Tetrahedron Vol. 47, No. 12/13, pp. 2221–2228, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A GENERAL SYNTHESIS OF CALIX[4]ARENE MONOALKYL ETHERS

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(*Received in UK 23 November* 1990)

Abstract - A method for the first general and high yield synthesis of calix[4]arene monoalkyl ethers (4) has been developed by treating the easily available tetra-(2) or dialkyl ethers (3) with the equivalent amount of iodotrymethylsilane in $CHCl_3$.

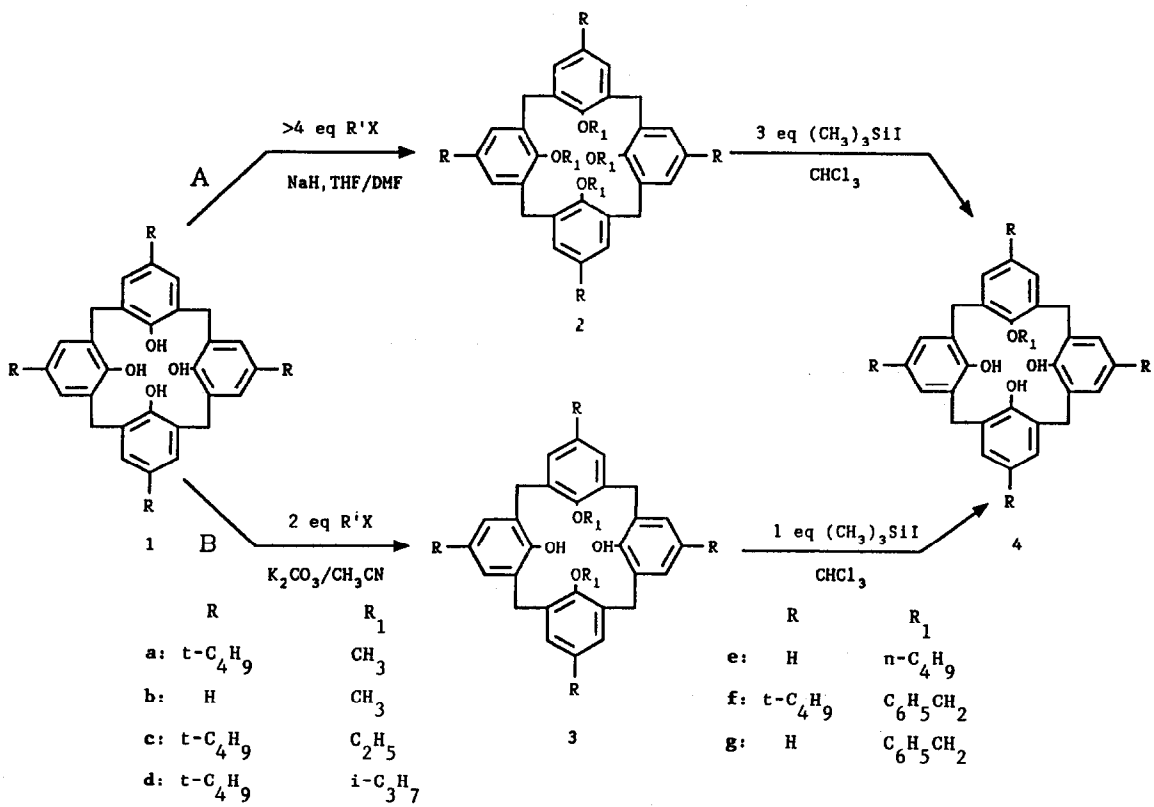
The extensive use of calixarenes and, in particular calix[4]arenes, in Supramolecular Chemistry,[1] justifies the efforts of several research groups to find synthetic methodologies for their selective functionalization both at the upper rim (aromatic nuclei) and at the lower rim (phenolic OH groups).

