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Original TDAE application: synthesis of 2-substituted-4,11-dimethoxy-anthra-[2,3-*b*]furan-5,10-diones via intramolecular Buchwald reaction

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ABSTRACT

We report herein an original and rapid synthesis of 2-substituted-4,11-dimethoxy-anthra[2,3-*b*]furan-5,10-diones by TDAE strategy followed by Palladium-catalyzed cyclo-etherification reaction.

Anthracycline derivatives such as daunomycin and adriamycin possess high antitumor activity due to their capability of intercalating DNA double helix to result dramatic changes in DNA conformation[1] and, furthermore, can also inhibit DNA replication and transcription.[2] Unfortunately, the clinical use is limited by both dose-related cumulative cardiotoxicity and development of drug-resistance.[3] Several synthesis of heterocyclic anthracycline analogs were developed by replacing the cyclohexane ring (A) of anthracycline by an heterocycle.[4] Interesting activity against drug-resistant cells is obtained by modification of the 4,11-dihydroxy-naphtho[2,3-*f*]indole-5,10-dione skeleton (Fig. 1).[5] On the other hand, the compounds possessing a furano or pyrano ring fused to polycyclic, aromatic system such as furanoxanthone,[6] benzopyranoxanthone,[7] and coumarin[8] exhibit interesting antitumor[9] and anti-inflammatory properties.[10]

Since 2003, we have introduced a new program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[11] We have shown that from *o*- and *p*-nitrobenzyl chloride, Tetrakis(dimethyl-amino)ethylene (TDAE) could generate a nitrobenzyl carbanion which is able to react with various electrophiles as aromatic aldehydes, α-ketoester, ketomalonate, and α-ketolactam derivatives. We have recently reported the extension of this reactivity in anthraquinone series with aromatic aldehyde and nitro-anthraquinonic with ketomalonate and α-keto-ester derivatives.[12] Moreover, in order to develop pharmacomodulation studies, our team is interested in the palladium-catalyzed reactions such as Suzuki–Miyaura and Heck reactions.[13] However, Pd-catalyzed coupling of Ar-X with alcohol remains still not explored in our laboratory despite its potential application in organic synthesis. Furthermore, aryl ethers, including oxygen heterocycles, are prominent in a large number of pharmacologically important molecules.[14]

In connection with our program centered on the synthesis of new quinonic compounds using the electron transfer methodology and the preparation of new potentially bioactive compounds as anticancer agents,[15] we report herein an original and efficient synthesis of new 2-substituted-4,11-dimethoxy-anthra[2,3-*b*]furan-5,10-diones (**6a**–**f**) by an intramolecular Pd-catalyzed C–O bond forming reaction of halide alcohol derivatives **5a**–**f** prepared by the TDAE strategy.

The required starting material, 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**3**), was synthesized in two steps from compound **1** as previously described[16] (see Scheme 1). The aromatic bromination of **1** using Sandmeyer reaction gave the bromo derivative **2**,[17] and was followed by a radical bromination using *N*-bromosuccinimide (NBS) giving the bromomethyl derivative **3**.[18] In contrast to 1,4-dimethoxy-2-methylanthracene-9,10-dione, whose bromination with an excess of NBS gave the dibromomethyl derivative,[12a] the bromination of **2** furnished only the monobromomethyl derivative **3**, even with a large excess of NBS. This difference of reactivity is probably due to the steric hindrance.

The reaction of 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**3**) with aromatic aldehydes **4a**–**d** and in the presence of TDAE at −20 °C for 1 h, followed by 8 h at rt led to the corresponding alcohols **5a**–**d** in moderate to good yields

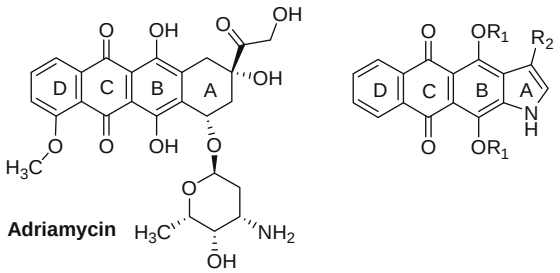

Figure 1.

