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Soluble and polymer-supported 2- and 3-benzylated furans for the preparation of α,β-ethylenic carbonyl compounds

Sébastien Albert,[a] Adrien Soret,[a] Luis Blanco[b,a] and Sandrine Deloisy[a,b,*]

[a]*Univ Paris-Sud, I.C.M.M.O., UMR 8182, Laboratoire de Synthèse Organique et Méthodologie, Bât. 420, Orsay Cedex F-91405, France*
[b]*CNRS, UMR 8182, Orsay Cedex F-91405, France*

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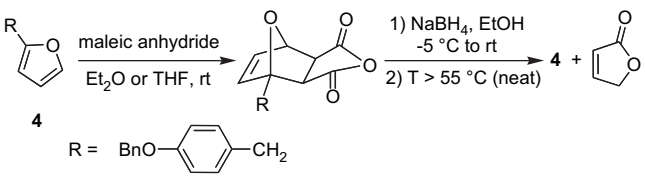
Abstract—Soluble and polymer-supported 2- and 3-benzylated furans were subjected to a sequence involving a Diels–Alder reaction with α,β-acetylenic carbonyl compounds, a Michael addition, and a subsequent retro-Diels–Alder reaction to yield olefinic compounds. On solid support, this traceless strategy is advantageous since pure compounds were released in the thermal cycloreversion step. The fur-2-ylated resin allowed a highly diastereoselective synthesis.

1. Introduction

The last step of a solid-phase synthesis is generally the release of the product in solution. Frequently, acidic/electrophilic or basic/nucleophilic labile linkers are used and one problem with these procedures is the compatibility of the core and the substituents of the molecule with the generally drastic conditions of the cleavage. Transition metal-mediated cleavage and silicon-based linkers are compatible with the presence of less robust substituents. Obviously the use of photolabile linkers leads to improved cleavage characteristics and allows the presence of structures and/or substituents, which are not stable in the above-cited conditions.[1–5] Thermolabile linkers may also be envisaged in order to preserve the integrity of a wide range of structures. To our knowledge only four groups have used a thermal cleavage step involving a retro-Diels–Alder reaction. The cycloreversion has allowed the release of furans,[6,7] buckminsterfullerene C_{60},[8] and benzoquinone.[9]

Moreover it was shown that C_{60} readily undergoes Diels–Alder cycloaddition with cyclopentadiene- and furan-functionalized polymers.[8] These reactions are just some of the numerous examples of Diels–Alder reactions performed on solid support.[10]

We have proposed the use of a furan-functionalized resin in a sequence involving a Diels–Alder cycloaddition to immobilize a dienophile and a retro-Diels–Alder reaction to release an olefinic compound after chemical transformation of the initial cycloadduct.[11,12] In preliminary experiments, Diels–Alder cycloaddition of maleic anhydride with the soluble furan derivative **4** afforded the expected cycloadduct at room temperature. Reduction of this compound with sodium borohydride followed by heating of the resulting lactone led to furan-2-(5*H*)-one and the starting compound **4** (Scheme 1). Reactions of the analogous polymer-bound furan **6** (vide infra) with maleic anhydride in tetrahydrofuran at various temperatures (from 20 °C to 50 °C) were unsuccessful. The ^{13}C NMR spectra of the resins showed mainly the signals of the starting material **6**; in some cases, tiny signals corresponding to the desired cycloadduct and to maleic anhydride were noticed. The presence of the dienophile was unexpected since the resins were carefully washed with THF before analysis by NMR. We concluded that it could have been released by cycloreversion from the polymer-supported cycloadduct after the washings. Thus, the retro-Diels–Alder reaction occurred at too low a temperature, precluding the use of such a polymer-bound cycloadduct in further transformations.



Scheme 1.

This paper deals with the use of 2- and 3-benzylated furans in a strategy involving acetylenic dienophiles, where the

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* Corresponding author. Tel.: +33 1 69 15 47 12; fax: +33 1 69 15 62 78; e-mail: sdeloisy@icmo.u-psud.fr

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thermally stable Diels–Alder cycloadducts could be functionalized before the retro-Diels–Alder reaction.

2. Results and discussion

2.1. Preparation of 2- and 3-benzylated furans

The 2- and 3-benzylated furans **4** and **7** were synthesized in a four-step sequence from commercially available ethyl 4-hydroxybenzoate, as shown in Scheme 2.

Reactions of the difuran-2-yl-[13] and the difuran-3-yllithiocuprate[14] with the benzylic bromide **3**[15,16] afforded furans **4** and **7**, respectively. For the synthesis of furan **4**, the optimum yield (94%) was obtained using a difuranyllithiocuprate prepared from $CuBr\cdot SMe_2$. However, the yields were erratic (from 20 to 94%) and depended on the quality of the cuprous complex. More reproducible results (76–87%) were observed with the higher order difuranylcyanocuprate $(C_4H_3O)_2Cu(CN)Li_2$.[17] The corresponding furan-substituted resins **6** and **9** were prepared by treatment of a chloromethylated Merrifield resin with the phenolic products **5** and **8** in the presence of cesium carbonate and sodium iodide in DMF.[18] Compounds **5** and **8** were obtained by hydrogenolysis of **4** and **7** with sodium in butan-1-ol.[19] Resins **6** and **9** were purified by successive washings with DMF, H_2O, DMF, acetone, and CH_2Cl_2 and subsequently dried under vacuum. Acidification of filtrates allowed recovery of excesses of phenols **5** and **8**. The resins **6** and **9** were characterized by IR and ^1H and ^{13}C Magic Angle Spinning (MAS) NMR spectroscopies.

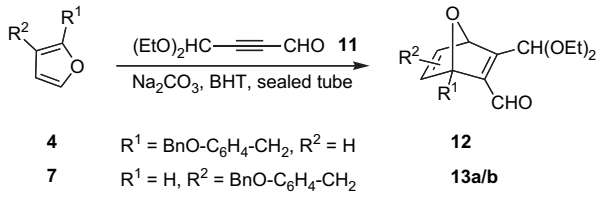
The soluble furans **4** and **7**, similar to the furan spacer appendage of the polymers **6** and **9**, were used for solution-state study of the reaction sequence to be applied on the solid support.

2.2. Diels–Alder reactions with acetylenic dienophiles

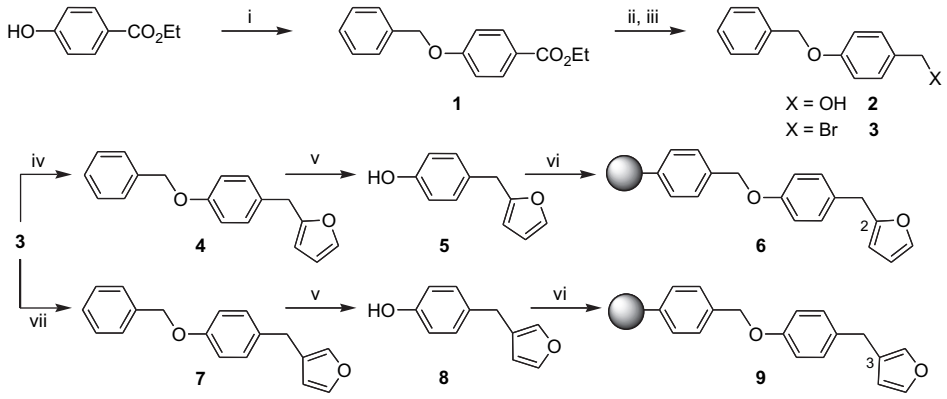
At first, 4,4-diethoxybut-2-ynal was selected as the dienophile since the presence of a free and a protected aldehyde should allow various chemical transformations.

Treatment of 1,1,4,4-tetraethoxybut-2-yne **10** with pure formic acid in chloroform gave 4,4-diethoxybut-2-ynal **11**[20,21] in 66% yield after distillation. As reported,[20b] tetraethoxybutyne **10** was prepared by reaction of diethyl phenyl orthoformate with bis(bromomagnesium)acetylide in variable yields (between 24 and 65%). A more reproducible synthesis (85% yield) was achieved by reaction of diethyl phenyl orthoformate with the bromomagnesium derivative of commercially available 3,3-diethoxypropyne (Scheme 3).

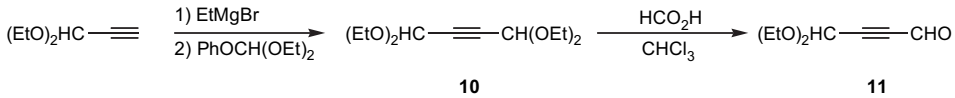
Using conditions described for 2-alkylfurans,[22] Diels–Alder reaction of the furan derivative **4** (1.2 equiv) with ynal **11** in a sealed tube at 90 °C under argon in the presence of small amounts of sodium carbonate and 2,6-di-*tert*-butyl-4-methylphenol (BHT) without solvent gave the cycloadduct **12** in 93% yield (Scheme 4, Table 1: entry 1). Since a liquid is necessary to swell the resin in cases of solid-supported reactions, various solvents were tested under different conditions for the preparation of the cycloaddition products **12** and **13**, despite the fact that a very slow reaction had been reported for the cycloaddition of ynal **11** with 2-alkylfurans in dichloromethane or toluene.[22]



Scheme 4.



Scheme 2. Reagents and conditions: (i) BnBr, K_2CO_3, Aliquat® 336 (1 mol %), 100 °C, 98%; (ii) $LiAlH_4$, Et_2O, rt, 100%; (iii) PBr_3, CH_2Cl_2, rt, 91%; (iv) furan, *n*-BuLi, Et_2O, 0 °C, then $CuBr\cdot SMe_2$, Et_2O/THF, −40 °C to rt, 94%; (v) Na, *n*-BuOH, 80 °C, 98% for **5**; 79% for **8**; (vi) Merrifield resin, Cs_2CO_3, NaI, DMF, rt; (vii) 3-bromofuran, *n*-BuLi, Et_2O, −78 °C, then $CuBr\cdot SMe_2$, Et_2O/THF, −65 °C to rt, 76%.



Scheme 3.

