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Reappraisal of the diastereoselectivity of intramolecular Diels–Alder reactions of some *o*-quinodimethanes generated by benzocyclobutene thermolysis: some complementary results and an improvement

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Abstract—In a synthetic approach to 19-nor steroids and in order to compare the diastereoselectivities observed for the intramolecular Diels–Alder reactions of *o*-quinodimethanes generated either from **1** or **2**, the thermolysis of benzocyclobutenes such as **2** was reexamined. The IMDA diastereoselectivity was highly dependent on the nature of the protective group of the hydroxyl substituent at the unique chiral stereocentre of the *o*-quinodimethane intermediate, in a position α to the double bond of the dienophile. Consistently with previous results reported for benzocyclobutenes **2**, the *trans*-fused cycloadducts were the major products, the *trans syn* or *trans anti* predominant isomer being determined by the hydroxyl protective group. In contrast with these previous reports, the *cis*-fused cycloadducts were always formed competitively, although as minor products. In the present work, the diastereoselectivity was improved by achieving the thermolysis of a benzocyclobutene **2** having a lithium alkoxide which afforded the *trans syn* adduct in high yield.

1. Introduction

For our study concerning the generation of *o*-quinodimethanes from precursors such as **1** and the diastereoselectivity of their intramolecular Diels–Alder reactions,[1,2] it was necessary to compare our results with those previously obtained by Kametani and Fukumoto for the thermolysis of the benzocyclobutenes **2**,[3] and hence to get the reference compounds $\mathbf{3_A}$, $\mathbf{4_A}$, $\mathbf{5_A}$ and $\mathbf{6_A}$ for the chemical filiation of the cycloadducts (Scheme 1).

Therefore, we reproduced the thermolysis of some compounds previously studied,[3] $\mathbf{2_A}$ and $\mathbf{2_D}$. We also examined some other protective groups in order to see if we might improve the IMDA diastereoselectivity and get a better understanding of the factors determining it in those examples.

2. Thermolysis of benzocyclobutenes: IMDA yield and diastereoselectivity (Table 1)

The racemic alcohol $\mathbf{2_A}$ was prepared according to Kametani,[3,4] and standard procedures afforded the corresponding derivatives $\mathbf{2_B}$ to $\mathbf{2_G}$ in high yields (82–91%). The lithium alkoxide $\mathbf{2_H}$ was generated in situ by addition of *n*-BuLi 1.6 M in hexane (1.1 equiv), at 0 °C, to the solution of $\mathbf{2_A}$ in toluene before sealing the tube under argon. All the thermolyses were achieved in sealed tubes (under argon), for solutions of precursors $\mathbf{2_A}$–$\mathbf{2_H}$ (0.11 M) in anhydrous toluene, at 180 °C for 22 h, to afford the cycloadducts in high yields (Table 1). In those conditions, the *o*-quinodimethane dimeric products were not observed. Each diastereoisomer was isolated by chromatography and characterized.[1] The structures of the cycloadducts were unambiguously assigned by identification of $\mathbf{3_A}$ and the derived ketone **7** with authentic samples provided by Roussel Uclaf,[5] and by chemical filiation for $\mathbf{4_A}$, $\mathbf{5_A}$ and $\mathbf{6_A}$. The structures of the other

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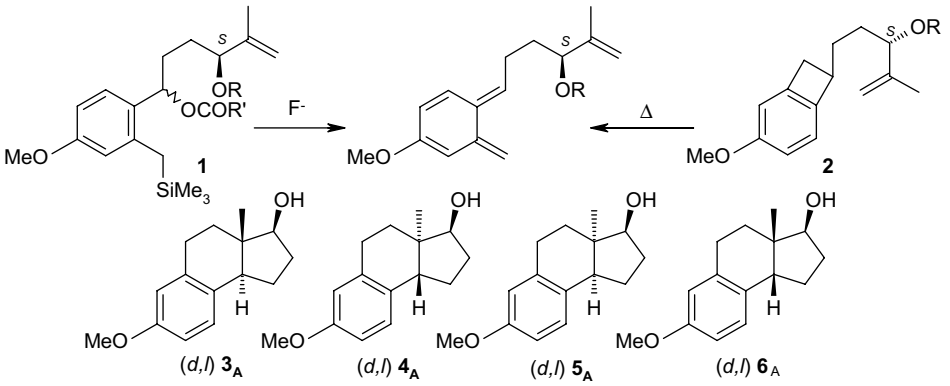