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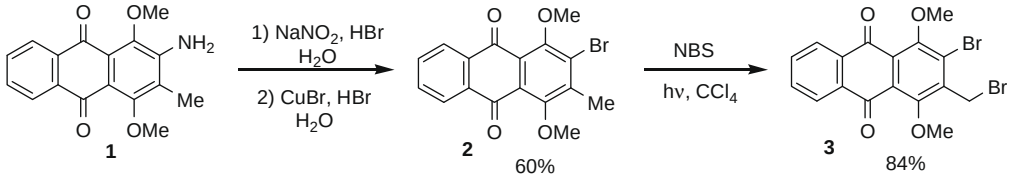
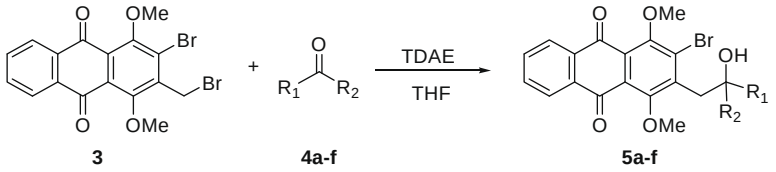
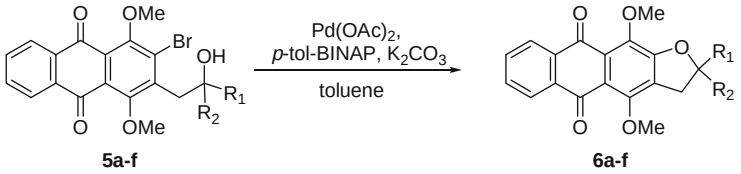


Scheme 1. Synthesis of the 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione **3**.



Scheme 2. Reaction of **3** with carbonyl derivatives in the presence of TDAE.



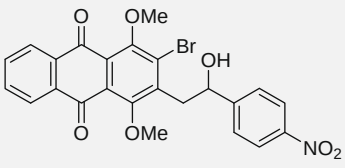
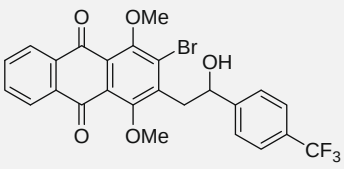
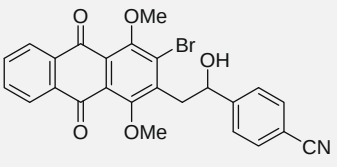
Scheme 3. Pd-catalyzed cyclization reaction of alcohols **5a**–**f**.

(53–70%).[19] Under the same conditions, we have studied the reaction of **3** with α-keto-esters **4e**,**f**[19] in the presence of TDAE which gives the corresponding α-hydroxy-ester derivatives **5e**,**f** in respectively, 67% and 46% yield (see Scheme 2, Table 1).

Compounds **5a**–**f** constitute promising candidates to effect an intramolecular Pd-catalyzed *ipso* substitution of an aryl halide with an alcohol. The first method which was tested to carry out palladium-catalyzed C–O bond forming reaction, used 15 mol % of *p*-tol-BINAP as supporting ligand, 10 mol % of $Pd(OAc)_2$ as palladium source, and 1.4 equiv of K_2CO_3 as base in toluene at 100 °C for 5–8 h.[20] From derivatives **5a**–**f**, this method furnished the corresponding 2-substituted-4,11-dimethoxy-anthra[2,3-*b*] furan-5,10-dione derivatives (**6a**–**f**) in good yields (70–84%)[21] as shown in Scheme 3, Table 2.

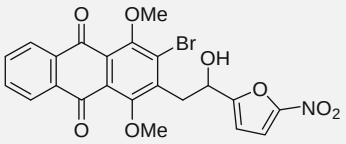
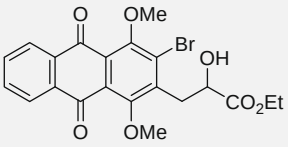
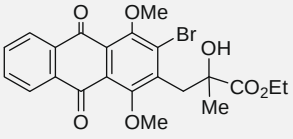
In conclusion, we developed the reaction of 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**3**) with various

Table 1
Reaction of 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione **3** and carbonyl derivatives using TDAE[a]