Several useful synthetic methodologies have been reported which allow the synthesis of tetrasubstituted calix[4]arenes at the lower rim.[1] More recently we[2,3] and other authors[4] have reported on the selective 1,3-dialkylation (diametral) of calix[4]arenes, whereas Pappalardo et al.[5] and ourselves[6] have published examples of 1,2-functionalization (proximal).

Continuing our efforts to synthesize new efficient cation receptors and carriers based on calixarenes,[7] we needed a series of monoprotected calix[4]arenes at the lower rim. Apart from one example by Gutsche and Nam, who reported the synthesis of monoallyloxycalix[4]arene,[8] no general methodology is available for the synthesis of calix[4]arene monoalkyl ethers. Several attempts to obtain these compounds by direct alkylation of calix[4]arenes 1 failed, this reaction giving tetra-[1] and dialkylated[2-4] products or mixture of compounds.

RESULTS AND DISCUSSION

As a result of a systematic study on the dealkylation of calixarene ethers in the presence of several ether cleavage reagents[6] we have found that by treating calix[4]arene tetraether 2 or the diether 3 derivatives with the stoichiometric amount of iodotrimethylsilane (Scheme) the monoalkyl ethers of calix[4]arenes are obtained in good yields (Table 1).



The procedure seems to be quite general and leads to new calix[4]arene derivatives useful for the construction of more complex receptor molecules. The calix[4]arene tetraalkyl ethers 2 are produced in quantitative yields by simple alkylation procedures, although with R_1 bulkier than CH_3, a mixture of stereoisomers (cone, partial cone, 1,2-alternate, 1,3-alternate) is usually obtained.[1,9]

The crude mixture is used for the dealkylation step and the yield of monoalkyl ethers 4 does not seem to be affected by the isomer distribution. Only in the case of tetrabenzyl ether of calix[4]arene 2g, which exists mainly in the 1,3-alternated structure,[10] the yield

of monobenzyloxycalix[4]arene 4g via procedure A is rather low and in this case it is better to use procedure B starting from the 1,3-dibenzyloxy derivative (3g).

Table 1
Isolated yield of monoalkyl ethers of calix[4]arenes

Compound	R	R_1	Procedure	Yield %
4a	t-C_4H_9	CH_3	A	85
4b	H	CH_3	A	65
4c	t-C_4H_9	C_2H_5	A	65
			B	80
4d	t-C_4H_9	i-C_3H_7	A	90
4e	H	n-C_4H_9	A	75
4f	t-C_4H_9	$C_6H_5CH_2$	A	60
			B	68
4g	H	$C_6H_5CH_2$	A	35
			B	77

Also compound 3g can be easily obtained in very good yield (96%) via a recently reported procedure.[3] At the moment it is not completely clear the reason for this high selectivity observed in the cleavage of calixarene ethers by iodotrimethylsilane, although this reagent has been shown to be of moderate activity in the cleavage of alkyl aryl ethers and very sensitive to the nature of the alkyl group.[11]

A possible explanation can be found by considering the steric bulkiness of the trimethylsilyl group, whose influence in other organic reaction has been well documented,[12] and the accepted mechanism for the cleavage of aryl-ethers by iodotrimethylsylane, which implies the formation of aryloxytrimethylsilane intermediates.[13] It is quite possible that as more silyl groups are introduced on the lower rim of the calix the more the reaction slows down favouring the unreacted substrate.

All the monoalkyl calix[4]arenes 4 show a cone conformation,[1] since their spectra are very similar to that of compound 4a (Figure 1) for which a cone structure have been indicated in solution by NOE experiments[14] and Molecular Mechanics Calculations.[15] In all compounds the ^1H NMR spectra show a typical pattern represented by a 4H doublet at ≈3.4 δ for the equatorial and two doublets for the axial protons of the bridging methylene (Ar-CH_2-Ar),[14] one centered at 4.2 δ and the second around 4.3 δ. Interestingly all compounds show two sharp signals for the three OH groups one at 9.5 δ (2H) and one at 10.1 δ (1H). This indicates that two H bonds are weaker than the other one and are those probably formed by the two opposite phenolic OH groups with the neighbour alkoxy oxygen

atom which, according to Molecular Mechanics calculations, bears less negative charge than a hydroxyl oxygen atom.[15]

