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Synthesis of 5-aza-analogues of angucyclines: manipulation of the 2-deoxy-*C*-glycoside subunit

Nguyen Quang Vu,[a] Gilles Dujardin,[a,*] Sylvain C. Collet,[b,*] Eun-Ang Raiber,[b] André Y. Guingant[b,*] and Michel Evain[c]

[a]*Laboratoire de Synthèse Organique, UMR CNRS 6011, Université du Maine, F-72085, Le Mans Cedex 9, France*
[b]*Laboratoire de Synthèse Organique, UMR CNRS 6513, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208-44322 Nantes Cedex 03, France*
[c]*Institut des Matériaux Jean Rouxel, 2, rue de la Houssinière, BP 92208-44322 Nantes Cedex 03, France*

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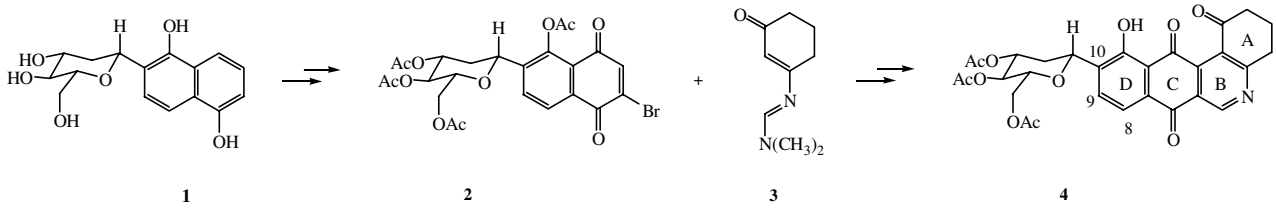
Abstract—Based on a heterocyclic Diels–Alder strategy, a concise synthesis of 5-aza-analogues of angucyclines bearing a 2-deoxy-*C*-glycoside subunit is reported. Starting from a common intermediate, a peracetylated D-2-deoxyglucose could be linked to carbons C9 or C10 of the tetracyclic framework. Further manipulations of the sugar residue allowed the installation of bromo and azido substituents at carbon C6′.

1. Introduction

Angucyclines belong to an ever-growing class of natural products characterized by a unique benz[*a*]anthraquinone core structure.[1] Angucyclines and their aglycones (angucyclinones) often display a broad range of interesting biological and pharmaceutical activities. Therefore, this class of compounds represents a source of inspiration for the design and synthesis of structural analogues, which could be of value for SAR studies. In this regard, we recently disclosed a simple and efficient strategy for the synthesis of 5-aza-analogues of angucyclines having the B-ring fully aromatized.[2] Our synthetic route, which relies on a hetero Diels–Alder reaction between a 2-bromo-[1,4]naphthoquinone and the 'push–pull' aza diene **3**, allows the extremely direct formation of 5-aza-analogues of angucyclines in good to excellent chemical yields. This strategy is particularly promising since structural diversity could be easily introduced by varying the nature and position of substituents on the diene and (or) the dienophile. As a first demonstrative example, we reported[2] the synthesis of the 5-aza-analogue **4**, bearing a 2-deoxy-*C*-glycoside unit at carbon C10 (angucycline numbering), by reaction of diene **3** with dienophile **2** prepared in few steps from **1** (Scheme 1).



Scheme 1.

Keywords: Angucycline; Angucyclinone; Angucycline-5-aza-analogue; 2-Aza-1,3-diene; 2-Bromo-naphthoquinone; Hetero-Diels–Alder reaction; *C*-Glycoside.
* Corresponding authors. Tel.: +33 (0)2 43 83 33 44; fax: +33 (0)2 43 83 39 02; e-mail: gilles.dujardin@univ-lemans.fr

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In continuation of our efforts to find 5-aza-analogues of angucyclines with significant biological activities, we next focused our attention on the possibility of introducing different substituents at carbon C6′ of the 2-deoxy-*C*-glycoside unit. These modifications could affect the bioactivity of the corresponding compounds as a result, inter alia, of alteration of hydrophilicity or lipophilicity. Additionally, we were also interested to find conditions that would allow the linkage of the 2-deoxy-*C*-glycoside unit at carbon C9, instead of C10 as previously realized.[3,4]

2. Substitution at C6′: synthesis of the angucycline 5-aza-analogues 9 and 13

We first envisaged to synthesize the angucycline 5-aza-analogue **9** having a bromine atom at carbon C6′ of the sugar moiety. The introduction of a versatile bromine atom at C6′ of **9** is particularly attractive since its displacement with various nucleophilic species (thiol, amine, etc.) should allow synthetic access to several other angucycline 5-aza-analogues. According to our hetero Diels–Alder protocol, compound **9** should be formed by reacting the 2-bromo-[1,4]naphthoquinone **7** with aza-diene **3**, followed by selective deacetylation at C11 (Scheme 2).