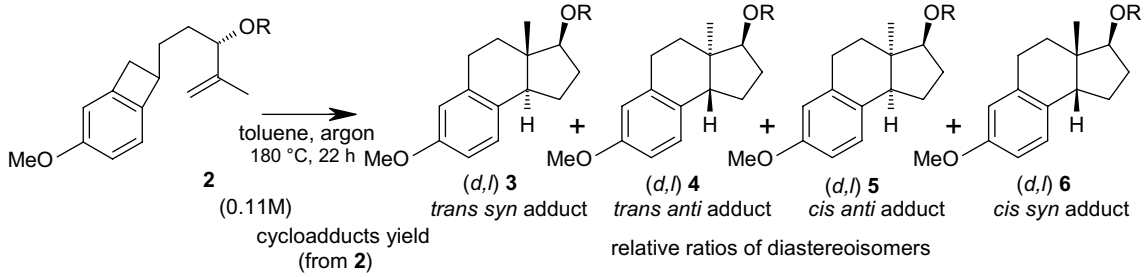
Scheme 1.

cycloadducts were established by cleavage of the hydroxyl protective group. For each IMDA experiment, the diastereoselectivities were measured on $\mathbf{3_A}$–$\mathbf{6_A}$ obtained after complete cleavage of the hydroxyl protective group on the crude product, by careful integration of the angular methyl group, by ^{1}H NMR (200 MHz, $CDCl_3$), and by HPLC (Lichrosorb Si 60 μm; eluent: 11:89:0.2 EtOAc–hexane–AcOH; flow rate: 2 mL/min).

The diastereoselectivities given in Table 1 were shown to be kinetic results, since each isolated cycloadduct ($\mathbf{3_B}$, $\mathbf{4_B}$, $\mathbf{5_B}$ or $\mathbf{6_B}$) remained unchanged when heated again in the same conditions (toluene, 180 °C, 24 h). No difference of diastereoselectivity was observed with or without BHT as a radical inhibitor.[6]

Kametani and Fukumoto previously reported the exclusive formation of the two *trans*-fused cycloadducts by thermolysis of benzocyclobutenes **2** (R = H, Si-*i*-Pr_3, TBS, TBDPS, BOM, THP, CPh_3).[3] However, they mentioned once that, in the case of the thermolysis of $\mathbf{2_A}$, a reexamination of the ^{1}H NMR spectra of the crude product confirmed that the cycloaddition gave *cis*-fused and *trans*-fused cycloadducts in a 1:4 ratio; however, the exact diastereoselectivity between the diastereomers $\mathbf{3_A}$–$\mathbf{6_A}$ was then not specified.[7] As shown in Table 1, thermolysis of the benzocyclobutenes $\mathbf{2_A}$–$\mathbf{2_H}$ led in each case to a mixture of four diastereoisomers. As previously reported,[3,7] the *trans*-fused cycloadducts are the major products and our structural assignments are consistent with the corrected assignments[3d] of Nemoto and Fukumoto which appeared during completion of the present work.[1] However, the *cis*-fused products are always formed to a non-negligible extent, mostly the *cis syn* adduct **6**. It is worth pointing out that the diastereoselectivity is often difficult to estimate on the hydroxyl protected cycloadducts and it was found to be the best measured on the derived alcohols $\mathbf{3_A}$–$\mathbf{6_A}$ after complete deprotection, with a good precision and calibration in the aforementioned HPLC conditions in which alcohols $\mathbf{3_A}$–$\mathbf{6_A}$ are well separated (t_R (min): $\mathbf{4_A}$, 13.66; $\mathbf{6_A}$, 14.75; $\mathbf{5_A}$, 16.38; $\mathbf{3_A}$, 18.21). On the other hand, the ^{1}H NMR angular methyl group signals are clearly separated for $\mathbf{3_A}$–$\mathbf{6_A}$ in $CDCl_3$ (δ/TMS: $\mathbf{3_A}$:0.65; $\mathbf{4_A}$:0.56; $\mathbf{5_A}$:1.08; $\mathbf{6_A}$:1.02).[1] With respect to the ratios of *trans anti* **4** to *trans syn* **3** adducts previously reported by Fukumoto and Nemoto for R = Si-*i*-Pr_3 (2:1), TBS (2.3:1) and TBDPS (1.5:1),[3d] here, the *trans anti* cycloadduct **4** is also the major product with silyl ethers as protective groups for $\mathbf{2_D}$–$\mathbf{2_G}$ R = $SiMe_2$-*i*-Pr (1.9:1), $SiMe_2$Thex