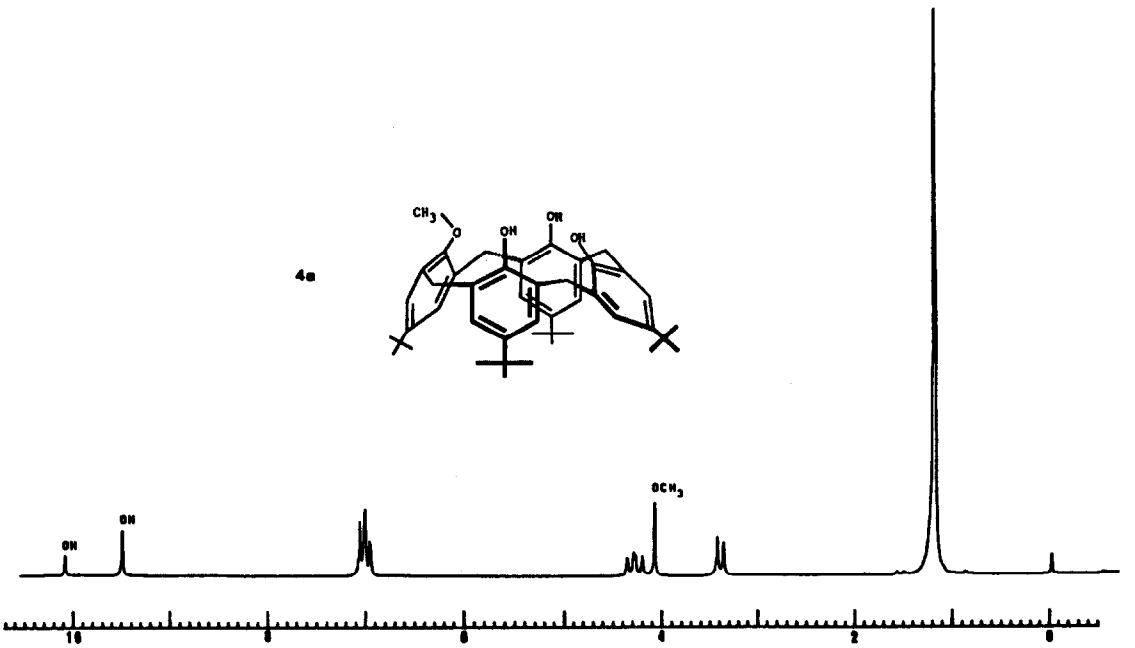


Figure 1. ^{1}H NMR spectrum (200 MHz, δ from TMS) of monomethoxy-p-tert-butylcalix[4]arene 4a in $CDCl_3$.

EXPERIMENTAL

Melting points were taken in capillary sealed in vacuo and are uncorrected. Mass spectra (EI) were recorded on a Finnigan mod. 1020 quadrupole instrument. ^{1}H NMR spectra (200 MHz) were recorded on a Bruker CXP 200 spectrometer and ^{13}C NMR (25 MHz) on a Bruker AC100 instrument of the Centro Interfacoltà di Misure (CIM) of the University of Parma in $CDCl_3$ (Me_4Si as an internal standard). IR spectra were recorded on a Perkin Elmer mod. 298 instrument. Analytical TLC were performed on precoated silica gel plates (Carlo Erba Stratochrom SiF_{254}).

Microanalyses were carried out at the Istituto di Chimica Farmaceutica of the University of Parma. All solvents were purified by standard procedures. Most Chemicals were purchased from Aldrich and used without further purification.

General procedure for the synthesis of calix[4]arene-monoalkyl ethers.

A.- Via tetraalkyl ethers 2.

Calix[4]arenes (1.0 mmol), NaH (50% oil, 5 mmol) and the proper alkyl iodide (10 mmol) in THF/DMF 9/1 were refluxed for several h, until TLC analysis (hexane 4, $CHCl_3$ 3) show no colour formation upon spraying with a $FeCl_3$ solution.