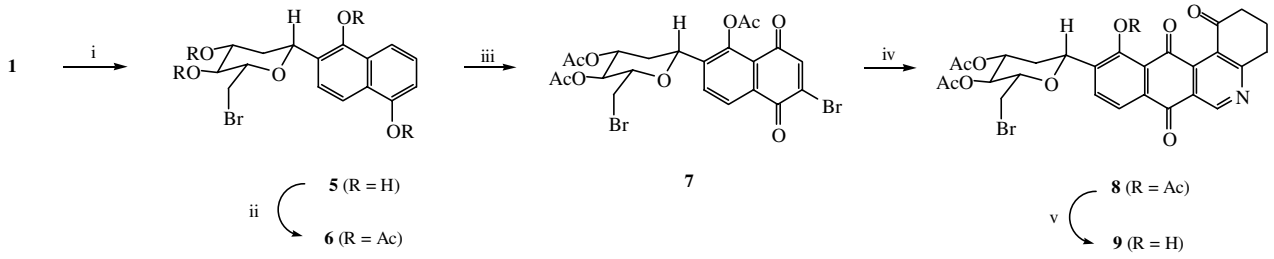
A possible precursor of **7** being the 1,5-naphthalene derivative **5**, we first attempted to reach this compound by treating the unprotected Toshima coupling product **1**[5] with PPh_3–Br_2, following a protocol developed for selective C6 halogenation of α-D-methyl glycosides.[6] Under these conditions, however, compound **5** was accompanied, inter alia, with di-bromo compounds from which it could only be separated after transformation to the peracetylated derivative **6**. Applying the Grunwell conditions[7] to **6** next afforded the key 2-bromo-[1,4]naphthoquinone **7** in good yield. Its subsequent condensation with diene **3** led, after in situ transformation of the primary adduct, to the tetracyclic trione **8**, which was selectively deacetylated to provide the angucycline 5-aza-analogue **9**[8] (84% yield for the two steps).

At this stage, we planned to introduce an azido group at C6′ by effecting a nucleophilic substitution of the bromine atom in **9**. Toward this end **9** was treated with sodium azide in DMSO at room temperature. These conditions, however, failed to give any traces of the expected angucycline 5-aza-analogue **13**. Fortunately, application of these same conditions to **6** effected the desired transformation to give **10** in moderate yield. As for the synthesis of **9**, the transformation of **10** to **13**[9] proceeded without incident over the course of three steps as outlined in Scheme 3.

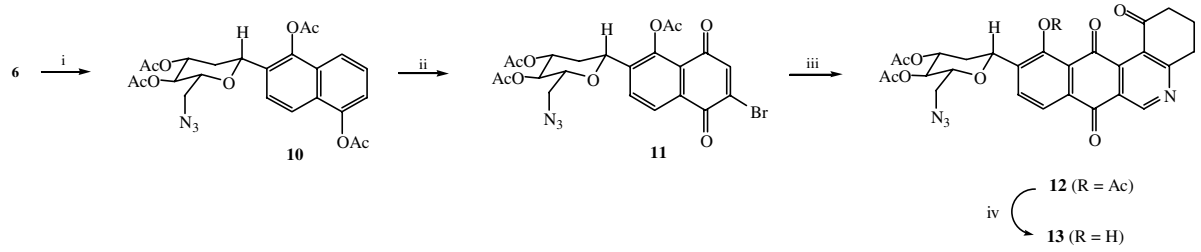
3. Introduction of a sugar unit at C9: synthesis of the angucycline 5-aza-analogue 14

Our next effort aimed at synthesizing the angucycline 5-aza-analogue **14** bearing a peracetylated D-2-deoxy-glucose residue linked at carbon C9. A retrosynthetic analysis based on a hetero Diels–Alder cycloaddition strategy allows to discern 2-bromo-[1,4]naphthoquinone **15** and diene **3** as key intermediates (Scheme 4).