Entry	R_1	R_2	Product	Yield[b] (%)
1	4-Nitrophenyl	**H**	**5a** 	64
2	4-(Trifluoromethyl)phenyl	**H**	**5b** 	53
3	4-Cyanophenyl	**H**	**5c** 	56

(*continued on next page*)

Table 1 (*continued*)

Entry	R_1	R_2	Product	Yield[b] (%)
4	5-Nitrofuran-2-yl	**H**	**5d** 	70
5	CO_2Et	**H**	**5e** 	67
6	CO_2Et	**Me**	**5f** 	46

[a] All the reactions are performed using 3 equiv of carbonyl derivatives, 1 equiv of bromide **3,** and 1 equiv of TDAE in anhydrous THF stirred at −20 °C for 1 h and then warmed up to rt for 2 h.
[b] All yields refer to chromatographically isolated pure products and are relative to bromide **3**.

Table 2
Pd-catalyzed C–O bond forming reaction[a]

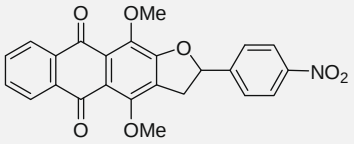
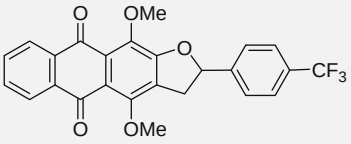
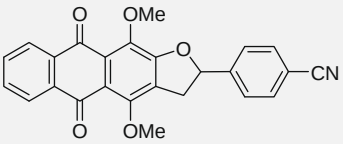
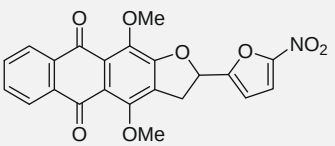
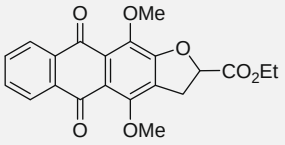
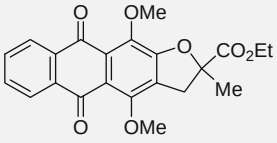
Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	**5a**	8	**6a** 	83
2	**5b**	8	**6b** 	70
3	**5c**	7	**6c** 	81
4	**5d**	7	**6d** 	83

Table 2 (*continued*)

Entry	Substrate	Time (h)	Product	Yield[b] (%)
5	**5e**	5	**6e** 	70
6	**5f**	6	**6f** 	84

[a] All the reactions are performed using 10 mol % $Pd(OAc)_2$, 15 mol % *p*-tol-BINAP, 1.4 equiv of K_2CO_3 in toluene at 80 °C.
[b] All yields refer to chromatographically isolated pure products and are relative to substrate **5a–f**.

aromatic aldehydes and α-keto-esters using TDAE, leading to the corresponding alcohols. The products obtained were good candidates for intramolecular palladium-catalyzed cyclo-etherification reaction, to synthesize 2-substituted-4,11-dimethoxy-anthra[2,3-*b*] furan-5,10-dione compounds. These last results constitute the first example of intramolecular Pd-catalyzed C–O bond forming reaction in anthraquinone series. The pharmacological evaluation of these compounds is under active investigation.

