A Diels–Alder Approach to Anthrapyran Antibiotics

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Abstract: A new entry to the synthesis of anthrapyran antibiotics has been accomplished through the synthesis of a 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione model. The key step features a Diels–Alder reaction between a substituted 5-vinyl-3,4-dihydro-2*H*-pyran and naphthoquinone as the dienophile. The resulting tetracyclic adduct is then processed towards the targeted trione in a few steps.

Key words: anthrapyran antibiotics, Diels–Alder reaction, quinones, Stille reaction, 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione

The pluramycins[1] are a group of naturally occurring anthrapyran antibiotics with antitumor activity. They display a 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione structure with *C*-glycoside moieties typically attached at C8 and C10 (or C5 and C10 for the subgroup of altromycins) and a lateral chain branched at C2 bearing one or two epoxide functionalities. These compounds intercalate in DNA with selective positioning of the chain epoxide in the major groove where it can form an adduct with the N7 of a guanine residue. In addition to the C-glycosylated pluramycins, the family of 4*H*-anthra[1,2-*b*]pyran antibiotics also contains bioactive compounds having no epoxide functionality and compounds bearing no carbohydrate moieties. For the purpose of illustration, Figure 1 gives an overview of their structural diversity.

The original structure and mode of action of pluramycins added to the promising antitumoral activity of some members of the family have spurred recently some synthetic interest. While no synthesis of a complete skeleton of a pluramycin has been achieved to date,[2] several syntheses of 4*H*-anthra[1,2-*b*]pyran antibiotics including pluramycin aglycones (pluramycinones) have appeared in the literature.[3] In these reported syntheses, anionic condensations and Diels–Alder reaction were mainly used to fashion the DCB framework of the molecules whereas ring A was elaborated by creation of the O1–C2 or the C4–C4a bonds from a suitable precursor. Our approach to this class of compounds is different and inspired from our previous work accomplished in the field of angucycline synthesis.[4] We thus planned to construct, in one single operation, a tetracyclic precursor to the 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione framework with creation of ring B by means of a hetero Diels–Alder reaction [ABCD → AB + CD strategy]. In addition to its convergency this strategy would allow the preparation of several analogues by changes in the structure of the diene and (or) of the dienophile. To test the feasibility of such an approach, the 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione (**1**) was chosen as a model compound. A retrosynthetic overview of our key strategic bond disconnections is depicted in Scheme 1.

We thus envisioned that trione **1** could be obtained by aromatisation of the A ring of **2a** or **2b**, which could in turn be prepared by aromatisation of the B ring of **3a** or **3b**, respectively. These latter could be the result of a Diels–