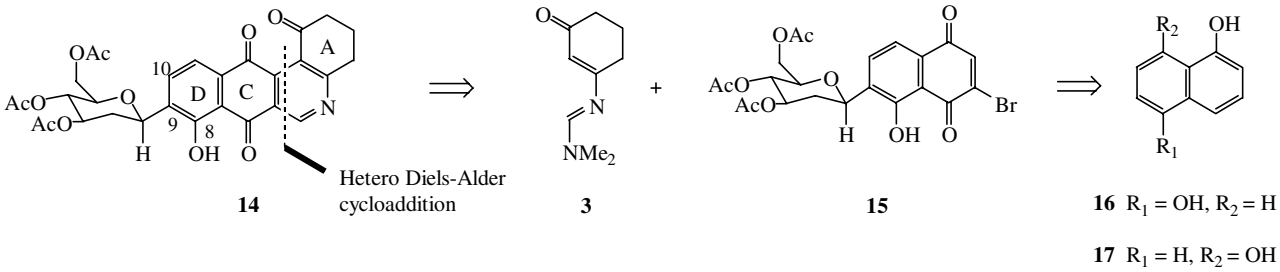
Prior experience gained in the synthesis of dienophile **2** from 1,5-naphthalene diol **16** suggested that its isomer



Scheme 2. Synthesis of the angucycline 5-aza-analogue **9**. Reagents and conditions: (i) Br_2 (1.5 equiv), PPh_3 (1.5 equiv), rt, 15 h; (ii) Ac_2O, Py, rt, 15 h (28%, two steps); (iii) NBS (6 equiv), AcOH–H_2O (1:2), 70 °C, 3 h, 77%; (iv) **3** (1.2 equiv), MeCN, 60 °C, 60 h; (v) NH_4OAc (8 equiv), MeOH–H_2O (4:1), rt, 7 h, 84% (two steps).



Scheme 3. Synthesis of the angucycline 5-aza-analogue **13**. Reagents and conditions: (i) NaN_3 (1.5 equiv), DMSO, rt, 12 h, 55%; (ii) NBS (6 equiv), AcOH–H_2O (1:2), 70 °C, 3 h, 38%; (iii) **3** (1.2 equiv), MeCN, 60 °C, 60 h; (iv) NH_4OAc (8 equiv), MeOH–H_2O (4:1), rt, 7 h, 84% (two steps).

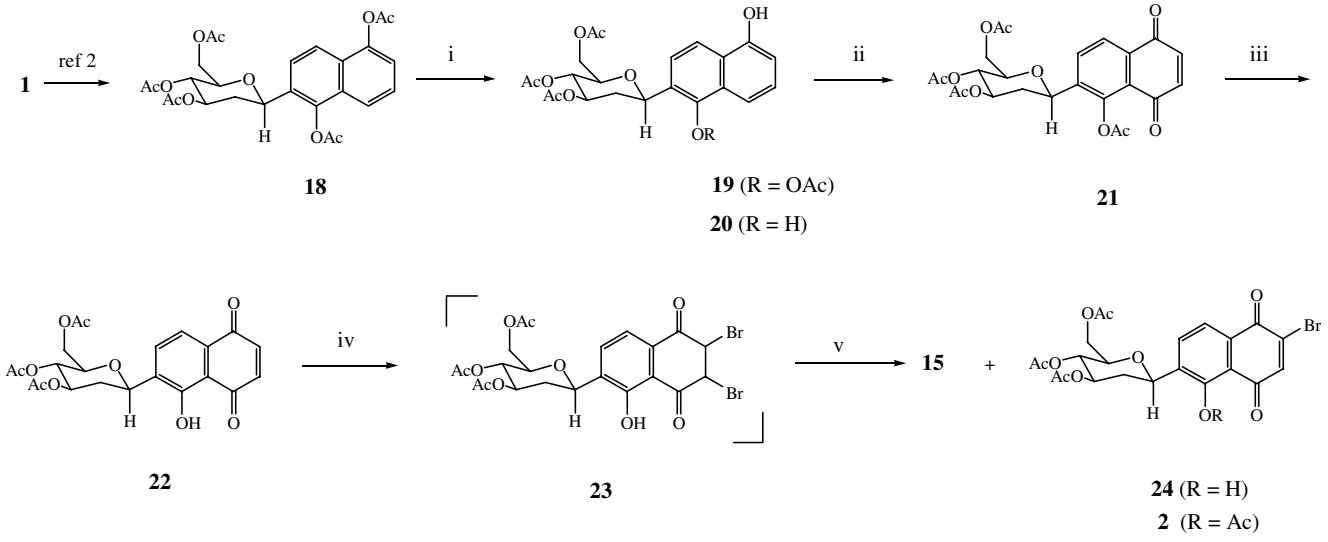


Scheme 4.