Table 1. Diels–Alder reactions of furan **4** or **7** with ynal **11** in homogeneous phase[a]

Entry	Furan	Solvent	Temp (°C)	Time (h)	Cycloadduct	Yield (%)
1	**4**	None[b]	90	40	**12**	93
2	**4**	Toluene[c]	90	48	**12**	0[d]
3	**4**	Toluene	90	48	**12**	86
4	**4**	Toluene	125	24	**12**	47
5	**4**	Toluene	125	72	**12**	42
6	**4**	1,4-Dioxane	90	48	**12**	77
7	**4**	CH_3CN	90	48	**12**	69
8	**4**	THF	90	48	**12**	72
9	**4**	DMF	90	48	**12**	0[d]
10	**4**	DMF	110	48	**12**	0[d]
11	**7**	Toluene	90	48	**13a/13b**	73[e]
12	**7**	Toluene	124	48	**13a/13b**	87[f]

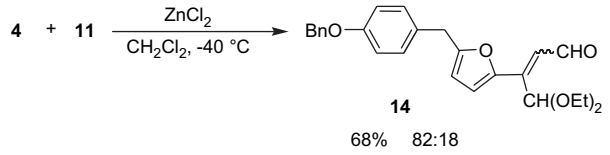
[a] Unless otherwise noted, reactions were performed in vacuum-sealed tubes after freeze-pump-thaw cycles.
[b] Reaction was performed under argon.
[c] Reaction was performed under argon in an open vessel after bubbling of argon in the reaction mixture.
[d] Degradation.
[e] Regioisomeric ratio of 57:43.
[f] Regioisomeric ratio of 55:45.

Degassed solutions of dienophile **11** (1.1 equiv) and substituted furan **4** or **7** in the presence of sodium carbonate (0.1 equiv) and BHT (0.1 equiv) were heated, then the cycloadducts **12** and **13** were isolated by chromatography (Table 1).

When a toluene solution of **4** and **11** was heated at 90 °C for 48 h under an argon atmosphere after bubbling of argon in the solution for 15 min, the ynal was totally transformed and some furan remained unchanged, but no cycloadduct **12** was observed in the reaction mixture (entry 2). On the other hand, the expected product **12** was isolated using toluene, 1,4-dioxane, acetonitrile or tetrahydrofuran as solvent after heating in vacuum-sealed tubes previously degassed solutions by freeze-pump-thaw cycles (entries 3–8). The best result (86% yield) for this extremely air-sensitive reaction was obtained by maintaining a toluene solution at 90 °C for 48 h (entry 3). Heating the toluene reaction mixture to 125 °C for 24 or 72 h (entries 4 and 5) led to the product **12** in decreased yields, 47 and 42%, respectively. With a well-degassed DMF solution heated at 90 °C (entry 9) or 110 °C (entry 10) no cycloadduct **12** was detected, despite the fact that ynal **11** was totally transformed after 48 h at 110 °C. ^1H and ^{13}C NMR spectra of all samples of compound **12** indicated the presence of only one diastereomer. The reported structure with the aldehyde function close to the benzylic appendage was proved by NOESY experiments (cross-peaks are present between the acetal proton and the bridgehead proton of the oxabicyclo[2.2.1]heptadiene core).

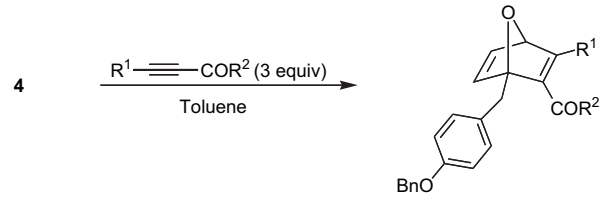
The 3-substituted furan **7** was less reactive with ynal **11**. When a degassed toluene solution was heated at 90 °C for 48 h in a vacuum-sealed tube, a 57:43 mixture of the two regioisomers **13a** and **13b** (entry 11) was isolated in 73% yield and unreacted ynal **11** was still present in the reaction mixture. A slightly better yield of the cycloadduct **13** (87% yield) was obtained by increasing the reaction temperature to 124 °C (entry 12). The ratio of regioisomers was similar to the previous case and the ^1H NMR spectrum of the crude reaction mixture showed the absence of ynal **11**.

It is noteworthy that the $ZnCl_2$-catalyzed reaction of ynal **11** and furan **4** in methylene chloride at −40 °C gave only Michael adduct **14** (Scheme 5). A similar Michael addition product was observed in the cycloaddition of furan[20a] and 2-alkylfurans[22] with ynal **11** in the absence of sodium carbonate.



Scheme 5.

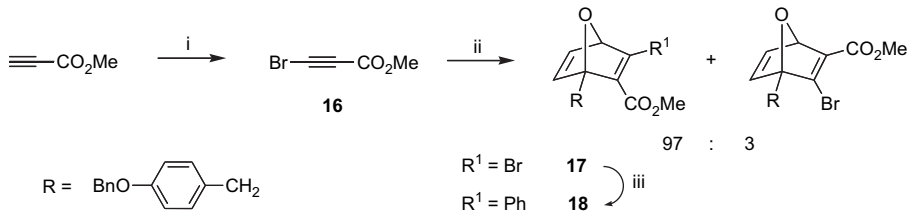
Most of the reported Diels–Alder reactions of acetylenic dienophiles with furan derivatives involve acetylenedicarboxylates.[23] Moreover, with the exception of intramolecular reactions,[24] unsymmetrical acetylenic carbonyl compounds used in such cycloadditions generally bear a second electron-withdrawing group.[25] To prepare other 1-substituted 7-oxabicycloheptadiene adducts, Diels–Alder reactions with furan **4** were attempted using 3 equiv of commercially available dimethyl acetylenedicarboxylate (DMAD) or methyl 3-phenylpropiolate or the synthesized 3-phenylpropynal[26] (Scheme 6). With DMAD, a toluene solution was heated at 110 °C in a round-bottomed flask for 3 h (the reaction is not air-sensitive) and the cycloadduct **15** was isolated quantitatively. After heating degassed toluene solutions of furan **4** and methyl phenylpropiolate or phenylpropynal in the presence of sodium carbonate and BHT in vacuum-sealed tubes at 90 °C during 24 h, no cycloadducts were detected.[27,28]



$R^1 = CO_2Me$	$R^2 = OMe$	110 °C, 3 h	**15**	99%
$R^1 = Ph$	$R^2 = OMe$	a	**18**	0%
$R^1 = Ph$	$R^2 = H$	a		0%

Scheme 6. (a) Sealed tube, BHT (0.1 equiv), Na_2CO_3 (0.1 equiv), 90 °C, 24 h.

In order to prepare the expected phenyl product **18**, we envisaged a two-step synthesis via the brominated intermediate **17** obtained by Diels–Alder reaction of furan **4** with methyl 3-bromopropiolate **16** (Scheme 7). Treatment of methyl propiolate with *N*-bromosuccinimide in acetone in the presence of silver nitrate afforded methyl bromopropiolate **16**.[29] In our hands, only impure lachrymatory samples of the ester **16** were isolated, with difficulty. To obviate purification, the bromination was run in acetonitrile, then a solution of ester **16** (about 3 equiv) in this solvent was collected by distillation under low pressure and used in the cycloaddition step. After heating at 110 °C in a vacuum-sealed tube for two days, a 97:3 mixture of the 3-brominated cycloadduct **17** and the 2-brominated isomer was isolated in 60% yield. A similar regioselectivity was recently reported in the cycloaddition of 2-methylfuran with the same bromopropiolate



Scheme 7. Reagents and conditions: (i) NBS, $AgNO_3$, CH_3CN, rt, 1 h; (ii) **4**, CH_3CN (sealed tube), 110 °C, 48 h, 60%; (iii) $PhB(OH)_2$, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, KF, THF, rt, 3.5 h, 90%.

16.[30] Reaction of phenylboronic acid (1.1 equiv) with the adduct **17** in the presence of potassium fluoride, $Pd_2(dba)_3$, and tris(*tert*-butyl)phosphine[31] furnished the phenyl cycloadduct **18** in high yield (90%). When standard Suzuki coupling conditions were used ($Pd(OAc)_2$, triphenylphosphine, aqueous solution of sodium carbonate in a 5:1 mixture of benzene and methanol at 50 °C for 2.5 h), the product **18** was only obtained in 56% yield.[32] Stille cross-coupling of the brominated adduct **17** with tributylphenyltin was unsuccessful or gave the expected product in a very low yield under classical conditions.[33]

The formation of the 3-phenyl compound **18** and, consequently, the regioselective synthesis of the 3-brominated cycloadduct **17** were ascertained by the presence of cross-peaks between aromatic protons and the bridgehead proton in the NOESY spectrum of compound **18**.

2.3. Functionalization by Michael addition and retro-Diels–Alder reaction

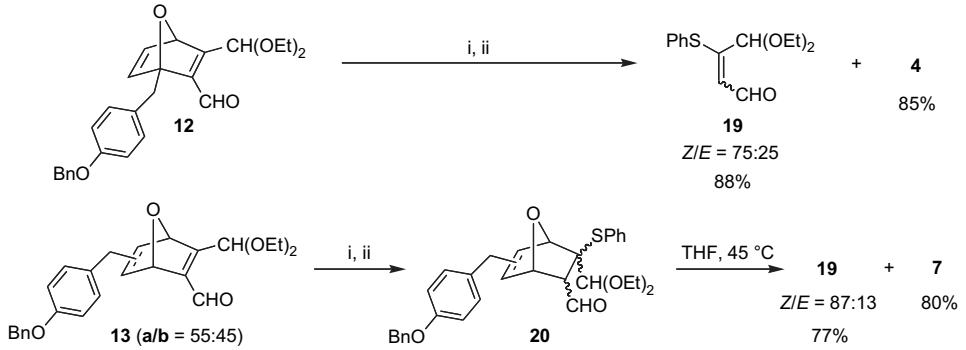
The functionalization of α,β-ethylenic aldehydes **12** and **13** was envisaged by Michael addition of benzenethiol using a catalytic amount of sodium hydride (Scheme 8). When the reaction with the cycloadduct **12** was run in THF at −78 °C, surprisingly a mixture of the starting furan **4** and (*Z*)- and (*E*)-4,4-diethoxy-3-(phenylsulfanyl)butenal **19** (*Z*/*E*=75:25) was isolated after a basic aqueous work-up at 0 °C and no Michael addition compound was detected. Performing the reaction at room temperature yielded the furan **4**, the aldehydes (*E*)-**19** and (*Z*)-**19**, and a small amount of 4,4-diethoxy-3,3-bis(phenylsulfanyl)butanal resulting from a second Michael addition reaction on the aldehyde **19**.[34]

Treatment of a 55:45 mixture of cycloadducts **13a/13b** with sodium benzenethiolate at −78 °C, as previously described, gave a mixture of Michael addition products **20**, which were stable enough to be isolated at room temperature. The ^{1}H NMR spectrum of the crude isolated product **20** showed the presence of two major isomers and (at least) four minor diastereomers. An 87:13 mixture of enals (*Z*)-**19** and (*E*)-**19** and the furan **7** resulting from a retro-Diels–Alder reaction were easily obtained after heating this mixture of diastereomers **20** for 3 h at 45 °C in THF (Scheme 8).

