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Synthesis of substituted 1-alkylidenephthalanes via lithium promoted 5-*exo*-*dig* cyclization

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Abstract: A one-pot synthesis of substituted 1-alkylidenephthalanes from 3-(2-bromophenyl)propyne derivatives has been developed. 3-(2-Bromophenyl)propynal acetals **9** and corresponding orthoesters **19** were treated successively with *n*-butyllithium and various aldehydes and ketones at low temperature to obtain 1-alkylidenephthalanes **10** and **20** with various functional groups at the exocyclic methylene moiety. Halogen-metal exchange, nucleophilic addition to various carbonyl compounds, regioselective 5-*exo*-*dig* cyclization of the respective intermediate lithium alcoholate and hydrolysis represent the key steps in this Domino reaction. A two-step mechanism involving at first a synchronous cyclization to form a vinyl lithium

intermediate and then a methanolate elimination leading to the respective 1-methoxy allenes is suggested based on DFT-calculations.

Key words; alkylidenephthalanes; phenylpropynal acetals; orthoesters; DFT calculations; 5-*exo*-*dig* cyclization, Domino reaction

Introduction

1,3-Dihydro-2-benzofuran, also known as phthalane, is frequently found as core structure in functional organic molecules, natural products and pharmacologically active compounds. For example, the pH indicator phenolphthalein synthesized first by Adolf von Baeyer in 1871 contains the 2-benzofuran-1(3*H*)-one ring system (phthalide), which is crucial for its pH sensitivity.[1] The phthalane containing natural product pestacin (**1**) isolated from *Pestalotiopsis microspora* shows antifungal and strong antioxidative properties.[2] Paecilospirone (**2**), a spirocyclic phthalane isolated from marine fungus *Paecilomyces* species, represents a potential antimitotic agent.[3] The phthalanes **3** with a spirocyclic connected piperidine ring represent potent and selective σ_1 receptor ligands.[4][5] The ^{18}F-labeled 2-fluoroethyl derivative fluspidine (**3a**: n = 2, R = Bn) is currently investigated as PET tracer in clinical studies.[6–8] The aminopropyl substituted phthalane citalopram (**4**) is a selective serotonin reuptake inhibitor, which is used in more than 65 countries for the treatment of major depression and anxiety disorders. In 2012, 1-alkylidenephthalanes **5** were found to have moderate antibacterial and antidepressant effect.[9][10] (Figure 1)

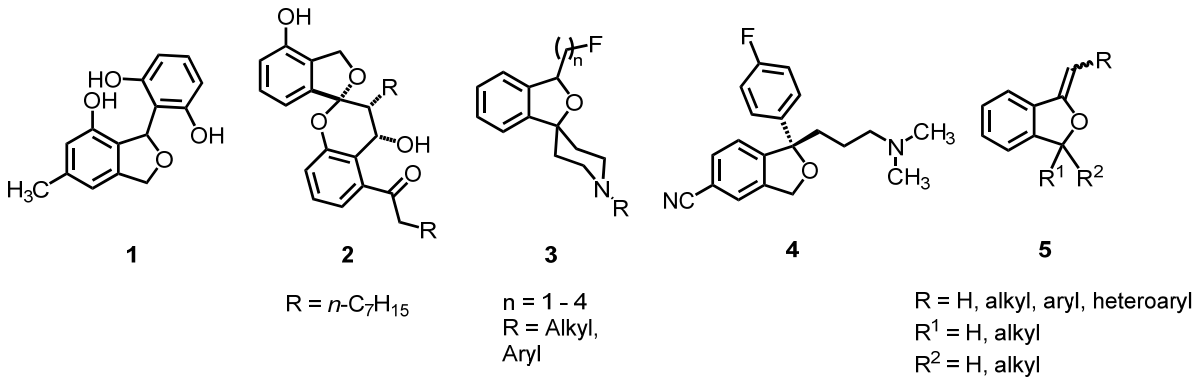


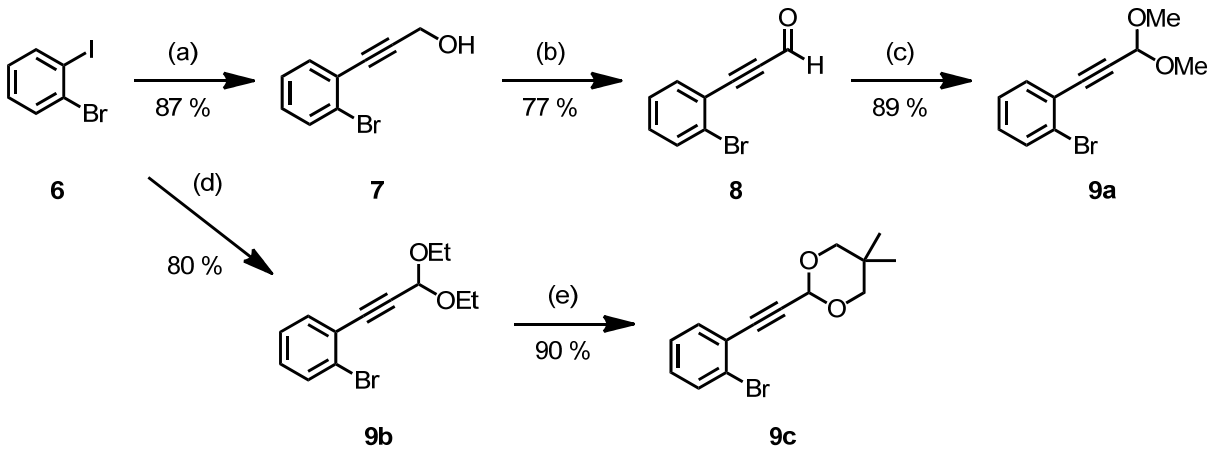
Figure 1. Natural products **1** and **2** and pharmacologically active compounds **3** - **5** with phthalane scaffold.