15 could be generated from 1,8-naphthalene diol **17** by application of an identical sequence of reactions. However, coupling of **17** with D-2-deoxyglucose under the conditions described by Toshima[5] proved unfruitful. We thus anticipated that the precursor of **2** (i.e., **1**) could also serve as an effective precursor to the 2-bromo-[1,4]naphthoquinone **15** as well, provided that appropriate modifications of experimental procedure, especially with respect to regioselectivity of the crucial bromination step, could be accomplished. The realization of this objective is outlined in Scheme 5.

The synthesis of **15** began with the chemoselective deacetylation of **18**, which, when treated with ammonium acetate,[10] afforded a 5:1 ratio of acetate **19** and diol **20**. These compounds were subsequently separated by column chromatography, thereby affording **19** in 63% isolated yield. Oxidation of **19** to 1,4-naphthoquinone **21** was best accomplished by treatment with an excess of diacetoxyiodobenzene (DAIB) in an acidic medium. Because **21** appeared to be somewhat unstable on silica, it was employed without further purification for the next step, which consisted in the chemoselective hydrolysis of the remaining acetoxy substituent on the naphthoquinone ring. After some unsuccessful experimentation, it was discovered that this transformation could be accomplished by exposure of **21** to an excess of BF_3–Et_2O in methylene chloride at room temperature for 5 days.[11] Under these experimental conditions, the 1,4-naphthoquinone **22** could be isolated in 62% overall yield. We were now in a position to effect the crucial bromination reaction. Treatment of **22** with bromine in chloroform followed by mild warming in EtOH led to a 4/1 mixture of isomeric bromo-[1,4]naphthoquinones **15** and **24**, that could not be easily separated by chromatography. However, when the crude primary di-bromo adduct **23** was heated in ethanol in the presence of BF_3–Et_2O,[12] the desired 2-bromo-[1,4]naphthoquinone **15** was formed, along with only a small amount of **24**. After crystallization from AcOEt–petroleum ether, **15** could be isolated in 65% yield and its structure confirmed by single-crystal X-ray analysis[13] (Fig. 1). Parenthetically, and unsurprisingly, bromination of the 1,4-naphthoquinone **21** led principally to the corresponding 2-bromo-5-acetoxy-[1,4]naphthoquinone **2**.

Finally, with the 2-bromo-[1,4]naphthoquinone **15** in hand, its cycloaddition with aza-diene **3** could be attempted. Admixture of both partners in acetonitrile at room temperature smoothly led to the desired angucycline 5-aza-analogue **14**[16] in a 61% yield.



Scheme 5. Synthesis of the 2-bromo-8-hydroxy-[1,4]naphthoquinone **15**. Reagents and conditions: (i) NH_4OAc (4 equiv), MeOH–H_2O, 4:1, 70 °C, 6 h, 63%; (ii) DAIB (3 equiv), TFA–AcOH–H_2O (6:3:1), 40 °C, 1 h; MeOH, rt, 2 h; (iii) BF_3–Et_2O (10 equiv), CH_2Cl_2, rt, 5 days (62%, two steps); (iv) Br_2 (1.1 equiv), $CHCl_3$, 0 °C, 2 h; (v) BF_3–Et_2O, EtOH, 60 °C, 15 min (65%).

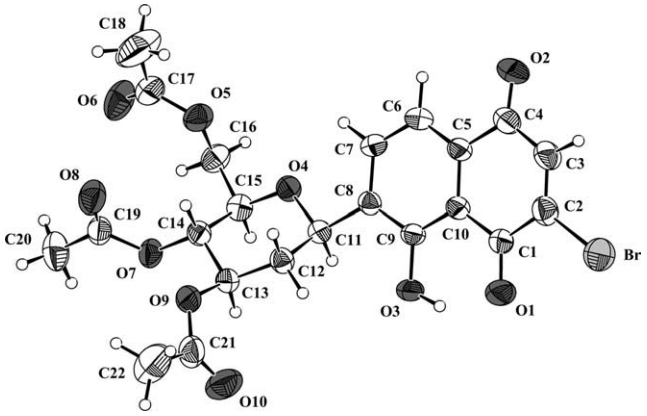


Figure 1. ORTEP drawing of compound **15**.