Table 1. Yields and diastereoselectivity of the Diels–Alder reaction from the *o*-quinodimethane generated in situ from benzocyclobutenes $\mathbf{2_A}$ to $\mathbf{2_H}$



R = H	$\mathbf{2_A}$	92%	$\mathbf{3_A}$ 34%	$\mathbf{4_A}$ 48%	$\mathbf{5_A}$ 8%	$\mathbf{6_A}$ 10%
R = MEM	$\mathbf{2_B}$	99%	$\mathbf{3_B}$ 49%	$\mathbf{4_B}$ 35%	$\mathbf{5_B}$ 3%	$\mathbf{6_B}$ 12%
R = MOM	$\mathbf{2_C}$	96%	$\mathbf{3_C}$ 48%	$\mathbf{4_C}$ 36%	$\mathbf{5_C}$ 3%	$\mathbf{6_C}$ 12%
R = TBS	$\mathbf{2_D}$	80%	$\mathbf{3_D}$ 23%	$\mathbf{4_D}$ 60%	$\mathbf{5_D}$ 4%	$\mathbf{6_D}$ 13%
R = $SiMe_2Ph$	$\mathbf{2_E}$	97%	$\mathbf{3_E}$ 32%	$\mathbf{4_E}$ 54%	$\mathbf{5_E}$ 5%	$\mathbf{6_E}$ 9%
R = $SiMe_2$*i*Pr	$\mathbf{2_F}$	99%	$\mathbf{3_F}$ 30%	$\mathbf{4_F}$ 56%	$\mathbf{5_F}$ 6%	$\mathbf{6_F}$ 8%
R = $SiMe_2$Thex	$\mathbf{2_G}$	98%	$\mathbf{3_G}$ 31%	$\mathbf{4_G}$ 52%	$\mathbf{5_G}$ 6%	$\mathbf{6_G}$ 10%
R = Li	$\mathbf{2_H}$	94%	$\mathbf{3_A}$ 67%	$\mathbf{4_A}$ 15%	$\mathbf{5_A}$ 2%	$\mathbf{6_A}$ 16%

(1.7:1), $SiMe_2Ph$ (1.7:1) and TBS (2.6:1) whereas the MEM or MOM ethers, $\mathbf{2_B}$ and $\mathbf{2_C}$, afford with a slight preference (1.3–1.4:1) the *trans syn* adduct $\mathbf{3_B}$ or $\mathbf{3_C}$. For alcohol $\mathbf{2_A}$, unlike the previously reported 1:1 ratio for $\mathbf{3_A}$ and $\mathbf{4_A}$,[3] we found that the *trans anti* adduct $\mathbf{4_A}$ is slightly favoured (1.4:1). Noteworthy, thermolysis of the lithium alkoxide $\mathbf{2_H}$ affords the cycloadducts in high yield (94%) and, from all the derivatives of $\mathbf{2_A}$ examined till now,[1,3] gives the best diastereoselectivity, moreover affording after aqueous work-up the *trans syn* adduct $\mathbf{3_A}$ in a 4.5:1 ratio with respect to $\mathbf{4_A}$; however, in those conditions, the relative ratio of the *cis syn* adduct $\mathbf{6_A}$ increases to 16% and is presently the highest observed. On the other hand, the thermolysis of the TBS ether $\mathbf{2_D}$ gives the best access to the *trans anti* adduct. It is also worth pointing out that the thermolysis of the benzocyclobutenes $\mathbf{2_A}$–$\mathbf{2_H}$ always affords a mixture of four diastereoisomers and in a comparable 4:1 ratio of *trans*- to *cis*-fused cycloadducts, whatever the nature of the derivative examined here.