1-Alkylidenephthalanes **5** can be synthesized by cyclization of functionalized 2-ethynylbenzyl alcohols. According to Baldwin's rules both 5-*exo*-*dig* and 6-*endo*-*dig* cyclization reactions are favored leading to 1-alkylidenephthalanes (1-alkylidene-2-benzofurans) and/or 1*H*-2-benzopyrans.[11] A large variety of catalysts enables the regioselective synthesis of 1-alkylidenephthalanes.[10,12–14] A one-step transformation of silylated 2-ethynylbenzyl alcohols into 1-alkylidenephthalanes has also been reported.[15] Another method is the Michael addition of 2-iodobenzyl alcohols to activated alkynes, followed by intramolecular Heck reaction.[16] The additional activating functional group at the original alkyne (e.g. a C=O-moiety) allows further modifications. Another method to obtain 1-alkylidenephthalanes with a C=O-moiety in the sidechain uses the Sonogashira reaction of 2-ethynylbenzyl alcohol with various aryl iodides under CO pressure.[17]

In our research devoted to novel receptor ligands, we became interested in variously substituted phthalanes. Therefore, a novel method for the synthesis of 1-alkylidenephthalanes with additional functional groups at the exocyclic double bond, such as hydroxymethyl, formyl or alkoxycarbonyl should be developed.

Results and Discussion

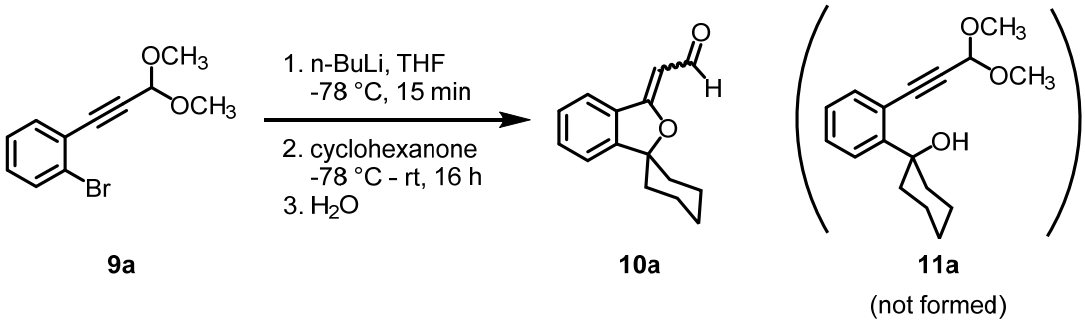
At first, propynal dimethyl acetal **9a** was synthesized in three steps from 1-bromo-2-iodobenzene (**6**) comprising a Sonogashira reaction[18] with propargyl alcohol, oxidation with TEMPO and (diacetoxyiodo)benzene[19] and acetalization with methanol. The diethyl acetal **9b** was prepared by Sonogashira reaction of 1-bromo-2-iodobenzene (**6**) with propynal diethyl acetal, which are both commercially available Furthermore, the cyclic acetal **9c** was synthesized by transacetalization of diethyl acetal **9b** with 2,2-dimethylpropane-1,3-diol. (Scheme 1)



Scheme 1. Synthesis of 3-(2-bromophenyl)propynal acetals **9a**-**c**. Reagents and reaction conditions: (a) $HC{\equiv}CCH_2OH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 15 h; (b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 4.5 h; (c) $CH(OCH_3)_3$, Amberlyst® 15, MeOH, 75 °C, 2.5 h, microwave; (d) $HC{\equiv}CCH(OEt)_2$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 20 h; (e) $(CH_3)_2C(CH_2OH)_2$, Amberlyst® 15, toluene, 60 °C, 5.5 h, reduced pressure.

The next step in the synthesis of phthalanes should be the generation of benzylic alcohols **11** by reaction of aryl bromides **9** with *n*-BuLi and aldehydes or ketones. Unexpectedly, successive treatment of **9a** with *n*-BuLi and cyclohexanone at -78 °C provided the aldehyde **10a** instead of the expected benzylic alcohol **11a** after aqueous work-up and purification by flash chromatography. (Scheme 2) Instead of simple hydroxyalkylation, a Domino reaction comprising of halolgen-metal exchange,

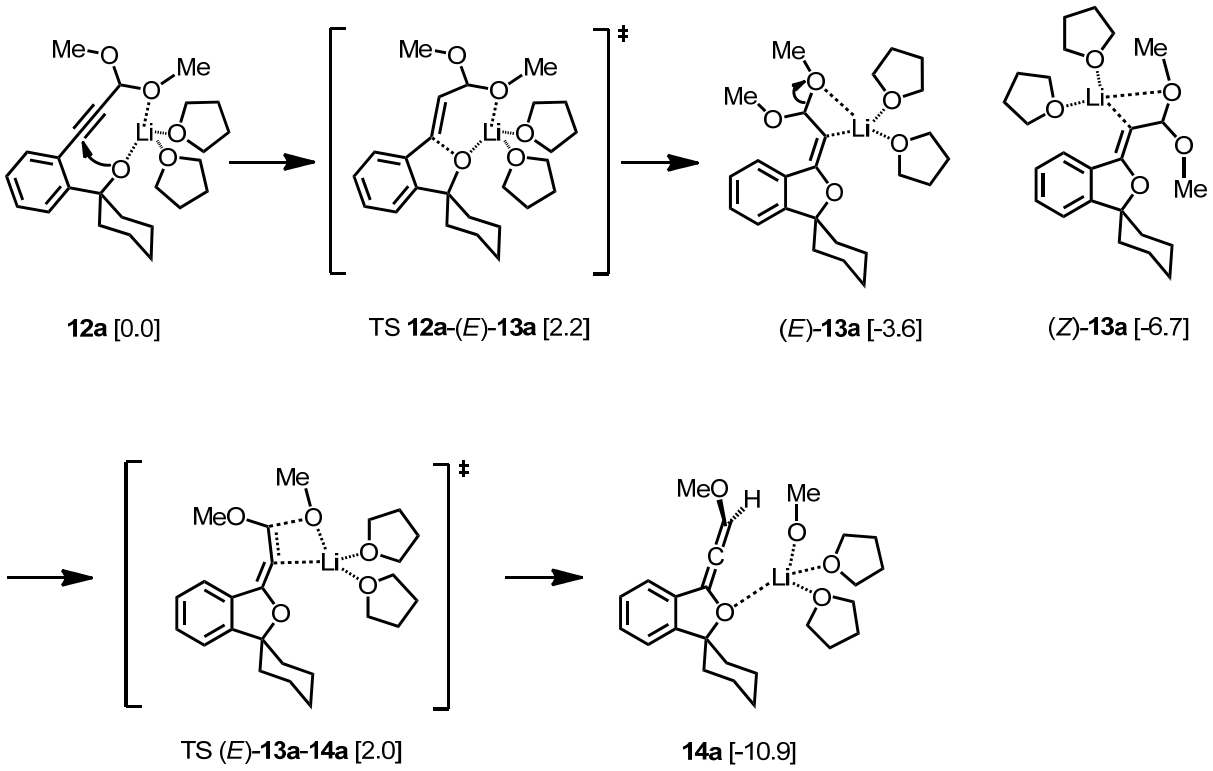
nucleophilic addition to cyclohexanone. cyclization of the intermediate alcoholate, and formal hydrolysis had occurred.