4. Conclusion

In conclusion, a convergent synthesis of the angucycline 5-aza-analogues **9**, **13**, and **14** has been achieved. A key feature of this synthetic work includes a [4+2] cycloaddition between a 2-aza-1,3-diene **3** and a 2-bromo-[1,4]naphthoquinone bearing a C6′-substituted (OAc, Br, N_3) *C*-glycoside moiety. Also of note is the preparation of dienophiles **2** and **15** from the common precursor **1**. We believe that the present work would facilitate the synthesis of a small library of angucycline 5-aza-analogues for biological evaluation.[17]

Acknowledgments

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8. Spectral data for compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (ddd, $J = 12.9$ Hz, $J = 11.4$ Hz, $J = 11.4$ Hz, 1H), 2.03 (s, 3H), 2.11 (s, 3H), 2.30 (dt, $J = 6.8$ Hz, $J = 6.1$ Hz, 2H), 2.67 (ddd, $J = 12.9$ Hz, $J = 5.2$ Hz, $J = 2.0$ Hz, 1H), 2.98 (t, $J = 6.8$ Hz, 2H), 3.22 (t, $J = 6.1$ Hz, 2H), 3.51 (dd, $J = 11.4$ Hz, $J = 5.6$ Hz, 1H), 3.60 (dd, $J = 11.4$ Hz, $J = 2.8$ Hz, 1H), 3.84 (ddd, $J = 8.3$ Hz, $J = 5.6$ Hz, $J = 2.8$ Hz, 1H), 5.06 (dd, $J = 11.4$ Hz, $J = 2.0$ Hz, 1H), 5.09 (dd, 1H, $J = 9.4$ Hz, $J = 9.4$ Hz, 1H), 5.28 (ddd, $J = 11.4$ Hz, $J = 9.4$ Hz, $J = 5.2$ Hz, 1H), 7.87 (d, $J = 8.1$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 9.51 (s, 1H), 12.05 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 21.4, 31.8, 33.2, 36.4, 39.2, 60.4, 71.3, 71.6, 71.7, 76.8, 116.2, 119.7, 126.4, 128.9, 131.1, 134.1, 136.8, 138.9, 151.6, 158.1, 169.1, 169.9, 170.3, 181.0, 186.9, 198.1. MS (CIN): 585 ($[C_{27}H_{24}NO_9{}^{79}Br]^-$, 94), 586 ($[C_{27}H_{24}NO_9{}^{81}Br-H]^-$, 29); 587 ($C_{27}H_{24}NO_9{}^{81}Br]^-$, 100). HRMS (ESP) $[M+Na]^+$: calcd for $C_{27}H_{24}NO_9BrNa$: 608.0532, found 608.0545. HRMS (ESP) $[M+K]^+$: calcd for $C_{27}H_{24}NO_9BrK$: 624.0272, found 624.0276. Anal. Calcd for $C_{27}H_{24}NO_9Br$: C, 55.30; H, 4.13; N, 2.39; Br, 13.63. Found: C, 55.31; H, 4.26; N, 2.32; Br, 13.34.
9. Spectral data for compound **13**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (ddd, $J = 12.7$ Hz, $J = 11.6$ Hz, $J = 11.6$ Hz, 1H), 2.03 (s, 3H), 2.09 (s, 3H), 2.30 (dt, $J = 6.6$ Hz, $J = 6.6$ Hz, 2H), 2.68 (ddd, $J = 12.7$ Hz, $J = 5.2$ Hz, $J = 2.0$ Hz, 1H), 2.97 (t, $J = 6.6$ Hz, 2H), 3.22 (t, $J = 6.6$ Hz, 2H), 3.37 (dd, $J = 13.4$ Hz, $J = 5.6$ Hz, 1H), 3.46 (dd, $J = 13.4$ Hz, $J = 2.5$ Hz, 1H), 3.84 (ddd, $J = 9.6$ Hz, $J = 5.6$ Hz, $J = 2.5$ Hz, 1H), 5.06 (dd, $J = 11.6$ Hz, $J = 2.0$ Hz, 1H), 5.09 (dd, $J = 9.6$ Hz, $J = 9.6$ Hz, 1H), 5.28 (ddd, $J = 11.6$ Hz, $J = 9.6$ Hz, $J = 5.2$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 9.50 (s, 1H), 12,06 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 21.4, 29.7, 33.2, 36.4, 39.2, 51.4, 70.2, 71.67, 71.69, 75.5, 116.2, 119.7, 126.4, 128.9, 131.1, 133.7, 136.6, 138.9, 151.6, 158.1, 169.1, 170.0, 170.3, 181.0, 187.0, 198.1. FT-IR (liquid film, cm^{-1}): 1746, 1778, 2108. MS (EI) $m/z = 548$ ($[M]^{+\cdot}$, 100); 520 ($[M-N_2]^{+\cdot}$, 3). HRMS (ESP) $[M+Na]^+$: calcd for $C_{27}H_{24}N_4O_9Na$: 571.1441, found 571.1436. HRMS (ESP) $[M+K]^+$: calcd for $C_{27}H_{24}N_4O_9K$: 587.1180, found 587.1179.
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13. X-ray crystallographic analysis—A plate-like (approximately $0.25 \times 0.25 \times 0.08$ mm^3 in dimension), orange colored crystal was attached at the tip of a glass Lindeman capillary by means of silicon glue. Data collection was performed on a Brüker-Nonius KappaCCD diffractometer with graphite monochromatized MoK-$L_{2,3}$ radiation. After the usual absorption correction (Gaussian integration), the structure was solved by direct methods (Sir2002[14]) and refined (Jana2000[15]) with anisotropic atomic displacement parameters for all non-H atoms. H atoms were defined with fully restrained angle (all H atoms but that of the OH group) and distance (all H atoms) geometry and riding isotropic displacement parameters (×1.2). Absolute configuration was unambiguously determined by refining the Flack enantiopole parameter (1.0018(19)) using Friedel pairs. The structure data are as