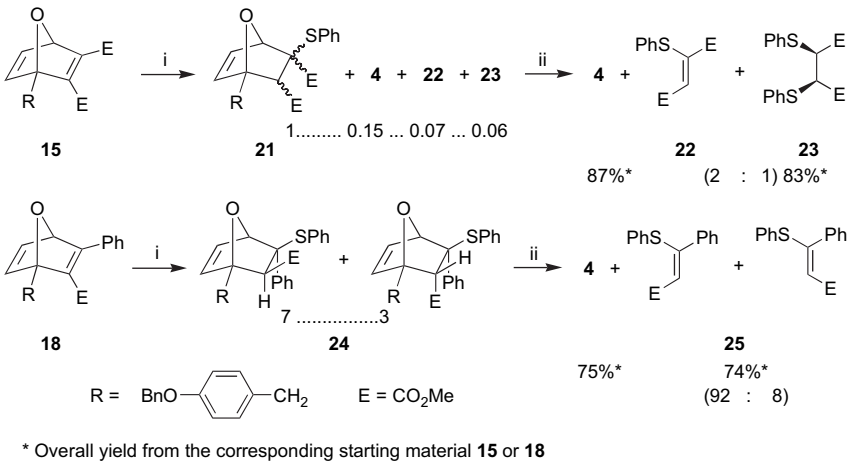
Treatment of esters **15** and **18** with benzenethiol in the presence of a catalytic amount of NaH at −78 °C and subsequent thermal retro-Diels–Alder reaction gave mainly the furan **4** and the unsaturated esters **22** and **25**, respectively (Scheme 9).

The ^{1}H NMR spectrum of the crude product obtained from reaction of the diester **15** with sodium benzenethiolate showed various signals, which could be attributed to three isomers of the expected Michael adducts **21** (one set of signals at 6.72 (d), 6.48 (dd), and 5.34 ppm (d), another set at 6.52 (d), 6.31 (dd), and 4.92 ppm (d), and the last set at 6.25 (d), 6.21 (dd), and 5.02 ppm (d) attributed, respectively, to the protons H-6, H-5, and H-4 of the bicyclic core; a 0.7:0.3:1 mixture of these isomers was present). But a retro-Diels–Alder reaction had occurred and furan **4**, dimethyl phenylsulfanylfumarate **22**, and *meso*-dimethyl 2,3-bis(phenylsulfanyl)succinate **23**[35,36] were also present. The NMR spectrum also showed minor signals, which could be attributed to dimethyl phenylsulfanylmaleate[37] and *dl*-dimethyl 2,3-bis(phenylsulfanyl)succinate.[35,36] The adducts **21** were too unstable to be isolated by silica gel chromatography. After heating of this mixture for 16 h at 75 °C in toluene, the Michael adducts **21** were totally transformed. Furan **4** and a 2:1 mixture of fumarate **22** and *meso*-bis-(phenylsulfanyl)diester **23** were isolated in, respectively, 87 and 83% yields for this two-step sequence.[38]

Reaction of sodium benzenethiolate with the monoester **18** yielded the adduct **24** as a 7:3 mixture of two diastereomers.



Scheme 8. Reagents and conditions: (i) PhSH (3 equiv), NaH (0.3 equiv), THF, −78 °C to 0 °C; (ii) treatment with aqueous NaOH, 0 °C.



Scheme 9. Reagents and conditions: (i) PhSH (3 equiv), NaH (0.3 equiv), THF, −78 °C to 0 °C, then treatment with aqueous NaOH, 0 °C; (ii) toluene, 75 °C, 16 h.

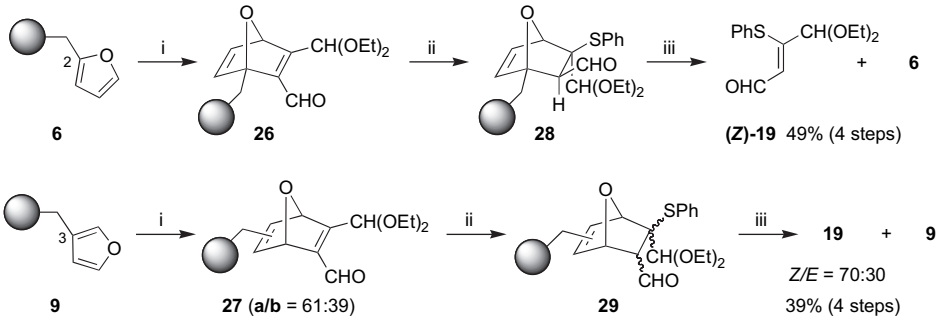
Column chromatography allowed the complete separation of these isomers but a retro-Diels–Alder reaction occurred and furan **4** and the olefinic esters **25** were present in each sample. Nevertheless, the main ^{1}H and ^{13}C NMR signals were observed and an attempt was made to establish the stereochemical relationships. With such 7-oxabicycloheptadienic compounds addition generally occurs on the *exo*-face[39] and the *exo*-position of the phenylsulfanyl group in the two diastereomers was proposed. The *exo*-position of the ester group of the major isomer was proved by NOESY experiments (cross-peaks are present between the protons in the positions 2 and 6 of the oxabicyclo[2.2.1]heptene core). Furan **4** and a mixture of (*E*)- and (*Z*)-isomers of the olefinic ester **25** were isolated in good yields after heating each stereomer for 16 h at 75 °C. The *Z*/*E* ratio obtained for ester **25** was fairly constant, regardless of the starting diastereomer **24** (from major isomer: *Z*/*E*=93:7; from minor isomer: *Z*/*E*=90:10).

2.4. Reactions on solid support

Treatment of the furan-substituted resins **6** and **9** at 90 °C for 72 h with 4 equiv of butynal **11**, in the same conditions as those used in homogeneous phase, gave, respectively, the supported Diels–Alder adducts **26** and **27** after successive washings with CH_2Cl_2, acetone, H_2O, acetone, and CH_2Cl_2 (Scheme 10). The excess of ynal **11** was mainly present in the first solvent washing and could be recovered.

Comparison of ^{1}H and ^{13}C MAS NMR spectra of the Diels–Alder adduct-functionalized resins **26** and **27** with those of the soluble analogs **12** and **13** indicated a similar selectivity of these solid-phase reactions to that observed with furans **4** and **7** in solution. Only one diastereomer was observed for the resin **26** obtained from the fur-2-ylated polymer **6**. Similarly to the analogous compound **13** prepared in solution-phase, the major isomer of the resin **27** is the one with the lower field aldehyde proton signal and a similar regioselectivity was observed (for **27**, a 61:39 diastereomeric ratio was obtained; for **13**, this ratio was 55:45).

Additions of excess benzenethiol to the resins **26** and **27** in the presence of a catalytic amount of sodium hydride were run at −40 °C (at a lower temperature, no swelling of the resins was observed). Upon increasing the reaction mixture temperature, GC analyses of the solvent showed the presence of the α,β-unsaturated aldehyde **19** resulting from a retro-Diels–Alder reaction above −35 °C in the former case and above −20 °C in the latter one. Thus, the Michael adduct-functionalized resins **28** and **29** were washed, respectively, at −35 °C and −25 °C with THF, THF/MeOH, and THF in order to remove excess of benzenethiol and sodium benzenethiolate. After addition of THF to the washed resin **28** the temperature was allowed to increase to −2 °C. Filtration at −2 °C after 15 h at this temperature and concentration of filtrates under vacuum at 20 °C allowed isolation of only pure (*Z*)-aldehyde **19** in 49% overall yield based on



Scheme 10. Reagents and conditions: (i) ynal **11**, Na_2CO_3, BHT, toluene, 90 °C, vacuum-sealed tube; (ii) PhSH, cat. NaH, THF; for **28**: −40 °C, then −35 °C and filtration and washings at −35 °C; for **29**: −40 °C, then −25 °C and filtration and washings at −25 °C; (iii) THF; with **28**: −35 °C, then −2 °C; with **29**: −25 °C, then rt and 40 °C.

Merrifield resin for this four-step sequence. Further increase of the temperature to 20 °C of a suspension of the recovered resin in THF did not release any more olefinic product. Partial isomerization of the (*Z*)-aldehyde **19** to the (*E*)-isomer was observed when the water bath was set to 40 °C during concentration. Stirring of the resin **29** in THF at 20 °C for 24 h gave a 71:29 mixture of (*Z*)- and (*E*)-aldehydes **19** in 23% yield. After the reported time no release of olefinic compounds was noticed at 20 °C. When a suspension of the recovered resin in THF was stirred for 24 h at 40 °C more aldehyde **19** was isolated (*Z*/*E*=70:30; 16% yield). No reaction was observed upon increasing the reaction time at 40 °C or at higher temperatures. Thus, it seems that the retro-Diels–Alder reactions occur at different temperatures for the various isomers linked to the resin **29**.

