A Facile Cross-Metathesis–Radical-Cyclisation Approach to Monobenz-annulated Spiroketals

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Abstract: The synthesis of a series of 5,5-, 5,6-, and 6,6-monobenzannulated spiroketals using a novel cross-metathesis–radical-cyclisation approach is reported. Cross metathesis between two olefin coupling partners resulted in the formation of a heterodimer which upon hydrogenation furnished a saturated alcohol product. Oxidative radical cyclisation then afforded the desired monobenzannulated spiroketals in good overall yield.

Key words: cross metathesis, radical cyclisation, spiroketal, rubromycins, berkelic acid

Nature has historically provided the most important source of lead compounds for the development of new therapeutic agents. By modification of a biologically active lead compound, libraries of simplified analogues can be synthesised that maintain or improve the desired biological activity.[1]

Spiroketals are a common structural element in a plethora of natural products of medicinal and environmental importance.[2] One such set of compounds, the rubromycins (Figure 1) are a class of natural antibiotics that display a broad range of biological activity[3] that includes inhibition of human telomerase by β-rubromycin (**2**) and γ-rubromycin (**3**, IC_{50} 3.06 ± 0.85 μM and 2.64 ± 0.09 μM, respectively). Intriguingly, α-rubromycin (**1**), derived from ring opening of the spiroketal core of β-rubromycin (**2**), exhibits much lower inhibition of telomerase (IC_{50} > 200 μM) than other members of the family. The absence of a spiroketal moiety in α-rubromycin (**1**) implies that the spiroketal unit is an essential structural unit for inhibition of telomerase.[4] Another natural product, berkelic acid (**4**), possesses a monobenzannulated 6,5-spiroketal as well as an additional oxygen-containing six-membered ring which is fused to both rings of the chroman unit. It is an inhibitor of matrix metalloproteinase-3 (MMP-3) and caspase-1, and was shown to exhibit selectivity toward ovarian cancer cell line OVCAR-3 (GI_{50} 91 nM).[5] Inspired by the biological activity of compounds **1**–**4**, we envisioned building simplified analogues of the central benzannulated spiroketal core of β-rubromycin (**2**), γ-rubromycin (**3**), and berkelic acid (**4**) in order to see if the biological activity was maintained.

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Our research group has a longstanding interest in the synthesis of simplified analogues of the unique aryl spiroketal moiety of the rubromycins. For example, we reported the synthesis of a series of 5,6-bisbenzannulated[6] and 6,6-bisbenzannulated[7] spiroketals as well as a series of 6,6-bisbenzannulated spiroketals containing additional oxygen atoms[8] by a common acid-catalysed cyclisation of their respective dihydroxyketone precursors.

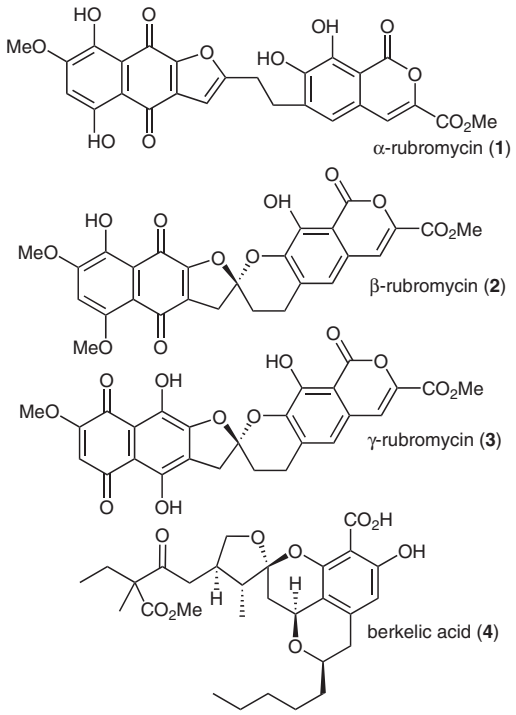
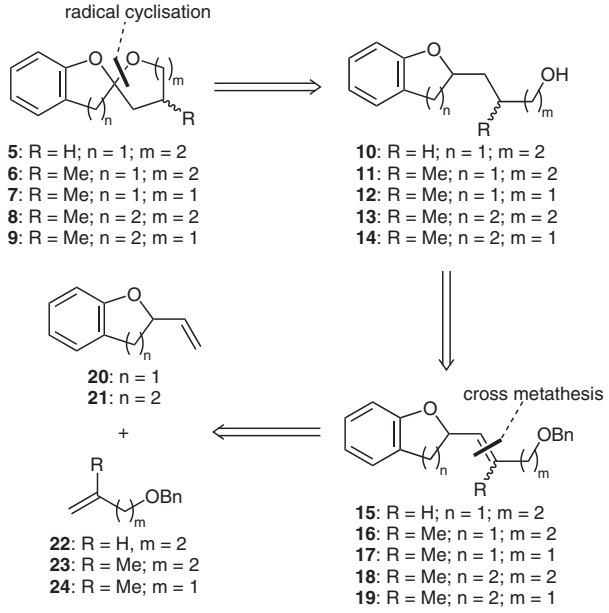