The tetrabenzylation gives better results by refluxing the calix[4]arene (1.0 mmol) and benzyl chloride (10 mmol) in acetonitrile for 24 h, in the presence of K_2CO_3 (10 mmol).

After the removal of most of the solvent under reduced pressure the mixture was taken up in CH_2Cl_2 and washed with 1N HCl (2x50 ml) and brine. The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated to afford a white solid, which was dried under vacuum. The crude solid was dissolved $CHCl_3$ (50 ml), treated, under nitrogen, with iodotrimethylsilane (3 mmol) and refluxed for 3 h. The debenzylation was performed at room temperature. After TLC control, which should show a single spot, the solid reaction mixture was treated with 3N HCl, the chloroform layer separated and the water extracted with CH_2Cl_2 (2x50 ml). After evaporation of the solvent the white solid was recrystallized (vide infra).

B.- Via dialkyl ethers 3.

Following the procedure reported in literature for the selective 1,3-dialkylation (diametral) of calix[4]arenes,[2,3] a suspension of 1 (1 mmol) K_2CO_3 (1.1 mmol), and the proper alkyl iodide or benzyl bromide (2 mmol) in CH_3CN (20 ml) was refluxed for 12 h. After evaporation of the solvent the mixture was taken up in CH_2Cl_2 and washed with 1N HCl (2x25 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated to yield a white solid which was dissolved in $CHCl_3$ (50 ml), treated with iodotrimethytilsilane (1 mmol) under nitrogen, and refluxed (room temperature for the debenzylation) for 3 h. For the isolation of the pure compounds 4 the procedure of via A was then followed.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-28-methoxypentacyclo[19.3.1.$1^{3,7}$.1.^{9,13}-$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,27-triol (4a). Crystallized from $CHCl_3$-MeOH: m.p. 203-204°C; IR (KBr) 3340 and 3200 cm^{-1} (OH stretching); ^1H NMR δ 1.19, 1.20 and 1.21 (36H, s, $C(CH_3)_3$), 3.42 (4H, d, H_{eq}), 4.12 (3H, s, OCH_3), 4.27 (2H, d, H_{ax}, J = 13.7 Hz), 4.35 (2H, d, H_{ax}, J = 13.0 Hz), 6.98-7.09 (8H, m, ArH), 9.55 (2H, s, OH), 10.14 (1H, s, OH); ^{13}C NMR δ 31.2 and 31.5 (q, $C(\underline{C}H_3)_3$), 32.1 and 33.0 (t, $ArCH_2Ar$), 33.9, 34.0, and 34.3 (s, $\underline{C}(CH_3)_3$), 63.2 (q, OCH_3), 125.7, 125.8, and 126.5 (d, Ar meta), 127.9 and 128.2 (s, Ar para), 133.4, 143.2, and 143.6 (s, Ar ortho), 147.8, 148.3, and 148.4 (s, ArO); EI-MS (+) m/e 662 (M^+, 100%), 647 (30%). Anal Calcd. for $C_{45}H_{58}O_4$: C, 81.53; H, 8.82. Found: C, 81.35; H, 8.60.