9a **10a** **11a** (not formed)

Scheme 2. One-step transformation of acetal **9a** into aldehyde **10a**.

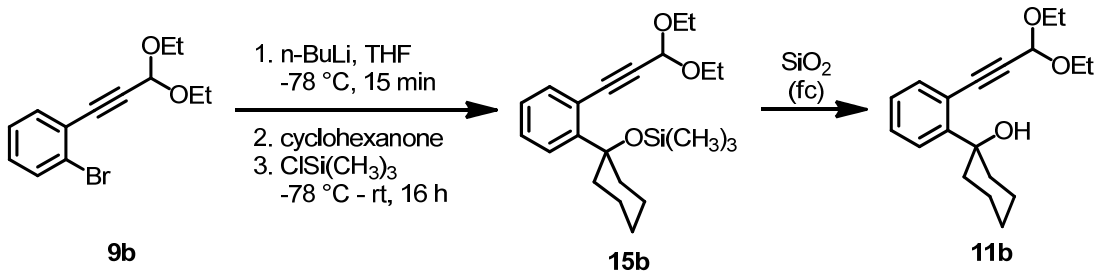
In order to understand the reaction mechanism leading to the unexpected direct formation of the aldehyde **10a**, DFT calculations (TPSS/def2-TZVP including GD3BJ dispersion interaction and the polarizable continuum model (PCM) for THF)[20–22] were performed for the 5-*exo*-*dig*-cyclization as key step of the reaction. Starting point of the reaction is the lithium alcoholate **12a**, which was formed upon addition of the aryllithium intermediate to cyclohexanone. The Gibbs free energies of the lithium alcoholate **12a**, whose lithium counterion was solvated by two molecules of THF, of the corresponding intermediates (*Z*)- and (*E*)-**13a**, the lithium coordinated allene **14a** and the related transition states were calculated.



Scheme 3. Calculated reaction mechanism for the formation of **14a** starting from alcoholate **12a**; Gibbs free energies [298 K, kcal/mol].

Stepwise shortening of the alcoholate-O – alkynyl-C-distance of **12a** led over a tiny barrier (only 2.2 kcal/mol) in a slightly exothermic reaction (-3.6 kcal/mol) to the vinyllithium compound (*E*)-**13a**. The isomeric form (*Z*)-**13**a is lower in energy (-6.7 kcal/mol). Elongation of one of the methoxy C-O bonds in (*E*)-**13a** as reaction coordinate led via the transition state TS (*E*)-**13a-14a** (2.0 kcal/mol) to the allene **14a**, representing the global minimum of this part of the energy surface (-10.9 kcal/mol). (Scheme 3) Thus, from the data obtained compounds **13a** may be considered to be kinetic reaction products, which will be interconverted into the thermodynamic product **14a** depending on the temperature applied. Both products **13a** and **14a** will give the aldehyde **10a** upon hydrolysis.

A comparable reaction was already observed for ω-lithioalk-2-ynyl methyl ethers affording alkenylidinecycloalkanes.[23] Lavoisier-Gallo and Rodriguez were able to perform an intramolecular S_N2' reaction of potassium 6-bromohex-4-ynolats leading to 2-vinylidenetetrahydrofurans by elimination of bromide.[24] Patil *et al.* demonstrated with their synthesis of 1-(2-alkoxyvinylidne)-2-benzopyrans the general stability of the 1,3-dialkoxyallene structure.[25] The base catalyzed cyclization of pent-4-yn-1-ol derivatives to afford 2-methylenetetrahydrofurans can be regarded as related transformation. This transformation was used for the synthesis of various furans.[12,14,26–28]



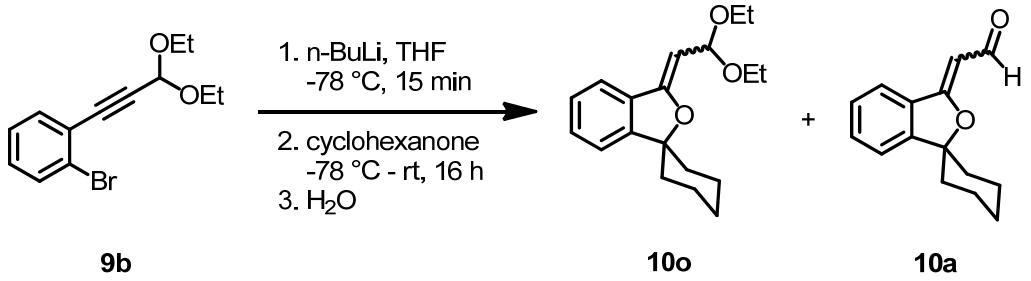
9b **15b** **11b**

Scheme 4. Reaction of **9b** with n-BuLi and cyclohexanone and subsequent trapping with $ClSi(CH_3)_3$ to form **15b** confirms the existence of the alcoholate of **11b** corresponding to **12a** in Scheme 3 as intermediate of the transformation.

In order to support the calculated reaction mechanism, various experiments were conducted. The formation of the intermediate alcoholate **12b** (diethyl acetal) was confirmed by trapping it with $ClSiMe_3$ affording the silyl ether **15b**. After aqueous work-up and flash chromatography, the tertiary alcohol **11b** was isolated as sole product in 24 % yield. (Scheme 4)

Careful aqueous work-up of the reaction of diethyl acetal **9b** with cyclohexanone and subsequent analysis of the crude product by ^1H NMR spectroscopy revealed the presence of acetal **10o** and aldehyde **10a** in the ratio of 4 : 1. (Scheme 5) A second ^1H

NMR spectrum of the same sample recorded after storage in DMSO-d_6 for 10 h showed further transformation of acetal **10o** into aldehyde **10a** (ratio **10o** : **10a** = 1 : 1). It is assumed that water in the NMR solvent DMSO-d_6 was responsible for the further hydrolysis of diethyl acetal **10o** to yield aldehyde **10a**. Probably the vinylogous orthoester structure in **10o** is responsible for its facile hydrolysis.