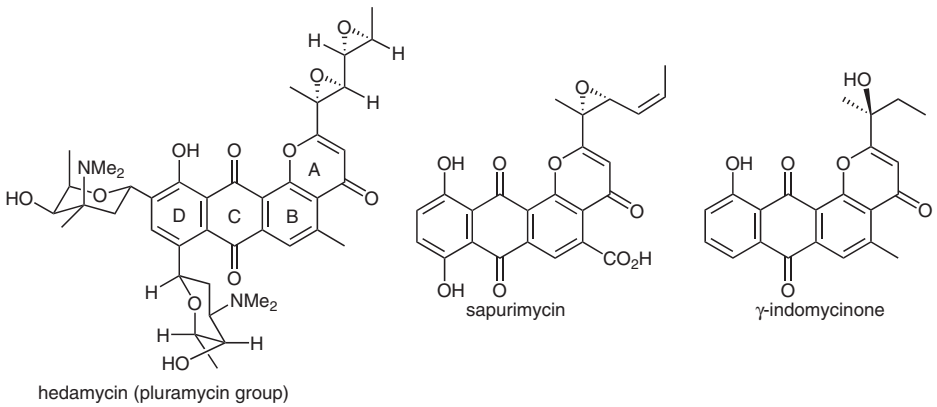

Figure 1 Selected natural anthrapyran antibiotics

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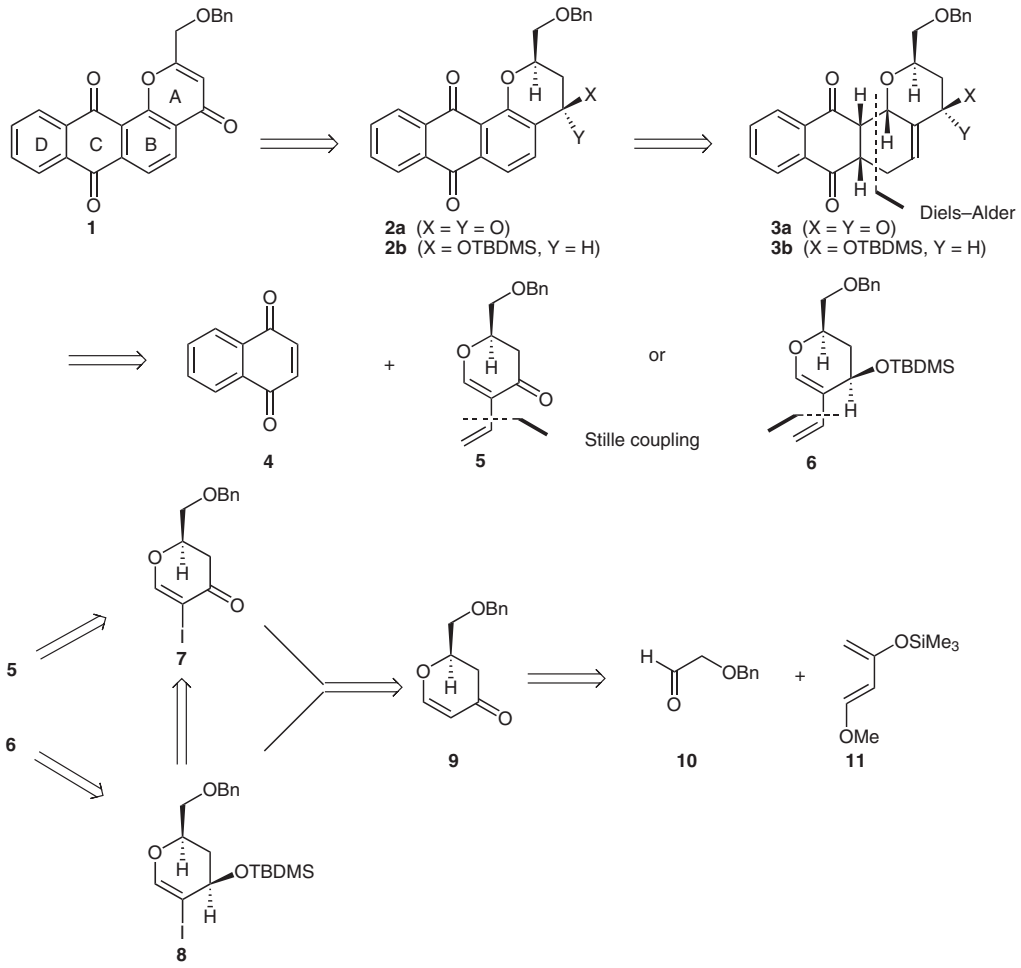
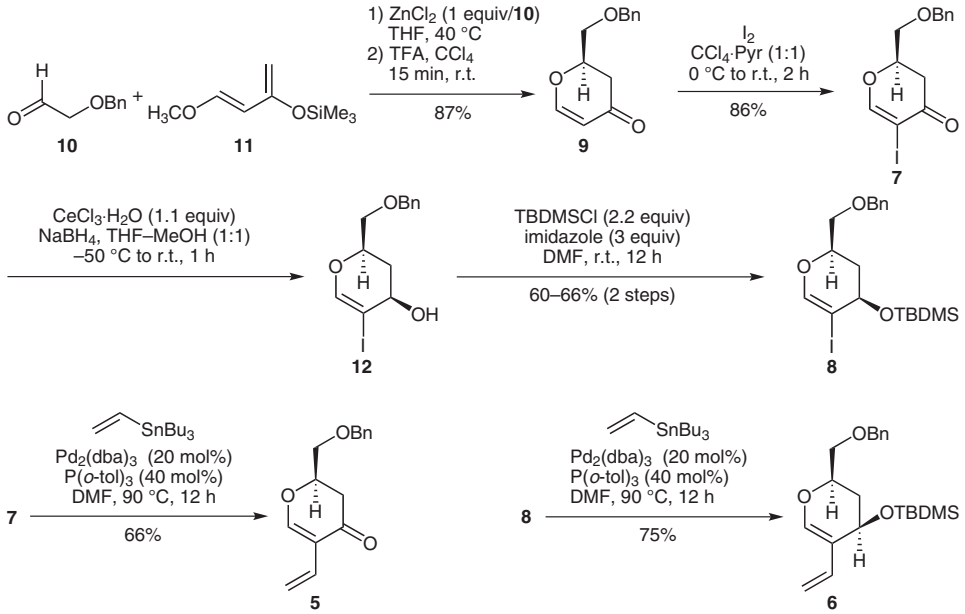


