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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 18):[1] Demethylation and Methylation of the C-8 Position of the Decalin Portion of Azadirachtin.

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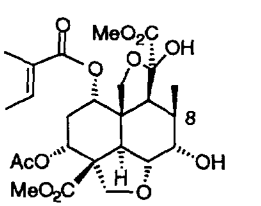
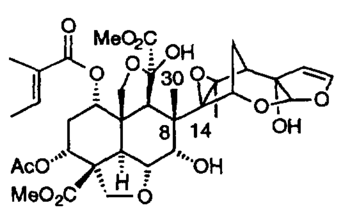
***Abstract*:** The degradation of azadirachtin (1) to the demethylated decalin 4 and the subsequent remethylation to the protected fragment 5 are described. The crucial steps in the degradation sequence were the decarbonylation of 14 and the selective removal of the hydroxy group at C8 in 16. Reaction of the silyl enolether of 4 with Eschenmoser's salt and subsequent reduction of enone 24 gave 5.

Introduction

Azadirachtin (1) is a naturally occurring compound, which was isolated from *Azadirachta Indica* A Juss (the Indian neem tree).[2] It is a potent insect antifeedant, growth disruptant and possesses anti-malaria activity.[3] However, it has also been shown to be non-toxic for mammals, non-mutagenic and biodegradable. Although readily available from natural resources, the fact that this molecule contains a plethora of oxygen functionality and sixteen stereocentres, seven of which are quaternary, makes it a challenging target for synthetic chemistry.



2 left-hand decalin fragment



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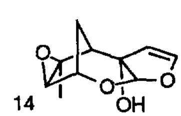
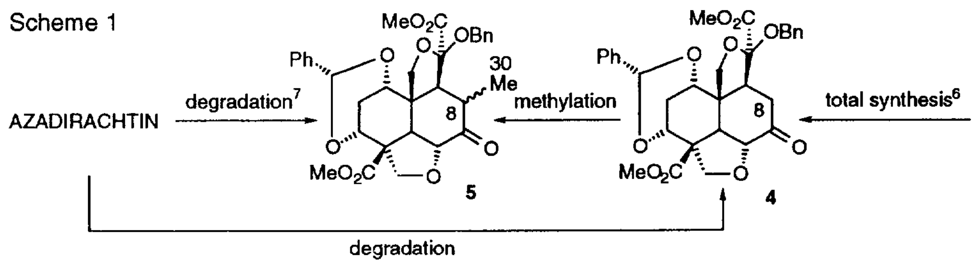


3 right-hand hydroxyfuran acetal

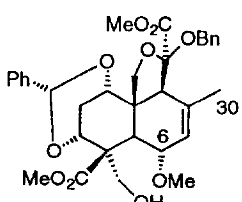
Over the past few years an intensive study has been carried out in these laboratories towards the total synthesis of azadirachtin,[4] and more recently for the preparation of various model compounds of azadirachtin in order to find simple analogues displaying similar biological activity.[1] The projected synthesis of azadirachtin consists of a separate preparation of the left-hand decalin fragment 2 and the right-hand hydroxyfuran acetal fragment **3**, the crucial step being the formation of the C8-C14 bond between these two fragments. The synthesis of suitably protected units equivalent to **3** is complete.[5] Furthermore, a synthesis of decalin **4** has been developed, which contains most of the required functionalities, but lacks a methyl group (C30) at C8.[6] Although it was initially planned that this C30 methyl might be introduced after the coupling of the right-hand furan acetal fragment with **4**, we later also required quantities of the methylated decalin **5**. In order to make **4** and **5** more accessible, we devised a degradation route from azadirachtin. Previously, we established a degradation route to **5**, which was efficient,[7] although a degradation route directly to **4** was not available. This paper therefore deals with the demethylation **5** and the subsequent remethylation of **4**, thereby not only connecting the total synthesis- and degradation route but also giving ready access to **4** for possible coupling studies with the right-hand side and the synthesis of important model compounds (Scheme 1).

Scheme 1

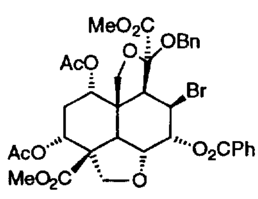


Demethylation Studies

Previous research indicated that it is very difficult to oxidise the C30 methyl of **5** to an aldehyde in the presence of the ketone functional group.[8] We therefore decided to remove the carbonyl group by introduction of a C7-C8 double bond *via* a Shapiro reaction.[9] Treatment of dihydroxyketone **6** with tosylhydrazide and a catalytic amount of *p*-TsOH in methanol gave hydrazone **7** in 60% yield (Scheme 2). As the tosylhydrazone group in **7** failed to eliminate under several basic reaction conditions, the diol moiety of **7** was protected as its benzylidene acetal **8**. When this protected hydrazone **8** was stirred in a boiling solution of sodium methoxide in methanol, the desired elimination product **9** was obtained in 79% yield along with a minor side product. This side product was thought to be compound **10**, which could arise by a substitution reaction at C6 after the elimination of the tosylhydrazone group. The assignment of the stereochemistry at C6 of **10** was based on the coupling constant $J_{H5\text{-}H6}$ = 10.8 Hz, indicating that H6 was in the axial position.



10



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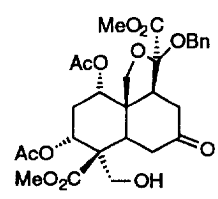

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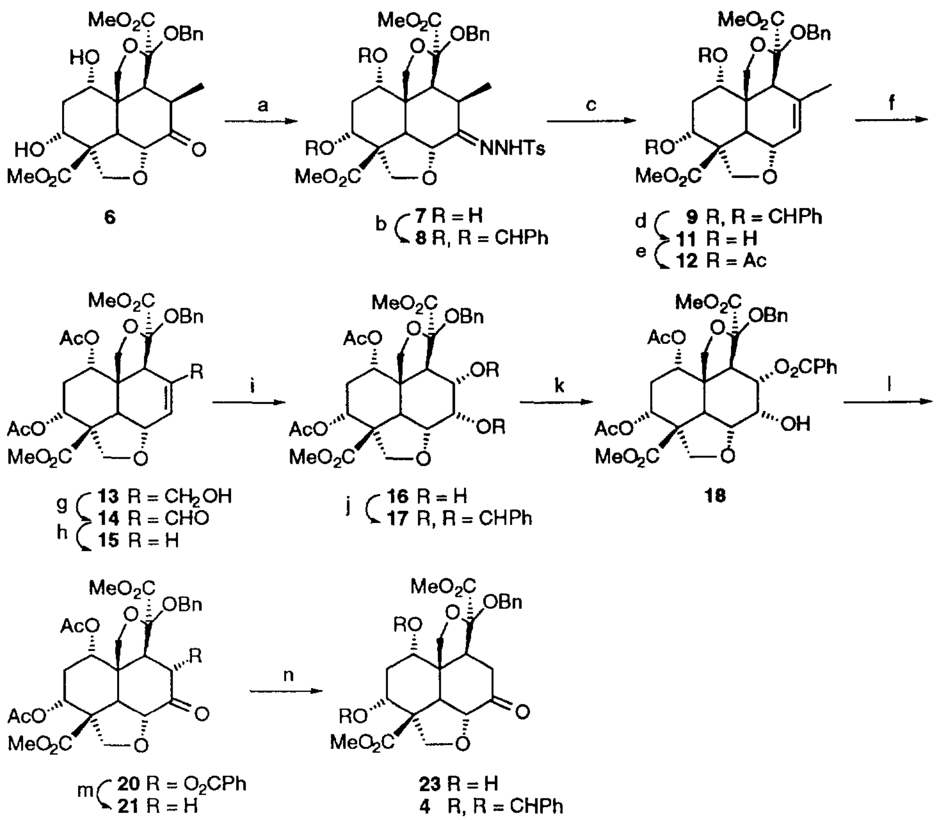
As the C30 methyl substituent is allylic, selenium dioxide was used as the reagent to effect its oxidation.[10] Firstly, the benzylidene protecting group in **9** was removed by acidic aqueous methanol to give **11**, as this was not stable to treatment with selenium dioxide. The hydroxy groups of **11** were then reprotected as their acetates **12**. Both the deprotection and the acylation reactions proceeded very smoothly giving **12** in 85% yield over the two steps. Oxidation with selenium dioxide/*tert*-butylperoxide in dichloromethane at 35 °C gave the allylic alcohol **13** but in only 30% yield while 65% of **12** was recovered intact. However, when the oxidation was carried out in 1,2-dichloroethane at 80 °C, the α,β-unsaturated aldehyde **14** was obtained in 60-80% yield together with **13** in 30-10% yield. Subsequent oxidation of **13** to **14** with pyridinium chlorochromate proceeded smoothly.

