Sonogashira Reactions of 2,3,4,5-Tetrabromofuran: Synthesis of 2,3,4,5-Tetraalkynylfurans, 2,3,5-Trialkynylfurans and 2,5-Dialkynylfurans

Imran Malik,[a,b] Zeeshan Ahmad,[a] Sebastian Reimann,[a,c] Muhammed Nawaz,[a] Tamás Patonay,[d] Peter Langer*[a,c]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany

[b] Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, Pakistan

[c] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany

[d] Department of Organic Chemistry, University of Debrecen, Egyetem tér 1, 4032 Debrecen, Hungary

Received: 21.03.2012; Accepted: 23.03.2012

Abstract: 2,3,4,5-Tetrabromofuran is transformed into a variety of alkynyl-substituted furans by regioselective Sonogashira cross-coupling reactions. In this context, the first 2,3,4,5-tetraalkynylfurans and 2,3,5-trialkynylfurans were prepared. 2,3,4,5-Tetraalkynylfurans and 2,5-dialkynyl-3,4-diarylfurans show interesting fluorescence properties.

Key words: catalysis, palladium, Sonogashira reaction, furan, regioselectivity, fluorescence

Furan derivatives represent important building block in synthetic organic chemistry. Substituted furans have attracted attention, due to their remarkable pharmacological and photophysical properties.[1] Furan is found in many natural products, e.g. lophotoxin, pukalide, the cembranolides, the plakorsins A–C, rosefuran, kallolide, adociacetylene B, XH-14, perillene, and dendrolasin.[2] The furan derivative ranitidine (commercial name Zantac) is used for the treatment of peptic ulcer and gastroesophageal reflux disease. Nitrofurantoin is used for the treatment of urinary tract infections and nifuroxazide is suggested for colitis and diarrhea treatment.[3] A great deal of research efforts on furan derivatives revealed also other biological properties, such as anti-inflammatory, antituberculosis, anticancer, and antifungal activities.[4] Furan derivatives have been also reported to show excellent photophysical properties and have, thus, gained attention in material sciences. In recent years, 2,5-bis(phenylethynyl)furans,[5] furanyl nucleosides,[6] bisfuranylethenes,[7] and furopyrimidine derivatives[8] have been reported to show nonlinear optical (NLO), fluorescence and photochromic properties.

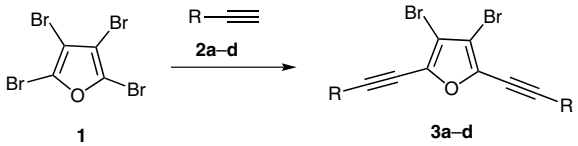
Various strategies have been developed for the synthesis of furans. Furans can be synthesized by cyclodehydrations of 1,4-diketones (Paal–Knorr synthesis),[9] by condensations of α-halocarbonyl compounds with 1,3-dicarbonyl compounds (Feist–Benary reaction),[10] by cyclizations of β,γ–epoxyketones,[11] by cyclodehydrations of γ-hydroxy-α,β-unsaturated ketones,[12] by heteroannulation reactions along with transition-metal-catalyzed cyclizations,[13] by cyclocondensations of phosphoranes with α-haloketones,[14] by base-mediated cyclizations of allenyl alcohols and epoxides,[15] by [3+2] annulations of alkynes with aldehydes,[16] and by cyclizations of 1,4-diones in the presence of catalytic amounts of *p*-toluenesulfonic acid.[17]