Scheme 1 Retrosynthetic analysis

Alder reaction between naphthoquinone **4** and dienes **5** (→ **3a**) or **6** (→ **3b**). Each of these dienes could be accessed from an iodoether precursor (**7** or **8**) through an organometallic coupling reaction. Finally, the preparation of **7** and **8** could be envisaged from a same precursor **9**, itself being the result of a heterocyclic Diels–Alder reaction between aldehyde **10** and Danishefsky's diene **11**.



Scheme 2

The synthesis of dienes **5** and **6** commenced with the hetero Diels–Alder condensation of 3-benzyloxyacetaldehyde (**10**) with the Danishefsky's diene (**11**) to afford the dihydropyran-4-one **9**.[5] The latter was next treated with an excess of iodine (ca. 2 equiv) in a 1:1 mixture of CCl_4 and pyridine to give the iododihydropyran-4-one **7** in good yield.[6] Reduction of **7** under Luche conditions[7] provided the sole iodo alcohol **12** which was subsequently OTBDMS-protected to give the iodo ether **8**. Dienes **5** and **6** could then be reached by palladium-catalysed Stille coupling reaction between tributylvinylstannane[8] and iodo ethers **7** and **8**, respectively (Scheme 2).

With access to dienes **5** and **6**, we were poised to study the key cycloaddition reaction to form **3a** and **3b** (Scheme 3). Initial reaction conducted with naphthoquinone **4** showed a clear difference of reactivity between dienes **5** and **6**. If diene **6** smoothly condensed with **4** to give adduct **3b** in good yield,[9,10] diene **5** failed to react in the same conditions. Diene **5**, however, reacted smoothly with the bromo-activated naphthoquinone **13** to give adduct **14** in good yield.[11] Diene **6** reacted similarly to give adduct **15**. Additionally, diene **6** was also reacted with juglone **16** to furnish adduct **17**[10] (Scheme 4).

Although our synthetic strategy implies subsequent aromatisation of the B-ring of Diels–Alder adducts, it is not without interest to point out that all the above adducts were isolated as single diastereomers. The structure of adduct **17** could be fully ascertained by single-crystal X-ray diffraction[12] (Figure 2) and structures of adducts **3b**, **14**, and **15** were attributed by analogy. The complete stereoselectivity of the cycloaddition process can be accounted for by an *endo* transition state with minimisation of steric interactions (i.e., attack of the dienophile on the face of the diene opposite the OTBDMS and CH_2OBn groups) as pictured in Scheme 4 for cycloaddition of juglone (**16**) with diene **6**.

