, dd, *J* = 13.9, 2.5 Hz), 2.56 (1H, td, *J* = 12.0, 12.0, 3.0 Hz), 2.67 (1H, dt, *J* ≈ 18.0, 5.0, 5.0 Hz), 3.20 (1H, q., *J* = 6.3 Hz), 3.23 (3H, s), 3.9 (1H, d, *J* = 4.5 Hz), 4.04 (1H, dd, *J* = 8.7, 4.7 Hz), 5.94 (1H, dd, *J* = 10.0, 2.4 Hz), 6.90 (1H, ddd, *J* = 10.0, 5.9, 1.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 2.7 (3C), 12.4, 26.4, 28.2, 28.6, 30.5, 41.8, 43.9, 57.1, 77.4, 80.5, 81.3, 85.0, 107.8, 129.4, 148.5, 200.2. EI HRMS $(M - Me)^+$ found: 353.1779; $C_{18}H_{29}O_5Si$ calcd: 353.1774. **18d**: ketone **17d** (0.204 g, 0.68 mmol) in THF (6 mL), 1.6 mol/L BuLi (6.6 mL, 10.6 mmol), *i*-Pr_2NH (1.2 mL, 8.6 mmol) in THF (6 mL), TMSCl (1.8 mL, 13.73 mmol), $Pd(OAc)_2$ (82.4 mg, 0.37 mmol) in DMSO (8 mL). Yield: 98.3 mg (47%) and 27.4 mg of recovered starting material (**17d**). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.08 (9H, s), 1.15 (3H, d, *J* = 6.2 Hz), 1.45 (3H, s), 1.78 (1H, dd, *J* = 14.2, 11.4 Hz), 1.94–2.22 (4H, m), 2.65–2.75 (1H, m), 3.2 (1H, q, *J* = 6.2 Hz), 3.27 (3H, s), 3.90 (1H, dd, *J* = 8.0, 5.0 Hz), 4.27 (1H, d, *J* = 5.0 Hz), 5.98 (1H, dd, *J* = 10.0, 1.8 Hz), 6.92 (1H, m). EI LRMS *m*/*z*: 353 $[M - Me]^+$ (10), 309 $[M - MeCHOMe]^+$ (90), 251 (100), 73 (30).

11-Hydroxy-10-methoxy-2-trimethylsilyloxy-2-(1′-methoxyethyl)-3,4-di-*O*-isopropylidene-1,2,3,4,4a,5,12,12a-octahydronaphthacen-12-one (21a)

A solution of tetracycle **20a**[4b] (120 mg, 0.232 mmol) and DDQ (79 mg, 0.348 mmol) in benzene (18 mL) was refluxed for 4 h. The solution was cooled, diluted with ether and water, and extracted with ether (3 × 20 mL). The organic extracts were combined, washed with water and then with brine, and dried over $MgSO_4$. The solvents were removed and the residue chromatographed (hexanes / ethyl acetate, 8:1) and the bright fluorescent band (R_f = 0.38) was separated from the starting material (R_f = 0.26), which did not fluoresce. Yield: 25.1 mg (21%); starting material recovered: 48.8 mg (41%). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J* = 6.3 Hz), 1.31 (3H, s), 1.54 (3H, s), 1.98 (dd, *J* = 14.7, 7.4 Hz), 2.45 (1H, dd, *J* = 14.5, 4 Hz), 2.49–2.54 (1H, m), 2.80 (3H, s), 2.94 (1H, m), 3.02 (1H, dd, *J* = 15.8, 3.8 Hz), 3.05 (1H, q, *J* = 6.3 Hz), 3.08 (1H, dd, *J* =15.8, 3.8 Hz), 3.83 (1H, d, *J* = 5.3 Hz), 3.92 (1H, dd, *J* = 9, 5.3 Hz), 3.99 (3H, s), 6.76 (1H, d, *J* = 7.9 Hz), 6.97 (1H, s), 7.17 (1H, d, *J* = 7.9 Hz), 7.42 (1H, t, *J* = 8 Hz). EI HRMS M^+ found: 514.2380; $C_{28}H_{38}O_7Si$ calcd: 514.2374.