An alternative approach to substituted furans relies on palladium-catalyzed cross-coupling reactions of brominated furans. However, the low stability of furans, in particular under aerobic and acidic conditions, makes their cross-coupling reactions more fragile and the product isolation more difficult than in the thiophene series. In recent years, site-selective reactions[18] of polybrominated furan derivatives have been studied. Negishi, Stille, Suzuki, and Sonogashira reactions and nucleophilic aromatic substitution reactions have been reported for 2,3-, 2,4- and 2,5-dibromofurans and proceed with excellent site selectivity in favor of position C-2.[19] Bellina, Sulikowski and Rossi and their co-workers reported site-selective transition-metal-catalyzed reactions of several dibromofuranones.[20] 2,3,4,5-Tetrabromofuran represents an interesting substrate for transition-metal-catalyzed cross-coupling reactions as all four carbon atoms of the furan moiety are halogenated. Recently, we have reported Suzuki–Miyaura reactions of 2,3,4,5-tetrabromofuran which were the first palladium(0)-catalyzed cross-coupling reactions of this substrate.[21] The synthesis of tetraarylthiophenes[22] and tetra(alkynyl)thiophenes[23] by Suzuki and Sonogashira reactions of tetrabromothiophene has been previously reported, respectively. The synthesis of tetra(alkynyl)pyrroles has also been reported.[24] Herein, we report what are, to the best of our knowledge, the first Sonogashira reactions of 2,3,4,5-tetrabromofuran. The reactions proceed with very good site selectivity and provide a convenient access to the first 2,3,4,5-tetraalkynylfurans and 2,3,5-trialkynylfurans and to a variety of other derivatives. The UV-Vis absorption and fluorescence properties of the products were studied.

2,3,4,5-Tetrabromofuran (**1**) was prepared following a literature procedure.[25] The Sonogashira reaction of **1** with 2.4 equivalents of acetylenes **2a**–**d** afforded the 2,5-di(arylethynyl)-3,4-dibromofuranfurans **3a**–**d** in 71–81% yield with very good site-selectivity (Scheme 1, Table 1).[26] The selectivity is observed as expected. The first attack occurs at the electronically more deficient positions 2 and 5.[18d] The reactions were carried out under standard conditions using $Pd(PPh_3)_2Cl_2$ (10 mol%) and CuI (5 mol%) as the catalyst and diisopropylamine (DIPA) as the base and solvent. The decrease of the catalyst loading resulted in a de-

SYNLETT 2012, 23, 1463–1466
Advanced online publication: 18.05.2012
DOI: 10.1055/s-0031-1291007; Art ID: ST-2012-B0262-L

crease of the yield. Attempts to carry out a monoalkynylation (using one equivalent of the alkyne) resulted in the formation of mixtures of mono- and dialkynylated products.



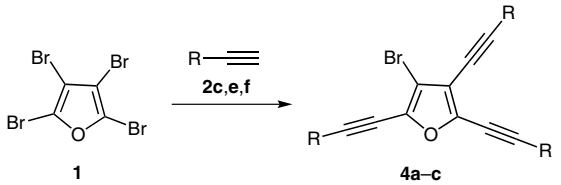
Scheme 1 Synthesis of **3a**–**d**. *Reagents and conditions*: **1** (1.0 equiv), **2a**–**d** (2.4 equiv), CuI (5 mol%), $Pd(PPh_3)_2Cl_2$ (10 mol%), DIPA, 60 °C, 2 h

Table 1 Synthesis of **3a**–**d**

2, **3**	R	Yield (%)[a] of **3**
a	4-*t*-BuC_6H_4	78
b	Ph	71
c	3-(MeO)C_6H_4	81
d	6-methoxynaphth-2-yl	76

[a] Yields of isolated products.

The Sonogashira reaction of **1** with 3.6 equivalents of **2c**,**e**,**f** afforded the 2,3,5-tri(arylethynyl)-4-bromofurans **4a**–**c** in 64–77% yield (Scheme 2, Table 2). The reactions were carried out under identical conditions as discussed for the synthesis of **3a**–**d**.