Scheme 2



a) $TsNHNH_2$, pTsOH.H_2O, MeOH, 60%. b) $PhCH(OMe)_2$, PPTS, PhH, Dean-Stark, 91%. c) MeONa, MeOH, reflux, 79%. d) H_2O, H_2SO_4, MeOH, 92%. e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 92%. f) SeO_2, t-BuO_2H, $ClCH_2CH_2Cl$, 80 °C, **14** 60% and **13** 30%. g) PCC, 4Å mol sieves, CH_2Cl_2, 81%. h) $RhCl(PPh_3)_3$, PhCN, 130 °C, 70%. i) OsO_4, t-BuOH, H_2O, 80 °C, 83%. j) $PhCH(OMe)_2$, PPTS, PhH, Dean-Stark, 90%. k) NBS, hv, H_2O, $BaCO_3$, CCl_4, 50%. l) PCC, 4Å mol sieves, CH_2Cl_2, 84%. m) SmI_2, THF, MeOH, -110°C → r.t., 79%. n) 1) MeONa, MeOH. 2) $PhCH(OMe)_2$, PPTS, PhH, Dean-Stark, 83% over 2 steps.

The aldehyde function in **14** was removed in the presence of Wilkinson's catalyst ($RhCl(PPh_3)_3$).[11] To drive this decarbonylation reaction to completion the reaction was performed at 130 °C in benzonitrile with three equivalents of the rhodium complex. In this way, **15** was obtained in 70% yield.

Now that the C30 methyl had been removed, we needed to reintroduce the oxygen functionality at C7. However, regioselective hydroxylation reactions such as borane additions, oxymercuration and halohydrin formation reactions afforded the wrong regioisomer or failed to work. As this regioselective hydroxylation process was unsuccesful, we devised an alternative sequence. The *cis*-hydroxylation of **15** in the presence of a stoichiometric amount of osmium tetroxide worked well, affording diol **16** in 83% yield. Any trace of phosphonium compounds present from the previous reaction were also removed during this step and aided reaction clean-up.

With **16** in hand, we first tried to selectively oxidize the hydroxy group at C7. However, both Swern oxidation of **16** and consecutive treatment of **16** with dibutyldimethoxy tin and bromine,[12] resulted in mixtures of the hydroxyketones in very low yield. Eventually, the diol was protected as its benzylidene acetal by treatment of **16** with the dimethoxy acetal of benzaldehyde in the presence of PPTS, to give **17** as an inseparable 4:1 mixture of diastereoisomers in high yield. It was reasoned that the major product was the α-isomer, because of the large upfield shift in ^1H NMR of one the acetoxy groups. Pleasingly, oxidation of the benzylidene acetal with NBS afforded **18** in 50% yield, along with some side products of which the major one was thought to be **19** (*ca.* 20%).[13] The succinimide formed in this reaction also co-ran with **18**, but did not interfere in the subsequent oxidation reaction (*vide infra*). The obtained selectivity in this ring opening oxidation was somewhat puzzling as the literature indicated a preference for the benzoate to be formed on the axially orientated hydroxy group.[14] A possible explanation might be that the benzoate was formed at C7 first, but migrated to the neighbouring hydroxy group under the reaction conditions or during work-up. The formation of **19**, in which the benzoate is positioned at C7, seems to be in agreement with this explanation. However, the formation of **18** was advantageous for our synthesis, as the hydroxy group at C8 was protected as a benzoate while the hydroxy group at C7 was available for oxidation.

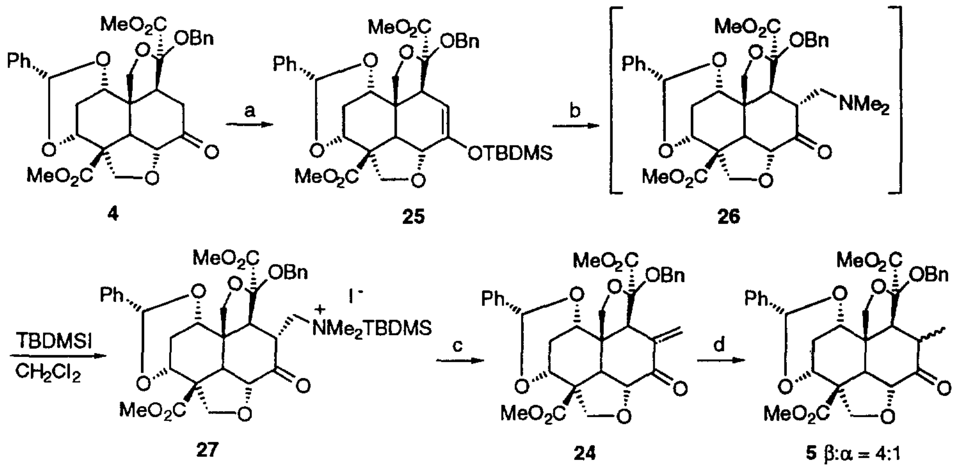
Pyridinium chlorochromate was used for the oxidation of **18** to **20**. The purified α-benzoate ketone **20** was then treated with samarium(II)iodide to remove the α-benzoate group.[15] We were pleased to find that the benzoate was removed selectively to give **21** in good yield, although a sideproduct was formed in this reaction. On the basis of ^1H NMR, we assumed that this product was **22** but it was not fully characterised. Its formation was probably due to further reaction of **21** with samarium(II)iodide, as it is known that samarium(II)iodide is also able to remove alkoxy functions α to the ketone function. However, no products containing the benzoate functionality were detected.

Finally, the ketone **21** was converted into the benzylidene protected ketone **4** by consecutive deprotection with sodium methoxide in methanol and reprotection with the dimethoxy acetal of benzaldehyde in the presence of PPTS. The intermediate diol **23** was not purified and the crude product was used for the next reaction, affording **4** in an overall yield of 83%. Spectral data of ketone **4** were identical to those obtained from the ketone synthesised previously by our group, except for a small difference between the optical rotations.[6c] The original ketone had an optical rotation $[\alpha]^{19}_D$ -25.5 (*c* 0.51, $CHCl_3$), while the new sample had an optical rotation $[\alpha]^{30}_D$ -30.4 (*c* 0.75, $CHCl_3$).

Methylation Studies

After succeeding in the demethylation of the left-hand side, the only missing piece in the connection of the total synthesis of the left-hand side and the degradation of azadirachtin was the remethylation of **4**. As the acetal ring will shield the β face of the decalin fragment for direct methylation, it was decided that the best way to introduce the methyl group in the β position at C8 might be *via* the enone **24** followed by the hydrogenation of the *exo* methylene double bond.[16] A well known method to introduce a methylene function α to a ketone, is the alkylation of the ketone with Eschenmoser's salt and subsequent elimination of the dimethylamino group by quaternisation.[17] Unfortunately, treatment of **4** with potassium hydride or LHMDS followed by quenching with Eschenmoser's salt, only resulted in the recovery of starting material. When LDA was used as base, only baseline products were formed. Therefore, we decided to modify the reaction. First, the *tert*-butyldimethylsilyl enolether **25** was made using *tert*-butyldimethylsilyl triflate and triethylamine in acetonitrile (Scheme 3). Subsequently, the enolether **25** was reacted with Eschenmoser's salt in dichloromethane.[18] It appeared that as soon as dimethylaminoketone **26** was formed, it reacted with the liberated *tert*-butyldimethylsilyl iodide, resulting in the formation of dimethylammonium salt **27**. However, the alkylation reaction proceeded very sluggishly and there was still some enolether present after stirring for 2 days at 35 °C. After aqueous work-up, the crude product mixture was not purified further, instead it was dissolved in a slurry of silica and dichloromethane. After stirring overnight, this mixture gave the desired enone **24** in 68% yield from **25** together with recovered **25** (25%). Finally, reduction of **24** in the presence of Pd/C gave **5** as a 4:1 mixture of the β and α isomer in 60% yield.[19]

Scheme 3



a) TBDMSOTf, Et_3N, CH_3CN, 77%. b) $CH_2{=}N(Me)_2^+$ I^-, CH_2Cl_2, 35 °C. c) SiO_2, CH_2Cl_2, 68% over 2 steps. d) H_2, 10% Pd/C, MeOH, 60%.

In conclusion we have established a degradation route from azadirachtin to the demethylated left-hand decalin **4**. Furthermore, we have been able to synthesise left-hand fragment **5** from **4** thereby connecting our research on the total synthesis and degradation of azadirachtin. Additionally, this work also provides useful compounds for biological evaluation.