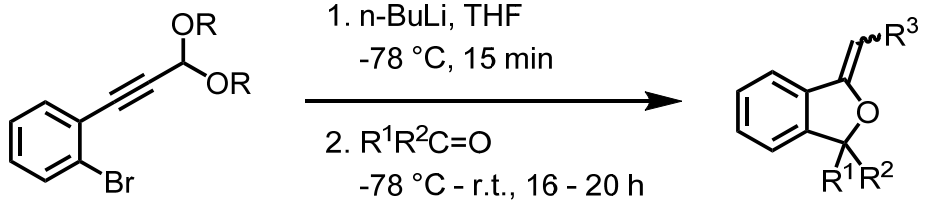
9b **10o** **10a**

Scheme 5. 1-Alkylidenephthalanes **10o** and **10a** observed after aqueous work-up.

In a further experiment, cyclohexanone was added to lithiated **9b** at -80 °C. Then, THF was removed in vacuo at room temperature, the residue was dissolved in THF-d_8 and NMR spectra were recorded. Finally, the same experiment was conducted in THF-d_8 at -80 °C and the NMR spectra were recorded immediately after addition of cyclohexanone. Both experiments showed the formation of diethyl acetal **10o** as the major product, which obviously represents the first identifiable intermediate. The ^{1}H NMR spectrum confirmed unequivocally the structure of the acetal **10o** displaying two characteristic duplets at 5.04 ppm and 5.50 ppm originating from adjacent protons of the diethoxyethylidene ($(EtO)_2CH$-CH=) side chain.

In order to investigate the scope and limitations of this novel transformation the dimethyl acetal **9a**, the diethyl acetal **9b** and the cyclic acetal **9c** were reacted with *n*-BuLi and subsequently with various ketones and aldehydes to provide a large series of substituted 1-alkylidenephthalanes **10**. The results are summarized in Table 1.

Table 1. One-pot transformation of acetals **9a**-**c** into substituted 1-alkylidenephthalanes **10**.



9a-c **10a-n**

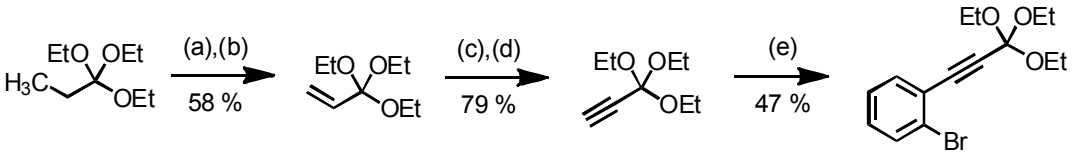
compd.	R	R^1	R^2	R^3	Product	yield	(*E*)/(*Z*)[a]
9a	Me		$(CH_2)_5$	CHO	**10a**	42	5:95
9a	Me	Me	Ph	CHO	**10b**	76[b]	5:95
9a	Me	H	*t*-Bu	CHO	**10c**	40[b]	5:95
9b	Et		$(CH_2)_5$	CHO	**10a**	62	10:90
9b	Et	Me	Ph	CHO	**10b**	59	10:90
9b	Et	Me	Me	CHO	**10d**	69	10:90
9b	Et	Me	*n*-Bu	CHO	**10e**	53	10:90
9b	Et		$(CH_2)_4$	CHO	**10f**	52	10:90
9b	Et	H	Ph	CHO	**10g**	15	5:95
9b	Et	H	*t*-Bu	CHO	**10c**	68	5:95
9b	Et	H	*i*-Pr	CHO	**10h**	43	5:95
9b	Et	H	*i*-Bu	CHO	**10i**	24	5:95
9b	Et	H	cyclohexyl	CHO	**10j**	54	10:90
9c	$CH_2C(CH_3)_2CH_2$		$(CH_2)_5$	$CH(OCH_2)_2C(CH_3)_2$	**10k**	45	<1:>99
9c	$CH_2C(CH_3)_2CH_2$	Me	Ph	$CH(OCH_2)_2C(CH_3)_2$	**10l**	32	<1:>99
9c	$CH_2C(CH_3)_2CH_2$	H	Ph	$CH(OCH_2)_2C(CH_3)_2$	**10m**	-	-
9c	$CH_2C(CH_3)_2CH_2$	H	*t*-Bu	$CH(OCH_2)_2C(CH_3)_2$	**10n**	-	-

[a] The ratio of (*E*) : (*Z*)-configured diastereomers was determined from ^{1}H NMR spectra of purified products.

[b] Transformation was performed at -90 °C.

Since diethyl acetal **9b** was accessible in only one reaction step from commercially available compounds, it represented the preferred starting material in this study. Both dimethyl acetal **9a** and diethyl acetal **9b** resulted in the direct formation of the aldehydes **10a**-**j**. However, the cyclic acetal of **9c** was not cleaved, but was retained in

the produced 1-alkylidenephthalanes **10k+l**. Reactions with aldehydes appear to give lower yields than reactions with ketones with exception of pivalaldehyde providing the aldehyde **10c** in 68 % yield. Unexpectedly, transformations with benzaldehyde afforded either low yields of aldehyde **10g** (15 %) or failed to give acetal **10m**.

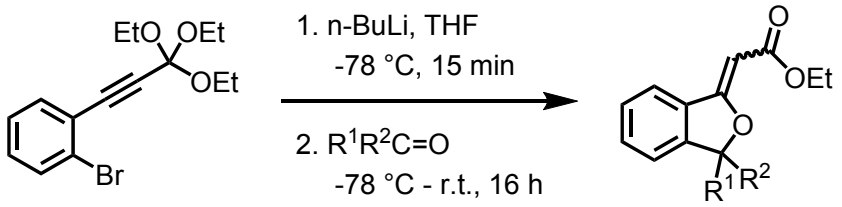


16 **17** **18** **19**

Scheme 6: Synthesis of orthoester **19**. Reagents and reaction conditions. (a) Br_2, pyridine, 0 °C, 2 h; (b) KO*t*Bu, DMSO, rt, 6 h; (c) Br_2, CH_2Cl_2, 0 °C, 1 h; (d) KOH, 18-crown-6, heptane, 98 °C, 18 h; (e) C_6H_4BrI, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 15 h;

In addition to various acetals, the orthoester **19** was included into the study. Orthoester **19** was obtained by Sonogashira reaction of 1-bromo-2-iodobenzene (**6**) with triethyl orthopropynoate (**18**). The alkyne **18** was prepared from triethyl orthopropanoate (**16**) by alternate bromination and HBr elimination via orthoacrylate **17**.[29][30] (Scheme 6)

Table 2. Reaction of orthoester **19** with various ketones and aldehydes to afford ethoxycarbonyl substituted 1-alkylidenephthalanes **20**.