28-Methoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecene-25,26,27-triol (4b). Crystallized from $CHCl_3$-MeOH: m.p. 276-277°C; IR (KBr) 3340, 3200 cm^{-1} (OH); ^1H NMR δ 3.46 (4H, d, H_{eq}), 4.13 (3H, s, OCH_3), 4.27 (2H, d, H_{ax}, J = 13.6 Hz), 4.37 (2H, d, H_{ax}, J = 13.0 Hz), 6.7-7.1 (12H, m, ArH), 9.35 (2H, s, OH), 9.70 (1H, s, OH); ^{13}C NMR δ 31.3 and 31.9 (t, $ArCH_2Ar$), 63.4 (q, OCH_3), 121.0, 121.9 (d, Ar para), 126.2, 128.5, 128.7, 128.9, 129.4 (d, Ar meta), 128.6 and 134.1 (s, Ar ortho), 149.3, 150.7, 152.6 (s, ArO); EI-MS (+) m/e 438 (M^+, 100%). Anal Calcd. for $C_{29}H_{26}O_4$: C, 79.43; H, 5.98. Found: C, 80.15; H, 6.22.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-28-ethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,27-triol (4c). Crystallized from MeOH: m.p. 200-201°C; IR (KBr) 3340 and 3190 cm^{-1} (OH); ^1H NMR δ 1.19, 1.21 and 1.22 (36H, s, $C(CH_3)_3$), 1.75 (3H, t, OCH_2CH_3, J = 7.1 Hz), 3.42 (4H, d, H_{eq}), 4.23 (2H, q, OCH_2CH_3, J = 7.1 Hz), 4.28 (2H, d, H_{ax}, J = 13.6 Hz), 4.36 (2H, d, H_{ax}, J = 12.9 Hz), 6.98-7.1 (8H, m, ArH), 9.65 (2H, s, OH), 10.23 (1H, s, OH); ^{13}C NMR δ 15.25 (q, OCH_2CH_3), 31.3 and 31.5 (q, $C(CH_3)_3$), 32.3 and 33.0 (t, $ArCH_2Ar$), 33.9 and 34.2 (s, $C(CH_3)_3$), 72.4 (t, OCH_2CH_3), 125.6, 125.7 and 126.3 (d, Ar meta), 127.9, 128.3 (s, Ar para), 133.7, 143.1, 143.5 (s, Ar ortho), 147.9, 148.1, 148.4 and 149.3 (s, ArO); EI-MS (+) m/e 677 (M, 100%). Anal Calcd. for $C_{46}H_{60}O_4$: C, 81.60; H, 8.93. Found: C, 81.25; H, 8.50.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-28-(1-methylethoxy)pentacyclo[19.3.1.1^{3,7}.-1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,-27-triol (4d). Crystallized from $CHCl_3$-MeOH: m.p. 129-130°C dec.; IR (KBr) 3320 and 3190 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.19, 1.21 and 1.22 (36H, s, $C(CH_3)_3$), 1.58 (6H, d, $CH(CH_3)_2$, J = 6.1 Hz), 3.39 (2H, d, H_{eq}, J = 12.9 Hz), 3.42 (2H, d, H_{eq}, J = 13.7 Hz), 4.30 (2H, d, H_{ax}, J = 13.7 Hz), 4.45 (2H, d, H_{ax}, J = 12.9 Hz), 4.55 (1H, m, $CH(CH_3)_2$, J = 6.1 Hz), 6.9-7.1 (8H, m, ArH), 9.59 (2H, s, OH), 10.23 (1H, s, OH); ^{13}C NMR δ 22.1 (q, $CH(CH_3)_2$), 31.4 and 31.6 (q, $C(CH_3)_3$), 32.9 and 33.2 (t, $ArCH_2Ar$), 34.0 and 34.3 (s, $C(CH_3)_3$), 79.2 (d, $CH(CH_3)_2$), 125.8 and 126.5 (d, Ar meta), 127.7, 128.5 (s, Ar para), 134.3, 143.1, 143.7 (s, Ar ortho), 147.3, 147.8, 147.9 and 148.7 (s, ArO); EI-MS (+) m/e 691 (M^+, 100%). Anal Calcd. for $C_{47}H_{62}O_4$: C, 81.70; H, 9.04. Found: C,81.00; H, 8.80.