3. Compared diastereoselectivities obtained from *o*-quinodimethane precursors 1 and 2

In the preceding communication, we reported the efficient in situ formation of *o*-quinodimethanes from **1** and their intramolecular Diels–Alder reaction, with the corresponding diastereoselectivities.[2] Comparison of the data respectively obtained from precursors **1** and **2** (R = MEM, MOM and TBS) shows that in each case, for the same protective group, the diastereoselection was slightly improved when the *o*-quinodimethane intermediate was generated by fluoride induced 1,4 elimination from **1**, at 80 °C. Thus, the ratio of the *trans*- to the *cis*-fused cycloadducts is about 9:1, at 80 °C, instead of 4:1 by the thermolysis of benzocyclobutenes at 180 °C. Depending on the hydroxyl protective group, the major diastereomer is the same by the two procedures and the diastereoselectivity improvement is only due to the temperature effect, and its incidence is relatively weak as anticipated for an IMDA. This was clearly shown by examining the reactions of $\mathbf{1_B}$ (R = MEM, R′ = Ph) at different temperatures, and the diastereoselectivity was also shown to be identical at 180 °C with that obtained at the same temperature by thermolysis of $\mathbf{2_B}$.[1,2]

4. Structural assignments of the cycloadducts

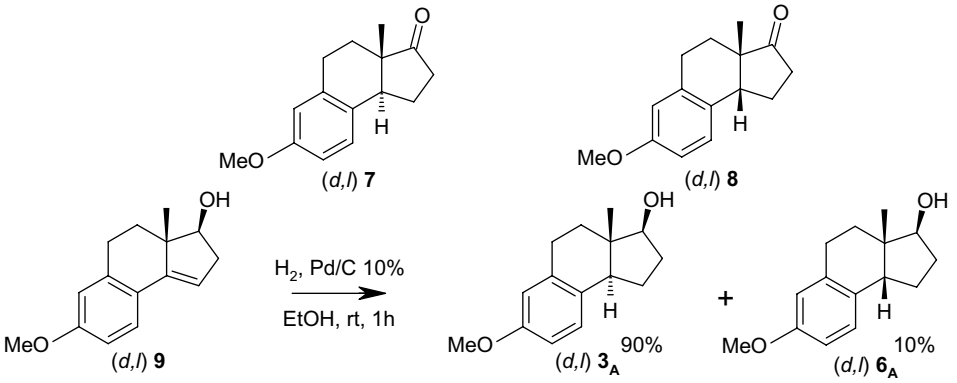
In order to establish the structure and the stereochemistry of each cycloadduct, compounds **3** to **6** were deprotected in classical conditions to afford $\mathbf{3_A}$, $\mathbf{4_A}$, $\mathbf{5_A}$ and $\mathbf{6_A}$. Compound $\mathbf{3_A}$ was identical with an authentic sample provided by Roussel Uclaf.[5] Oxidation of $\mathbf{3_A}$ and $\mathbf{4_A}$ with PCC afforded the same ketone, identical with an authentic sample of the *trans*-hydrindanone **7** provided by Roussel Uclaf.[5] Compound $\mathbf{3_A}$ was also converted into $\mathbf{4_A}$, via a Mitsunobu reaction (*p*-nitrobenzoic acid 1.2 equiv/PPh_3 1.2 equiv/DEAD 1.2 equiv, toluene, 80 °C, 3 h, 91%) and subsequent cleavage of the ester (KOH 8 equiv, MeOH, rt, 1 h, 95%).[8]