Acknowledgement: We thank the Niels Stensen Foundation for a Research Fellowship (to W.-J.K), and Ciba Central Research Basel together with the BP endowment (to S.V.L.) at Cambridge for further financial support.

Experimental

General information. Infrared spectra were obtained from films using a Perkin Elmer 1600 Series FTIR and are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in $CDCl_3$ unless otherwise stated, using a Bruker AM 200 (200 MHz) or Bruker AM 400 (400 MHz). Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as internal reference. ^{13}C NMR spectra were recorded on the same instruments (50 or 100 MHz, respectively) in $CDCl_3$, using $CDCl_3$ as internal reference (δ_C = 77.0 ppm). Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Mass spectra were recorded on a Kratos MS890MS spectrometer. Flash chromatography was performed on Merck 9385 Kieselgel 60 silica (230-400 mesh). All reactions were carried out under argon unless stated otherwise. Diethyl ether and THF solvents were distilled from sodium-benzophenone ketyl; CH_2Cl_2, toluene and acetonitrile from calcium hydride and methanol from magnesium methoxide.

[2a*R*, 4*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-dihydroxy-4-methyl-3-(*p*-toluene)sulfonylhydrazonoperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 7. A solution of **6** (354 mg, 0.72 mmol), $TsNHNH_2$ (400 mg, 2.15 mmol) and *p*-$TsOH{\cdot}H_2O$ (34 mg, 0.18 mmol) in MeOH (12 mL) was stirred for 19 h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ (50 mL) and the water layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:1 → 4:1) gave **7** (284 mg, 0.43 mmol) in 60% yield as a white foam. IR: 3484, 3237, 2952, 1750, 1727, 1166, 1092, 1060; ^1H NMR (400 MHz): 8.80 (broad s, 1 H, N-H), 7.86 (d, 1 H, *J* 8.2 Hz, *o*-C_6H_4-SO_2), 7.20 - 7.40 (m, 7 H, Ph & *m*-C_6H_4-SO_2), 4.78 (d, 1 H, *J* 11.6 Hz, *H*CH-Ph), 4.38 (d, 1 H, *J* 11.6 Hz, HC*H*-Ph), 4.33 (m, 1 H, H-3), 4.26 (d, 1 H, *J* 13.3 Hz, H-6), 3.91 (m, 3 H, 2 × H-28 & H-1), 3.78 (s, 3 H, CO_2Me), 3.46 (d, 1 H, *J* 9.6 Hz, H-19), 3.38 (s, 3 H, CO_2Me), 3.31 (d, 1 H, *J* 9.4 Hz, H-19'), 2.92 (d, 1 H, *J* 5.8 Hz, H-9), 2.73 (d, 1 H, *J* 13.3 Hz, H-5), 2.54 (m, 1 H, H-8), 2.41 (s, 3 H, Ar-CH_3), 2.26 (dt, 1 H, *J* 15.7, 2.6 Hz, H-2), 2.19 (dt, 1 H, *J* 15.8, 1.8 Hz, H-2'), 2.24 (d, 3 H, *J* 6.6 Hz, C30 Me); ^{13}C NMR (100 MHz): 173.8, 169.3, 158.1, 143.5, 137.3, 136.2, 129.4 (2 × C), 128.7 (2 × C), 128.0 (2 × C), 127.7 (2 × C), 106.1, 73.3, 73.0, 72.5, 68.1, 67.1, 65.6, 56.6, 52.8, 52.5, 52.0, 46.9, 40.0, 37.3, 36.1, 35.2, 21.6, 13.3; exact mass spectrum, calcd for $C_{32}H_{39}N_2O_{11}S$ (M^+ + H) *m/e* 659.22743, found *m/e* 659.22500.

[2a*R*, 4*R*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-4-methyl-8,10-phenylmethylenedioxy-3-(*p*-toluene)sulfonylhydrazonoperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 8. A solution of **7** (346 mg, 0.52 mmol), $PhCH(OMe)_2$ (1.5 mL, 10 mmol) and PPTS (13 mg, 0.05 mmol) in benzene (50 mL) was boiled for 20 min using a Dean-Stark trap and 4Å mol sieves to remove the water. The reaction was poured into saturated aqueous $NaHCO_3$ (50 mL) and the water layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:3 → 2:1) gave **8** (353 mg, 0.47 mmol) in 91% as a white foam. IR: 3256, 2953, 2902, 1749, 1730, 1453, 1167, 1111, 1056; ^1H NMR (200 MHz): 8.61 (broad s, 1 H, N-H), 7.90 (d, 2 H, *J* 8.2 Hz, *o* -C_6H_4-SO_2), 7.21 - 7.44 (m, 12 H, 2 × Ph & *m*-C_6H_4-SO_2), 6.20 (s, 1 H, CH-Ph), 4.78 (d, 1 H, *J* 4.6 Hz, H-3), 4.77 (d, 1 H, *J* 11.4 Hz, *H*CH-Ph), 4.45 (d, 1 H, *J* 11.6 Hz, HC*H*-Ph), 4.38 (d, 1 H, *J* 4.2 Hz, H-1), 4.28 (d, 1 H, *J* 13.8 Hz, H-6), 3.89 (d, 1 H, *J* 8.4 Hz, H-28), 3.83 (d, 1 H, *J* 8.4 Hz, H-28'), 3.78 (s, 3 H, CO_2Me), 3.71 (d, 1 H, *J* 9.8 Hz, H-19), 3.55 (d, 1 H, *J* 9.9 Hz, H-19'), 3.50 (s, 3 H,