Figure 1 Spiroketal-containing natural products

Recent novel methods for the synthesis of monobenzannulated spiroketals include montmorillonite K-10 clay mediated formation of spirochromans from substituted 2-vinylpyrans via a glycosylation, Claisen rearrangement and intramolecular ring-closure sequence,[9] gold-catalysed double intramolecular alkyne hydroalkoxylation,[10] lactone alkylidenation with a functionalised titanium carbenoid bearing a protected hydroxyl group, followed by acid-mediated intramolecular cyclisation of the formed exocyclic enol ether,[11] and a hetero-Diels–Alder cycloaddition between an *o*-quinone methide and an *exo*-enol ether.[12] We now report the synthesis of a series of 5,5-, 5,6-, and 6,6-monobenzannulated spiroketals related to

the central spiroketal core of β-rubromycin (**2**), γ-rubromycin (**3**), and berkelic acid (**4**) using a novel cross-metathesis–radical-cyclisation approach.



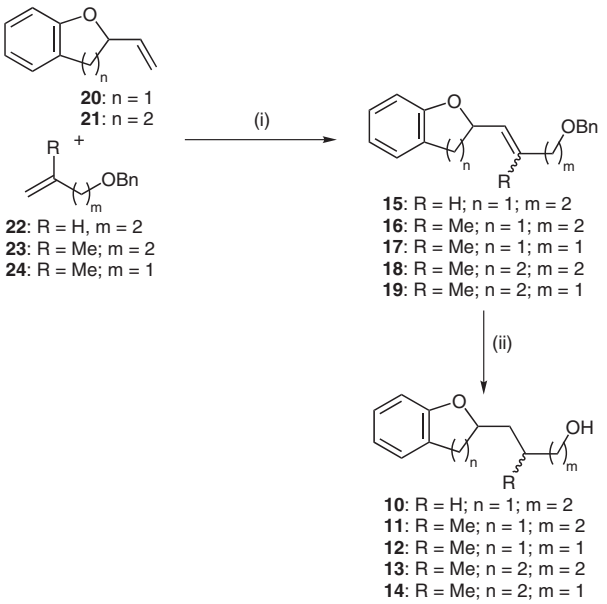
Scheme 1 Retrosynthesis of monobenzannulated spiroketals **5**–**9**

It was envisaged that monobenzannulated spiroketals **5**–**9** could be synthesised by oxidative radical cyclization[13] of alcohols **10**–**14** which in turn could be formed by concomitant hydrogenation of the olefin and hydrogenolysis of the benzyl group from olefin adducts **15**–**19**. Each of the olefin adducts **15**–**19** could in turn be assembled via cross metathesis of an appropriate terminal olefin **20** or **21** with an appropriate coupling partner **22**–**24** (Scheme 1). This convergent approach was envisaged to provide rapid access to a range of monobenzannulated spiroketals that would be amenable to analogue design.

Initially, the synthesis of the two heterocyclic alkenes **20** and **21** was conducted. Olefin **20** was synthesised from phenol in two steps using the procedure reported by Stoltz et al.,[14] and olefin **21** was readily available by the palladium-catalysed annulation of 2-iodophenol with 1,4-pentadiene.[15] Benzyl-protected olefin coupling partners **22**–**24** were obtained by benzylation of their appropriate alcohol precursors under standard conditions; thus, olefin **22**[16] was prepared from 3-buten-1-ol, olefin **23**[17] from 3-methyl-3-buten-1-ol, and olefin **24**[18] from 2-methyl-2-propen-1-ol.