19 **20a-d**

R^1	R^2	product	yield (%)	(*E*)/(*Z*)[a]
$(CH_2)_5$		**20a**	47	<1:>99
Me	Ph	**20b**	47	10:90
H	*t*-Bu	**20c**	50	<1:>99
H	Ph	**20d**	-	-

[a] The ratio of (*E*) : (*Z*)-configured diastereomers was determined from ^{1}H NMR spectra of purified products.

Treatment of orthoester **19** with *n*-BuLi and various aldehydes and ketones led to the ethoxycarbonyl substituted 1-alkylidenephthalanes **20a**-**c**. (Table 2) Again the aromatic aldehyde benzaldehyde failed to give the phenyl substituted derivative **20d**.

Gas phase DFT calculations (without solvating THF molecules) for the reaction of the lithiated trimethyl orthoester (in analogy of **12a**) resulted in a one-step reaction with a barrier of 9.1 kcal/mol and direct formation of the corresponding allene species (-7.3 kcal/mol). (see Supporting Information)

According to ^{1}H NMR spectra, the formed aldehydes **10a**-**j**, acetals **10k**-**l** and esters **20a**-**c** exist as mixtures of (*Z*)- and (*E*)-configured diastereomers. Usually, the ratio (*Z*) : (*E*) is in the range of 90 : 10 to 95 : 5. For the cyclic acetals **10k** and **10l** as well as the esters **20a** and **20c** signals for the minor (*E*)-configured diastereomer could not be detected in the ^{1}H and ^{13}C NMR spectra.

Conclusion

Herein, a novel method is reported for the synthesis of variously substituted 1-alkylidenephthalanes **10** and **20** bearing an additional carbonyl moiety at the exocyclic double bond. Starting from 1-bromo-2-iodobenzene (**6**) allowed the synthesis of 1-alkylidenephthalanes **10** with a formyl moiety in only two reaction steps via propynal diethyl acetal **9b**. 1-Alkylidenephthalanes **20** with an ethoxycarbonyl moiety at the double bond were obtained by reaction of orthoester **19** with aldehydes and ketones. The key step is a Domino reaction comprising a halogen-metal exchange, nucleophilic addition to various carbonyl compounds, 5-*exo*-*dig* cyclization of resulting alcoholates and formal hydrolysis. DFT calculations resulted in a two-step reaction

mechanism starting from intermediate alcoholate **12** producing a vinyl lithium compound **13** in the first step and formation of allene **14** in the second step by methanolate elimination

Experimental Section

Chemistry, General Methods

Oxygen and moisture sensitive reactions were carried out under nitrogen, dried with silica gel with moisture indicator (orange gel, VWR, Darmstadt, Germany) and in dry glassware (Schlenk flask or Schlenk tube). Temperatures were controlled with dry ice/acetone (-78 °C), ice/water (0 °C), Cryostat (Julabo TC100E-F, Seelbach, Germany), magnetic stirrer MR 3001 K (Heidolph, Schwalbach, Germany) or RCT CL (IKA, Staufen, Germany), together with temperature controller EKT HeiCon (Heidolph) or VT-5 (VWR) and PEG or silicone bath. All solvents were of analytical or technical grade quality. Demineralized water was used. CH_2Cl_2 was distilled from CaH_2; THF was distilled from sodium/benzophenone; MeOH was distilled from magnesium methanolate. Thin layer chromatography (tlc): tlc silica gel 60 F_{254} on aluminum sheets (VWR). Flash chromatography (fc): Silica gel 60, 40–63 µm (VWR); parentheses include: diameter of the column (d), length of the stationary phase (l), fraction size (V) and eluent. Automated flash chromatography: Isolera™ Spektra One (Biotage®); parentheses include: cartridge size, flow rate, eluent, fractions size was always 20 mL. Melting point: Melting point system MP50 (Mettler Toledo, Gießen, Germany), open capillary, uncorrected. MS: MicroTOFQII mass spectrometer (Bruker Daltonics, Bremen, Germany); deviations of the found exact masses from the calculated exact masses were 5 mDa or less; the data were analyzed with DataAnalysis® (Bruker Daltonics). NMR: NMR spectra were recorded in deuterated solvents on Agilent DD2 400 MHz and 600 MHz spectrometers (Agilent, Santa Clara CA, USA); chemical shifts

(*δ*) are reported in parts per million (ppm) against the reference substance tetramethylsilane and calculated using the solvent residual peak of the undeuterated solvent; coupling constants are given with 0.5 Hz resolution; assignment of ^{1}H and ^{13}C NMR signals was supported by 2-D NMR techniques where necessary.IR: FT/IR IR Affinity®-1 spectrometer (Shimadzu, Düsseldorf, Germany) using ATR technique.

HPLC method for the determination of the purity

Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (equipment and software from Thermo Fisher Scientific, Lauenstadt, Germany); column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized water with 0.05 % (V/V) trifluoroacetic acid, B: CH_3CN with 0.05 % (V/V) trifluoroacetic acid; gradient elution (% A): 0 - 4 min: 90 %; 4 - 29 min: gradient from 90 % to 0 %; 29 - 31 min: 0 %; 31 - 31.5 min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %.

Synthetic procedures

2-(3*H*-Spiro[[2]benzofuran-1,1'-cyclohexan]-3-yliden)acetaldehyde (10a)

Method A: Diethyl acetal **9b** (430 mg, 1.52 mmol, 1.0 eq) was dissolved in THF (35 mL) and the solution was cooled to -78 °C. A solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.73 mL, 1.82 mmol, 1.2 eq) was added dropwise and the solution was stirred for 15 min at -78 °C. A solution of cyclohexanone (0.28 mL, 2.73 mmol, 1.8 eq) in absolute THF (3 mL) was added dropwise within 15 min. Afterwards, the reaction mixture was warmed up to rt within 16 h. H_2O was added and the reaction mixture was stirred for further 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 x). Brine was added

after the first extraction step to afford better phase separation. The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The residue was purified by twofold flash column chromatography (1. 100 g cartridge, cyclohexane:ethyl acetate = 9:1, 2. 50 g cartridge, CH_2Cl_2:ethyl acetate = 95:5). The product was isolated as red resin, yield 214 mg (62 %).