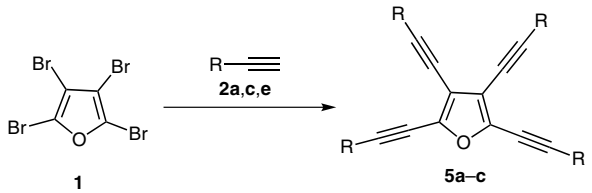
Scheme 2 Synthesis of **4a**–**c**. *Reagents and conditions*: **1** (1.0 equiv), **2c**,**e**,**f** (3.6 equiv), CuI (5 mol%) $Pd(PPh_3)_2Cl_2$ (10 mol%), DIPA, 60 °C, 2 h

Table 2 Synthesis of **4a**–**c**

2	**4**	R	Yield (%)[a] of **4**
c	**a**	3-(MeO)C_6H_4	77
e	**b**	3-MeC_6H_4	73
f	**c**	*n*-Pr	64

[a] Yields of isolated products.

The Sonogashira reaction of **1** with 4.8 equivalents of acetylenes **2a**,**c**,**e** afforded the 2,3,4,5-tetra(arylethynyl)furans **5a**–**c** in 75–83% yield (Scheme 3, Table 3). During the optimization, the temperature had to be increased from 60 °C to 75 °C. The catalyst loading did not have to be increased. The use of 10 mol% of Pd catalyst corresponds to 2.5 mol% per coupling step.



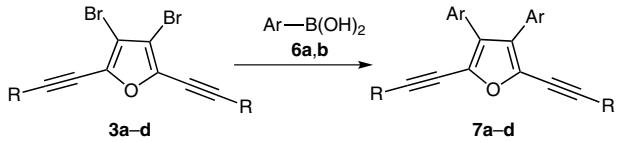
Scheme 3 Synthesis of **5a**–**c**. *Reagents and* conditions: **1** (1.0 equiv), **2a**,**c**,**e** (4.8 equiv), CuI (5 mol%) $Pd(PPh_3)_2Cl_2$ (10 mol%), DIPA (5 mL), 75 °C, 2 h

Table 3 Synthesis of **5a**–**c**

2	**2**, **5**	R	Yield (%)[a] of **5**
c	**a**	3-(MeO)C_6H_4	83
a	**b**	4-*t*-BuC_6H_4	81
e	**c**	3-MeC_6H_4	75

[a] Yields of isolated products.

The Suzuki–Miyaura reaction of 2,5-di(arylethynyl)-3,4-dibromofurans **3a**–**d** with (4-methoxyphenyl)boronic acid (**6a**) and (4-methylphenyl)boronic acid (**6b**), in the presence of 10 mol% of $Pd(PPh_3)_2Cl_2$ (70 °C, 2 h), resulted in the formation of products **7a**–**d** in 69–79% yields (Scheme 4, Table 4). Other types of coupling reactions, such as cyanation and formylation, are currently being studied.



Scheme 4 Synthesis of **7a**–**d**. *Reagents and* conditions: **3a**–**d** (1.0 equiv), **6a**,**b** (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), K_2CO_3 (3 equiv), dioxane, 70 °C, 2 h.

Table 4 Synthesis of **7a**–**d**

3, **7**	**6**	R	R^1	Yield (%)[a] of **7**
a	**a**	4-*t*-BuC_6H_4	4-(MeO)C_6H_4	76
b	**a**	Ph	4-(MeO)C_6H_4	69
c	**a**	3-(MeO)C_6H_4	4-(MeO)C_6H_4	79
d	**b**	6-methoxynaphth-2-yl	4-MeC_6H_4	74

[a] Yields of isolated products.