With the appropriate starting materials to hand, attention turned to the cross-metathesis step (Scheme 2). Unfortunately, cross metathesis of olefin **20** with olefin **22** only afforded a low yield of heterodimer **15** exclusively as the *E*-isomer, unsurprisingly as both **20** and **22** are both classified as type I olefins.[19] As a result of this observation, disubstituted type III olefins **23** and **24** were envisioned as suitable coupling partners for heterocyclic olefins **20** and **21**. It was found that using one equivalent of olefin **20** and six equivalents of olefin **23** provided the best yield of the desired heterodimer **16** as an inconsequential mixture of *E*/*Z* isomers.

Based on this result, the synthesis of heterodimers **17**–**19** could thus be carried out in a similar fashion in moderate yields. Thus, **17** was obtained from olefin coupling partners **20** and **24**, **18** from **21** and **23**, and **19** from **21** and **24**, respectively. Heterodimers **16**–**19** were all produced as a mixture of *E*/*Z* isomers (Scheme 2).

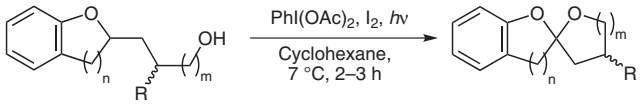


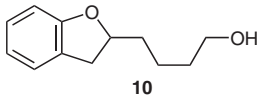
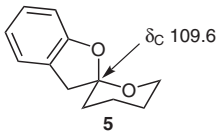
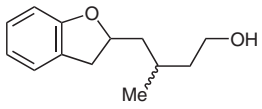
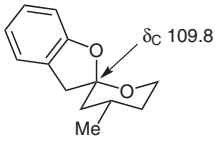
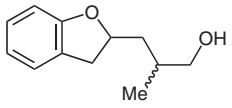
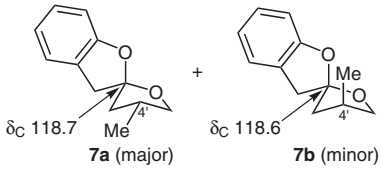
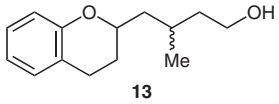
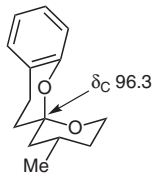
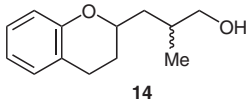
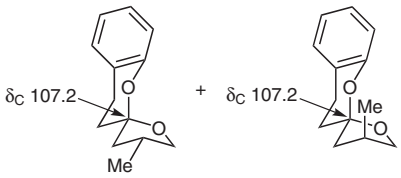
Scheme 2 *Reagents and conditions*: (i) Grubbs II, 60 °C, 14–70 h, **15**, 19% (*E*/*Z* = 1:0); **16**, 58%, (*E*/*Z* = 2.1:1); **17**, 57% (*E*/*Z* = 4:1); **18**, 38% (*E*/*Z* = 1.1:1); **19**, 51% (*E*/*Z* = 3.5:1); (ii) H_2, $Pd(OH)_2$/C, MeOH, r.t., 2.5–5 h, **10**, 44%; **12**, 83%; **14**, 76%, or H_2, 10% Pd/C, EtOAc, r.t., 3.5 h, **11**, 100%; **13**, 63%.

Having synthesised the required heterodimer products **15**–**19**, hydrogenation of the double bond and hydrogenolysis of the benzyl ethers could be conducted (Scheme 2). Thus, alcohols **10**,[20] **12**, and **14** were prepared from heterodimers **15**, **17**, and **19** respectively, using Pearlman's catalyst in methanol under an atmosphere of hydrogen. Alcohols **11** and **13** were prepared from heterodimers **16** and **18** in a similar fashion; however, it was necessary to change the catalyst system to 10% palladium on carbon in ethyl acetate. This was done to prevent further hydrogenolysis of the long-chain alcohols **10**, **11**, and **13** (m = 2) frequently observed using Pearlman's catalyst, interestingly not observed with the short-chain alcohols **12** and **14** (m = 1). Alcohols **11**–**14** were all isolated as an inseparable 1:1 mixture of diastereomers as determined by ^{1}H NMR.