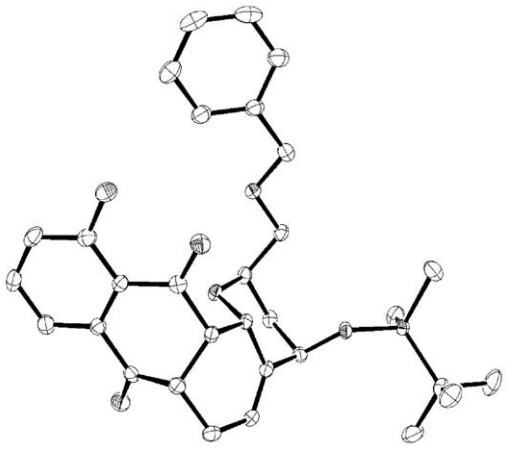
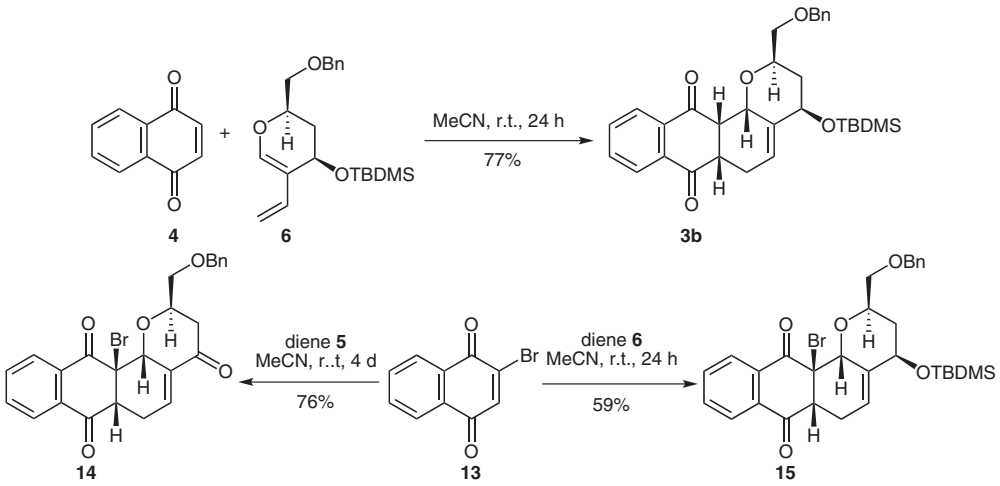
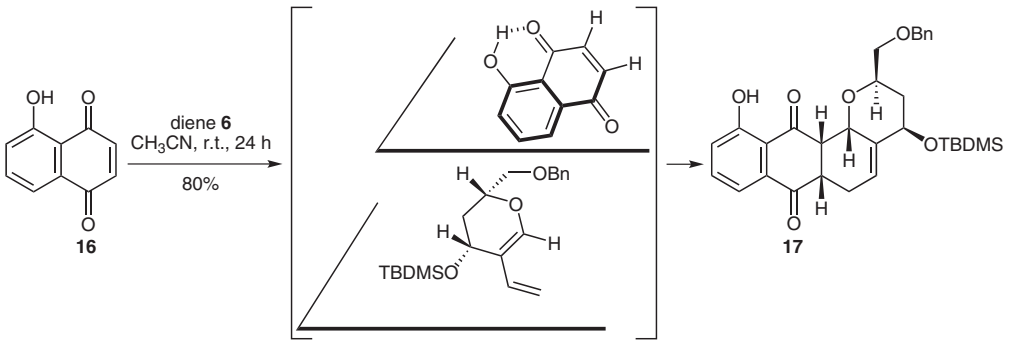


Figure 2 X-ray structure of **17**



Scheme 3



Scheme 4

Processing further on to reach trione **1**, we next considered the possibility of carrying out the aromatisation of ring B in adducts **14**, **15**, and **3b**. Treatment of adduct **14** with triethylamine resulted in the formation of the B-ring-opened product **18** (Scheme 5) and we also failed to isolate compound **2a** in several other conditions. Adduct **15** behaved similarly in similar conditions.