CO_2Me), 3.22 (d, 1 H, *J* 13.6 Hz, H-5), 2.99 (d, 1 H, *J* 5.9 Hz, H-9), 2.95 (dt, 1 H, *J* 15.9, 4.7 Hz, H-2), 2.69 (m, 1 H, H-8), 2.41 (s, 3 H, Ar-CH_3), 1.80 (d, 1 H, *J* 15.9 Hz, H-2'), 1.24 (d, 3 H, *J* 6.7 Hz, C30 Me); ^{13}C NMR (100 MHz): 173.1, 169.2, 158.7, 143.4, 137.4, 136.4, 129.7, 129.3 (2 × C), 128.7 (2 × C), 128.6 (2 × C), 128.0 (2 × C), 127.9 (2 × C), 127.6, 126.1 (2 × C), 106.3, 93.1, 74.6, 72.5, 71.7, 68.6, 67.8, 65.8, 56.0, 53.6, 53.4, 52.7, 52.2, 47.9, 39.9, 36.4, 24.4, 21.6, 13.3; exact mass spectrum, calcd for $C_{39}H_{43}N_2O_{11}S$ (M^+ + H) *m/e* 747.25873, found *m/e* 747.26300.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-4-methyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydro-8,10-phenylmethylenedioxynaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 9. A solution of tosylhydrazone **8** (449 mg, 0.60 mmol) and MeONa (3 mL of 1 M solution in MeOH, 3 mmol) in MeOH (150 mL) was heated at reflux for 18 h. The resulting cooled solution was poured into saturated aqueous $NaHCO_3$ (150 mL), and the water layer was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:2 → 1:1 → 2:1) gave in order of elution **9** (268 mg, 0.48 mmol) in 79% yield as a white foam and **10** (35 mg, 0.06 mmol) in 10% yield as a white foam. For **9**: IR: 3032, 2952, 2893, 1747, 1453, 1296, 1244, 1200, 1118; ^1H NMR (400 MHz): 7.23 - 7.41 (m, 10 H, 2 × Ph), 6.19 (d, 1 H, *J* 1.2 Hz, H-7), 6.16 (s, 1 H, CH-Ph), 4.78 (d, 1 H, *J* 4.6 Hz, H-3), 4.64 (d, 1 H, *J* 12.2 Hz, *H*CH-Ph), 4.53 (d, 1 H, *J* 12.1 Hz, HC*H*-Ph), 4.51 (dd, 1 H, *J* 1.2, 11.6 Hz, H-6), 4.43 (d, 1 H, *J* 4.4 Hz, H-1), 4.03 - 4.08 (m, 3 H, 2 × H-28 & H-19), 3.77 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 3.67 (d, 1 H, *J* 10.3 Hz, H-19'), 3.39 (s, 1 H, H-9), 3.04 (d, 1 H, *J* 11.8 Hz, H-5), 2.93 (dt, 1 H, *J* 15.7, 4.8 Hz, H-2), 1.90 (s, 3 H, C30 Me), 1.72 (d, 1 H, *J* 15.7 Hz, H-2'); ^{13}C NMR (100 MHz): 173.8, 170.0, 138.9, 138.0, 134.8, 129.4, 128.5 (2 × C), 128.2 (2 × C), 127.1 (2 × C), 126.8, 126.6 (2 × C), 105.0, 93.6, 72.5, 72.0, 71.4, 69.1, 67.8, 65.3, 56.3, 55.6, 52.8, 52.2, 49.6, 42.6, 23.8, 23.7 (2 × C); exact mass spectrum, calcd for $C_{32}H_{33}O_9$ (M^+ - H) *m/e* 561.21244, found *m/e* 561.20960; exact mass spectrum, calcd for $C_{32}H_{35}O_9$ (M^+ + H) *m/e* 563.22809, found *m/e* 563.23140. For **10**: IR: 3426, 2952, 1748, 1736, 1726, 1454, 1436, 1396, 1221, 1114; ^1H NMR (400 MHz): 7.27 - 7.43 (m, 10 H, 2 × Ph), 6.09 (s, 1 H, CH-Ph), 5.84 (s, 1 H, H-7), 4.82 (d, 1 H, *J* 4.3 Hz, H-3), 4.63 (d, 1 H, *J* 12.1 Hz, *H*CH-Ph), 4.53 (d, 1 H, *J* 10.9 Hz, H-6), 4.44 (d, 1 H, *J* 3 Hz, H-1), 4.43 (d, 1 H, *J* 12.1 Hz, HC*H*-Ph), 4.01 (d, 1 H, *J* 6.7 Hz, OH), (d, 1 H, *J* 10.3 Hz, H-19), 3.87 (m, 2 H, 2 × H-28), 3.75 (s, 3 H, CO_2Me), 3.73 (s, 3 H, CO_2Me), 3.65 (d, 1 H, *J* 10.3 Hz, H-19'), 3.45 (s, 3 H, OMe), 3.31 (s, 1 H, H-9), 2.86 (d, 1 H, *J* 10.8 Hz, H-5), 2.84 (m, 1 H, H-2), 1.95 (d, 1 H, *J* 15.8 Hz, H-2'), 1.90 (broad s, 3 H, C30 Me); ^{13}C NMR (100 MHz): 173.1, 170.3, 138.2 (2 × C), 132.2, 129.2, 128.4 (2 × C). 128.2 (2 × C), 127.4, 127.2, 126.9 (2 × C), 126.7 (2 × C), 104.6, 92.4, 75.9, 74.0, 71.5, 69.9, 68.4, 65.5, 56.4, 55.9, 55.6, 52.8, 52.0, 51.9, 41.9, 23.0, 22.2; exact mass spectrum, calcd for $C_{33}H_{37}O_{10}$ (M^+ - H) *m/e* 593.23865, found *m/e* 593.23740.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-dihydroxy-4-methyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 11. A solution of **9** (180 mg, 0.32 mmol), H_2O (0.75 mL, 42 mmol) and 2 drops of H_2SO_4 (98%) in MeOH (40 mL) was stirred for 20 min. The resulting solution was quenched with saturated aqueous $NaHCO_3$ (60 mL) and the water layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:1 → EtOAc) gave **11** (140 mg, 0.30 mmol) in 92% yield as a white foam. IR: 3374, 2952, 1747, 1728, 1435, 1259, 1112, 1095, 1057; ^1H NMR (400 MHz): 7.22 - 7.33 (m, 5 H, Ph), 6.09 (s, 1 H, H-7), 4.59 (d, 1 H, *J* 12.3 Hz, *H*CH-Ph), 4.54 (d, 1 H, *J* 12.3 Hz, HC*H*-Ph), 4.52 (d, 1 H, *J* 12 Hz, H-6), 4.44 (m, 1 H, H-3), 4.12 (d, 1 H, *J* 8.5 Hz, H-28), 4.02 (d, 1 H, *J* 8.5 Hz, H-28'), 3.97 (m, 1 H, H-1), 3.79 (s, 3 H, CO_2Me), 3.78 (broad d, 1 H, *J* 7 Hz, OH), 3.75 (d, 1 H, *J* 9.9 Hz, H-19), 3.62 (s, 3 H, CO_2Me), 3.58 (m, 1 H, OH), 3.48 (d, 1 H, *J* 9.7 Hz, H-19'), 3.35 (s, 1 H, H-9), 2.44