Next, the key oxidative radical cyclisation of alcohols **10**–**14** was undertaken (Table 1). Using a procedure developed in our laboratory,[13c] irradiation of alcohols **10**–**14** with a desk lamp (60 W) in the presence of iodobenzene diacetate and iodine in cyclohexane at 7 °C delivered spiroketals **5**–**9** in variable yields.[21] Higher yields were

Table 1 Oxidative Radical Cyclisation of Alcohols **10**–**14**



Starting material	Product	Yield (%)	dr
 **10**	 **5**	40	
 **11**	 **6**	42	
 **12**	 **7a** (major) + **7b** (minor)	73	1.4:1
 **13**	 **8**	58	
 **14**	 **9a** (major) + **9b** (minor)	92	1.4:1

observed for the formation of the five-membered rings compared to their six-membered counterparts.

Spiroketal **5** was isolated as a single isomer wherein the C–O bond of the five-membered ring adopts an axial position with respect to the six-membered ring. For spiroketals **7** and **9**, two inseparable racemic diastereomers were observed for each spiroketal. With respect to diastereomeric spiroketals **7a** and **7b** (Figure 2), it was found that the methyl group at C-4′ in spiroketal **7a** was more upfield than the corresponding methyl group in **7b** where it occupied a position *syn* to the oxygen atom of the dihydrobenzofuran moiety. Similarly, the signal for H-4′ in spiroketal **7a** was further downfield than that for H-4′ in **7b** due to H-4′ in **7a** being *syn* to the oxygen atom of the dihydrobenzofuran moiety. Based on this and NOE evidence, spiroketal **7a** was assigned as the major diastereomer with the methyl group adopting a pseudoequatorial position.

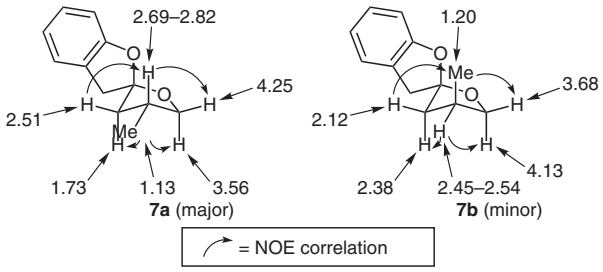


Figure 2 Selected δ_H values (ppm) and NOE correlations in spiroketals **7a** and **7b**

Surprisingly, spiroketals **6** and **8** were obtained as a single racemic diastereomer. It was established that the methyl substituent adopted an equatorial position on the six-membered ring, and the corresponding spiroketal bearing a methyl group in the axial position was not observed.

Presumably, once spiroketal formation had taken place, ring opening and ring closure occurred leading to formation of the thermodynamically favoured spiroketal in which the methyl group is equatorial and the C–O bond of the five-membered ring is axial with respect to the six-membered ring thus gaining maximum stability from the anomeric effect.[22] Thus, the formation of two racemic diastereomers for each of spiroketals **7** and **9** can be rationalised by the fact that the anomeric effect was weaker in five-membered ring systems (for spiroketals **7** and **9**) than in six-membered ring systems (for spiroketals **6** and **8**).[22]

In conclusion, the synthesis of substituted monobenzannulated spiroketals **5**–**9** was achieved using two key reactions, namely cross metathesis between two olefin coupling partners using Grubbs second-generation catalyst and intramolecular oxidative radical cyclisation of a tethered alcohol. Studies toward the synthesis of the rubromycins **1**–**3**, berkelic acid (**4**) and analogues using this methodology are ongoing.