After several unfruitful research efforts we finally discovered that compound **2b** could be derived from **3b** through a two-step process featuring epoxidation[13] of **3b** to give epoxide **19** (one single diastereomer) and treatment of the latter with an excess of triethylamine. Moreover, we found that a substantial improvement of the yield (49% to 67%) could be achieved when a one-pot procedure was applied (Scheme 6).

At this point, completion of the synthesis of trione **1** required deprotection and oxidation of the C4 alcohol and introduction of the C2–C3 double bond. Treatment of **2b** with the Jones reagent effected both deprotection of the OTBDMS ether and oxidation of the resulting alcohol to give ketone **20** (Scheme 7). The same transformation was also achieved in two steps, that is, OTBDMS deprotection ($CuCl_2 \cdot 7H_2O$, acetone–H_2O, reflux, 48h; 70%)[14] and PCC oxidation (3 equiv of reagent, CH_2Cl_2, reflux, 3 d; 80%), without significant yield improvement. Finally, introduction of the C2–C3 double bond to reach trione **1** was best accomplished by exposure of **20** to iodine in DMSO at 80 °C.[15] Under these conditions, the targeted trione **1**[16] could be isolated in 93% yield (Scheme 7).

In summary, we have achieved the synthesis of the 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione (**1**) embodying the tetracyclic framework displayed by pluramycins and related natural products. The key step is a Diels–Alder cycloaddition, which allows, in one single operation, the regioselective assemblage of a CD unit to a A-ring precursor with formation of an advanced tetracyclic intermediate. Investigations directed towards the implementation of this strategy for the synthesis of more elaborated targets including natural products are ongoing.

Acknowledgment

We thank Aurélien Planchat for X-ray crystallographic structure determination.

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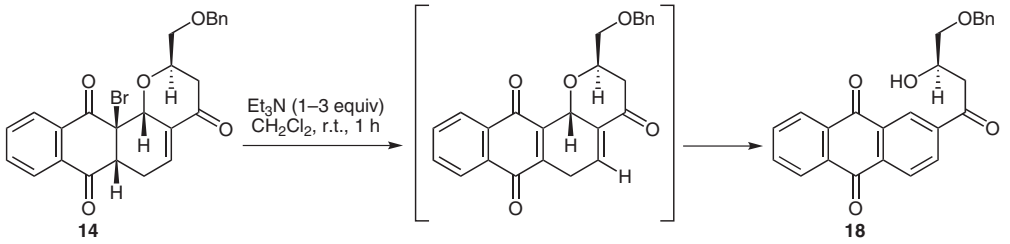
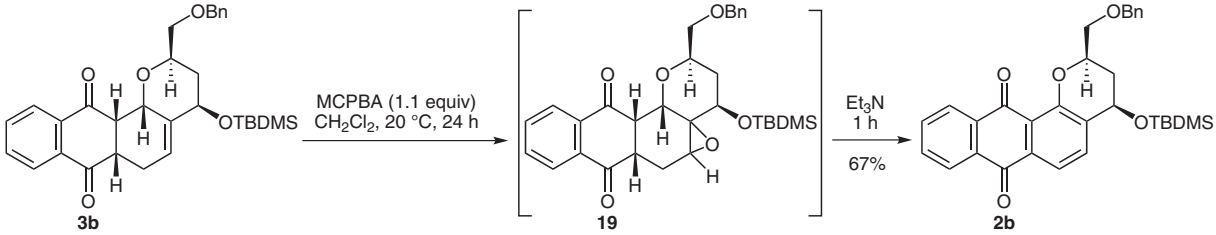
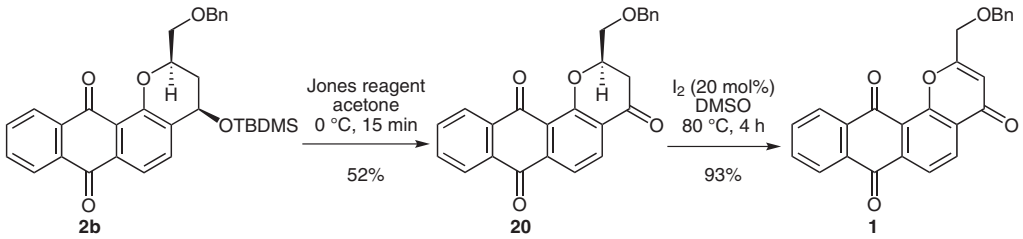