(d, 1 H, *J* 11.5 Hz, H-5), 2.26 (dt, 1 H, *J* 15.6, 2.7 Hz, H-2), 2.07 (dt, 1 H, *J* 15.6, 2.4 Hz, H-2'), 1.85 (s, 3 H, C30 Me); ^{13}C NMR (100 MHz): 174.4, 170.4, 138.4, 134.4, 128.5, 128.2 (2 × C), 127.2, 126.8 (2 × C), 105.2, 72.9, 72.6, 70.8, 68.2, 67.9, 65.5, 56.7, 54.5, 52.9, 52.1, 48.7, 43.0, 34.5, 23.6; exact mass spectrum, calcd for $C_{25}H_{29}O_9$ (M^+ - H) *m/e* 473.18114, found *m/e* 473.18510; exact mass spectrum, calcd for $C_{25}H_{31}O_9$ (M^+ + H) *m/e* 475.19679, found *m/e* 475.19940.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S* , 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-4-methyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c*']difuran-5,10a-dicarboxylate 12. A solution of **11** (200 mg, 0.42 mmol), pyridine (780 µL, 9.6 mmol), acetic anhydride (460 µL, 4.88 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (30 mL) was stirred for 2.5 h. The resulting solution was poured into saturated aqueous $NaHCO_3$ (30 mL) and the water layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:2 → 2:1) gave **12** (216 mg, 0.39 mmol) in 92% yield as a white foam. IR: 3029, 2953, 2897, 1744, 1437, 1376, 1247, 1115, 1045; ^1H NMR (400 MHz): 7.22 - 7.33 (m, 5 H, Ph), 6.11 (d, 1 H, *J* 1 Hz, H-7), 5.45 (t, 1 H, *J* 2.8 Hz, H-3), 5.07 (t, 1 H, *J* 2.8 Hz, H-1), 4.61 (d, 1 H, *J* 12.3 Hz, *H*CH-Ph), 4.57 (d, 1 H, *J* 12.3 Hz, HC*H*-Ph), 4.50 (d, 1 H, *J* 1.5, 11.5 Hz, H-6), 4.06 (d, 1 H, *J* 8.8 Hz, H-28), 3.78 (s, 3 H, CO_2Me), 3.76 (d, 1 H, *J* 8.8 Hz, H-28'), 3.63 (s, 3 H, CO_2Me), 3.61 (d, 1 H, *J* 9.8 Hz, H-19), 3.57 (d, 1 H, *J* 9.8 Hz, H-19'), 2.97 (s, 1 H, H-9), 2.53 (d, 1 H, *J* 11.6 Hz, H-5), 2.40 (dt, 1 H, *J* 16.8, 2.5 Hz, H-2), 2.32 (dt, 1 H, *J* 16.8, 3.3 Hz, H-2'), 2.04 (s, 3 H, CH_3-CO), 2.03 (s, 3 H, CH_3-CO), 1.83 (s, 3 H, C30 Me); ^{13}C NMR (100 MHz): 173.5, 169.7, 169.6, 169.5, 138.4, 133.8, 128.2 (2 × C), 128.1, 127.2, 126.8 (2 × C), 105.2, 72.9, 72.3, 71.0, 67.6, 67.5, 65.6, 57.1, 52.8, 52.5, 52.4, 47.0, 46.2, 31.0, 23.6, 21.0 (2 × C); exact mass spectrum, calcd for $C_{29}H_{33}O_{11}$ (M^+ - H) *m/e* 557.20227 found *m/e* 557.19920.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-4-hydroxymethyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c*']difuran-5,10a-dicarboxylate 13 and [2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] dimethyl 5-benzyloxy-8,10-diacetoxy-4-formyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c*']difuran-5,10a-dicarboxylate 14. A solution of **12** (208 mg, 0.37 mmol), SeO_2 (257 mg, 2.32 mmol) and *t*-BuO_2H (260 µL of 3 M in *i*-octane, 0.78 mmol) in 1,2-dichloroethane (7 mL) was stirred at 80 °C for 3 h. The resulting solution was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the water layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:3 → 2:1 → EtOAc → acetone) gave, in order of elution, **14** (128 mg, 0.22 mmol) in 60% yield as a white foam and **13** (65 mg, 0.11 mmol) in 30% yield as a white foam. (Over several reactions, the yield of **14** varied from 60% to 80% and the yield of **13** from 10% to 30% but the overall yield was always 90%) For **14**: IR: 2955, 1744, 1686, 1436, 1376, 1246, 1045; ^1H NMR (400 MHz): 9.46 (s, 1 H, CHO), 7.18 - 7.32 (m, 6 H, Ph & H-7), 5.46 (t, 1 H, *J* 2.7 Hz, H-3), 5.12 (t, 1 H, *J* 2.6 Hz, H-1), 4.72 (d, 1 H, *J* 12.1 Hz, H-6), 4.71 (d, 1 H, *J* 12.1 Hz, *H*CH-Ph), 4.48 (d, 1 H, *J* 12.1 Hz, HC*H*-Ph), 4.09 (d, 1 H, *J* 8.8 Hz, H-28), 3.82 (s, 3 H, CO_2Me), 3.76 (d, 1 H, *J* 8.8 Hz, H-28'), 3.73 (s, 1 H, H-9), 3.59 (d, 1 H, *J* 9.7 Hz, H-19), 3.59 (s, 3 H, CO_2Me), 3.51 (d, 1 H, *J* 9.8 Hz, H-19'), 2.56 (d, 1 H, *J* 12.1 Hz, H-5), 2.43 (dm, 1 H, *J* 16.8 Hz, H-2), 2.34 (dt, 1 H, *J* 16.8, 3.3 Hz, H-2'), 2.03 (s, 3 H, CH_3-CO), 1.99 (s, 3 H, CH_3-CO); ^{13}C NMR (100 MHz): 192.3, 173.0, 169.6 (2 × C), 168.2 , 151.1, 139.8, 138.4, 128.3 (2 × C), 127.4, 127.3 (2 × C), 104.6, 73.5, 72.6, 71.1, 67.6, 67.2, 66.0, 52.9, 52.7, 51.9, 50.5, 46.6, 46.0, 31.0, 21.0 (2 × C); exact mass spectrum, calcd for $C_{29}H_{33}O_{12}$ (M^+ + H) *m/e* 573.19718, found *m/e* 573.20020. For **13**: IR: 3582, 3454, 2954, 1743, 1436, 1376, 1247, 1045; ^1H NMR (200 MHz): 7.25 - 7.37 (m, 5 H, Ph), 6.36 (s, 1 H, H-7), 5.46 (t, 1 H, *J* 2.8 Hz, H-3), 5. 12 (t, 1 H, *J* 2.8 Hz, H-1), 4.63 (d, 1 H, *J* 12.1 Hz, *H*CH-Ph), 4.55 (d, 1 H, *J* 12.1 Hz, HC*H*-Ph), 4.54 (d, 1 H, *J* 11.6 Hz, H-6), 4.31 (broad dd, 1 H, *J* 6.4, 13.0 Hz, *H*CH-OH), 4.08 (d, 1 H, *J* 8.8 Hz, H-28), 4.07 (obscured, 1 H, HC*H*-OH), 3.80 (s, 3 H, CO_2Me), 3.78 (d, 1 H, *J* 8.8 Hz, H-28'), 3.69 (d, 1 H, *J* 9.8 Hz, H-19), 3.67 (s, 3 H, CO_2Me), 3.61 (d, 1 H, *J* 9.8 Hz, H-19'), 3.36 (s, 1 H, H-9), 2.57 (d, 1 H, *J* 11.6 Hz, H-5), 2.41 (dt, 1 H, *J* 16.9, 2.8 Hz, H-2), 2.30 (dt, 1 H, *J* 16.9, 2.8 Hz, H-2'), 2.17 (t, 1 H, *J* 6.6 Hz, OH), 2.06 (s, 3 H, CH_3-CO), 2.04 (s, 3 H, CH_3-CO); ^{13}C NMR (50 MHz): 173.8, 170.2, 169.8, 168.7, 137.4, 128.6 (2 × C), 127.9, 127.7 (2 × C), 105.3, 74.1, 72.4, 71.5, 67.4, 67.1, 66.0, 65.8, 63.3, 56.8, 53.2, 52.4, 51.8, 49.6, 48.7, 37.2, 30.7, 21.1, 21.0.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-4-formyl-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 14 from 13. A solution of **13** (16 mg, 0.028 mmol), powdered molecular sieves (4Å, 30 mg), pyridine (40 µL, 0.50 mmol) and PCC (30 mg, 0.139 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 40 min. The resulting mixture was poured into saturated aqueous $NaHCO_3$ (3 mL) and the water layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:2 → 1:1) gave **14** (13 mg, 0.023 mmol) in 81%. For spectroscopic data see previous experiment.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 15. A solution of **14** (48 mg, 0.048 mmol) and $RhCl(PPh_3)_3$ (233 mg, 0.25 mmol) in benzonitrile (4 mL) was stirred at 130 °C for 13 h. The solvent was evaporated and the residue was dissolved in MeOH (25 mL). The resulting mixture was stirred for 20 min then filtered over Florisil/Celite®. The residue was washed with EtOAc/Hexanes (1:1, 100 mL) and the combined organic layers were concentrated *in vacuo*. Purification by flash chromatography (EtOAc:Hex = 2:3) gave **15** (33 mg, 0.061 mmol) in 72% yield as a white solid, slightly contaminated with triphenylphosphine which was inseparable from the product. IR: 2953, 1743, 1436, 1376, 1248, 1045; ^1H NMR (400 MHz): 7.22 - 7.33 (m, 5 H, Ph), 6.35 (dt, 1 H, *J* 10.3, 1.5 Hz, H-7), 5.73 (ddd, 1 H, *J* 2.1, 4.6, 10.3 Hz, H-8), 5.45 (t, 1 H, *J* 2.8 Hz, H-3), 5.04 (t, 1 H, *J* 2.8 Hz, H-1), 4.63 (d, 1 H, *J* 12.2 Hz, *H*CH-Ph), 4.55 (dq, 1 H, *J* 11.5, 1.8 Hz, H-6), 4.47 (d, 1 H, *J* 12.2 Hz, HC*H*-Ph), 4.07 (d, 1 H, *J* 8.9 Hz, H-28), 3.77 (d, 1 H, *J* 8.9 Hz, H-28'), 3.75 (s, 3 H, CO_2Me), 3.74 (d, 1 H, *J* 9.9 Hz, H-19), 3.67 (s, 3 H, CO_2Me), 3.61 (d, 1 H, *J* 9.9 Hz, H-19'), 3.17 (m, 1 H, H-9), 2.62 (d, 1 H, *J* 11.5 Hz, H-5), 2.42 (dt, 1 H, *J* 16.7, 2.5 Hz, H-2), 2.24 (dt, 1 H, *J* 16.7, 3.3 Hz, H-2'), 2.05 (s, 3 H, CH_3-CO), 2.03 (s, 3 H, CH_3-CO); ^{13}C NMR (100 MHz): 173.4, 169.7 (2 × C), 169.2, 138.0, 131.1, 128.3 (2 × C), 127.4, 127.0 (2 × C), 125.6, 104.9, 72.7, 71.9, 70.9, 67.7, 67.5, 65.8, 52.8, 52.6 (2 × C), 52.1, 47.3, 45.5, 30.7, 21.1, 21.0.

[2a*R*, 3*S*, 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-3,4-dihydroxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 16. A solution of **15** (196 mg, 0.36 mmol) and OsO_4 (150 mg, 0.59 mmol) in *t*-BuOH (9 mL) / H_2O (3 mL) was stirred at 80 °C for 30 min. Aqueous $NaHSO_3$ (0.5 M, 50 mL) was added to the resulting black mixture and stirring was continued at rt for 15 min. The water layer was extracted with Et_2O (4 × 100 mL) and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc → acetone) gave **16** (173 mg, 0.30 mmol) in 83% yield as a white foam. IR: 3548, 2955, 1741, 1435, 1378, 1252, 1049; ^1H NMR (200 MHz): 7.25 - 7.36 (m, 5 H, Ph), 5.48 (t, 1 H, *J* 2.9 Hz, H-3), 4.95 (t, 1 H, *J* 2.8 Hz, H-1), 4.78 (d, 1 H, *J* 11.1 Hz, *H*CH-Ph), 4.44 (d, 1 H, *J* 11.1 Hz, HC*H*-Ph), 4.43 (m, 1 H, H-7), 4.22 (dd, 1 H, *J* 2.6, 12.2 Hz, H-6), 4.17 (dt, 1 H, *J* 9.3, 2.6 Hz, H-8), 4.03 (d, 1 H, *J* 8.7 Hz, H-28), 4.02 (d, 1 H, *J* 10.3 Hz, H-19), 3.77 (d, 1 H, *J* 8.7 Hz, H-28'), 3.75 (s, 3 H, CO_2Me), 3.72 (s, 3 H, CO_2Me), 3.65 (d, 1 H, *J* 9.7 Hz, H-19'), 3.37 (d, 1 H, *J* 2.8 Hz, C8-OH), 3.30 (d, 1 H, *J* 12.4 Hz, H-5), 3.05 (d, 1 H, *J* 9.6 Hz, H-9), 2.44 (s, 1 H, C7-OH), 2.41 (dt, 1 H, J 16.6, 2.5 Hz, H-2), 2.06 (s, 3 H, CH_3-CO), 2.05 (s, 3 H, CH_3-CO), 2.04 (obscured, 1 H, H-2'); ^{13}C NMR (100 MHz): 173.1, 169.7 (2 × C), 169.6, 136.7, 128.6 (2 × C), 128.2, 127.7 (2 × C), 105.6, 74.8, 73.2, 69.7, 69.6, 69.5, 66.9, 67.6, 67.2, 53.1, 52.7, 52.4, 51.5, 48.2, 36.2, 30.0, 21.0, 20.9; exact mass spectrum, calcd for $C_{28}H_{35}O_{13}$ (M^+ + H) *m/e* 579.20774, found *m/e* 579.20760.