In both cases, IR spectroscopy of the recovered resins after the retro-Diels–Alder reactions showed only the characteristic bands of the furan-functionalized resins **6** and **9**. It should be noticed that the recovered resin **6** could be reused in another Diels–Alder reaction/Michael addition/retro-Diels–Alder reaction sequence.

3. Conclusion

We have shown that Diels–Alder reaction of soluble and polymer-supported 2- and 3-benzylated furans with 4,4-diethoxybut-2-ynal, followed by Michael addition of a nucleophile, then retro-Diels–Alder reaction allows the preparation of a β-substituted α,β-ethylenic aldehyde. On solid-phase, this sequence is another example of a safety-catch strategy since the Michael adduct is stable enough at low temperature to remove unreacted reagents by filtration and the thermal cycloreversion is induced at a higher temperature. Thus, the released olefinic aldehyde is pure enough to avoid further purification. The fur-2-ylated resin appears more promising from a synthetic point of view since only one regioisomer was obtained in the Diels–Alder reaction, a better diastereoselectivity was observed in the Michael addition, and the yield of the final olefinic product was higher. α,β-Ethylenic esters were also obtained, using a similar sequence via 7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylates prepared from dimethyl acetylenedicarboxylate or from methyl 3-bromopropiolate and a subsequent substitution of the bromine atom. Synthetic applications of this traceless methodology using various nucleophiles will be published in due course.

4. Experimental

4.1. General

In solution-phase, reactions were monitored by TLC on silica gel 60 F_{254} precoated plates (0.25 mm thickness) with UV detection (254 nm) and by heating after dipping in ethanolic solutions of phosphomolybdic acid or *p*-anisaldehyde. The products were isolated by column chromatography on silica gel (SDS 70–220 mesh or SDS 220–440 mesh for flash chromatography). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200 (200 and 50.3 MHz, respectively) or Bruker AC250 (250 and 62.9 MHz, respectively) spectrometers. Chemical shifts (δ) are given in parts per million using solvent ($CDCl_3$) signals as internal standards ($CHCl_3$ δ=7.27 ppm; $CDCl_3$ δ=77.14 ppm). Assignments were aided by DEPT-135 pulse, NOESY, and heteronuclear two-dimensional experiments. Mass spectra (MS) were obtained by electronic impact (EI, 70 eV) or positive chemical ionization (CI) on a Nermag R10-10 spectrometer coupled with an OK1 DP125 gas chromatographer. Electrospray (ES^+) mass spectra were performed on a Finnigan MAT 95S spectrometer. Relative percentages are shown in brackets. High resolution mass spectra (HRMS) were recorded with a Finnigan MAT 95S (electronic impact or electrospray) spectrometer. Elemental analyses were performed with a Perkin–Elmer 240C analyzer by the Service de Microanalyse of the Institut de Chimie des Substances Naturelles of Gif-sur-Yvette (France). Melting points were determined with a Büchi B-545 apparatus and were uncorrected. As the solid support, Merrifield resin (loading 0.8 mmol/g, styrene–1%DVB, 200–400 mesh) was purchased from Fluka. For MAS NMR experiments, the resins were swollen with the minimal volume of deuterated solvent ($CDCl_3$) after introducing them into the rotor. ^{1}H and ^{13}C NMR data were collected using a 4 mm MAS solid state probe on a Bruker DRX-400 (400 and 100 MHz, respectively) spectrometer with a spinning rate of 3 kHz. Signals of the polymeric matrix were indicated by Pm. Proofs of purity of aldehyde **19** released from the resins were provided by their ^{1}H NMR spectrum (>95% pure). Infrared (IR) spectra of products and resins were recorded using an FT-IR Perkin–Elmer spectrophotometer (Spectrum One). Solvents were dried according to standard procedures and all reactions requiring anhydrous conditions were performed under argon. Degassed solutions were prepared by freeze-pump-thaw cycles.

4.2. Preparation of fur-2-ylated and fur-3-ylated resins 6 and 9

4.2.1. Ethyl 4-(benzyloxy)benzoate (1). A mixture of ethyl 4-hydroxybenzoate (8.30 g, 50.0 mmol), potassium carbonate (7.25 g, 52.5 mmol), Aliquat® 336[40] (250 mg, 0.50 mmol), and benzyl bromide (6.25 mL, 52.5 mmol) was stirred at 100 °C for 6 h, and then cooled to room temperature. After dilution with Et_2O (100 mL) and water (100 mL), the decanted aqueous layer was extracted with Et_2O. The combined organic extracts were successively washed with 1 M HCl and water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O: 90/10) to afford **1** (12.52 g, 98%) as a white solid: mp 44 °C (lit.[41] mp 45.5 °C). Spectroscopic data were in agreement with reported values.[42]

4.2.2. [4-(Benzyloxy)phenyl]methanol (2). To a suspension of lithium aluminum hydride (1.28 g, 33.7 mmol) in dry Et_2O (80 mL) maintained under argon in an ice bath was added dropwise a solution of ester **1** (11.55 g, 45.1 mmol) in dry Et_2O (100 mL). The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The excess of lithium aluminum hydride was decomposed by slow addition (violent reaction) of hydrated Na_2SO_4 until a clear solution was obtained (approximately 30 g of Na_2SO_4). Filtration through a pad of anhydrous sodium sulfate and removal of solvent under reduced pressure gave the benzylic alcohol **2** (9.69 g, 100%) as a white solid: mp 86 °C

(lit.[43] mp 85–86 °C). The crude alcohol showed a very satisfactory ^{1}H NMR spectrum[43] and was used in the subsequent reaction without further purification. ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 64.9, 70.0, 115.0, 127.5, 128.0, 128.6, 128.7, 133.5, 137.0, 158.4.

4.2.3. 1-(Benzyloxy)-4-(bromomethyl)benzene (3). Benzylic bromide **3** (4.50 g) was prepared by reaction of alcohol **2** (3.37 g, 15.7 mmol) with phosphorus tribromide (1.9 mL, 20.2 mmol) in dry methylene chloride (70 mL) as described by Cushman et al.[15b] NMR data were in agreement with reported values. Recrystallization from *n*-hexane gave **3** (3.97 g, 91%) as white needles: mp 84 °C (lit.[15d] mp 85–86 °C). However, due to its allergenic properties (by contact and inhalation), compound **3** could be rapidly used in the next step without purification.

4.2.4. 2-[4-(Benzyloxy)phenylmethyl]furan (4). To a stirred solution of freshly distilled furan (0.75 mL, 10.3 mmol) in anhydrous Et_2O (5 mL) under argon at 0 °C was added dropwise a 1.6 M solution of *n*-butyllithium in hexane (6.25 mL, 10.0 mmol). After stirring at room temperature for 1 h a pale yellow precipitate of fur-2-yllithium was formed and dry THF (2 mL) was added. The resulting solution was transferred by a cannula to a suspension of cuprous bromide–dimethyl sulfide complex (1.03 g, 5.0 mmol) in THF (7 mL) under argon at −40 °C. The dark red solution was then stirred for 30 min at −40 °C. A solution of bromide **3** (0.817 g, 2.94 mmol) in Et_2O (4 mL) was then added dropwise. The reaction mixture was allowed to warm slowly to room temperature overnight and then hydrolyzed during 3 h with a saturated aqueous solution of ammonium chloride. After three extractions with Et_2O, the combined organic fractions were dried over sodium sulfate and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/Et_2O: 99.5/0.5) to give compound **4** (0.729 g, 94%) as a pale yellow molten solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.93 (s, 2H), 5.06 (s, 2H, PhCH_2), 6.00 (d, J=2.8 Hz, 1H, H-3), 6.30 (dd, J=2.0 Hz, J=2.8 Hz, 1H, H-4), 6.94 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 7.32–7.50 (m, 6H, Ph and H-5). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.5, 69.9, 105.9 (C-3), 110.1 (C-4), 114.8, 127.4, 127.8, 128.5, 129.6, 130.4, 137.1, 141.3 (C-5), 154.9 (C-2), 157.4. IR (neat): 1615, 1580, 1513, 1453, 1255, 1246, 1049, 1010 cm^{-1}. MS (EI) *m*/*z* (%): 264 (23) [M$^{+\bullet}$], 91 (100). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.79; H, 6.13.

4.2.5. 4-(Fur-2-ylmethyl)phenol (5). Small shavings of sodium (6.0 g, 261 mmol) were added over 1.5 h to a solution of furanic compound **4** (1.5 g, 5.7 mmol) in dried distilled butan-1-ol (63 mL) maintained at 80 °C. The solution was stirred at 80 °C for an additional 15 h (TLC showed complete disappearance of compound **4**, if necessary more butanol and sodium could be added). After cooling to room temperature, the dark red-brown reaction mixture was acidified with 1 M HCl aqueous solution and Et_2O was added. The ethereal layer was separated and the aqueous phase was extracted three times with Et_2O. The combined organic fractions were washed with water, dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (pentane/Et_2O: 90/10, then 50/50) to afford phenol **5** (0.974 g, 98%) as a gray oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.90 (s, 2H), 5.25 (br s, 1H, OH), 6.00 (d, J=2.9 Hz, 1H, H-3), 6.31 (dd, J=2.0 Hz, J=2.9 Hz, 1H, H-4), 6.80 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.35 (d, J=2.0 Hz, 1H, H-5). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.6, 106.0 (C-3), 110.3 (C-4), 115.5, 129.9, 130.3, 141.4 (C-5), 154.1 (C-2), 155.0. MS (EI) *m*/*z* (%): 174 (100) [M$^{+\bullet}$]. HRMS (EI): calcd mass for $C_{11}H_{10}O_2$: 174.0681. Found: 174.0676.