Acknowledgments

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17. For procedure see: Huszthy, P.; Kontos, Z.; Vermes, B.; Pinter, A. *Tetrahedron* **2001**, *57*, 4967–4975. Compound **2**: yellow solid; mp 195 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.53 (s, 3H); 3.91 (s, 3H); 3.99 (s, 3H); 7.72–7.76 (m, 2H); 8.15–8.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.5 (CH_3); 61.7 (OCH_3); 61.8 (OCH_3); 125.6 (C); 125.7 (C); 126.4 (CH); 126.5 (CH); 131.0 (C); 133.6 (2CH); 133.7 (C); 133.9 (C); 142.9 (C); 153.7 (C); 155.3 (C); 182.0 (CO); 182.5 (CO). Anal. Calcd for $C_{17}H_{13}BrO_4$: C, 56.53; H, 3.63. Found: C, 56.16; H, 3.62.
18. For procedure see: Shchekotikhin, A. E.; Luzikov, Y. N.; Buyanov, V. N.; Preobrazhenskaya, M. N. *Chem. Heterocycl. Compd.* **2006**, *42*, 1236–1241. Compound **3**: yellow solid; mp 168 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.02 (s, 3H); 4.09 (s, 3H); 4.82 (s, 2H); 7.75–7.79 (m, 2H); 8.17–8.22 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.0 (CH_2Br); 61.9 (OCH_3); 63.3 (OCH_3); 128.8 (C); 126.6 (2CH); 127.8 (C); 130.9 (C); 133.5 (C); 133.6 (C); 133.8 (2CH); 140.9 (C); 153.8 (C); 155.9 (C); 181.7 (2CO). Anal. Calcd for $C_{17}H_{12}Br_2O_4$: C, 46.40; H, 2.75. Found: C, 46.36; H, 2.80.
19. General procedure for TDAE reaction: Into a two-necked flask equipped with a drying tube (silica gel) and a nitrogen inlet was added 10 mL of anhydrous THF solution of 2-bromo-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**3**) (0.3 g, 0.68 mmol) and corresponding carbonyl derivatives (3 equiv). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.15 g, 0.75 mmol). A red color immediately developed with the formation of a fine white precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to rt for 8 h. After this time, TLC analysis (CH_2Cl_2) clearly showed that compound (**3**) was totally consumed. The solution was filtered (to remove the octamethyl-oxamidinium dibromide) and hydrolyzed with 70 mL of H_2O. The aqueous solution was extracted with chloroform (3 × 40 mL), the combined organic layers washed with H_2O (2 × 40 mL), and dried over $MgSO_4$. Evaporation of the solvent yield to an orange viscous liquid as a crude product. Purification by silica gel chromatography (CH_2Cl_2/diethyl ether: 95/5) and recrystallization