28-Buthoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecene-25,26,27-triol (4e). Crystallized from hexane: m.p. 239-240°C; IR (KBr) 3340 and 3100 cm^{-1} (OH stretching); ^1H NMR δ 1.10 (3H, t, $OCH_2CH_2CH_2CH_3$, J = 7.1 Hz), 1.70 (2H, m, $OCH_2CH_2CH_2CH_3$,), 2.16 (2H, m, $OCH_2CH_2CH_2CH_3$, J = 7.0 Hz), 3.45 (4H, d, H_{eq}, J = 13.3 Hz), 4.14 (2H, t, $OCH_2CH_2CH_2CH_3$, J = 6.9 Hz), 4.28 (2H, d, H_{ax}, J = 13.7 Hz), 4.36 (2H, d, H_{ax}, J = 12.9 Hz), 6.6-7.1 (12H, m, ArH), 9.43 (2H, s, OH), 9.75 (1H, s, OH); ^{13}C NMR δ 14.0 (q, $OCH_2CH_2CH_2CH_3$), 19.27 (t, $OCH_2CH_2CH_2CH_3$) 31.5 and 32.0 (t, $ArCH_2Ar$), 77.2 (t, $OCH_2CH_2CH_2CH_3$), 120.9, 121.9 (d, Ar para), 126.1, 128.4, 128.7, 128.8, and 129.3 (d, Ar meta), 134.3, 149.2, 150.8 and 151.6 (s, Ar ortho and ArO); EI-MS (+) m/e 480 (M^+,

100%), 423 (M-57, 80%). Anal Calcd. for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71. Found: C,79.85; H, 6.88.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-28-phenylmethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,27-triol (4f). Crystallized from $CHCl_3$-MeOH: m.p. 202-203°C; IR (KBr) 3320 (OH); ^{1}H NMR ($CDCl_3$) δ 1.20, and 1.21 (36H, s, $C(CH_3)_3$), 3.40 (4H, d, H_{eq}), 4.22 (2H, d, H_{ax}, J = 12.6 Hz), 4.35 (2H, d, H_{ax}, J = 12.8 Hz), 5.17 (2H, s, OCH_2Ph), 6.9-7.1 (8H, m, ArH), 7.4-7.7 (5H, m, PhH), 9.40 (2H, s, OH), 10.02 (1H, s, OH); ^{13}C NMR δ 31.2 and 31.5 (q, $C(\underline{C}H_3)_3$), 32.5 and 33.0 (t, $ArCH_2Ar$), 33.9, 34.0 and 34.3 (s, $\underline{C}(CH_3)_3$), 79.2 (t, OCH_2Ph), 125.6, 125.7, 125.9 and 126.5 (d), 127.6, 128.0 and 128.3 (s), 128.9, 129.0 and 129.2 (d), 133.6, 135.6, 143.0 and 143.5 (s) (Ar+Ph), 147.7, 148.2, 148.5 and 149.3 (s, ArO); EI-MS (+) m/e 739 (M^+, 20%), 648 (M^+-91, 100%). Anal Calcd. for $C_{51}H_{62}O_4$: C, 82.88; H, 8.45. Found: C, 82.75; H, 8.80.

28-Phenylmethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,27-triol (4g). Crystallized from hexane: m.p. 225-226°C; IR (KBr) 3280 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ 3.42 (4H, d, H_{eq}), 4.22 (2H, d, H_{ax}, J = 13.3 Hz), 4.35 (2H, d, H_{ax}, J = 12.8 Hz), 5.18 (2H, s, OCH_2Ph), 6.5-7.1 (12H, m, ArH), 7.4-7.8 (5H, m, PhH), 9.23 (2H, s, OH), 9.58 (1H, s, OH); ^{13}C NMR δ 31.7 and 31.9 (t, $ArCH_2Ar$), 79.3 (t, OCH_2Ph) 120.9, 122.0, 126.3, 126.9, 127.0, 127.8, 128.4, 128.8, 129.0, 129.1 and 129.5 (d), 131.3, 134.4 and 135.6 (s) (Ar+Ph), 149.2, 150.9, and 151.3 (s, ArO); EI-MS (+) m/e 514 (M^+, 100%), 423 (M^+-91, 40%). Anal Calcd. for $C_{35}H_{30}O_4$: C, 81.68; H, 5.87. Found: C, 81.32; H, 6.05.

ACKNOWLEDGEMENTS - This work was supported by the Consiglio Nazionale delle Ricerche (C.N.R.), Italy.

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