The UV–Vis and fluorescence spectroscopic data of various furan derivatives, measured in chloroform at 25 °C, are summarized in Table 5. A typical spectrum is depicted in Figure 1. The absorption wavelengths (λ_{abs}) are in the

UV region (303–374 nm) and their emission wavelengths (λ_{em}) (fluorescence) are in the UV or blue region (418–442 nm). Di- and trialkynylfurans **3a**–**d** and **4a**–**c** are not fluorescent. In contrast, tetraalkynylfurans **5a**–**c** possess excellent fluorescence properties and exhibit absorptions at $\lambda_{abs(max)}$ = 309, 303, 304 nm and emissions at $\lambda_{em(max)}$ = 425, 422, 420 nm with Stokes shift values 116, 119, 116 nm, respectively. 2,5-Dialkynyl-3,4-diarylfurans **7a**–**d** also exhibit good fluorescence properties. While the emission wavelengths of **7a**–**d** are in the same range as the emissions of **5a**–**c**, the Stokes shifts of **7a**–**d** are considerably lower as compared to **5a**–**c**. Since higher Stokes shifts generally correspond to better fluorescence properties, tetraalkynylfurans **5a**–**c** are the best derivatives with respect to possible technical applications. The absorptions of the alkynylated products show a significant bathochromic shift as compared to parent furan. Tetra(alkynyl)thiophenes[23a] and 2,5-bis(alkynyl)thiophenes[23b] have been previously prepared. However, their photophysical properties were, to the best of our knowledge, not studied. Therefore, a comparison is not possible. While 2,5-bis(alkynyl)-3,4-dicyanothiophenes have been reported to form liquid crystals,[23b] 2,5-dialkynylfurans **3** and **7** did not show liquid crystalline properties.

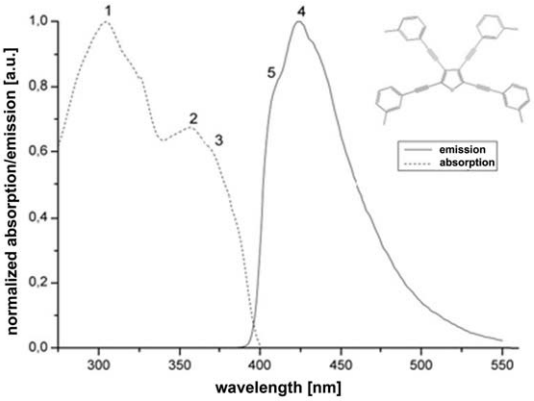


Figure 1 Absorption and emission spectra of compound **5c**

Table 5 Absorption and Emission Spectroscopic Data of Alkynylated Furans ($c = 10^{-6}$ mol/L, in $CHCl_3$)

Product	$\lambda 1_{abs}$ [nm]	lg ε	$\lambda 4_{em}$ [nm]	Stokes shift [nm]
5a	309	3.83	425	116
5b	303	4.07	422	119
5c	304	4.16	420	116
7a	356	4.06	418	62
7b	355	4.25	420	65
7c	356	3.70	420	64
7d	374	3.47	442	68

We have reported the synthesis of di-, tri- and tetraalkynylated furans by the first Sonogashira reaction of 2,3,4,5-tetrabromofuran. The synthesis of 2,3,4,5-tetraalkynylfurans has been reported for the first time. 2,3,4,5-Tetraalkynylfurans and 2,5-dialkynyl-3,4-diarylfurans show a bright fluorescence. The properties of the tetraalkynylated furans are particularly promising because of the excellent Stokes shifts. Our current studies are directed towards exploring the scope of the methodology, studying the quantum yields and further optimizing the fluorescence properties by variation of the substitution pattern.

Acknowledgment

Financial support by the State of Pakistan (scholarships for I.M., Z.A. and M.N.), by the DAAD (scholarships for I.M. and M.N.) and by the Interdisciplinary Faculty of the University of Rostock (scholarship for S.R.) is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References

(1) (a) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Vol. 15; Gribble, G. W.; Gilchrist, T. L., Eds.; Pergamon: Oxford, **2003**, 167. (b) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry*; Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Amsterdam, **1996**, 359. (c) Shea, K. M. *Palladium in Heterocyclic Chemistry*; Vol. 26; Elsevier: Amsterdam, **2007**, 303.