Method B: As described in method A, dimethyl acetal **9a** (231 mg, 0.91 mmol, 1.0 eq) was reacted with a solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.44 mL, 1.09 mmol, 1.2 eq) and cyclohexanone (0.11 mL, 1.09 mmol, 1.2 eq) in THF (15 mL). The residue was purified by threefold flash column chromatography (1. 100 g cartridge, cyclohexane:ethyl acetate = 95:5 → 90:10, 2. 50 g cartridge, cyclohexane:ethyl acetate = 90:10, 3. 25 g cartridge, CH_2Cl_2:ethyl acetate = 95:5). The product was isolated as red resin, yield 87.8 mg (42 %).

R_f = 0.33 (CH_2Cl_2:ethyl acetate = 9:1); ^{1}H NMR (600 MHz, CD_2Cl_2): δ [ppm] = 1.75 - 1.91 (m, 10H, $(CH_2)_5$), 5.66 (d, *J* = 8.5 Hz, 0.9H, C=CH), 5.84 (d, *J* = 8.1 Hz, 0.1H, C=CH*), 7.34 (dt, *J* = 7.6/0.8 Hz, 1H, 7-$H_{arom.}$), 7.45 (td, *J* = 7.7/1.0 Hz, 1H, 5-$H_{arom.}$), 7.55 (td, *J* = 7.5/1.0 Hz, 1H, 6-$H_{arom.}$), 7.63 (dt, *J* = 7.7/0.9 Hz, 0.9H, 4-$H_{arom.}$), 8.22 (d, *J* = 8.0 Hz, 0.1H, 4-$H_{arom.}$*), 10.17 (d, *J* = 8.5 Hz, 0.9H, CHO*), 10.32 (d, *J* = 8.1 Hz, 0.1H, CHO); ^{13}C NMR (151 MHz, CD_2Cl_2): δ [ppm] = 23.1 (2C, CH_2), 25.4 (1C, CH_2), 36.9 (2C, CH_2), 94.2 (1C, C-1), 98.5 (1C, C=*C*H), 121.6 (1C, C-$7_{arom.}$), 123.2 (0.9C, C-$4_{arom.}$), 126.4 (0.1C, C-$4_{arom.}$*), 129.3 (1C, C-$5_{arom.}$), 132.0 (1C, C-$3a_{arom.}$), 132.8 (1C, C-$6_{arom.}$), 150.3 (1C, C-$7a_{arom.}$), 171.5 (1C, *C*=CH), 187.6 (0.1C, CHO*), 189.3 (0.9C, CHO). Compound **10a** was isolated as a mixture of (*Z*)- and (*E*)-isomers. In the NMR spectra a ratio of 90:10 is observed. Signals for the (*E*)-isomer are marked with an asterisk. HPLC (method A): t_R = 22.2 min, purity 96.8 %; IR: $\tilde{\nu}$ [cm^{-1}] = 2932, 2859 (C-$H_{aliph.}$), 1647 (CH=O), 1620 (C=C_{alkene}), 1466 (CH_2 deform.), 1053 (C-O-C), 806 (=C-

H_{alkene}), 764 (=C-$H_{arom.}$ deform.); Exact Mass (APCI**)**: m/z = 229.1219 (calcd. 229.1223 for $C_{15}H_{17}O_2$ $[MH]^+$).

2-(3-*tert*-Butyl-2-benzofuran-1(3*H*)-yliden)acetaldehyde (10c)

Method A: Diethyl acetal **9b** (242 mg, 0.85 mmol, 1.0 eq) was dissolved in THF (15 mL) and the solution was cooled to -78 °C. A solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.41 mL, 1.03 mmol, 1.2 eq) was added dropwise and the solution was stirred for 15 min at -78 °C. A solution of 2,2-dimethylpropanal (0.09 mL, 0.85 mmol, 1.0 eq) in THF (2 mL) was added dropwise within 14 min. Afterwards, the reaction mixture was warmed up to rt within 22 h. H_2O was added and the reaction mixture was stirred for further 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 x). Brine was added after the first extraction step to afford better phase separation. The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The residue was purified by flash column chromatography (100 g cartridge, CH_2Cl_2:ethyl acetate = 95:5). The product was isolated as yellow solid, mp 106 °C, yield 126 mg (68 %).

Method B: As described in method A, dimethyl acetal **9a** (192 mg, 0.75 mmol, 1.0 eq) was reacted as in method A described with a solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.36 mL, 0.90 mmol, 1.2 eq) and 2,2-dimethylpropanal (0.15 mL, 1.35 mmol, 1.8 eq) in THF (25 mL) at -90 °C. The residue was purified by flash column chromatography (100 g cartridge, CH_2Cl_2:ethyl acetate = 95:5). The product was isolated as yellow solid, yield 65.4 mg (40 %).

R_f = 0.43 (CH_2Cl_2:ethyl acetate = 9:1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ [ppm] = 1.00 (s, 0.45H, $C(CH_3)_3$*), 1.03 (s, 8.55H, $C(CH_3)_3$), 5.28 (s, 0.05H, ArC*H*O*), 5.38 (s, 0.95H, ArC*H*O), 5.66 (d, *J* = 8.5 Hz, 0.95H, C=CH), 5.86 (d, *J* = 8.2 Hz, 0.05H, C=CH*), 7.45