[2a*R*, 3*R* (*SR*), 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-3,4-phenylmethylenedioxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 17. A solution of **16** (90 mg, 0.156 mmol), $PhCH(OMe)_2$ (470 µL, 3.13 mmol) and PPTS (4 mg, 0.016 mmol) in benzene (15 mL) was heated at reflux for 30 min using a Dean-Stark trap and 4Å mol sieves to remove the water. The resulting cooled reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and the water layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:3 → 2:1) gave an inseparable 4:1 mixture of the α and β isomer of **17** (94 mg, 0.141 mmol) in 90% yield as a white foam. For major α-isomer of **17**: ^1H NMR (400 MHz): 7.62 (m, 2 H, Ph), 7.28 - 7.40 (m, 8 H, Ph), 5.66 (s, 1 H, CH-Ph), 5.50 (t, 1 H, J 2.7 Hz, H-3), 5.02 (t, 1 H, J 2.6 Hz, H-1), 4.79 (d, 1 H, J 7.6 Hz, H-8), 4.41 - 4.52 (m, 3 H, CH_2-Ph & H-7), 4.21 (dd, 1 H, J 4.6, 12.5 Hz, H-6), 4.02 (d, 1 H, J 8.4 Hz, H-28), 3.83 (s, 3 H, CO_2Me), 3.72 (d, 1 H, J 8.4 Hz, H-28'), 3.61 - 3.73 (obscured, 2 H, H-19 & H-19'), 3.66 (s, 3 H, CO_2Me), 3.29 (d, 1 H, J 12.5 Hz, H-5), 2.77 (s, 1 H, H-9), 2.43 (dm, 1 H, J 16.8 Hz, H-2), 2.29 (dm, 1 H, J 16.8 Hz, H-2'), 2.08 (s, 3 H, CH_3-CO), 1.69 (s, 3 H, CH_3-CO); ^{13}C NMR (100 MHz): 173.4, 170.7, 169.6, 167.7, 136.6, 136.0, 128.6 (2 × C), 128.2, 128.1, 128.1 (2 × C), 128.0 (2 × C), 127.4 (2 × C), 105.0, 102.4, 76.3, 73.4, 73.1, 72.8, 71.7, 67.6, 67.4, 66.3, 53.0, 52.4, 52.3, 52.0, 47.7, 38.7, 31.3, 21.0 (2 × C); exact mass spectrum, calcd for $C_{35}H_{39}O_{13}$ (M^+ + H) *m/e* 667.23904, found *m/e* 667.23260. Distinguishable for minor β-isomer of **17**: ^1H NMR (400 MHz): 7.46 (m, 2 H, Ph), 7.28 - 7.40 (m, 6 H, Ph), 7.21 (m, 2 H, Ph), 6.32 (s, 1 H, CH-Ph), 5.46 (t, 1 H, J 2.7 Hz, H-3), 5.06 (t, 1 H, J 2.7 Hz, H-1), 4.66 (d, 1 H, J 7.3 Hz, H-8), 4.41 - 4.52 (m, 2 H, *H*CH-Ph & H-7), 4.35 (d, 1 H, J 11.1 Hz, HC*H*-Ph), 4.13 (dd, 1 H, J 4.6, 12.7 Hz, H-6), 4.03 (d, 1 H, J 8.4 Hz, H-28), 3.80 (s, 3 H, CO_2Me), 3.78 (d, 1 H, J 8.6 Hz, H-28'), 3.61 - 3.73 (obscured, 2 H, H-19 & H-19'), 3.61 (s, 3 H, CO_2Me), 3.19 (d, 1 H, J 12.5 Hz, H-5), 2.80 (s, 1 H, H-9), 2.43 (dm, 1 H, J 16.8 Hz, H-2), 2.33 (dm, 1 H, J 16.8 Hz, H-2'), 2.12 (s, 3 H, CH_3-CO), 2.06 (s, 3 H, CH_3-CO); ^{13}C NMR (100 MHz): 173.5, 170.4, 169.6, 167.6, 138.9, 136.5, 129.7 (2 × C), 128.6 (2 × C), 128.4 (2 × C), 125.7, 104.8, 103.1, 74.9, 73.0, 72.9, 71.7, 52.9, 52.8, 47.7, 38.8, 31.2, 21.2, 20.9.

[2a*R*, 3*R*, 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 4-benzoyloxy-5-benzyloxy-8,10-diacetoxy-3-hydroxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 18 and [2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] dimethyl 3-benzoyloxy-5-benzyloxy-4-bromo-8,10-diacetoxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 19. A solution of **17** (40 mg, 0.060 mmol), water (110 µL, 6.11 mmol), NBS (12 mg, 0.067 mmol) and $BaCO_3$ (60 mg, 0.30 mmol) in CCl_4 (4 mL) was irradiated with a Hg-lamp (254 nm, 5.5 W, 2 × 2 min with a 10 min interval). The resulting reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the water layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:1 → 2:1 → EtOAc) gave in order of elution **19** (impure, ca 20%) and **18** (24 mg, 0.030 mmol) contaminated with succinimide in 50% yield as a colourless oil. Distinguishable signals for **19**: IR: 2955, 1742, 1731; ^1H NMR (400 MHz): 8.18 (d, 2 H, J 7.3 Hz, *o*-O_2CPh), 7.57 (t, 1 H, J 7.4 Hz, *p*-O_2CPh), 7.26 - 7.47 (m, 7 H, *m*-O_2CPh & Ph), 6.01 (t, 1 H, J 2.3 Hz, H-7), 5.54 (t, 1 H, J 2.5 Hz, H-3), 5.09 (t, 1 H, J 2.6 Hz, H-1), 4.79 (d, 1 H, J 11.1 Hz, *H*CH-Ph), 4.48 (d, 1 H, J 10.9 Hz, HC*H*-Ph), 4.42 (m, 2 H), 4.07 (d, 1 H, J 10.0 Hz, H-19), 3.95 (d, 1 H, J 9.0 Hz, H-28), 3.77 (s, 3

H, CO_2Me), 3.72 (s, 3 H, CO_2Me), 3.36 (d, 1 H, *J* 12.5 Hz, H-5), 3.30 (d, 1 H, *J* 2.7 Hz, H-9), 2.97 (dm, 1 H, *J* 16.8 Hz, H-2), 2.19 (s, 3 H, CH_3-CO), 1.95 (s, 3 H, CH_3-CO); ^{13}C NMR (400 MHz): 172.9, 169.4, 169.3, 165.0, 136.5, 133.1, 129.7 (2 × C), 128.6 (2 × C), 128.5, 128.2, 128.1 (2 × C), 127.8 (2 × C), 105.5, 73.8, 73.2, 71.0, 69.9, 69.2, 67.8, 67.7, 67.1, 53.2, 52.8, 52.4, 52.1, 48.4, 38.4, 29.5, 20.9, 20.8; exact mass spectrum, calcd for $C_{35}H_{39}O_{13}$ (M^+ - Br + 2 H) *m/e* 667.23904, found *m/e* 667.23570. For **18**: ^1H NMR (200 MHz): 7.99 (m, 2 H, *o*-$PhCO_2$), 7.37 - 7.59 (m, 3 H, *m* & *p*-$PhCO_2$), 6.91 - 7.07 (m, 5 H, Ph), 5.55 (dd, 1 H, *J* 2.6, 10.4 Hz, H-8), 5.52 (broad s, 1 H, H-3), 5.08 (t, 1 H, *J* 2.7 Hz, H-1), 4.65 (t, 1 H, *J* 2.4 Hz, H-7), 4.55 (d, 1 H, *J* 11.3 Hz, *H*CH-Ph), 4.38 (dd, 1 H, *J* 2.4, 12.5 Hz, H-6), 4.30 (d, 1 H, *J* 11.3 Hz, HC*H*-Ph), 4.02 (d, 1 H, *J* 8.9 Hz, H-28), 3.97 (d, 1 H, *J* 9.9 Hz, H-19), 3.79 (obscured, 1 H, H-19'), 3.78 (s, 3 H, CO_2Me), 3.67 (s, 3 H, CO_2Me), 3.63 (obscured, 1 H, H-28'), 3.41 (d, 1 H, *J* 12.5 Hz, H-5), 3.40 (d, 1 H, *J* 10.4 Hz, H-9), 2.43 (dt, 1 H, *J* 16.9, 2.4 Hz, H-2), 2.12 (s, 3 H, CH_3-CO), 2.07 (s, 3 H, CH_3-CO), 2.07 - 2.12 (obscured, 1 H, H-2'); exact mass spectrum, calcd for $C_{35}H_{38}O_{14}Na$ (M^+ + Na) *m/e* 705.21593, found *m/e* 705.21800.