11-Hydroxy-10-methoxy-2-trimethylsilyloxy-2-(1′-methoxyethyl)-3,4-di-*O*-isopropylidene-1,2,3,4,4a,5,12,12a-octahydronaphthacen-12-one (21c)

Silyl ether **20c**[4b] (286 mg, 0.55 mmol) was dissolved in benzene (55 mL) under argon. The solution was then treated with 2,3-dichloro-5,6-dicyanobenzoquinone (197 mg, 0.87 mmol) in one portion at 25 °C. The reaction was stirred for 5 h at 25 °C and then quenched with water. The product was extracted into Et_2O and washed sequentially with saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexanes, 1.9) to afford the desired product **21c** (282 mg, 0.515 mmol, 100%) as a bright green amorphous solid. $[\alpha]_D$ = +32.4 ($CHCl_3$). R_f 0.36 (EtOAc/hexanes, 1:4). ^1H NMR ($CDCl_3$, 500 MHz): data are shown in Table 1. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 2.7 (3C), 12.5, 26.4, 28.6 (2C), 33.9, 41.4, 44.7, 56.1, 57.2, 77.5, 80.4, 81.3, 85.1, 105.4, 107.8, 111.1, 115.1, 116.6, 119.7, 130.8, 137.8, 140.1, 159.8, 165.7, 204.9. EI HRMS calcd for $C_{28}H_{38}O_7Si$ *m*/*z*: 514.2387; found: 514.2380.

2,11-Dihydroxy-10-methoxy-2-(1′-methoxyethyl)-3,4-di-*O*-isopropylidene-1,2,3,4,4a,5,12,12a-octahydronaphthacen-12-one (22)

To ensure complete dissolution, THF (0.60 mL) was added to a solution containing silyl ether **20c** (95.7 mg, 0.186 mmol) partially dissolved in HPLC grade MeOH (6.0 mL). The solution was cooled to 0 °C prior to adding pyridinium *p*-toluenesulfonate (52.8 mg, 0.210 mmol) as a solid in one portion. The reaction mixture was stirred in the dark under an Ar atmosphere at 0 °C for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ (0.5 mL) at 0 °C and the organic solvent removed in vacuo. The crude mixture was redissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexanes, 2:3) to give the tetracyclic diol **22** (82.5 mg, 0.186 mmol, 100%) as a fluorescent green, amorphous solid. R_f 0.29 (EtOAc/hexanes, 3:7). ^1H NMR ($CDCl_3$, 500 MHz): data are shown in Table 1. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.2, 25.1, 25.6, 27.3, 34.9, 39.2, 43.9, 56.1, 57.0, 73.7, 76.2, 79.9, 80.9, 105.5, 108.6, 111.2, 115.1, 116.6, 119.7, 130.9, 137.4, 140.1, 159.8, 165.7, 204.6. EI HRMS calcd for $C_{25}H_{30}O_7$ *m*/*z*: 442.1992; found: 442.1990.

4,11-Dihydroxy-10-methoxy-2-[1′-methoxyethyl]-2β,3β,-di-*O*-isopropylidene-1,2,3,4,5,12,12a-octahydronaphthacen-12-one (23)

To a vial containing a solution of **21c** (16.6 mg, 0.032 mmol) in THF (0.40 mL) was added H_2O (0.10 mL) as a co-solvent. To the vial was then added a catalytic amount of *p*-toluenesulfonic acid monohydrate (2.0 mg, 0.011 mmol) and the reaction stirred at 25 °C for 48 h. The reaction was terminated by removal of the solvent in vacuo. The crude reaction was applied directly to silica gel and purified by flash column chromatography (EtOAc/hexanes, 2:3) to afford **23** (6.0 mg, 0.014 mmol, 42%) as a fluorescent yellow-green amorphous solid, recrystallized from CH_2Cl_2/hexane. $[\alpha]_D$ = –26.3 ($CHCl_3$). R_f 0.51 (EtOAc/hexanes, 1:1). ^1H NMR ($CDCl_3$, 500 MHz): data are shown in Table 1. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.6, 26.9, 28.4, 28.9, 33.0, 40.3, 46.3, 56.1, 56.7, 74.2, 81.5, 82.4, 83.3, 105.4, 108.8, 111.2, 115.1, 116.6, 119.8, 130.9, 137.6, 140.2, 159.8, 165.8, 204.5. EI HRMS calcd for $C_{25}H_{30}O_7$ *m*/*z*: 442.1992; found: 442.1988.