follows: $C_{22}H_{21}BrO_{10}$, $M_r = 525.3$, monoclinic, $P2_1$, $a = 5.6871(3)$ Å, $b = 13.0649(6)$ Å, $c = 15.6320(11)$ Å, $\beta = 99.054(5)°$, $V = 1147.01(11)$ Å^3, $Z = 2$, $D_{calcd} = 1.520$ g cm^{-3}, $F(000) = 536$, $\mu(MoK\text{-}L_{2,3}) = 1.845$ mm^{-1}, $T = 293$ K, $R(obs) = 0.0661$, $S(obs) = 1.87$ (6315 *hkl*, 4769 gt, 300 parameters, cutoff for observed: $I/\sigma(I) = 2$). Crystallographic details have been deposited at the Cambridge Crystallographic Data Center (deposition number: CCDC 278803).

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16. Spectral data for compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 (ddd, $J = 12.6$ Hz, $J = 11.7$ Hz, $J = 11.7$ Hz, 1H), 2.03 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.29 (qt, $J = 6.6$ Hz, 2H), 2.67 (ddd, $J = 12.6$ Hz, $J = 5.1$ Hz, $J = 1.8$ Hz, 1H), 2.95 (t, $J = 6.6$ Hz, 2H), 3.23 (t, $J = 6.6$ Hz, 2H), 3.84 (ddd, $J = 9.6$ Hz, $J = 4.8$ Hz, $J = 2.1$ Hz, 1H), 4.20 (dd, $J = 12.3$ Hz, $J = 1.8$ Hz, 1H), 4.37 (dd, $J = 12.3$ Hz, $J = 5.1$ Hz, 1H), 5.02 (d, $J = 9.9$ Hz, 1H), 5.09 (dd, 1H, $J = 9.6$ Hz, $J = 9.6$ Hz, 1H), 5.26 (m, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 7.8$ Hz, 1H), 9.51 (s, 1H), 12.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.85, 20.9, 21.0, 21.6, 33.5, 36.6, 39.2, 62.9, 69.6, 71.6, 72.1, 76.5, 114.8, 120.2, 126.6, 129.0, 133.7, 134.2, 136.5, 141.2, 151.3, 158.4, 169.8, 170.0, 170.4, 170.9, 181.8, 187.5, 197.5. FT-IR (KBr, cm^{-1}): 1571, 1636, 1683, 1710, 1748. MS (EI) $m/z =$ 566 ($[M+H]^+$, 1), 505 ($[M-OAc+H]^+$, 2); 385 (100). HRMS (ESP) $[M+Na]^+$: calcd for $C_{29}H_{27}NO_{11}Na$: 588.1482, found 588.1478. HRMS (ESP) $[M+K]^+$: calcd for $C_{29}H_{27}NO_{11}K$: 604.1221, found 624.1223.
17. Results of the cytotoxic tests will be reported elsewhere.