[2a*R*, 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 4-benzoyloxy-5-benzyloxy-8,10-diacetoxy-3-oxoperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 20. A solution of **18** (24 mg, 0.035 mmol), molecular sieves (4Å, 75 mg) and PCC (75 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) was stirred for 45 min before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The water layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:3 → 2:1) gave **20** (20 mg, 0.029 mmol) in 84% yield as a colourless oil. IR: 2954, 2925, 1743, 1736, 1730, 1455, 1436, 1377, 1273, 1246, 1102, 1048; ^1H NMR (400 MHz): 8.04 (dd, 2 H, *J* 1.3, 8.3 Hz, *o*-$PhCO_2$), 7.57 (m, 1 H, *p*-PhCO2), 7.43 (m, 2 H, *m*-$PhCO_2$), 7.02 - 7.13 (m, 5 H, Ph), 6.05 (dd, 1 H, *J* 1.4, 8.9 Hz, H-8), 5.52 (t, 1 H, *J* 2.9 Hz, H-3), 5.11 (t, 1 H, *J* 2.8 Hz, H-1), 5.01 (dd, 1 H, *J* 1.4, 14.1 Hz, H-6), 4.63 (d, 1 H, *J* 11.6 Hz, *H*CH-Ph), 4.47 (d, 1 H, *J* 11.6 Hz, HC*H*-Ph), 4.24 (d, 1 H, *J* 10.1 Hz, H-19), 4.08 (d, 1 H, *J* 9.1 Hz, H-28), 3.83 (d, 1 H, *J* 9.1 Hz, H-28'), 3.78 (s, 3 H, CO_2Me), 3.73 (d, 1 H, *J* 10.1 Hz, H-19'), 3.67 (s, 3 H, CO_2Me), 3.50 (d, 1 H, *J* 9.0 Hz, H-9), 2.96 (d, 1 H, *J* 14.2 Hz, H-5), 2.45 (dt, 1 H, *J* 16.8, 2.6 Hz, H-2), 2.10 (dm, 1 H, *J* 17 Hz, H-2'), 2.03 (s, 3 H, CH_3-CO)l, 2.00 (s, 3 H, CH_3-CO); ^{13}C NMR (100 MHz): 198.3, 172.1, 169.5, 169.4, 168.6, 164.8, 136.5, 133.2, 130.0 (2 × C), 129.6, 128.3 (2 × C), 128.2 (2 × C), 128.1, 127.7 (2 × C), 104.3, 76.8, 73.5, 73.3, 69.7, 68.5, 67.4, 66.7, 56.5, 53.2, 53.0 (2 × C), 48.5, 45.5, 30.1, 20.9, 20.8; exact mass spectrum, calcd for $C_{35}H_{37}O_{14}$ (M^+ + H) *m/e* 681.21831, found *m/e* 681.21210.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-diacetoxy-3-oxoperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 21. A solution of SmI_2 (680 µL of 0.1 M solution in THF, 0.068 mmol) was added to a solution of **20** (23 mg, 0.034 mmol) in THF (600 µL) / MeOH (300 µL) at -110 °C. The resulting reaction mixture was stirred at -78 °C for 15 min, then allowed to come to rt over 10 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the water layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:1 → 2:1) gave in order of elution **22** (4 mg, 0.007 mmol) in 21% yield as a colourless oil, and **21** (15 mg, 0.027 mmol) in 79% yield as a colourless oil. For **21**: IR: 2954, 1736, 1436, 1376, 1428, 1067, 1042; ^1H NMR (200 MHz): 7.19 - 7.39 (m, 5 H, Ph), 5.45 (t, 1 H, *J* 2.9 Hz, H-3), 5.00 (t, 1 H, *J* 2.7 Hz, H-1), 4.52 (d, 1 H, *J* 11.3 Hz, *H*CH-Ph), 4.45 (d, 1 H, *J* 11.3 Hz, HC*H*-Ph), 4.35 (d, 1 H, *J* 14.3 Hz, H-6), 4.02 (d, 1 H, *J* 8.8 Hz, H-28), 3.75 (s, 3 H, CO_2Me), 3.73 (s, 2 H, 2 × H-19), 3.62 (obscured, 1 H, H-28'), 3.60 (s, 3 H, CO_2Me), 2.96 (d, 1 H, *J* 17.0 Hz, H-8eq), 2.94 (d, 1 H, *J* 14.3 Hz, H-5), 2.67 (d, 1 H, *J* 8.4 Hz, H-9), 2.57 (dd, 1 H, *J* 7.4, 17.1 Hz, H-8ax), 2.31 - 2.51 (m, 2 H, 2 × H-2), 2.05 (s, 3 H, CH_3-CO), 2.04 (s, 3 H, CH_3-CO); ^{13}C NMR (50 MHz): 205.3, 172.8, 169.6, 169.4, 167.6, 136.2, 128.6 (2 × C), 128.2, 127.9 (2 × C), 105.2, 73.2, 72.9, 67.1, 66.8, 66.4, 52.9, 52.6, 51.9, 50.3, 46.0, 43.9, 37.9, 30.9, 21.0, 20.9.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-3-oxo-8,10-phenylmethylenedioxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 4 *via* [2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-8,10-dihydroxy-3-oxoperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 23. MeONa (65 mL of a 1 M solution in MeOH, 0.065 mmol) was added to a solution of **21** (18 mg, 0.032 mmol) in MeOH (3 mL). The resulting solution was stirred for 15 min before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The water layer was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organic layers were dried over $MgSO_4$ to give crude **23** (16 mg). {^{1}H NMR (200 MHz) of **23**: 7.21 - 7.37 (m, 5 H, Ph), 4.55 (d, 1 H, *J* 11.5 Hz, *H*CH-Ph), 4.48 (obscured, 1 H, H-3), 4.46 (d, 1 H, *J* 11.5 Hz, HC*H*-Ph), 4.38 (d, 1 H, *J* 14.2 Hz, H-6), 4.05 (d, 1 H, *J* 8.5 Hz, H-28), 3.98 (d, 1 H, *J* 8.4 Hz, H-28'), 3.97 (obscured, 1 H, H-1), 3.87 (d, 1 H, *J* 9.7 Hz, H-19), 3.75 (s, 3 H, CO_2Me), 3.60 (d, 1 H, *J* 9.7 Hz, H-19'), 3.59 (s, 3 H, CO_2Me), 3.53 (broad s, 1 H, OH), 3.00 (dd, 1 H, *J* 3.2, 7.4 Hz, H-9), 2.90 (dd, 1 H, *J* 3, 18 Hz, H-8eq), 2.89 (d, 1 H, *J* 14.3, H-5), 2.58 (dd, 1 H, *J* 7.4, 17.9 Hz, H-8ax), 2.27 (dt, 1 H, *J* 15.8, 2.9 Hz, H-2), 2.13 (dt, 1 H, *J* 16, 2.5 Hz, H-2').}