The chemical shift of the angular methyl group is characteristic of the *trans*-fused hydrindanes $\mathbf{3_A}$ and $\mathbf{4_A}$ (δ/TMS = 0.65 and 0.56, respectively, in $CDCl_3$), and of the *cis*-fused hydrindanes for $\mathbf{5_A}$ and $\mathbf{6_A}$ (δ/TMS = 1.08 and 1.02, respectively, in $CDCl_3$). For $\mathbf{4_A}$, the signal of the *pro*-17 hydrogen is a doublet ($J = 6.1$ Hz), compatible with an envelope or a half-chair of the five-membered ring with a dihedral angle $H_{17\alpha}$–C_{17}–C_{16}–$H_{16\beta}$ of about 90°. For $\mathbf{3_A}$, the signal of the *pro*-17 hydrogen is a doublet of doublet ($J = 7.5$ Hz and $J = 9.0$ Hz).[9] Considering the ^{13}C NMR data in $CDCl_3$, the signal of the angular methyl group of $\mathbf{3_A}$ ($\delta = 10.4$) is at higher field with respect to that in $\mathbf{4_A}$ ($\delta = 16.3$), which is consistent with the assigned relative configurations, OH and Me *syn* in $\mathbf{3_A}$, OH and Me *anti* in $\mathbf{4_A}$, according to the work of Roberts on 2-methylcyclopentanols,[10] and with the γ effect due to the OH group.[11] With respect to $\mathbf{3_A}$ (C_{12}, $\delta = 33.6$; C_{14}, $\delta = 45.4$), the strong shielding of C_{12} ($\delta = 28.9$) and the higher field shift of C_{14} ($\delta = 43.7$) observed for $\mathbf{4_A}$ are consistent with the pseudo-axial orientation of the OH group in that cycloadduct. Noteworthy, although also being γ to the OH, C_{15} is not shielded in $\mathbf{4_A}$, but slightly deshielded ($\delta = 24.5$) with respect to $\mathbf{3_A}$ ($\delta = 23.0$), probably due to the different geometric situation in an envelope or a half-chair conformation of the five-membered ring with a pseudo-axial OH in $\mathbf{4_A}$.

On the other hand, the structures of $\mathbf{5_A}$ and $\mathbf{6_A}$ were unambiguously assigned since their oxidation with PCC afforded the same ketone **8**, different from **7**. The chemical shift of the angular methyl group ($\delta = 1.11$, $CDCl_3$) of the ketone derived from $\mathbf{5_A}$ and $\mathbf{6_A}$, significantly different from that in **7** ($\delta = 0.73$, $CDCl_3$), is in good agreement with that reported for **8**.[3d,12] The *cis*-fused ring junction was definitely proven by hydrogenation of (*d*,*l*)-**9**, sample provided by Roussel Uclaf, which afforded $\mathbf{3_A}$ as the major product, but also a minor compound identical to $\mathbf{6_A}$, thus establishing unambiguously the *cis syn* structure of the latter (Scheme 2). Furthermore, $\mathbf{6_A}$ was converted into $\mathbf{5_A}$, via a Mitsunobu reaction (*p*-nitrobenzoic acid 1.5 equiv/PPh_3 1.5 equiv/DEAD 1.2 equiv, toluene, rt, 2 h, 47%) and further cleavage of the ester ($LiAlH_4$ 1.2 equiv, THF, rt, 10 min, 95.5%).[8]