Scheme 5



Scheme 6



Scheme 7

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(10) **Procedure for the Preparation of 3b**
To a solution of (2-benzyloxymethyl-5-vinyl-3,4-dihydro-2*H*-pyran-4-yloxy)-*tert*-butyl(dimethyl)silane (diene 6, 890 mg, 2.45 mmol) in MeCN (13 mL) was added 1,4-naphthoquinone (4, 465 mg, 2.94 mmol). The reaction was stirred for 24 h at r.t. H_2O (30 mL) was then added, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (Et_2O–PE = 1:4) to yield Diels–Alder adduct **3b** (1.18 g, 77%) as a white solid (mp 97 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.02 (m, 1 H, H_{11}), 7.95–7.89 (m, 1 H, H_8), 7.65–7.59 (m, 2 H, H_9 and H_{10}), 7.34–7.18 (m, 5 H, H-Ph), 5.81 (dd, $J_{5–6}$ = 5.9 Hz, $J_{5–6'}$ = 1.6 Hz, 1 H, H_5), 4.79 (dd, $J_{12b–12a}$ = 5.2 Hz, $J_{12b–6b}$ = 1.2 Hz, 1 H, H_{12b}), 4.30 (X part of an ABX system, J_{XA} = 4.2 Hz, J_{XB} = 3.7 Hz, 1 H, H_4), 4.31 and 4.26 (AB system, J_{AB} = 12.0 Hz, 2 H, CH_2Ph), 3.76 and 3.32 (AB part of an ABX system, J_{AB} = 11.0 Hz, J_{AX} = 7.6 Hz, J_{BX} = 4.5 Hz, 2 H, CH_2O), 3.64–3.56 (m, X part of 2 ABX systems, 1 H, H_2), 3.44 (M part of an AMX system, $J_{12a–12b}$ = 5.2 Hz, $J_{12a–6a}$ = 5.8 Hz, 1 H, H_{12a}), 3.37 (M part of an ABMX system, $J_{12a–6a}$ = 5.8 Hz, $J_{6a–6}$ = 6.0 Hz, $J_{6a–6'}$ = 1.2 Hz, 1 H, H_{6a}), 3.0 and 2.13 (AB part of an ABXY system, J_{AB} = 18 Hz, $J_{6–7}$ = 6 Hz, $J_{6–6a}$ = 1.2 Hz, $J_{6'–6a}$ = 6.0 Hz, $J_{6'–5}$ = 1.6 Hz, $J_{6'–12b}$ = 1.2 Hz, 2 H, H_6 and $H_{6'}$), 1.92 and 1.66 (AB part of ABXY system, J_{AB} = 14.1 Hz, $J_{3–2}$ = 6.0 Hz, $J_{3–4}$ = 4.2 Hz, $J_{3'–4}$ = 3.7 Hz, $J_{3'–2}$ = 3.7 Hz, 2 H, H_3 and $H_{3'}$), 0.84 (s, 9 H, H_{22}), 0.02 (s, 3 H, H_{20}), –0.01 (s, 3 H, $H_{20'}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5 and 196.44 (2 Cq, C_7 and C_{12}), 138.7 (Cq, C_{16}), 137.2 and 136.4 (2 Cq, C_{7a} and C_{11a}), 136.8 (Cq, C_{4a}), 133.5 and 133.1 (2 CH, C_9 and C_{10}), 128.2 (2 CH, C_{17} and $C_{17'}$), 127.5 (2 CH, C_{18} and $C_{18'}$), 127.3 (CH, C_{19}), 126.2 and 125.7 (2 CH, C_8 and C_{11}), 121.6 (CH, C_5), 72.8 (CH, C_2), 72.5 (CH_2, C_{15}), 70.8 (CH, C_4), 70.7 (CH_2, C_{13}), 63.1 (CH, C_{12b}), 51.8 (CH, C_{12a}), 43.65 (CH, C_{6a}), 37.4 (CH_2, C_3), 25.7 (3 CH_3, C_{22}), 22.31 (CH_2, C_6), 17.9 (Cq, C_{21}), –4.6 (CH_3, C_{20}), –5.1 (CH_3, $C_{20'}$). IR (KBr): 2930, 1699, 1254, 1095, 1052 cm^{-1}. MS (EI): *m/z* (%) = 386 (16), 370 (8), 353 (14), 327 (7), 295 (7), 265 (13), 261 (7), 133 (22) 91 (100), 73 (25). MS (CI, NH_3): *m/z* = 536 [$(M + NH_4)^+$]. HRMS (Maldi DHB/MeCN + PEG600): *m/z* calcd for $C_{31}H_{38}O_5SiNa$ $[MNa]^+$: 541.2381; found: 541.2397, Δ = 2.3 ppm.