from isopropanol gave corresponding alcohol derivatives (**5a**–**f**). New products: **5a**: yellow solid; mp 209 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.39 (dd, J = 13.3 Hz, J = 9.0 Hz, 1H); 3.48 (dd, J = 13.3 Hz, J = 5.2 Hz, 1H); 3.99 (s, 6H); 5.20 (dd, J = 9.0 Hz, J = 5.2 Hz, 1H); 7.64 (d, J = 8.5 Hz, 2H); 7.76–7.81 (m, 2H); 8.18–8.23 (m, 2H); 8.21 (d, J = 8.5 Hz, 2H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 41.2 (CH_2); 61.8 (OCH_3); 62.8 (OCH_3); 71.0 (CH); 123.8 (2 × CH); 125.8 (C); 126.6 (2 × CH); 126.8 (C), 127.3 (2 × CH), 131.0 (C), 133.8 (C), 134.1 (C), 134.5 (CH), 134.6 (CH), 142.3 (C); 147.1 (C); 153.2 (C); 153.5 (C); 156.4 (C); 181.9 (CO); 182.2 (CO). Anal. Calcd for $C_{24}H_{18}BrNO_7$: C, 56.27; H, 3.54; N, 2.73. Found: C, 56.41; H, 3.72; N, 2.69. Compound **5b**: yellow solid; mp 168 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.33 (dd, J = 13.5 Hz, J = 9.4 Hz, 1H); 3.49 (dd, J = 13.5 Hz, J = 3.8 Hz, 1H); 3.98 (s, 3H); 4.00 (s, 3H); 5.16 (dd, J = 9.4 Hz, J = 3.8 Hz, 1H); 7.60 (d, J = 8.7 Hz, 2H); 7.65 (d, J = 8.7 Hz, 2H); 7.75–7.80 (m, 2H); 8.17–8.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 41.3 (CH_2); 62.0 (OCH_3); 62.7 (OCH_3); 72.9 (CH); 124.1 (q, J = 271.0 Hz, CF_3); 125.5 (q, J = 32.2 Hz, 2 × CH); 125.8 (C);125.9 (2 × CH); 126.7 (2 × CH); 127.0 (C); 129.9 (q, J = 3.7 Hz, C); 131.4 (C); 133.7 (C); 133.8 (C); 133.9 (CH); 134.0 (CH); 141.9 (C); 148.1 (C); 154.2 (C); 155.9 (C); 182.0 (CO); 182.3 (CO). Anal. Calcd for $C_{25}H_{18}BrF_3O_5$: C, 56.09; H, 3.39. Found: C, 55.49; H, 3.86. Compound **5c**: yellow solid; mp 173 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.35 (dd, J = 13.5 Hz, J = 9.0 Hz, 1H); 3.46 (dd, J = 13.5 Hz, J = 4.0 Hz, 1H); 3.99 (s, 3H); 4.00 (s, 3H); 5.17 (dd, J = 9.0 Hz, J = 4.0 Hz, 1H); 7.59 (d, J = 8.3 Hz, 2H); 7.68 (d, J = 8.3 Hz, 2H); 7.76–7.81 (m, 2H); 8.18–8.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 41.3 (CH_2), 61.8 (OCH_3); 62.8 (OCH_3); 71.2 (CH); 110.2 (C); 119.4 (C); 125.8 (C); 126.6 (2 × CH); 126.7 (C); 127.1 (2 × CH); 131.1 (C); 132.6 (2 × CH); 133.8 (C); 134.1 (C); 134.5 (CH); 134.6 (CH); 142.4 (C); 151.3 (C); 153.2 (C); 156.4 (C); 181.8 (CO); 182.2 (CO). Anal. Calcd for $C_{25}H_{18}BrNO_5$: C, 60.99; H, 3.69; N, 2.85. Found: C, 61.02; H, 3.78; N, 2.79. Compound **5d**: yellow solid; mp 80 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.55 (dd, J = 13.4 Hz, J = 7.8 Hz, 1H); 3.61 (dd, J = 13.4 Hz, J = 5.4 Hz, 1H); 3.97 (s, 3H), 3.98 (s, 3H); 5.17 (dd, J = 7.8 Hz, J = 5.4 Hz, 1H); 6.63 (d, J = 3.7 Hz, 2H); 7.28 (d, J = 3.7 Hz, 2H); 7.74–7.79 (m, 2H); 8.15–8.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.7 (CH_2); 62.1 (OCH_3); 62.8 (OCH_3); 67.2 (CH); 109.6 (CH); 112.4 (CH); 125.8 (C); 126.7 (2 × CH); 127.3 (C); 131.4 (C); 133.6 (C); 133.8 (C); 134.0 (CH); 134.1 (CH); 140.1 (C); 151.8 (C); 154.2 (C); 155.8 (C); 159.2 (C); 181.9 (CO); 182.2 (CO). HRMS (EI): m/z calcd for $[M+H]^+$: 502.0132. found: 502.0143. Compound **5e**: yellow solid; mp 132 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20 (t, J = 7.1 Hz, 3H); 3.31 (dd, J = 13.2 Hz, J = 8.1 Hz, 1H); 3.41 (dd, J = 13.2 Hz, J = 6.5 Hz, 1H); 3.92 (s, 3H), 3.96(s, 3H); 4.20 (q, J = 7.1 Hz, 2H); 4.54 (dd, J = 8.1 Hz, J = 6.5 Hz, 1H); 7.70–7.75 (m, 2H); 8.12–8.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (CH_3); 36.4 (CH_2); 61.8 (OCH_3); 62.0 (OCH_2); 62.6 (OCH_3); 69.0 (CH); 125.4 (C); 126.6 (2 × CH); 126.8 (C); 131.3 (C); 133.6 (C); 133.8 (2 × CH); 141.0 (2 × C); 153.7 (C); 156.3 (C); 174.0 (C); 181.9 (CO); 182.2 (CO). Anal. Calcd for $C_{21}H_{19}BrO_7$: C, 54.44; H, 4.13. Found: C, 54.43; H, 4.23. Compound **5f**: yellow solid; mp 101 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 7.1 Hz, 3H); 1.50 (s, 3H); 3.50 (s, 2H); 3.87 (s, 3H); 3.96 (s, 3H); 4.24 (q, J = 7.1 Hz, 2H); 7.73–7.78 (m, 2H); 8.15–8.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (CH_3); 25.4 (CH_3); 41.2 (CH_2); 61.8 (OCH_3); 62.2 (OCH_2); 62.2 (OCH_3); 74.8 (C); 125.2 (C); 126.5 (CH); 126.6 (CH); 126.8 (C); 132.8 (C); 133.6 (C); 133.8 (2 × CH); 140.6 (2 × C); 153.8 (C); 156.3 (C); 175.8 (C); 181.9 (CO); 182.0 (CO). Anal. Calcd for $C_{22}H_{21}BrO_7$: C, 55.36; H, 4.43. Found: C, 55.67; H, 4.58.