(2) (a) Culver, P.; Jacobs, R. S. *Toxicon* **1981**, *19*, 825. (b) Missakian, M. G.; Burreson, B. J.; Schever, P. J. *Tetrahedron* **1975**, *31*, 2513. (c) Shen, Y. C.; Chatervedula, V. S. P.; Kuo, Y. H. *J. Nat. Prod.* **2001**, *64*, 324. (d) Karasawa, D.; Shatar, S.; Erdenechimeg, A.; Okamoto, Y.; Tateba, H.; Shimizu, S. *J. Essent. Oil. Res.* **1995**, *7*, 255. (e) Look, S. A.; Burch, N. T.; Fenical, W. *J. Org. Chem.* **1985**, *50*, 5741. (f) Kobayashi, M.; Mahmud, T.; Tajima, H.; Wang, W.-Q.; Aoki, S.; Nakagawa, S.; Mayumi, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 720. (g) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537. (h) Bernard, R.; Cardani, C.; Selva, D.; Baggini, A.; Pavan, M. *Tetrahedron Lett.* **1967**, 3893. (i) Barma, D. K.; Kundu, A.; Baati, R.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2002**, *4*, 1387.

(3) (a) Brunton, L.; Lazo, J.; Keith, P. *The Pharmacological Basis of Therapeutics*; McGraw-Hill: New York, **2005**. (b) Cadwallader, D. E. *J. Am. Pharm. Assoc.* **1975**, *NS15*, 409.

(4) (a) Tangallapally, R. P.; Lee, R. E. B.; Lenaerts, A. J. M.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2584. (b) Srivastava, V.; Negi, A. S.; Kumar, J. K.; Faridu, U.; Sisodia, B. S.; Darokar, M. P.; Luqman, S.; Khanuja, S. P. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 911. (c) Nagaraja, G. K.; Kumaraswamy, M. N.; Vaidya, V. P.; Mahadeven, K. M. *ARKIVOC* **2006**, *(x)*, 1. (d) Sondhi, S. M.; Jain, S.; Rani, R.; Kumar, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2007**, *46*, 1848.