4.2.6. Fur-2-ylated resin (6): derivatization of Merrifield resin with 5. In a 50 mL polypropylene Erlenmeyer flask was swollen a suspension of Merrifield resin (0.687 g, 0.55 mmol) in DMF (4 mL) for 10 min. Cesium carbonate (0.537 g, 1.65 mmol) and sodium iodide (83 mg, 0.55 mmol) were added, followed by a solution of phenolic compound **5** (0.287 g, 1.65 mmol) in DMF (0.7 mL). The mixture was stirred at room temperature for 24 h under argon using an orbital shaker. The resin was then filtered off and washed successively with DMF, H_2O, DMF, acetone, and CH_2Cl_2. After evaporation of solvents under reduced pressure and standing in vacuo in the presence of P_2O_5, a pale yellow furan-substituted resin **6** (0.707 g, 0.55 mmol) was obtained. The combined filtrates from DMF and water washings were acidified with 1 M HCl aqueous solution and extracted four times with Et_2O. The combined ethereal fractions were washed twice with water and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, unreacted starting phenol **5** (186 mg) was recovered. ^{1}H MAS NMR (400 MHz, $CDCl_3$) δ 1.50–2.04 (m, CH_2-Pm), 2.04–2.67 (m, C*H*-Pm), 4.24 (br s), 5.12–5.32 (m), 6.31 (br s, H-Fur), 6.60 (br s, H-Fur), 6.64–7.17 (m, H_{Ar}-Pm), 7.17–7.76 (m, H_{Ar}-Pm), 7.62 (br s, H-Fur). ^{13}C MAS NMR (100 MHz, $CDCl_3$) δ 33.8 (s), 38.7–47.0 (m, *C*H-Pm), 40.5 (br s, *C*H_2-Pm), 70.1 (s), 106.1 (s, C-Fur), 110.3 (s, C-Fur), 114.9 (s), 125.8 (br s, *C*H_{Ar}-Pm), 126.3–132.5 (m, *C*H_{Ar}-Pm), 129.8 (s), 141.5 (s, C-Fur), 144.1–147.5 (m, C_{Ar}-Pm), 155.1 (s, C-Fur), 157.8 (br s). IR (KBr): 1943, 1871, 1799, 1724, 1600, 1584, 1509, 1492, 1450, 1238, 1173, 1009 cm^{-1}.

4.2.7. 3-[4-(Benzyloxy)phenylmethyl]furan (7). To a solution of *n*-butyllithium (7.7 mL, 12.3 mmol) in anhydrous Et_2O (6 mL) at −78 °C under argon was added dropwise a solution of 3-bromofuran (1.14 mL, 12.7 mmol) in Et_2O (2 mL). After stirring for 1 h at −78 °C, this solution was transferred by a cannula to a suspension of cuprous bromide–dimethyl sulfide complex (1.26 g, 6.1 mmol) in anhydrous THF (11 mL) under argon at −78 °C and the reaction mixture was stirred for 2 h at −65 °C. Bromide **3** (1.0 g, 3.6 mmol) dissolved in anhydrous Et_2O (8 mL) was then added dropwise to the resulting dark red solution. The reaction mixture was allowed to warm slowly to room temperature overnight and then poured into a saturated aqueous solution of ammonium chloride. After stirring for 3 h, the aqueous layer was extracted twice with Et_2O. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (pentane/Et_2O: 95/5) afforded compound **7** (0.730 g, 76%) as a pale yellow molten solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 2H), 5.05 (s, 2H, PhCH_2), 6.24 (br s, 1H, H-4), 6.93 (d, J=8.5 Hz, 2H), 7.14 (d, J=8.5 Hz, 2H), 7.21 (br s, 1H, H-Fur), 7.29–7.49 (m, 6H,

Ph and H-Fur). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 30.3, 70.0, 111.2 (C-4), 114.8, 124.7 (C-3), 127.5, 127.9, 128.6, 129.5, 132.7, 137.2, 139.5 (C-Fur), 143.0 (C-Fur), 157.3. IR (neat): 1614, 1580, 1511, 1461, 1451, 1253, 1244, 1177, 1017 cm^{-1}. MS (EI) *m/z* (%): 264 (12) [M$^{+\bullet}$], 91 (100). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10; O, 12.11. Found: C, 81.65; H, 6.16; O, 11.87.

4.2.8. 4-(Fur-3-ylmethyl)phenol (8). Compound **8** was synthesized following the procedure described in Section 4.2.5. After reaction of compound **7** (0.846 g, 3.2 mmol) with sodium (2.3 g, 100 mmol) in butan-1-ol (30 mL) at 80 °C for 3 h, phenol **8** (0.440 g, 79%) was isolated by silica gel column chromatography (petroleum ether/Et_2O: 90/10). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.73 (s, 2H), 5.62 (br s, 1H, OH), 6.26 (br s, 1H, H-4), 6.78 (d, *J*=8.5 Hz, 2H), 7.09 (d, *J*=8.5 Hz, 2H), 7.21 (br s, 1H, H-Fur), 7.37 (br s, 1H, H-Fur). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 30.3, 111.3 (C-4), 115.4, 124.7 (C-3), 129.7, 132.7, 139.5 (C-Fur), 143.0 (C-Fur), 153.7. MS (EI) *m/z* (%): 174 (100) [M$^{+\bullet}$]. HRMS (EI): calcd mass for $C_{11}H_{10}O_2$: 174.0681. Found: 174.0684.

4.2.9. Fur-3-ylated resin (9): derivatization of Merrifield resin with 8. Resin **9** was prepared following the procedure described in Section 4.2.6. From Merrifield resin (0.310 g, 0.25 mmol) swollen in DMF (2 mL), cesium carbonate (0.242 g, 0.74 mmol), sodium iodide (37 mg, 0.25 mmol), and a solution of phenolic compound **8** (0.129 g, 0.74 mmol) in DMF (0.7 mL), a beige furan-substituted resin **9** (0.319 g, 0.25 mmol) was obtained after shaking under argon for 24 h at room temperature, washings, and evaporation of solvents under reduced pressure. ^{1}H MAS NMR (400 MHz, $CDCl_3$) δ 1.50–2.02 (m, C*H*$_2$-Pm), 2.02–2.61 (m, C*H*-Pm), 4.05 (br s), 5.14–5.35 (m), 6.57 (br s, H-Fur), 6.61–7.11 (m, H_{Ar}-Pm), 7.11–7.62 (m, H_{Ar}-Pm), 7.67 (br s, H-Fur). ^{13}C MAS NMR (100 MHz, $CDCl_3$) δ 30.4 (s), 38.9–46.5 (m, *C*H-Pm), 40.5 (br s, *C*H$_2$-Pm), 70.1 (s), 111.3 (s, C-Fur), 114.9 (s), 125.8 (br s, *C*H$_{Ar}$-Pm), 126.4–130.0 (m, *C*H$_{Ar}$-Pm), 129.6 (s), 139.4 (s, C-Fur), 143.1 (s, C-Fur), 144.3–145.9 (m, C_{Ar}-Pm), 157.2 (br s). IR (KBr): 1944, 1873, 1802, 1720, 1600, 1584, 1507, 1490, 1449, 1218, 1172, 1019 cm^{-1}.

4.3. Preparation of dienophile 11

4.3.1. 1,1,4,4-Tetraethoxybut-2-yne (10). To a 0.94 M solution of ethylmagnesium bromide (9.1 mL, 8.6 mmol) in Et_2O maintained under argon at −10 °C was added dropwise a solution of 3,3-diethoxypropyne (1.1 mL, 7.8 mmol) in anhydrous THF (11 mL). The mixture was stirred for 2 h at −10 °C and a solution of diethyl phenyl orthoformate (2.3 mL, 11.7 mmol) in THF (11 mL) was added. The reaction mixture was stirred for 2 h at −10 °C and then overnight at room temperature. After hydrolysis with a saturated aqueous solution of ammonium chloride, the aqueous layer was extracted three times with Et_2O and the combined organic phases were washed twice with a 2 M sodium hydroxide aqueous solution, three times with water, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (pentane/Et_2O: 95/5) afforded compound **10** (1.53 g, 85%) as a clear oil: bp 58 °C/0.07 mmHg (lit.[20] bp 91–93 °C/0.6 mmHg). Spectroscopic data were in agreement with reported values.[20a]

4.3.2. 4,4-Diethoxybut-2-ynal (11). Using a modified procedure of Gorgues et al.,[20b] ynal **11** was prepared by monohydrolysis of diacetal **10** (3.1 g, 13.5 mmol) with 99% formic acid (12 mL, 318 mmol) in chloroform (24 mL) in the presence of water (40 mg; without addition of water, lower yields were obtained). Distillation of the crude product under reduced pressure gave compound **11** (1.4 g, 66%) as a clear oil: bp 32 °C/0.07 mmHg (lit.[20] bp 73–74 °C/4 mmHg). NMR data were in agreement with reported values.[20a]

4.4. Diels–Alder reactions with 4,4-diethoxybut-2-ynal in homogeneous phase

4.4.1. 1-[4-(Benzyloxy)phenylmethyl]-3-(diethoxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carbaldehyde (12). A solution of the 2-substituted furan **4** (1.0 g, 3.78 mmol) in toluene (5 mL) was added to a mixture of 4,4-diethoxybut-2-ynal **11** (0.650 g, 4.16 mmol), BHT (83 mg, 0.38 mmol), and sodium carbonate (40 mg, 0.38 mmol) placed in a high-pressure glass tube. The tube was degassed under low pressure and sealed. The reaction mixture was heated in the dark for 48 h at 90 °C. After cooling to room temperature and concentration in vacuo, the crude product was purified by silica gel column chromatography (pentane/Et_2O: 90/10, then 60/40) to afford adduct **12** (1.37 g, 86%) as a caramel oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.1 Hz, 6H), 3.41–3.71 (m, 4H), 3.58 (d, *J*=15.2 Hz, 1H) and 3.78 (d, *J*=15.2 Hz, 1H) (AB syst., C*H*$_2$-C-1), 5.03 (s, 2H, PhC*H*$_2$), 5.42 (d, *J*=0.9 Hz, 1H, H-4), 5.50 (s, 1H, C*H*(OEt)$_2$), 6.90 (d, *J*=8.6 Hz, 2H), 6.97 (s, 1H, H-5), 7.24 (d, *J*=8.6 Hz, 2H), 7.34–7.46 (m, 6H, Ph and H-6), 10.17 (s, 1H, C*H*O). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8, 34.4 (*C*H$_2$-C-1), 61.2, 61.7, 69.5 (Ph*C*H$_2$), 82.3 (C-4), 95.6 (C-1), 97.4 (*C*H(OEt)$_2$), 114.1, 127.1, 127.5, 128.2, 129.2, 130.9, 136.9, 142.8 and 144.9 (C-5, C-6), 151.1 (C-2), 157.1, 171.3 (C-3), 187.5 (*C*HO). IR (neat): 1664, 1612, 1512, 1454, 1379, 1243, 1177, 1120, 1051 cm^{-1}. MS (ES$^+$) *m/z* (%): 491 (8) [M+MeOH+K]$^+$, 459 (17) [M+K]$^+$, 443 (100) [M+Na]$^+$, 287 (17). HRMS (EI): calcd mass for $C_{26}H_{28}O_5$: 420.1936. Found: 420.1943.