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(12) **Crystal Structure Data for 17**
$C_{31}H_{38}O_6Si$, M_r = 534.7, monoclinic, *P*21/c, *a* = 11.1097 (11), *b* = 18.9124 (12), *c* = 13.8124 (15) Å, β = 106.699 (9), *V* = 2779.7 (5) Å^3, *Z* = 4, ρ_{calcd} = 1.2773 g cm^{-3}, μ = 1.27 mm^{-1}, *F*(000) = 1144, colourless block, 0.19 × 0.18 × 0.17 mm^3, $2c_{max}$ = 56°, *T* = 120 K, 48226 reflections, 6629 unique (98% completeness), R_{int} = 0.096, 346 parameters, *GOF* = 1.54, *wR*2 = 0.1231, *R* = 0.0563 for 4795 reflections with $I > 2\sigma(I)$. CCDC 855339 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(16) **Spectroscopic Data for Trione 1**
Tan solid (mp 165 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, $J_{6–5}$ = 8.3 Hz, 1 H, H_6), 8.37 (d, $J_{5–6}$ = 8.3 Hz, 1 H, H_5), 8.33–8.27 (m, 2 H, H_8 and H_{11}), 7.90–7.79 (m, 2 H, H_9 and H_{10}), 7.49–7.30 (m, 5 H, H-Ph), 6.68 (s, 1 H, H_3), 4.80 (s, 2 H, CH_2Ph), 4.57 (d, *J* = 0.8 Hz, 2 H, CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.4 and 181.3 (2 Cq, C_7 and C_{12}), 176.6 (Cq, C_4), 167,6 (Cq, C_{12b}), 154.7 (Cq, C_2), 137.9 (Cq, C_{6a}), 137.1 (Cq, C_{16}), 134.9 and 134.2 (2 CH, C_9 and C_{10}), 134.3 (Cq, C_{11a}), 132.3 (Cq, C_{7a}), 132.1 (CH, C_6), 128.8 (2 CH, C_{17}, $C_{17'}$), 128.5 (Cq, C_{4a}), 128.3 (CH, C_{19}), 128.0 (2 CH, C_{18} and $C_{18'}$), 127.3 and 127.2 (2 CH, C_8 and C_{11}), 123.3 (CH, C_5), 122.7 (Cq, C12a), 110.1 (CH, C_3), 73.8 (CH_2, C_{15}), 67.9 (CH_2, C_{13}). IR (KBr): 1674, 1657, 1589, 1418, 1324, 1283, 1122 cm^{-1}. MS (EI): *m/z* (%) = 280 (20), 125 (27), 111 (30), 97 (47), 83 (45), 71 (59), 57 (100), 43 (69). MS (CI, NH_3): *m/z* = 397 [$(M + H)^+$]. ESI-HRMS: *m/z* calcd for $C_{25}H_{17}O_5$ $[MH]^+$: 397.1071; found: 397.1056, Δ = 3.6 ppm.