- 7.58 (m, 3H, 4-$H_{arom.}$, 5-$H_{arom.}$, 6-$H_{arom.}$), 7.66 (d, *J* = 7.6 Hz, 0.95H, 7-$H_{arom.}$), 8.27 (d, *J* = 7.8 Hz, 0.05H, 7-$H_{arom.}$*), 10.17 (d, *J* = 8.5 Hz, 0.95H, CHO), 10.32 (d, *J* = 8.1 Hz, 0.05H, CHO*); ^{13}C NMR (101 MHz, CD_2Cl_2): δ [ppm] = 25.7 (3C, C(CH_3)$_3$), 37.2 (1C, *C*(CH_3)$_3$), 94.2 (0.05C, Ar*C*HO*), 96.0 (0.95C, Ar*C*HO), 97.9 (0.95C, C=*C*H), 104.6 (0.05C, C=*C*H*), 123.0 (0.95C, C-$7_{arom.}$), 123.7 (1C, C-$4_{arom.}$), 126.2 (0.05C, C-$7_{arom.}$*), 129.4 (1C, C-$6_{arom.}$), 132.4 (1C, C-$5_{arom.}$), 133.8 (1C, C-$7a_{arom.}$), 143.5 (0.95C, C-$3a_{arom.}$), 146.0 (0.05C, C-$3a_{arom.}$*), 172.7 (0.95C, *C*=CH), 174.1 (0.05C, *C*=CH*), 187.7 (0.05C, CHO*), 189.0 (0.95C, CHO). Compound **10c** was isolated as a mixture of (*Z*)- and (*E*)-isomers. In the NMR spectra a ratio of 95:5 is observed. Signals for the (*E*)-isomer are marked with an asterisk. HPLC (method A): t_R = 21.6 min, purity 97.6 %; IR: $\tilde{\nu}$ [cm^{-1}] = 2967, 2955, 2870 (C-$H_{aliph.}$), 1643 (CH=O), 1624 (C=C_{alkene}), 1389 (CH_3 deform.), 1026 (C-O-C), 837 (=C-H_{alkene}), 775 (=C-$H_{arom.}$ deform.); Exact Mass (APCI): m/z = 217.1229 (calcd. 217.1223 for $C_{14}H_{17}O_2$ $[MH]^+$).

(*Z*)-3-[(5,5-Dimethyl-1,3-dioxan-2-yl)methylen]-3*H*-spiro[[2]-benzofuran-1,1'-cyclohexane] (10k)

Cyclic acetal **9c** (180 mg, 0.61 mmol, 1.0 eq) was dissolved in THF (20 mL) and the solution was cooled to -78 °C. A solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.29 mL, 0.73 mmol, 1.2 eq) was added dropwise and the solution was stirred for 15 min at -78 °C. A solution of cyclohexanone (0.11 mL, 1.10 mmol, 1.8 eq) in THF (3.5 mL) was added dropwise *via* syringe pump (10 mL/h). Afterwards, the reaction mixture was warmed up to rt within 16 h. H_2O was added and the reaction mixture was stirred for further 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 x). Brine was added after the first extraction step to afford better phase separation. The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The residue was purified by twofold flash column chromatography (1. 100 g cartridge,

cyclohexane:Et_3N = 98:2, 2. 100 g cartridge, cyclohexane:ethyl acetate = 95:5). The product was isolated as yellow resin, yield 85.5 mg (45 %). R_f = 0.29 (cyclohexane:ethyl acetate = 9:1); ^{1}H NMR (600 MHz, Acetone-d_6): δ [ppm] = 0.75 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.63 - 1.86 (m, 10H, $(CH_2)_5$), 3.55 (d, *J* = 10.9 Hz, 2H, C(C*H*$_A$H$_B$)$_2$)), 3.59 (d, *J* = 10.5 Hz, 2H, C(CH$_A$*H*$_B$)$_2$)), 5.07 (d, *J* = 7.5 Hz, 1H, C=CH), 5.50 (d, *J* = 7.5 Hz, 1H, C*H*$(OCH_2)_2$), 7.33 - 7.42 (m, 3H, 5-H$_{arom.}$, 6-H$_{arom.}$, 7-H$_{arom.}$), 7.56 - 7.60 (m, 1H, 4-H$_{arom.}$); ^{13}C NMR (151 MHz, Acetone-d_6): δ [ppm] = 22.0 (1C, CH_3), 23.2 (2C, CH_2), 23.3 (1C, CH_3), 25.5 (1C, CH_2), 30.4 (1C, *C*$(CH_3)_2$), 37.3 (2C, CH_2), 77.7 (2C, CH(O*C*$H_2)_2$), 90.0 (1C, C-1), 93.8 (1C, C=*C*H), 98.6 (1C, *C*H$(OCH_2)_2$), 121.3 (1C, C-4$_{arom.}$), 121.7 (1C, C-7$_{arom.}$), 129.0 (1C, C-5$_{arom.}$), 130.2 (1C, C-6$_{arom.}$), 133.5 (1C, C-3a$_{arom.}$), 149.0 (1C, C-7a$_{arom.}$), 156.5 (1C, *C*=CH); HPLC (method A): t_R = 22.3 min, purity 91.2 %; IR: $\tilde{\nu}$ [cm^{-1}] = 3044 (=C-H$_{arom.}$), 2936, 2851 (C-H$_{aliph.}$), 1690 (C=C$_{alkene}$), 1462 (CH_2 deform.), 1393 (CH_3 deform.), 1088 (C-O-C), 1061 (C-O-C), 791 (=C-H$_{alkene}$), 752 (=C-H$_{arom.}$ deform.); Exact Mass (APCI): m/z = 315.1966 (calcd. 315.1955 for $C_{20}H_{27}O_3$ [MH]$^+$).

Ethyl (*Z*)-2-(spiro[[2]benzofuran-1,1'-cyclohexan]-3-yliden)acetate (20a)

Orthoester **19** (144 mg, 0.44 mmol, 1.0 eq) was dissolved in THF (25 mL) and the solution was cooled to -78 °C. A solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.21 mL, 0.53 mmol, 1.2 eq) was added dropwise and the solution was stirred for 15 min at -78 °C. A solution of cyclohexanone (0.08 mL, 0.79 mmol, 1.8 eq) in THF (2 mL) was added dropwise *via* syringe pump (10 mL/h). Afterwards, the reaction mixture was warmed up rt within 17 h. H_2O was added and the reaction mixture was stirred for further 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 x). Brine was added after the first extraction step to afford better phase separation. The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The residue was