4.4.2. 5- and 6-[4-(benzyloxy)phenylmethyl]-3-(diethoxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carbaldehyde (13). Compound **13** was prepared following the procedure described above. From a solution of the 3-substituted furan **7** (303 mg, 1.15 mmol) and 4,4-diethoxybut-2-ynal **11** (196 mg, 1.26 mmol) in toluene (3.5 mL) in the presence of BHT (25 mg, 0.11 mmol) and few milligrams of sodium carbonate, crude compound **13** was obtained after heating the vacuum-sealed tube in the dark for 48 h at 124 °C. After concentration in vacuo, ^{1}H NMR spectrum of the residue shows adduct **13** as a mixture of regioisomers (52:48 ratio). Purification by silica gel column chromatography (pentane/Et_2O: 60/40) gave a mixture of the unseparated isomers **13a/13b** (421 mg, 87%, **13a/13b**=55:45) as a pale brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14–1.33 (m, 6H), 3.41–3.70 (m, 6H, OC*H*$_2$CH$_3$ and C*H*$_2$-C-5/C*H*$_2$-C-6), 4.96 (s, 0.55H, C*H*(OEt)$_2$ *major*), 5.05 (s, 2H, PhC*H*$_2$), 5.21 (d, *J*=1.3 Hz, 0.55H, H-4 or H-1 *major*), 5.44 (br s, 0.45H, H-4 or H-1 *minor*), 5.49 (s, 0.45H, C*H*(OEt)$_2$ *minor*), 5.51 (br s, 0.45H, H-1 or H-4 *minor*), 5.70 (br s, 0.55H, H-1 or H-4 *major*), 6.36 (d,

J=1.8 Hz, 0.45H, H-6 or H-5 *minor*), 6.55 (d, *J*=1.7 Hz, 0.55H, H-6 or H-5 *major*), 6.90 (d, *J*=8.6 Hz, H_{Ar} *minor*) and 6.92 (d, *J*=8.6 Hz, H_{Ar} *major*) (2H), 7.06 (d, *J*=8.6 Hz, 2H, H_{Ar}), 7.30–7.48 (m, 5H, Ph), 10.09 (s, 0.45H, C*H*O *minor*), 10.14 (s, 0.55H, C*H*O *major*). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 15.2, 34.4 (*C*H_2-C-5/*C*H_2-C-6), 61.1 (O*C*H_2CH$_3$ *major*), 61.4 (O*C*H_2CH$_3$ *minor*), 61.6 (O*C*H_2CH$_3$ *minor*), 62.3 (O*C*H_2CH$_3$ *major*), 69.9 (Ph*C*H_2), 82.2 (C-1 or C-4 *major*), 84.0 (C-1 or C-4 *minor*), 84.8 (C-4 or C-1 *minor*), 86.5 (C-4 or C-1 *major*), 97.7 (*C*H(OEt)$_2$ *major*), 97.9 (*C*H(OEt)$_2$ *minor*), 114.9 (*minor*), 115.0 (*major*), 127.3, 127.8, 128.4, 129.4, 129.6, 129.8, 133.1 (C-5 or C-6 *minor*), 135.2 (C-5 or C-6 *major*), 136.9 (*major*), 137.0 (*minor*), 151.5 (C-2 *minor*), 152.2 (C-2 *major*), 157.4 (*minor*), 157.6 (*major*), 157.7 (C-6 or C-5 *major*), 159.6 (C-6 or C-5 *minor*), 169.0 (C-3 *major*), 169.6 (C-3 *minor*), 186.7 (*C*HO *minor*), 186.8 (*C*HO *major*). IR (neat): 1658, 1612, 1511, 1454, 1242, 1176, 1055 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 491 (11) [M+MeOH+K]$^+$, 459 (15) [M+K]$^+$, 443 (100) [M+Na]$^+$, 287 (15). HRMS (ES$^+$): calcd mass for $C_{26}H_{28}O_5Na$: 443.1834. Found: 443.1835.

4.5. Lewis acid-catalyzed reaction with 4,4-diethoxybut-2-ynal

4.5.1. 3-{5-[4-(Benzyloxy)phenylmethyl]fur-2-yl}-4,4-diethoxybut-2-enal (14). To a suspension of anhydrous zinc chloride (93 mg, 0.682 mmol) in dichloromethane (0.5 mL) was added a solution of 4,4-diethoxybut-2-ynal **11** (106 mg, 0.684 mmol) in CH_2Cl_2 (0.6 mL). After stirring for 15 min at room temperature until complete solubilization of the Lewis acid, the resulting orange solution was cooled to −40 °C and furanic compound **4** (164 mg, 0.621 mmol) in dichloromethane (0.8 mL) was introduced. The dark brown solution was stirred for 2 h at −40 °C and hydrolyzed with water. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. ^{1}H NMR spectrum of the crude product shows Michael adduct **14** as a mixture of diastereomers (82:18 ratio). Purification by silica gel column chromatography (pentane/Et_2O: 70/30) afforded pure major diastereomer (23 mg) as a yellow oil and a mixture of the two diastereomers (154 mg, 68% overall yield). *Major diastereomer*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 6H), 3.47–3.71 (m, 4H), 3.96 (s, 2H, CH_2-Fur), 5.07 (s, 2H, PhCH_2), 5.23 (s, 1H, C*H*(OEt)$_2$), 6.12 (d, *J*=3.4 Hz, 1H, H-Fur), 6.20 (d, *J*=8.0 Hz, 1H, H-2), 6.87 (d, *J*=3.4 Hz, 1H, H-Fur), 6.95 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.6 Hz, 2H), 7.32–7.48 (m, 5H), 10.44 (d, *J*=8.0 Hz, 1H, C*H*O). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.2, 34.1 (*C*H_2-Fur), 62.1, 70.1 (Ph*C*H_2), 100.8, 108.9, 115.1, 116.9, 124.4, 127.5, 128.0, 128.7, 129.2, 129.9, 137.0, 141.8, 149.4, 157.8, 159.2, 194.6 (*C*HO). MS (ES$^+$) *m*/*z* (%): 443 (100) [M+Na]$^+$. HRMS (ES$^+$): calcd mass for $C_{26}H_{28}O_5Na$: 443.1834. Found: 443.1834. Anal. Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 73.84; H, 6.81.

4.6. Diels–Alder reactions with acetylenic esters

4.6.1. Dimethyl 1-[4-(benzyloxy)phenylmethyl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (15). A solution of the 2-substituted furan **4** (0.700 g, 2.65 mmol) and dimethyl acetylenedicarboxylate (1.10 g, 7.75 mmol) in dry toluene (3 mL) was heated at reflux, under argon, for 3 h. After cooling to room temperature and concentration in vacuo, the crude product was purified by silica gel column chromatography (petroleum ether/Et_2O: 2/1) to afford adduct **15** (1.065 g, 99%) as a caramel oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.47 (s, 2H, CH_2-C-1), 3.76 and 3.77 (2 s, 6H, 2 CO_2Me), 5.04 (s, 2H, PhCH_2), 5.68 (d, *J*=1.8 Hz, 1H, H-4), 6.91 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*=5.2 Hz, 1H, H-6), 7.14–7.21 (m, 3H, H-5 and 2 H_{Ar}), 7.31–7.46 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.9 (*C*H_2-C-1), 51.9 (2 CO_2*C*H$_3$), 69.6 (Ph*C*H_2), 83.1 (C-4), 97.5 (C-1), 114.3, 127.2, 127.6, 128.1, 128.3, 130.8, 136.8, 144.2 (C-5 or C-6), 144.8 (C-6 or C-5), 151.0 (C-2 or C-3), 155.5 (C-3 or C-2), 157.4, 162.3 (CO_2), 165.0 (CO_2). IR (neat): 3034, 2955, 1748, 1723, 1648, 1610, 1513, 1436, 1300, 1261, 1245, 1113, 1013 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 429 (100) [M+Na]$^+$. Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.93; H, 5.46. Found: C, 70.92; H, 5.64.

4.6.2. Methyl 1-[4-(benzyloxy)phenylmethyl]-3-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (17) and methyl 1-[4-(benzyloxy)phenylmethyl]-2-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-3-carboxylate. To a solution of methyl propiolate (0.942 g, 11.22 mmol) in dry acetonitrile (7.5 mL) were added silver nitrate (0.190 g, 1.1 mmol) and *N*-bromosuccinimide (2.30 g, 12.92 mmol). After stirring under argon for 1 h at room temperature, the flask was fitted with a glass distillation bridge connected to a receiving flask and the liquids were evaporated under low pressure (ca. 0.1 mbar) and collected at −78 °C. The solution of methyl 3-bromopropiolate **16** in acetonitrile was warmed up to room temperature and introduced in a high-pressure glass tube containing the 2-substituted furan **4** (0.987 g, 3.74 mmol). The tube was degassed under low pressure, sealed, and the green reaction mixture was heated in the dark for 48 h at 110 °C. After cooling to room temperature and concentration in vacuo, the crude product was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2: 3/1) to afford a 97:3 mixture of adduct **17** and methyl 1-[4-(benzyloxy)phenylmethyl]-2-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-3-carboxylate (0.959 g, 60%) as a brown oil. A preparative silica gel TLC (three elutions with pentane/Et_2O: 9/1) has allowed the isolation of pure samples of each regioisomer.