20. (a) Palucki, M.; Wolfe, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; (b) Torraca, K. E.; Kuwabe, S.-. I.; Buchwald, S. L. *J. Org. Chem.* **2000**, *122*, 12907–12908; (c) Kuwabe, S. I.; Torraca, K. E.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206; (d) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498–2500.

21. General procedure for Buchwald reaction: Into a two-necked flask equipped with an argon inlet, $Pd(OAc)_2$ (10 mol %), *p*-tol-BINAP (15 mol %), and K_2CO_3 (1.4 equiv) were added. Then the alcohol (0.15 g, 1 equiv) dissolved in toluene (6 mL) was added to the flask. The resulting mixture was heated at 100 °C until the disappearance of the starting material as monitored by TLC. The solution was cooled to rt, diluted with chloroform, filtered through Celite, and concentrated. The crude product was purified by silica gel chromatography (CH_2Cl_2/diethyl ether: 95/5) and recrystallized from isopropanol. New products: **6a**: yellow solid; mp 204 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.32 (dd, J = 16.6 Hz, J = 9.5 Hz, 1H); 3.88 (dd, J = 16.6 Hz, J = 8.1 Hz, 1H); 3.94 (s, 3H); 4.08 (s, 3H); 6.09 (dd, J = 9.5 Hz, J = 8.1 Hz, 1H); 7.57 (d, J = 8.6 Hz, 2H); 7.70–7.75 (m, 2H); 8.14–8.20 (m, 2H); 8.27 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.3 (CH_2); 61.2 (OCH_3); 61.3 (OCH_3); 84.7 (CH); 121.4 (C); 124.2 (2 × CH); 126.3 (2 × CH); 126.4 (CH); 126.5 (CH); 126.9 (C); 129.0 (C); 133.3 (CH); 133.6 (CH); 134.1 (C); 141.5 (C); 145.4 (C); 147.4 (C); 147.9 (C); 154.3 (C); 157.9 (C); 181.9 (CO); 183.3(CO). Anal. Calcd for $C_{24}H_{17}NO_7$: C, 66.82; H, 3.97; N, 3.25. Found: C, 66.63; H, 4.01; N, 3.22. Compound **6b**: yellow solid; mp 147 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.33 (dd, J = 16.6 Hz, J = 8.9 Hz, 1H); 3.90 (dd, J = 16.6 Hz, J = 7.9 Hz, 1H); 3.94 (s, 3H); 4.07 (s, 3H); 6.05 (dd, J = 8.9 Hz, J = 7.9 Hz, 1H); 7.53 (d, J = 8.2 Hz, 2H); 7.67 (d, J = 8.2 Hz, 2H);7.69–7.74 (m, 2H); 8.14–8.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.3 (CH_2); 61.1 (OCH_3); 61.2 (OCH_3); 85.3 (CH); 121.2 (C); 123.8 (q, J = 271.0, CF_3); 125.9 (2 × CH); 126.0 (q, J = 3.7, 2 × CH); 126.4 (CH); 126.5 (CH); 127.3 (C); 128.9 (C); 130.8 (q, J = 32.5 2 × CH C); 131.2 (C); 133.3 (CH); 133.6 (CH); 134.2 (C); 141.5 (C); 144.4 (C); 154.3 (C); 158.2 (C); 182.0 (CO); 183.4 (CO). Anal. Calcd for $C_{25}H_{17}F_3O_5$: C, 66.08; H, 3.77. Found: C, 65.64; H, 3.91. Compound **6c**: yellow solid; mp 175 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.30 (dd, J = 16.6 Hz, J = 9.5 Hz, 1H); 3.90 (dd, J = 16.6 Hz, J = 7.8 Hz, 1H); 3.94 (s, 3H); 4.07 (s, 3H); 6.05 (dd, J = 9.5 Hz, J = 7.8 Hz, 1H); 7.53 (d, J = 8.3 Hz, 2H); 7.71 (d, J = 8.3 Hz, 2H); 7.73–7.75 (m, 2H); 8.14–8.