purified by flash column chromatography (50 g cartridge, cyclohexane:ethyl acetate = 9:1). The product was isolated as yellow resin, yield 56.1 mg (47 %). R_f = 0.30. (cyclohexane:ethyl acetate = 8:2); ^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathit{H}_3$), 1.42 (m, 1H, $(CH_2)_5$), 1.58 (d, *J* = 13.3 Hz, 2H, $(CH_2)_5$), 1.69 - 1.83 (m, 5H, $(CH_2)_5$), 1.90 (td, *J* = 13.3/5.3 Hz, 2H, $(CH_2)_5$), 4.07 (q, *J* = 7.1 Hz, 2H, $OC\mathit{H}_2CH_3$), 5.56 (s, 1H, C=CH), 7.44 (ddd, *J* = 8.0/6.1/2.2 Hz, 1H, 5-$H_{arom.}$), 7.51 - 7.58 (m, 2H, 6-$H_{arom.}$, 7-$H_{arom.}$), 7.85 (d, *J* = 7.8 Hz, 1H, 4-$H_{arom.}$); ^{13}C NMR (151 MHz, DMSO-d_6): δ [ppm] = 14.4 (1C, $OCH_2\mathit{C}H_3$), 22.0 (2C, CH_2), 24.2 (1C, CH_2), 35.8 (2C, CH_2), 58.5 (1C, $O\mathit{C}H_2CH_3$), 85.0 (1C, C=*C*H), 92.5 (1C, C-1), 121.2 (1C, C-$7_{arom.}$), 122.1 (1C, C-$4_{arom.}$), 128.8 (1C, C-$5_{arom.}$), 131.6 (1C, C-$6_{arom.}$), 131.7 (1C, C-$3a_{arom.}$), 149.2 (1C, C-$7a_{arom.}$), 165.2 (1C, $\mathit{C}O_2Et$), 165.7 (1C, *C*=CH); HPLC (method A): t_R = 23.7 min, purity 94.8 %; IR: $\tilde{\nu}$ [cm^{-1}] = 2978, 2932, 2859 (C-$H_{aliph.}$), 1701 (C=O), 1636 (C=C_{alkene}), 1466 (CH_2 deform.), 1369 (CH_3 deform.), 1146 (CO-O-CH_2CH_3), 1069 (C-O-C), 802 (=C-H_{alkene}), 768 (=C-$H_{arom.}$ deform.); Exact Mass (ESI): m/z = 273.1488 (calcd. 273.1485 for $C_{17}H_{21}O_3$ $[MH]^+$).

Ethyl (*Z*)-2-[3-(*tert*-butyl)-2-benzofuran-1(3*H*)-yliden]acetate (20c)

Orthoester **19** (219 mg, 0.67 mmol, 1.0 eq) was dissolved in THF (25 mL) and the solution was cooled to -78 °C. A solution of *n*-butyllithium in *n*-hexane (2.5 M, 0.32 mL, 0.80 mmol, 1.2 eq) was added dropwise and the solution was stirred for 15 min at -78 °C. A solution of 2,2-dimethylpropanal (0.13 mL, 1.20 mmol, 1.8 eq) in THF (2 mL) was added dropwise *via* syringe pump (10 mL/h). Afterwards, the reaction mixture was warmed up rt within 19 h. H_2O was added and the reaction mixture was stirred for further 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 x). Brine was added after the first extraction step to afford better phase separation. The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The residue was

purified by flash column chromatography (100 g cartridge, cyclohexane:ethyl acetate = 9:1). The product was isolated as yellow resin, yield 86.3 mg (50 %). R_f = 0.22 (cyclohexane:ethyl acetate = 8:2); ^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 0.94 (s, 9H, C(CH_3)$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 4.02 - 4.14 (m, 2H, OCH_2CH_3), 5.47 (s, 1H, ArC*H*O), 5.56 (s, 1H, C=CH), 7.44 - 7.52 (m, 1H, 6-$H_{arom.}$), 7.54 - 7.58 (m, 2H, 4-$H_{arom.}$, 5-$H_{arom.}$), 7.89 (d, *J* = 7.8 Hz, 1H, 7-$H_{arom.}$); ^{13}C NMR (151 MHz, DMSO-d_6): δ [ppm] = 14.4 (1C, OCH_2CH_3), 24.9 (3C, C(CH_3)$_3$), 36.0 (1C, *C*(CH_3)$_3$), 58.5 (1C, OCH_2CH_3), 84.2 (1C, C=*C*H), 94.0 (1C, Ar*C*HO), 121.9 (1C, C-7$_{arom.}$), 123.1 (1C, C-4$_{arom.}$), 128.7 (1C, C-6$_{arom.}$), 131.1 (1C, C-5$_{arom.}$), 133.6 (1C, C-7a$_{arom.}$), 142.4 (1C, C-3a$_{arom.}$), 165.1 (1C, *C*O_2Et), 166.9 (1C, *C*=CH); HPLC (method A): t_R = 23.1 min, purity 96.0 %; IR: $\tilde{\nu}$ [cm^{-1}] = 2959, 2936, 2901, 2870 (C-$H_{aliph.}$), 1705 (C=O), 1639 (C=C_{alkene}), 1466 (CH_2 deform.), 1366 (CH_3 deform.), 1142 (CO-O-CH_2CH_3), 1072 (C-O-C), 806 (=C-H_{alkene}), 768 (=C-$H_{arom.}$ deform.); Exact Mass (APCI): m/z = 261.1491 (calcd. 261.1485 for $C_{16}H_{21}O_3$ [MH]$^+$).

Supporting Information Available

Supporting Information includes the Experimental procedures and spectroscopic data of all compounds and additional information for DFT calculations. Additionally, all ^{1}H and ^{13}C NMR spectra are included.

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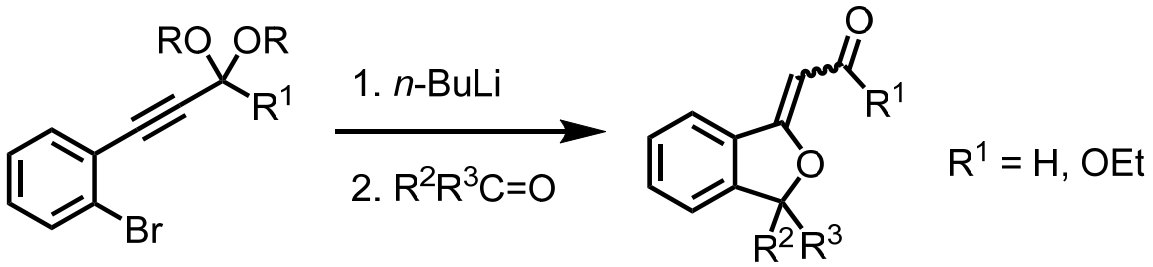
Graphical Abstract



Text for Graphical Abstract

The 1-alkylidenephthalane scaffold is found in several biological active compounds. In order to synthesize 1-alkylidenephthalanes a Domino reaction was developed using 2-alkynyl substituted bromobenzenes. Successive bromine/lithium exchange, nucleophilic addition at aldehydes or ketones 5-*exo*-*dig* cyclization and hydrolysis resulted in aldehydes or esters in high yield. The 5-*ex*-*dig* cyclization key step was theoretically analyzed by DFT calculations.