*Methyl 1-[4-(benzyloxy)phenylmethyl]-3-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (**17**).* ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.57 (d, *J*=15.2 Hz, 1H) and 3.68 (d, *J*=15.2 Hz, 1H) (AB syst., CH_2-C-1), 3.80 (s, 3H, CO_2Me), 5.03 (s, 2H, PhCH_2), 5.25 (d, *J*=1.9 Hz, 1H, H-4), 6.90 (d, *J*=8.7 Hz, 2H), 7.05 (d, *J*=5.3 Hz, 1H, H-6), 7.11 (dd, *J*=5.2 Hz, *J*=1.8 Hz, 1H, H-5), 7.20 (d, *J*=8.6 Hz, 2H), 7.30–7.47 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.7 (*C*H_2-C-1), 51.7 (CO_2*C*H$_3$), 69.9 (Ph*C*H_2), 87.9 (C-4), 97.4 (C-1), 114.5, 127.5, 127.9, 128.5, 128.7, 131.1, 137.1, 142.2 (C-5 or C-6), 143.7 (C-2 or C-3), 145.7 (C-6 or C-5), 149.2 (C-3 or C-2), 157.6, 163.8 (CO_2). IR (neat): 2951, 1710, 1611, 1512, 1454, 1435, 1310, 1242 cm^{-1}.

Methyl 1-[4-(benzyloxy)phenylmethyl]-2-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-3-carboxylate. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.33 (d, *J*=15.2 Hz, 1H) and 3.46 (d,

J=15.2 Hz, 1H) (AB syst., CH_2-C-1), 3.79 (s, 3H, CO_2Me), 5.03 (s, 2H, PhCH_2), 5.66 (d, J=1.7 Hz, 1H, H-4), 6.87–6.94 (m, 3H, H-6 and 2 H_{Ar}), 7.13 (dd, J=5.2 Hz, J=1.3 Hz, 1H, H-5), 7.25 (d, J=9.0 Hz, 2H), 7.30–7.47 (m, 5H, Ph).

4.7. Suzuki coupling reaction

4.7.1. Methyl 1-[4-(benzyloxy)phenylmethyl]-3-phenyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (18). To a solution of the brominated adduct **17** (0.200 g, 0.47 mmol), phenylboronic acid (63 mg, 0.52 mmol), and potassium fluoride (90 mg, 1.55 mmol) in dry THF (1 mL) under argon were successively added a 0.1 M solution of tris(*tert*-butyl)phosphine in THF (0.560 mL, 0.06 mmol) and a solution of bis(benzylideneacetone)palladium (13.6 mg, 0.02 mmol) in THF (0.5 mL). After stirring for 3.5 h at room temperature, the reaction mixture was diluted with Et_2O, filtrated over Celite®, and the adsorbent was washed with Et_2O. After concentration of the filtrate in vacuo, the crude product was purified by silica gel column chromatography (pentane/Et_2O: 4/1) to afford the phenylated product **18** (0.180 g, 90%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.58 (d, J=15.0 Hz, 1H) and 3.68 (d, J=15.0 Hz, 1H) (AB syst., CH_2-C-1), 3.73 (s, 3H, CO_2Me), 5.05 (s, 2H, PhCH_2), 5.55 (d, J=1.5 Hz, 1H, H-4), 6.93 (d, J=8.6 Hz, 2H), 7.12 (d, J=5.0 Hz, 1H, H-6), 7.17 (dd, J=5.0 Hz, J=1.6 Hz, 1H, H-5), 7.24 (d, J=8.7 Hz, 2H), 7.32–7.55 (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.1 (*C*H_2-C-1), 51.5 (CO_2*C*H_3), 70.0 (Ph*C*H_2), 86.1 (C-4), 97.3 (C-1), 114.6, 127.2, 127.5, 127.9, 128.2, 128.6, 129.5, 131.1, 132.8 (C-2 or C-3), 137.3, 140.4 (C-3 or C-2), 142.3 (C-5), 146.1 (C-6), 157.6, 164.6 (C_{Ar} or CO_2), 165.9 (CO_2 or C_{Ar}). IR (neat): 3033, 2949, 1713, 1612, 1581, 1512, 1494, 1455, 1434, 1331, 1269, 1240, 1177, 1001 cm^{-1}.

4.8. Functionalization by Michael addition and retro-Diels–Alder reaction in solution

4.8.1. (*Z*)- and (*E*)-4,4-diethoxy-3-(phenylsulfanyl)but-2-enal (19). *From Diels–Alder adduct **12***. To a mixture of a 60% dispersion of sodium hydride (3.3 mg, 0.082 mmol) in mineral oil and THF (1 mL) under argon was added dropwise benzenethiol (85 μL, 0.828 mmol) at room temperature. A gas release was observed and the suspension was then stirred for 15 min at room temperature. After cooling at −78 °C, a solution of adduct **12** (116 mg, 0.276 mmol) in THF (1.5 mL) was added. The reaction mixture was stirred for 2 h at −78 °C and the temperature was allowed to increase to 0 °C over 3 h. A 2.5 M sodium hydroxide aqueous solution was then added at 0 °C and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed twice with a 2.5 M sodium hydroxide aqueous solution, with water to neutrality, dried over sodium sulfate, and concentrated under reduced pressure (water bath at room temperature). ^{1}H NMR spectrum of the crude residue shows the Z and E enals **19** with a ratio (*Z*)-**19**/(*E*)-**19**=75:25. Chromatography on silica gel (pentane/Et_2O: 90/10, then 60/40) gave the furanic compound **4** (62 mg, 85%), enals (*Z*)-**19** (50 mg, 68%) and (*E*)-**19** (15 mg, 20%).

*From Diels–Alder adduct **13***. Following the same procedure as described above, cycloadduct **13** (**13a**/**13b**=55:45, 155 mg, 0.369 mmol) dissolved in anhydrous THF (1.2 mL) was added at −78 °C to a suspension of sodium benzenethiolate in THF (1.0 mL) prepared from benzenethiol (114 μL, 1.11 mmol) and a 60% dispersion of sodium hydride (4.4 mg, 0.11 mmol) in mineral oil. After slow warming of the reaction mixture to 0 °C over 4 h, treatment at this temperature with a 2.5 M sodium hydroxide aqueous solution followed by extractions with Et_2O and washings as previously described, a crude mixture of Michael addition products **20** was isolated. ^{1}H NMR spectrum of the residue shows traces of furan **7** and enal (*Z*)-**19** and especially the presence of two major diastereomers and, at least, four minor isomers. This mixture was dissolved in anhydrous THF (3 mL) and then stirred under argon at 45 °C for 3 h. After cooling to room temperature and concentration in vacuo, ^{1}H NMR spectrum of the crude residue shows furan **7** and enals **19** with a ratio (*Z*)-**19**/(*E*)-**19**=87:13. Purification by silica gel column chromatography (pentane/Et_2O: 80/20) afforded furan **7** (78 mg, 80%), enals (*Z*)-**19** (60 mg, 61%) and (*E*)-**19** (16 mg, 16%).

*(Z)-4,4-Diethoxy-3-(phenylsulfanyl)but-2-enal (Z)-**19***. Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 6H), 3.25–3.36 (m, 2H), 3.44–3.56 (m, 2H), 4.71 (s, 1H, H-4), 6.64 (d, J=6.9 Hz, 1H, H-2), 7.36–7.41 (m, 3H, H_{Ar}), 7.51–7.56 (m, 2H, H_{Ar}), 10.19 (d, J=6.9 Hz, 1H, C*H*O). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.9, 62.2, 99.1 (C-4), 127.5 (C-2), 129.0, 129.2, 130.2, 133.8, 156.5 (C-3), 190.6 (*C*HO). MS (ES^+) m/z (%): 321 (17) $[M+MeOH+Na]^+$, 289 (100) $[M+Na]^+$. HRMS (ES^+): calcd mass for $C_{14}H_{18}O_3SNa$: 289.0874. Found: 289.0874.

*(E)-4,4-Diethoxy-3-(phenylsulfanyl)but-2-enal (E)-**19***. Pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, J=7.1 Hz, 6H), 3.61–3.89 (m, 4H), 5.38 (d, J=7.7 Hz, 1H, H-2), 5.70 (s, 1H, H-4), 7.32–7.58 (m, 5H, H_{Ar}), 9.99 (d, J=7.7 Hz, 1H, C*H*O). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 15.0, 62.7, 99.0 (C-4), 123.5 (C-2), 128.5, 130.1, 130.2, 135.6, 166.2 (C-3), 188.0 (*C*HO). MS (CI/NH_3) m/z (%): 267 (23) $[M+H]^+$, 221 (100) $[M+H-EtOH]^+$. Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; O, 18.02. Found: C, 63.07; H, 6.97; O, 17.98.

4.8.2. Dimethyl phenylsulfanylfumarate 22 and *meso*-dimethyl 2,3-bis(phenylsulfanyl)succinate 23. Following the procedure described in Section 4.8.1 from Diels–Alder adduct **12**, a solution of cycloadduct **15** (108 mg, 0.27 mmol) in anhydrous THF (1.5 mL) was added at −78 °C to a suspension of sodium benzenethiolate in THF (1.5 mL) prepared from benzenethiol (93 μL, 0.93 mmol) and a 60% dispersion of sodium hydride (3.2 mg, 0.08 mmol) in mineral oil. The reaction mixture was stirred for 2 h at −78 °C and the temperature was allowed to increase to 0 °C over 3 h. After treatment with a 2.5 M sodium hydroxide aqueous solution at 0 °C, a crude mixture of Michael addition products **21** was isolated. ^{1}H NMR spectrum of the residue shows the presence of three diastereomers but also products resulting from a retro-Diels–Alder reaction (see Section 2.3). This mixture was dissolved in anhydrous toluene (2 mL) and then stirred under argon at 75 °C for 16 h. After cooling to room temperature and concentration in vacuo, purification by silica gel column chromatography (petroleum ether/Et_2O: 4/1) afforded furan **4** (62 mg, 87%) and a 2:1 mixture of dimethyl

phenylsulfanylfumarate **22**[37,44] and *meso*-dimethyl 2,3-bis(phenylsulfanyl)succinate **23**[36] (97 mg, 83%).