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.2 (CH_2); 61.2 (OCH_3); 61.3 (OCH_3); 84.9 (CH); 112.5 (C); 118.3 (C); 121.3 (C); 126.2 (2 × CH); 126.4 (CH); 126.5 (CH); 127.0 (C); 129.0 (C); 132.8 (2 × CH); 133.3 (CH); 133.6 (CH); 134.1 (C); 141.4 (C); 145.6 (2 × C); 154.3 (C); 158.0 (C); 181.9 (CO); 183.3 (CO). Anal. Calcd for $C_{25}H_{17}NO_5$: C, 72.99; H, 4.16; N, 3.40. Found: C, 72.81; H, 4.24; N, 3.40. Compound **6d**: yellow solid; mp 205 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.68 (dd, J = 16.7 Hz, J = 9.5 Hz, 1H); 3.71 (dd, J = 16.7 Hz, J = 7.7 Hz, 1H); 3.98 (s, 3H); 4.01 (s, 3H); 6.00 (dd, J = 9.5 Hz, J = 7.7 Hz, 1H); 6.71 (d, J = 3.7 Hz, 1H); 7.31 (d, J = 3.7 Hz, 1H); 7.70–7.74 (m, 2H); 8.13–8.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 32.7 (CH_2); 61.3 (2 × OCH_3); 78.2 (CH); 111.8 (CH); 112.0 (CH); 121.6 (C); 126.4 (C); 126.5 (CH); 126.6 (CH); 129.1 (C); 133.3 (CH); 133.6 (CH); 134.0 (C); 134.1 (C); 141.6 (C); 154.2 (C); 154.4 (C); 157.2 (C); 159.9(C); 181.9 (CO); 183.2 (CO). HRMS (EI): m/z calcd for $[M+H]^+$: 422.0870. found: 422.0877. Compound **6e**: yellow solid; mp 128 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (t, J = 7.1 Hz, 3H); 3.48 (dd, J = 16.9 Hz, J = 10.5 Hz, 1H); 3.71 (dd, J = 16.9 Hz, J = 6.0 Hz, 1H); 3.95 (s, 3H); 4.07 (s, 3H); 4.26 (q, J = 7.1 Hz, 2H); 5.38 (dd, J = 10.5 Hz, J = 6.0 Hz, 1H); 7.68–7.75 (m, 2H); 8.12–8.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (CH_3); 32.1 (CH_2); 61.1 (OCH_3); 61.2 (OCH_3); 62.1 (OCH_2); 80.5 (CH); 121.3 (C); 126.3 (C); 126.4 (CH); 126.5 (CH); 128.8 (C); 133.2 (CH); 133.5 (CH); 134.0 (C); 134.1 (C); 141.6 (C); 154.0 (C); 157.9 (C); 169.8 (C); 181.9 (CO); 183.2 (CO). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.74. Found: C, 66.06; H, 4.84. Compound **6f**: yellow solid; mp °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.29 (t, J = 7.1 Hz, 3H); 1.82 (s, 3H); 3.24 (d, J = 17.0 Hz, 1H); 3.75 (d, J = 17.0 Hz, 1H); 3.94 (s, 3H); 4.06 (s, 3H); 4.23 (q, J = 7.1 Hz, 2H); 7.68–7.73 (m, 2H), 8.12–8.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (CH_3); 24.4 (CH_3); 38.8 (CH_2); 61.1 (2OCH_3); 62.1 (OCH_2); 89.4 (CIV); 121.0 (C); 126.3 (CH); 126.4 (CH); 126.8 (C); 128.7 (C); 133.2 (CH); 133.4 (CH); 134.1 (C); 134.2 (C); 141.5 (C); 154.0 (C); 157.6 (C); 171.8 (C); 181.9 (CO); 183.3 (CO). Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.81; H, 5.24.