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References and Notes

(1) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.
(2) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. *The Total Synthesis of Spiroketal-Containing Natural Products, In Total Synthesis of Natural Products*, Vol. 8; ApSimon, J., Ed.; John Wiley and Sons, **2007**.
(3) Brasholz, M.; Sörgel, S.; Azap, C.; Reißig, H.-U. *Eur. J. Org. Chem.* **2007**, 3801.
(4) Ueno, T.; Takahashi, H.; Oda, M.; Mizunuma, M.; Yokoyama, A.; Goto, Y.; Mizushina, Y.; Sakaguchi, K.; Hayashi, H. *Biochemistry* **2000**, *39*, 5995.
(5) Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357.
(6) (a) Tsang, K. Y.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425. (b) Tsang, K. Y.; Brimble, M. A. *Tetrahedron* **2007**, *63*, 6015.
(7) Brimble, M. A.; Flowers, C. L.; Trzoss, M.; Tsang, K. Y. *Tetrahedron* **2006**, *62*, 5883.
(8) Brimble, M. A.; Liu, Y.-C.; Trzoss, M. *Synthesis* **2007**, 1392.
(9) van Hooft, P. A. V.; van Swieten, P. F.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Synlett* **2001**, 269.
(10) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, 940.
(11) Main, C. A.; Rahman, S. S.; Hartley, R. C. *Tetrahedron Lett.* **2008**, *49*, 4771.
(12) (a) Huang, Y.; Pettus, T. R. R. *Synlett* **2008**, 1353. (b) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477. (c) Bray, C. D. *Org. Biomol. Chem.* **2008**, *6*, 2815. (d) Bray, C. D. *Synlett* **2008**, 2500.
(13) (a) Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, *61*, 3999. (b) Brimble, M. A.; Horner, G. M.; Stevenson, R. J. *Aust. J. Chem.* **1996**, *49*, 189. (c) Brimble, M. A. *Molecules* **2004**, *9*, 394. (d) Meilert, K.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 2184.
(14) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.
(15) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.
(16) Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063.
(17) Cleary, P. A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 5531.
(18) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.
(19) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(20) Normant, A. *Bull. Soc. Chim. Fr.* **1940**, *7*, 37.
(21) **General Procedure – Oxidative Radical Cyclisation**
A mixture of alcohol (0.052 mmol), $PhI(OAc)_2$ (0.106 mmol), and I_2 (0.118 mmol) in anhyd cyclohexane (4.3 mL) was degassed with argon at r.t. for 15 min. The resulting solution was cooled in an ice–water bath (7 °C) and irradiated with a desk lamp (60 W) for 2–3 h after which it was diluted with Et_2O (10 mL), then sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (10 mL) were added. After separation of both phases, the aqueous phase was extracted with Et_2O (4 × 15 mL). The organic phases were combined, dried over anhyd $MgSO_4$, filtered, and the solvents concentrated in vacuo. The crude product was purified by column chromatography on SiO_2 (100% *n*-pentane, then *n*-pentane–Et_2O, 12:1) to give the spiroketal product.
(±)-4′-Methyl-3′,4′5′,6′tetrahydro-3*H*-spiro(benzofuran-2,2′-pyran) (6)
Pale yellow oil (7 mg, 0.034 mmol, 42%); R_f = 0.31 (hexanes–Et_2O, 10:1). IR (film): 2946, 2925, 2869, 1597, 1479, 1461, 1377, 1238, 1216, 1121, 1096, 1084, 1034, 869, 826, 810, 791, 776, 747, 706 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.6 Hz, 3 H, C-4′-CH_3), 1.33 (qd, *J* = 12.8, 4.9 Hz, 1 H, H_{ax}-5′), 1.47 (dd, *J* = 13.1, 12.5 Hz, 1 H, H_{ax}-3′), 1.64 (dtd, *J* = 13.2, 3.8, 1.9 Hz, 1 H, H_{eq}-5′), 2.03 (ddd, *J* = 13.4, 3.8, 1.8 Hz, 1 H, H_{eq}-3′), 2.08–2.24 (m, 1 H, H_{ax}-4′), 3.05 (d, *J* = 16.3 Hz, 1 H, H_a-3), 3.12 (d, *J* = 16.3 Hz, 1 H, H_b-3), 3.74 (ddd, *J* = 11.4, 4.9, 1.5 Hz, 1 H, H_{eq}-6′), 4.06 (ddd, *J* = 11.3, 13.0, 2.4 Hz, 1 H, H_{ax}-6′), 6.80 (d, *J* = 7.9 Hz, 1 H, H-7), 6.85 (td, *J* = 7.4, 0.9 Hz, 1 H, H-5), 7.10–7.17 (m, 2 H, H-4 and H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3, C-4′-*C*H_3), 26.2 (CH, C-4′), 33.3 (CH_2, C-5′), 42.5 (CH_2, C-3′) 42.8 (CH_2, C-3), 62.6 (CH_2, C-6′), 109.7 (CH, C-7), 109.8 (C, C-2), 120.6 (CH, C-5), 124.9 (CH, C-4), 126.0 (C, C-3a), 127.9 (CH, C-6), 158.2 (C, C-7a). MS (EI, 70 eV): *m/z* (%) = 41 (30), 51 (12), 55 (15), 69 (16), 78 (41), 91 (12), 97 (70), 107 (29), 115 (4), 121 (4.5), 131 (21), 134 (10), 145 (3), 159 (2.5), 171 (1.5), 189 (59.5), 203 (5), 204 (100) $[M]^+$. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1146.
(±)-4′-Methyl-4′,5′-dihydro-3*H*,3′*H*-spiro(benzofuran-2,2′-furan) (7a,b)
Pale yellow oil (8 mg, 0.042 mmol, 73%); **7a/7b** = 1.4:1, mixture of inseparable major (**7a**) and minor* (**7b**) diastereomers; R_f = 0.33 (hexanes–EtOAc, 9:1). IR (film): 2954, 2924, 2855, 1598, 1479, 1462, 1377, 1241, 1120, 1082, 1010, 830, 779, 747, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.8 Hz, 3 H, C-4′-CH_3), 1.20 (d, *J* = 6.6 Hz, 2.1 H, C-4′-CH_3*), 1.73 (dd, *J* = 12.9, 10.1 Hz, 1 H, H_B-3′), 2.12 (dd, *J* = 13.6, 6.0 Hz, 0.7 H, H_A-3′*), 2.38 (dd, *J* = 13.4, 9.4 Hz, 0.7 H, H_B-3′*), 2.45–2.54 (m, 0.7 H, H-4′*), 2.51 (dd, *J* = 12.9, 7.0 Hz, 1 H, H_A-3′), 2.69–2.82 (m, 1 H, H-4′), 3.23–3.32 (m, 3.4 H, H-3 and H-3*), 3.56 (t, *J* = 8.0 Hz, 1 H, H_B-5′), 3.68 (t, *J* = 8.2 Hz, 0.7 H, H_A-5′*), 4.13 (t, *J* = 7.9 Hz, 0.7 H, H_B-5′*), 4.25 (t, *J* = 8.0 Hz, 1 H, H_A-5′), 6.76 (d, *J* = 8.4 Hz, 1 H, H-7), 6.79 (d, *J* = 8.9 Hz, 0.7 H, H-7*), 6.85 (t, *J* = 7.4 Hz, 1.7 H, H-5 and H-5*), 7.11 (t,