A solution of crude **23** (16 mg), $PhCH(OMe)_2$ (100 μL, 0.67 mmol) and a few crystals of PPTS in benzene (3 mL) was heated at reflux for 25 min using a Dean-Stark trap and 4Å mol sieves to remove the water. The resulting solution was poured into saturated aqueous $NaHCO_3$ (5 mL) and the water layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 2:3 → 2:1) gave **4** (15 mg, 0.027 mmol) in 83% yield as a white foam. IR: 2954, 1732, 1454, 1291, 1264, 1121, 1096, 1057; ^{1}H NMR (400 MHz): 7.25 - 7.36 (m, 10 H, 2 × Ph), 6.20 (s, 1 H, CH-Ph), 4. 85 (d, 1 H, *J* 4.8 Hz, H-3), 4.58 (d, 1 H, *J* 11.5 Hz, *H*CH-Ph), 4.45 (d, 1 H, *J* 5.8 Hz, H-1), 4.43 (d, 1 H, *J* 11.6 Hz, HC*H*-Ph), 4.37 (d, 1 H, *J* 14.5 Hz, H-6), 4.27 (d, 1 H, *J* 10.2 Hz, H-19), 4.03 (d, 1 H, *J* 8.7 Hz, H-28), 4.01 (d, 1 H, *J* 8.7 Hz, H-28'), 3.73 (d, 1 H, *J* 10.2 Hz, H-19'), 3.70 (s, 3 H, CO_2Me), 3.68 (s, 3 H, CO_2Me), 3.39 (d, 1 H, *J* 14.6 Hz, H-5), 3.00 (dd, 1 H, *J* 3.2, 7.3 Hz, H-9), 2.98 (m, 1 H, H-2), 2.91 (dd, 1 H, *J* 3.2, 17.7 Hz, H-8eq), 2.59 (dd, 1 H, *J* 7.5, 17.7 Hz, H-8ax), 1.72 (d, 1 H, *J* 15.8 Hz, H-2'); ^{13}C NMR (100 MHz): 206.1, 172.8, 168.4, 137.3, 136.6, 129.4, 128.6 (2 × C), 128.4 (2 × C), 127.9, 127.8 (2 × C), 126.1 (2 × C), 105.2, 93.3, 76.1, 73.4, 72.7, 68.4, 67.4, 66.3, 55.2, 52.7, 52.3, 50.0, 48.8, 41.3, 38.4, 24.0; $[\alpha]^{30}_D$ -30.4 (*c* 0.75, $CHCl_3$).

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2a, 4a, 7a, 8, 9, 10, 10a, 10b-octahydro-8,10-phenylmethylenedioxynaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 25. A solution of **4** (14 mg, 0.025 mmol), Et_3N (40 μL, 0.287 mmol) and TBDMSOTf (30 μL, 0.131 mmol) in CH_3CN (1 mL) was stirred for 2 h. The resulting reaction mixture was poured into saturated aqueous $NaHCO_3$ (2 mL). The water layer was extracted with CH_2Cl_2 (4 × 2 mL) and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:Hex = 1:3 → 2:1) gave **25** (13 mg, 0.019 mmol) in 77% yield as a colourless oil. IR: 3034, 2953, 2892, 2856, 1737, 1635, 1454, 1251, 1222, 1124; ^{1}H NMR (400 MHz): 7.41 - 7.43 (m, 2 H, Ph), 7.27 - 7.41 (m, 6 H, Ph), 7.22 - 7.27 (m, 2 H, Ph), 6.14 (s, 1 H, Ph-CH), 4.84 (dd, 1 H, *J* 0.9, 3.9 Hz, H-8), 4.74 (d, 1 H, *J* 4.5 Hz, H-3), 4.62 (d, 1 H, *J* 11.6 Hz, *H*CH-Ph), 4.43 (d, 1 H, *J* 3.5 Hz, H-1), 4.42 (d, 1 H, *J* 11.8 Hz, H-6), 4.40 (d, 1 H, *J* 11.6 Hz, HC*H*-Ph), 4.09 (d, 1 H, *J* 10.4 Hz, H-19), 4.06 (s, 2 H, 2 × H-28), 3.72 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 3.70 (d, 1 H, *J* 10.4 Hz, H-19'), 3.63 (dd, 1 H, *J* 2.2, 3.3 Hz, H-9), 3.20 (d, 1 H, *J* 11.9 Hz, H-5), 2.89 (dt, 1 H, *J* 15.6, 4.8 Hz, H-2), 1.62 (d, 1 H, *J* 15.6 Hz, H-2'), 0.90 (s, 9 H, Si-$C(CH_3)_3$), 0.08 (s, 3 H, Si-Me), 0.04 (s, 3 H, Si-Me); ^{13}C NMR (100 MHz): 173.7, 170.4, 153.4, 137.9 (2 × C), 129.4, 128.4 (2 × C), 128.1 (2 × C), 127.8 (2 × C), 127.4, 126.7 (2 × C), 105.1, 103.9, 93.4, 72.4, 71.6, 70.8, 68.9, 67.9, 66.1, 56.4, 52.7, 52.3, 51.7, 49.8, 41.8, 25.8 (3 × C), 23.4, 18.2, -4.4, -4.8.

[2a*R*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-4-methylene-3-oxo-8,10-phenylmethylenedioxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 24. A solution of **25** (13 mg, 0.019 mmol) and Eschenmoser's salt (35 mg, 0.189 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 35 °C for 48 h. The resulting reaction mixture was poured into saturated aqueous $NaHCO_3$ (3 mL). The water layer was extracted with CH_2Cl_2 (4 × 3 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was redissolved in CH_2Cl_2 (2 mL) and silicagel was added (190 mg). The resulting slurry was stirred for 18 h, before being filtered. The residue was washed with acetone (20 mL) and the combined organic layers were evaporated *in vacuo*. Purification by flash chromatography (EtOAc:Hex = 2:3 → 3:1) gave in order of elution **25** (4 mg, 0.006 mmol) 30% yield as a colourless oil and **24** (7.5 mg, 0.013 mmol) in 68% yield as a colourless oil. For **24**: IR: 2954, 2899, 1747, 1723, 1454, 1126; ^{1}H NMR (400 MHz): 7.24 - 7.36 (m, 10 H, 2 × Ph), 6.41 (d, 1 H, *J* 1.2 Hz, H-30), 6.15 (s, 1 H, Ph-CH), 5.48 (s, 1 H, H-30'), 4.83 (d, 1 H, *J* 4.5 Hz, H-3), 4.56 (d, 1 H, *J* 11.5 Hz, *H*CH-Ph), 4.49 (d, 1 H, *J* 11.5 Hz, HC*H*-Ph), 4.46 (d, 1 H, *J* 4.0 Hz, H-1), 4.44 (d, 1 H, *J* 14.7 Hz, H-6), 4.29 (d, 1 H, *J* 10.1 Hz, H-19), 3.98 (d, 1 H, *J* 8.5 Hz, H-28), 3.93 (d, 1 H, *J* 8.5 Hz, H-28'), 3.74 (s, 3 H, CO_2Me), 3.71 (d, 1 H, *J* 10.1 Hz, H-19'), 3.68 (s, 1 H, H-9), 3.66 (s, 3 H, CO_2Me), 3.41 (d, 1 H, *J* 14.8 Hz, H-5), 2.99 (dt, 1 H, *J* 15.8, 4.8 Hz, H-2), 1.71 (d, 1 H, *J* 15.8 Hz, H-2'); ^{13}C NMR (100 MHz): 196.3, 172.8, 167.7, 141.3, 137.1, 136.6, 129.6, 128.6, 128.5 (2 × C), 128.4 (2 × C), 127.9, 127.8 (2 × C), 126.4 (2 × C), 106.0, 93.6, 75.3, 73.6, 72.8, 68.3, 67.4, 66.0, 57.6, 55.0, 52.7, 52.3, 48.6, 41.3, 24.0.

[2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S* (*R*), 10*R*, 10a*S*, 10b*R*] Dimethyl 5-benzyloxy-4-methyl-3-oxo-8,10-phenylmethylenedioxyperhydronaphto[1,8-*bc*:4,4a-*c'*]difuran-5,10a-dicarboxylate 5 and isomer. A solution of **24** (7.0 mg, 0.012 mmol) and Pd/C (10%, 6 mg) in MeOH (1 mL) was stirred under a hydrogen atmosphere for 1 h. The resulting reaction mixture was filtered over celite and the residue was washed with MeOH. Purification by flash chromatography (EtOAc:Hex = 2:3 → 1:1 → 2:1) gave **5** (4.5 mg, 0.008 mmol) as a 4:1 mixture of its β and α-methyl isomer in 60% yield as a colourless oil. ^{1}H NMR data of **5** were identical with the data of **5** obtained from the degradation of azadirachtin.[7]

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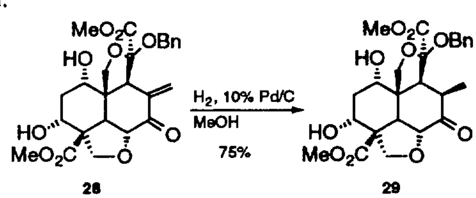
19) In addition to this: Reduction of the dihydroxy enone **28** under the same conditions resulted in exclusive formation of **29** in 75% yield:



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