11-Hydroxy-4,10-dimethoxy-2β,3β-di-*O*-isopropylidene-2α-(1′-methoxyethyl)-1,2,3,4,4a,5,12,12a-octahydronaphthacen-12-one (24)

Tetracyclic ketone **23** (6.0 mg, 0.014 mmol) dissolved in dry THF (1 mL) was treated with excess sodium hydride that had been previously rinsed with dry THF. Iodomethane (0.2 mL) was added and the mixture stirred at rt with occasional monitoring by TLC. After 1.5 h the starting material was completely consumed. The THF solution was poured into saturated aqueous ammonium chloride and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (ethyl acetate / hexanes, 5:7). Yield: 6 mg (94%) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (3H, d, J = 6.2 Hz), 1.35 (3H, s), 1.43 (1H, t, $J \approx$ 1.34 Hz), 1.45 (3H, s), 2.33 (1H, qd, $J \approx$ 12.4, 12.4, 3.5 Hz), 2.59–2.69 (2H, m), 2.80 (1H, dd, $J \approx$ 14, 3.6 Hz), 3.31 (3H, s), 3.39–3.47 (3H, m), 3.56 (3H, s), 4.0 (3H, s), 4.27 (1H, d, J = 3.25 Hz), 6.77 (1H, d, J = 7.9 Hz), 6.97 (1H, s), 7.19 (1H, d, J = 8 Hz), 7.44 (1H, t, $J \approx$ 8 Hz), 15.17 (1H, s). EI HRMS M$^+$ found: 456.2155; $C_{26}H_{32}O_7$ calcd: 456.2148.

2β,3β,11-Trihydroxy-4β,10-dimethoxy-2α-[1′-methoxyethyl]-1,2,3,4,4a,5,12,12a-octahydronaphthacen-12-one (25)

Tetracycle **24** (6.0 mg, 0.013 mmol) dissolved in THF (1 mL) was treated with 1 N aq HCl (0.4 mL) and stirred at rt with monitoring by TLC. After 36 h, the solution was poured into saturated aq $NaHCO_3$ and extracted with dichloromethane (4 × 10 mL). The extracts were combined, dried (Na_2SO_4), and the solvents removed. The residue was chromatographed (ethyl acetate / hexanes, 3:1) to obtain the triol **25**. Yield: 5 mg (91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (3H, d, J = 6.2 Hz), 1.54 (1H, s), 1.60 (1H, t, $J \approx$ 13 Hz), 2.25 (1H, qd, $J \approx$ 12.6, 12.6, 3.4 Hz), 2.57–2.65 (2H, m), 2.69 (1H, dd, $J \approx$ 13.6, 3.55 Hz), 2.79 (1H, s), 3.31 (1H, dd, J = 10.3, 2.7 Hz), 3.34 (3H, s), 3.37 (1H, q, J = 6.3 Hz), 3.49 (3H, s), 3.97 (1H, d, J = 2 Hz), 4.0 (3H, s), 6.78 (1H, d, $J \approx$ 7.9 Hz), 6.96 (1H, s), 7.18 (1H, d, J = 8 Hz), 7.45 (1H, t, J = 8 Hz), 15.07 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.5, 28.3, 33.4, 37.3, 45.7, 56.2, 57.0, 57.3, 69.7, 75.2, 79.7, 83.3, 105.5, 111.3, 115.1, 116.8, 119.8, 130.9, 137.7, 140.2, 159.8, 165.7, 204.3. EI HRMS M$^+$ found: 416.1832; $C_{23}H_{28}O_7$ calcd: 416.1835.

2β,11-Dihydroxy-4β,10-dimethoxy-2α-[1′-methoxyethyl]-1,2,3,4,4a,5,12,12-octahydronaphthacene-3,12-dione (26)

Triol **25** (5 mg, 0.012 mmol) in acetonitrile (1 mL) was heated to 70° with *o*-iodobenzoic acid and the progress of the reaction monitored by TLC. After 18 h, almost all the starting material had been consumed. The solvents were removed and the residue was chromatographed (ethyl acetate / hexanes, 4:1). The product **26** was isolated, but a small amount of starting material **25** also remained. Yield: 3.5 mg (70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (3H, d, J = 6.2 Hz), 2.27–2.35 (2H, m), 2.86 (1H, td, J = 13, 13, 1 Hz), 3.17 (1H, td, J = 12.5, 12.5, 3.7 Hz), 3.35 (3H, s), 3.41 (1H, q, J = 6.2 Hz), 3.44 (1H, dd, J = 15.8, 3.5 Hz), 3.56 (3H, s), 3.88 (1H, s), 4.0 (3H, s), 4.11 (1H, d, J = 11.1 Hz), 6.80 (1H, d, J = 8 Hz), 6.97 (1H, s), 7.19 (1H, d, J = 8.3 Hz), 7.47 (1H, t, J = 8 Hz), 14.99 (1H, s). EI HRMS M$^+$ found: 414.1687; $C_{23}H_{26}O_7$ calcd: 414.1679.