J = 7.9 Hz, 1.7 H, H-6 and H-6*), 7.16 (d, *J* = 7.4 Hz, 1.7 H, H-4 and H-4*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (CH_3, C-4′-*C*H_3), 18.0 (CH_3, C-4′-*C*H_3*), 32.3 (CH, C-4′), 32.9 (CH, C-4′*), 39.0 (CH_2, C-3), 40.1 (CH_2, C-3*), 44.6 (CH_2, C-3′*), 45.2 (CH_2, C-3′), 75.3 (CH_2, C-5′*), 75.5 (CH_2, C-5′), 109.4 (CH, C-7), 109.5 (CH, C-7*), 118.6 (C, C-2*), 118.7 (C, C-2), 120.46 (CH, C-5), 120.51 (CH, C-5*), 124.49 (CH, C-4*), 124.53 (CH, C-4), 125.7 (C, C-3a), 125.8 (C, C-3a*), 127.89 (CH, C-6*), 127.94 (CH, C-6), 157.7 (C, C-7a), 158.0 (C, C-7a*). MS (EI, 70 eV): *m/z* (%) = 37 (21), 47 (41.5), 78 (10), 83 (100), 85 (65.5), 107 (21), 131 (6), 134 (3.5), 175 (9), 190 (30) $[M]^+$. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{14}O_2$: 190.0994; found: 190.0990.

(22) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry, In Organic Chemistry Series*, Vol. 1; Baldwin, J. E., Ed.; Pergamon: Oxford, **1983**, 4.