(5) Lind, P.; Carlsson, M.; Eliasson, B.; Glimsdal, E.; Lindgren, M.; Lopes, C.; Boman, L.; Norman, P. *Mol. Phys.* **2009**, *107*, 629.
(6) Greco, N. J.; Tor, Y. *Tetrahedron* **2007**, *63*, 3515.
(7) Yamaguchi, T.; Irie, M. *J. Mater. Chem.* **2006**, *16*, 4690.
(8) Lechel, T.; Dash, J.; Brudgam, I.; Reissig, H. U. *Eur. J. Org. Chem.* **2008**, 3647.
(9) (a) Dulop, A. P.; Peters, F. N. *The Furans*; Reinhold Publishing: Baltimore, **1953**, 35. (b) Grieco, P.; Pogonowski, C.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542. (c) Scott, L. T.; Naples, J. O. *Synthesis* **1973**, 209.
(10) Bisagni, E.; Marquet, J. P.; Bourzat, J. D.; Depin, J. J.; Andre-Louisfert, J. *Bull. Chem. Soc. Fr.* **1971**, 4041.
(11) Courmier, R. A.; Grosshans, C. A.; Skibbe, S. L. *Synth. Commun.* **1988**, *7*, 677.
(12) Sammond, D. M.; Sammakia, T. *Tetrahedron Lett.* **1996**, *37*, 6065.
(13) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Kirsch, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47. (c) Marson, C.; Harper, S.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1879.
(14) Mross, G.; Holtz, E.; Langer, P. *J. Org. Chem.* **2006**, *71*, 8045.
(15) Marshall, J. A.; Bennett, C. *J. Org. Chem.* **1994**, *59*, 6110.
(16) Tso, H. H.; Tsay, H. *Tetrahedron. Lett.* **1997**, *38*, 6869.
(17) Mortensn, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838.
(18) For reviews of site-selective palladium(0)-catalyzed cross-coupling reactions, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (c) Wang, R.; Manabe, K. *Synthesis* **2009**, 1405. (d) For a simple guide for the prediction of the site selectivity of palladium-catalyzed cross-coupling reactions based on ^{1}H NMR data of the nonhalogenated derivatives, see: Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.
(19) (a) Bach, T.; Krüger, L. *Eur. J. Org. Chem.* **1999**, 2045. (b) Stock, C.; Höfer, F.; Bach, T. *Synlett* **2005**, 511. (c) Carpita, A.; Rossi, R. *Tetrahedron* **1985**, *41*, 1919. (d) Wellmar, U.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159. (e) Bach, T.; Krüger, L. *Synlett* **1998**, 1185. (f) Bach, T.; Krüger, L. *Eur. J. Org. Chem.* **1999**, 2045.
(20) (a) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. (b) Bellina, F.; Falchi, E.; Rossi, R. *Tetrahedron* **2003**, *59*, 9091.
(21) Hussain, M.; Khera, R. A.; Nguyen, T. H.; Langer, P. *Org. Biomol. Chem.* **2011**, *9*, 370.
(22) Dang, T. T.; Dang, T. T.; Rasool, N.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1595.
(23) (a) Neenan, T. X.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 2489. (b) For 2,5-di(alkynyl)thiophenes, see: Eichhorn, S. H.; Paraskos, A. J.; Kishikawa, K.; Swager, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 12742.
(24) Ullah, F.; Dang, T. T.; Heinicke, J.; Villinger, A.; Langer, P. *Synlett* **2009**, 838.
(25) Shoppee, C. W. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 45.
(26) **General Procedure for Sonogashira Coupling Reactions**
A suspension of tetrabromofuran (**1**), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (5 mol%) in diisopropylamine was degassed three times in a pressure tube. The acetylene (1.2 equiv per bromine atom) was added using a syringe. The mixture was heated at the indicated temperature (60–80 °C) for 2–4 h. The reaction mixture was filtered and the residue was washed with CH_2Cl_2. The filtrate was washed with a saturated solution of ammonium chloride (2 x 25 mL), water (2 x 25 mL) and was subsequently dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The product was purified by column chromatography (silica gel, EtOAc–heptanes).

3,4-Dibromo-2,5-bis[(4-*tert*-butylphenyl)ethynyl]furan (3a)

Starting with **1** (150 mg; 0.40 mmol), 4-*tert*-butylphenylacetylene (**2a**) (0.16 mL, 0.94 mmol), CuI (5 mol%), $Pd(PPh_3)_2Cl_2$ (10 mol%), and diisopropylamine (5 mL), **3a** was isolated as a white solid (163 mg, 78%); mp 197–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 18 H, CH_3), 7.40 (d, 4 H, *J* = 8.6 Hz), 7.51 (d, 4 H, *J* = 8.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 31.1 (CH_3), 34.9, 81.5, 98.8, 109.3, 118.8 (C), 125.5, 132.3 (CH), 136.7, 152.6 (C). IR (KBr): ν = 2952 (w), 1497 (m), 1461 (m), 1362 (m), 1266 (m), 1102 (m), 1013 (m), 923 (w), 833 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 536 (M^+, [^{79}Br, ^{79}Br], 30), 538 (M^+, [^{79}Br, ^{81}Br], 100), 540 (M^+, [^{81}Br, ^{81}Br], 62), 523 (52), 508 (2), 493 (4), 467 (3), 350 (3), 314 (18), 299 (26), 254 (15), 226 (9). HRMS (EI, 70 eV): calcd for $C_{28}H_{26}Br_2O$ (M^+, [^{79}Br, ^{79}Br]: 536.03449; found 536.03353; calcd for $C_{28}H_{26}Br_2O$ (M^+, [^{79}Br, ^{81}Br]: 538.03245; found 538.03238; calcd for $C_{28}H_{26}Br_2O$ (M^+, [^{81}Br, ^{81}Br]: 540.03040; found 540.03176.