The structures of $\mathbf{5_A}$ and $\mathbf{6_A}$ were also confirmed by NOE experiments proving the *cis* relation of the angular methyl group (Me_{18}) and H_{14} in those compounds, and also of $H_{17}/H_{14}/Me_{18}$ in $\mathbf{5_A}$. Concerning ^{13}C NMR data in $CDCl_3$, the signal of the angular methyl group consistently is at a higher field ($\delta = 19.3$) for $\mathbf{6_A}$ than in $\mathbf{5_A}$ ($\delta = 22.4$), due to the *syn* relative configuration of Me_{18} and the OH. The chemical shifts of C_{12} are also consistent with a stronger γ effect of the OH in $\mathbf{5_A}$ ($\delta = 30.6$), when compared to $\mathbf{6_A}$ ($\delta = 32.7$). Noteworthy, the difference of the ^{13}C chemical shifts for the homologous carbons (Me_{18}, C_{12}) of the two diastereomers are smaller for the *cis*-fused ($\mathbf{5_A}$, $\mathbf{6_A}$) than for the *trans*-fused ($\mathbf{3_A}$, $\mathbf{4_A}$) compounds, probably due to some conformational flexibility of the *cis*-hydrindanes.[13]

As a conclusion, we reexamined the benzocyclobutene thermolysis in order to analyze and compare the results



Scheme 2.

obtained by two different methods for the in situ generation of *o*-quinodimethanes. As shown previously in the pioneering work of Kametani, Fukumoto and Nemoto, IMDA diastereoselectivity is highly dependent on the nature of the hydroxyl protective group corresponding to a single chiral stereocentre at the allylic position of the dienophile. Consistent with the previously reported results,[3] the *trans syn* and *trans anti* cycloadducts are the major products, but we showed also in each case the formation of the *cis syn* and *cis anti* adducts as minor products. The best diastereoselectivity was obtained with the thermolysis of the lithium alkoxide $\mathbf{2_H}$ which afforded the *trans syn* adduct in high yield.