2,11-Dihydroxy-10-methoxy-2-hydroxy-2-(1′-methoxyethyl)-3,4-di-*O*-isopropylidene-2,3,4,5,12-hexahydronaphthacene-12-one (27)

To an oven-dried vial containing **21c** (10.4 mg, 0.020 mmol) dissolved in anhydrous THF (0.40 mL) was added a THF solution of TBAF (1 mol/L, 0.40 mL, 0.040 mmol) at 0 °C. The reaction mixture was stirred in darkness for 4.5 h at 0 °C and then at 25 °C for 18 h. The reaction was quenched by the addition of H_2O (0.30 mL) and purified directly by flash column chromatography using silica gel. The desired product was eluted using EtOAc/hexanes (2:3) to afford intermediate **27** (6.0 mg, 0.014 mmol, 70%) as a yellow-orange solid and crystallized from methylene chloride / hexane. $[\alpha]_D$ = –345 ($CHCl_3$). R_f 0.49 (EtOAc/hexanes, 2:3). ^{1}H NMR ($CDCl_3$, 500 MHz): data are shown in Table 1. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.7, 25.4, 27.4, 34.5, 39.0, 56.2, 56.8, 72.6, 76.8, 79.8, 80.6, 105.8, 109.3, 111.7, 115.2, 116.5, 119.9, 131.4, 135.3, 136.5, 138.1, 140.4, 159.9, 167.2, 189.7. EI HRMS calcd for $C_{25}H_{28}O_7$ *m/z*: 440.1835; found: 440.1837.

11,12a-Dihydroxy-10-methoxy-3,4-di-*O*-isopropylidene-2-(1′-methoxyethyl)-3,4,4a,5,11,12a-hexahydronaphthacen-12-one (28)

The enone **27** (16 mg, 0.036 mmol) dissolved in dry dichloromethane (5 mL) was treated with methylamine (0.2 mL) and DMAP (4 mg). The solution was cooled to 0 °C and methanesulfoxyl chloride (0.5 mL) was added. The mixture was stirred at 0 °C for 0.5 h and monitored by TLC for the disappearance of the starting material. It was poured into cold aqueous sodium bicarbonate and the solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and the residue chromatographed on silica (ethyl acetate / hexanes, 1:2). The greenish yellow fluorescent fraction, slightly slower on the TLC than **22** or **27**, was collected and evaporated. Further purification by column chromatography (dichloromethane/hexane, 85:15) resulted in the collection of a product that showed a single spot on the TLC, but still appeared to be contaminated by ~10% of an impurity (^{1}H and ^{13}C NMR). ^{1}H NMR ($CDCl_3$, 500 MHz): data are shown in Table 1. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.2, 19.2, 25.7, 27.1, 28.1, 41.8, 56.2, 56.5, 70.8, 71.7, 75.5, 77.4, 105.7, 105.9, 109.6, 109.7, 115.0, 117.2, 119.8, 124.9, 131.5, 137.3, 159.8, 163.7, 199. EI HRMS M$^+$ found: 440.1832; $C_{25}H_{28}O_7$ calcd: 440.1835.

Supplementary data

Supplementary data (general experimental methods; copies of ^{1}H NMR spectra for compounds **16a**, **16b**, **17a**–**17d**, **18a**–**18d**, **21c**, and **22**–**28**; ^{13}C or JMOD spectra for compounds **16a**, **16b**, **17a**–**17d**, **18a**, **18c**, **21c**, **22**, **23**, **25**, **27**, and **28**; H–H COSY spectrum for compound **28**; EIMS for compound **28**; and HPLC traces of compound **16a**) are available for this article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/v11-119. CCDC 814893–814898 contain the X-ray data (**17a**, **17b**, **18b**, **23**, **27**, and catalyst

B) in CIF format for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1Ez, UK; fax +44 1223 336033; or e-mail deposit@ccdc.cam.ac.uk).

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