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9. Steroid numbering for the compounds $\mathbf{3_A}$, $\mathbf{4_A}$, $\mathbf{5_A}$ and $\mathbf{6_A}$.
Compound $\mathbf{3_A}$: IR (cm^{-1}, $CHCl_3$): 3611 (OH), 1609, 1575, 1501 (Ar); UV (EtOH): $\lambda_{max} = 280$ nm ($\varepsilon = 2200$), $\lambda_{max} = 289$ nm ($\varepsilon = 2000$); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 0.65 (s, 3H, Me), 1.67 (br s, 1H, OH, exchangeable), 1.68 (m, 3H, H_{12}, H_{15}, H_{16}), 1.96 (m, 2H, H_{12}, H_{15}), 2.32 (m, 1H, H_{16}), 2.58 (dd, 1H, H_{14}, $J = 10.8$, $J = 11.0$), 2.91 (dd, 2H, H_{11}, $J = 4.8$, $J = 9.5$), 3.78 (s, 3H, OMe), 3.89 (dd, 1H, $H_{17\alpha}$, $J = 7.5$, $J = 9.0$), 6.68 (m, 2H, H_6, H_{10}), 6.91 (m, 1H, H_7); ^{13}C NMR (50.3 MHz, $CDCl_3$): 10.4 (Me), 23.0 (C_{15}), 26.9 (C_{11}), 31.1 (C_{16}), 33.6 (C_{12}), 43.1 (C_{13}), 45.4 (C_{14}), 55.1 (OMe), 80.8 (C_{17}), 110.9 (C_6), 113.5 (C_{10}), 113.6 (C_8), 126.3 (C_7), 137.2 (C_9), 157.4 (C_5); MS (EI, *m/z*): 232 (M^+), 214, 199, 188, 173 (100%), 161; $C_{15}H_{20}O_2 =$ 232.32. Anal. Calcd C, 77.6; H, 8.6. Found: C, 77.4; H, 8.5.
Compound $\mathbf{4_A}$: IR (cm^{-1}, $CHCl_3$): 3615 (OH), 1609, 1573, 1502 (Ar);); ^1H NMR (400 MHz, $CDCl_3$): δ/TMS 0.56 (s, 3H, Me), 1.42 (br s, 1H, OH, exchangeable), 1.50–1.76 (m, 3H, H_{12}, H_{15}, H_{16}), 2.03 (m, 1H, H_{12}), 2.24 (m, 1H, H_{15}), 2.38 (m, 1H, H_{16}), 2.95–3.00 (m, 3H, $2H_{11}$, H_{14}), 3.77 (s, 3H, OMe), 3.93 (d, 1H, H_{17}, $J = 6.1$); 6.67 (m, 2H, H_6, H_{10}), 6.98 (m, 1H, H_7); ^{13}C NMR (50.3 MHz, $CDCl_3$): 16.3 (Me), 24.5 (C_{15}), 27.2 (C_{11}), 28.9 (C_{12}), 33.4 (C_{16}), 43.7 (C_{14}), 45.3 (C_{13}), 55.1 (OMe), 79.1 (C_{17}), 110.9 (C_6), 113.5 (C_{10}), 127.1 (C_7), 132.5 (C_8), 137.3 (C_9), 157.4 (C_5); MS (EI, *m/z*): 232 (M^+), 214, 199 (100%), 173, 161; $C_{15}H_{20}O_2 = 232.32$.
Compound $\mathbf{5_A}$: IR (cm^{-1}, $CHCl_3$): 3612 (OH), 1610, 1576, 1502 (Ar); ^1H NMR (200 MHz, $CDCl_3$): δ/TMS 1.08 (s, 3H, Me), 1.48–1.82 (m, 4H, H_{12}, $2H_{15}$, H_{16}), 1.77 (br s, 1H, OH, exchangeable), 2.00–2.25 (m, 2H, H_{12}, H_{16}), 2.66 (t, 1H, H_{14}, $J = 9.0$), 2.78–2.90 (m, 2H, H_{11}), 3.82 (s, 3H, OMe), 4.01 (t, 1H, H_{17}, $J = 8.3$), 6.66 (d, 1H, H_{10}, $J = 2.4$), 6.75 (dd, 1H, H_6, $J = 2.4$, $J = 8.2$), 7.01 (d, 1H, H_7, $J = 8.2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 22.4 (Me), 22.9 (C_{15}), 22.9 (C_{11}), 30.6 and 30.7 (C_{12}, C_{16}), 42.3 (C_{13}), 46.2 (C_{14}), 55.1 (OMe), 82.3 (C_{17}), 112.2 (C_6), 113.3 (C_{10}), 130.1 (C_7), 132.2 (C_8), 136.2 (C_9), 157.4 (C_5); MS (EI, *m/z*): 232 (M^+), 214, 199, 173, 172 (100%); $C_{15}H_{20}O_2 =$ 232.32.
Compound $\mathbf{6_A}$: IR (cm^{-1}, $CHCl_3$): 3616 (OH), 1609, 1600, 1577, 1502 (Ar); ^1H NMR (200 MHz, $CDCl_3$): δ/TMS 1.02 (s, 3H, Me), 1.28–1.72 (m, 4H, $2H_{12}$, H_{15}, H_{16}), 1.67 (br s, 1H, OH, exchangeable), 1.80–2.34 (m, 2H, H_{15}, H_{16}), 2.59–2.75 (m, 2H, H_{11}), 2.86 (t, 1H, H_{14}, $J = 9.1$), 3.76 (s, 3H, OMe), 3.86 (dd, 1H, H_{17}, $J = 4.6$, $J = 5.7$), 6.18 (d, 1H, H_{10}, $J = 2.6$), 6.70 (dd, 1H, H_6, $J = 2.7$, $J = 8.3$), 7.01 ((d, 1H, H_7, $J = 8.3$); ^{13}C NMR (50.3 MHz,

$CDCl_3$): 19.3 (Me), 26.6 (C_{11}), 30.3 (C_{15}), 32.5 (C_{16}), 32.7 (C_{12}), 43.6 (C_{13}), 46.3 (C_{14}), 55.2 (OMe), 80.8 (C_{17}), 112.1 (C_6), 113.2 (C_{10}), 130.3 (C_7), 132.4 (C_8), 136.2 (C_9), 157.2 (C_5); MS (EI, *m*/*z*): 232 (M^+), 214, 199, 188, 173 (100%); $C_{15}H_{20}O_2 = 232.32$.

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