4.8.3. (*Z*)- and (*E*)-methyl 3-phenyl-3-phenylsulfanylpropenoate 25. Following the procedure described in Section 4.8.1 from Diels–Alder adduct **12**, a solution of cycloadduct **18** (101 mg, 0.24 mmol) in anhydrous THF (1.5 mL) was added at −78 °C to a suspension of sodium benzenethiolate in THF (1.0 mL) prepared from benzenethiol (85 μL, 0.83 mmol) and a 60% dispersion of sodium hydride (2.8 mg, 0.07 mmol) in mineral oil. The reaction mixture was stirred for 2 h at −78 °C and the temperature was allowed to increase to 0 °C over 3 h. After treatment with a 2.5 M sodium hydroxide aqueous solution at 0 °C, a crude mixture of Michael addition products **24** was isolated. Integration of the olefinic proton signals in the ^{1}H NMR spectrum of the residue shows the presence of a 7:3 mixture of two diastereomers. Fast silica gel column chromatography (pentane/Et_2O: 1/3) has allowed to separate these diastereomers but retro-Diels–Alder reaction occurred during the elution and impure compounds were isolated. The minor isomer was in the first eluted fraction (42 mg) and the major one was present in the second fraction (72 mg). The main spectroscopic characteristics of these adducts are reported below. The relative integrations of the ^{1}H NMR spectra were noted for clearly separated signals.

*Methyl 1-[4-(benzyloxy)phenylmethyl]-3-phenyl-3-phenylsulfanyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (**24**): minor isomer.* ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.08 (d, J=14.6 Hz, 1H) and 3.25 (d, J=14.6 Hz, 1H) (AB syst., CH_2-C-1), 3.50 (s, 1H, H-2), 3.78 (s, 3H, CO_2Me), 5.00 (s, 2H, PhCH_2), 5.40 (d, J=1.8 Hz, 1H, H-4), 6.68 (dd, J=5.1 Hz, J=1.8 Hz, H-5) and 6.71 (d, J=5.1 Hz, H-6) (2H), 6.80–7.53 (m, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 37.6 (*C*H_2-C-1), 52.0 (CO_2*C*H_3), 62.9 (C-2), 66.3 (C-3), 69.9 (Ph*C*H_2), 84.0 (C-4), 92.1 (C-1), 114.5 (C_{Ar}-H), 126.0–129.6 (various C_{Ar}-H), 130.9 (C_{Ar}-H), 134.0 (C_{Ar}-H), 134.9 (C_{Ar}-H), 135.4 (C-5), 137.1 (C_{Ar}), 138.2 (C-6), 145.1 (C_{Ar}), 157.5 (C_{Ar}), 170.6 (CO_2). IR (neat): 1731 cm^{-1}.

*Methyl 1-[4-(benzyloxy)phenylmethyl]-3-phenyl-3-phenylsulfanyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (**24**): major isomer.* ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.33 (s, 1H, H-2), 3.34 (d, J=14.4 Hz, 1H) and 3.59 (d, J=14.4 Hz, 1H) (AB syst., CH_2-C-1), 3.95 (s, 3H, CO_2Me), 5.02 (s, 2H, PhCH_2), 5.40 (d, J=1.3 Hz, 1H, H-4), 6.07 (d, J=5.5 Hz, H-6) and 6.11 (dd, J=5.5 Hz, J=1.3 Hz, H-5) (2H), 6.80–7.47 (m, H_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.3 (*C*H_2-C-1), 52.0 (CO_2*C*H_3), 58.2 (C-2), 67.6 (C-3), 69.8 (Ph*C*H_2), 84.3 (C-4), 91.4 (C-1), 114.6 (C_{Ar}-H), 126.0–129.6 (various C_{Ar}-H), 130.9 (C_{Ar}-H), 131.3 (C_{Ar}), 136.5 (C-5), 137.0 (C_{Ar}), 137.6 (C-6), 137.7 (C_{Ar}-H), 143.1 (C_{Ar}), 157.5 (C_{Ar}), 171.0 (CO_2). IR (neat): 1739 cm^{-1}.

The first fraction was dissolved in anhydrous toluene (0.4 mL) and was stirred under argon at 75 °C for 16 h. After cooling to room temperature and concentration in vacuo, purification by silica gel column chromatography (petroleum ether/Et_2O: 4/1) afforded furan **4** (18 mg, 28%) and a 90:10 mixture of (*Z*)- and (*E*)-methyl 3-phenyl-3-phenylsulfanylpropenoate **25**[45] (18 mg, 28%). After heating in the same conditions a solution of the second fraction in anhydrous toluene (0.7 mL), silica gel column chromatography (petroleum ether/Et_2O: 4/1) gave furan **4** (30 mg, 47%) and a 93:7 mixture of (*Z*)- and (*E*)-methyl 3-phenyl-3-phenylsulfanylpropenoate **25**[45] (30 mg, 46%).

4.9. Reactions on solid support

4.9.1. Diels–Alder adduct-functionalized resin (26). In a high-pressure glass tube were successively placed resin **6** (0.627 g, 0.49 mmol), sodium carbonate (20.6 mg, 0.19 mmol), BHT (42.9 mg, 0.19 mmol), and 4,4-diethoxybut-2-ynal **11** (302 mg, 1.93 mmol). The minimal quantity of toluene (4.8 mL) was then introduced in order to form a gel. The glass tube was degassed under low pressure and sealed. After heating at 90 °C for 72 h in the dark, the resin was filtered off and washed successively with CH_2Cl_2, acetone, H_2O, acetone, and CH_2Cl_2. After evaporation of solvents under reduced pressure and standing in vacuo in the presence of P_2O_5, an orange-brown resin **26** (0.689 g, 0.49 mmol) was obtained. Concentration in vacuo of the first filtrates obtained from washings with CH_2Cl_2 followed by a purification by silica gel column chromatography (pentane/Et_2O: 80/20) provided unreacted ynal **11** (183 mg). ^{1}H MAS NMR (400 MHz, $CDCl_3$) δ 1.52 (br s), 1.33–2.00 (m, CH_2-Pm), 2.00–2.50 (m, C*H*-Pm), 3.68–4.23 (m), 5.06–5.32 (m), 5.73 (br s), 5.80 (br s), 6.52–7.08 (m, H_{Ar}-Pm), 7.08–7.69 (m, H_{Ar}-Pm), 10.48 (br s, C*H*O). ^{13}C MAS NMR (100 MHz, $CDCl_3$) δ 15.2 (s), 34.8 (s), 38.1–46.7 (m, *C*H-Pm), 40.5 (br s, *C*H_2-Pm), 61.6 (s), 62.1 (s), 70.0 (s), 82.7 (s), 96.1 (s), 97.8 (s), 114.5 (s), 125.8 (br s, *C*H_{Ar}-Pm), 126.2–132.1 (m, *C*H_{Ar}-Pm), 131.3 (s), 143.2 (s), 144.3–146.7 (m, C_{Ar}-Pm), 151.5 (s), 157.7 (br s), 171.8 (s), 188.1 (s). IR (KBr): 1943, 1872, 1802, 1721, 1663, 1600, 1578, 1510, 1492, 1451, 1228, 1175, 1051, 1027 cm^{-1}.

4.9.2. Michael addition of benzenethiol on resin 26 and retro-Diels–Alder reaction. In a three-necked round-bottomed flask fitted with a bent solid addition bulb, a filtering cannula, an argon inlet, and a small magnetic stirring bar were placed a 60% dispersion of sodium hydride (1.3 mg, 0.032 mmol) in mineral oil and anhydrous THF (2 mL). Benzenethiol (42 μL, 0.409 mmol) was added dropwise and the suspension was stirred for 15 min at room temperature. The reaction mixture was cooled at −40 °C and resin **26** (115 mg, 0.081 mmol) previously placed in the solid addition bulb was added. After gentle stirring for 22 h at −35 °C, the liquid phase was removed through the filtering cannula under argon and the resin maintained at −35 °C was extensively washed with THF, mixtures of THF/MeOH (increasing and then decreasing MeOH ratios), and THF (the solvents being removed each time through the cannula under argon). Analysis by TLC and ^{1}H NMR spectrum of the residue obtained by concentration in vacuo of the combined filtrates show exclusively the presence of benzenethiol. After addition of distilled THF (2 mL), the heterogeneous reaction mixture was allowed to warm slowly to −2 °C and then gently stirred for 15 h at this temperature. The liquid phase was removed through the filtering cannula under argon and the resin was washed with distilled THF at −2 °C (the solvent being removed each time through the cannula). Concentration in vacuo (water bath at room temperature) of the combined filtrates gave enal (*Z*)-**19** (10.7 mg, 49% overall

yield with respect to Merrifield resin) as a single product, which was identical, in all spectroscopic details, with the synthesized material in solution-phase. Remaining resin was filtered off and, after drying under reduced pressure and standing in vacuo in the presence of P_2O_5, resin **6** (93 mg) was isolated (identified by IR spectroscopy).

4.9.3. Diels–Alder adduct-functionalized resin (27). Orange-brown resin **27** (0.314 g, 0.24 mmol) was prepared from resin **9** (0.306 g, 0.24 mmol), sodium carbonate (10.1 mg, 0.09 mmol), BHT (21.0 mg, 0.09 mmol), 4,4-diethoxybut-2-ynal **11** (149 mg, 0.95 mmol), and toluene (2.2 mL) analogously to the procedure described in Section 4.9.1. Concentration in vacuo of the first filtrates obtained from washings with CH_2Cl_2 followed by a purification by silica gel column chromatography (pentane/Et_2O: 90/10) provided unreacted ynal **11** (96 mg). ^{1}H MAS NMR spectrum of the resulting resin shows polymer-supported Diels–Alder adduct **27** as a mixture of regioisomers (61:39 ratio). ^{1}H MAS NMR (400 MHz, $CDCl_3$) δ 1.57 (br s), 1.33–2.04 (m, C*H*$_2$-Pm), 2.04–2.59 (m, C*H*-Pm), 3.75–4.11 (m), 5.14–5.38 (m), 5.57 (br s), 5.79 (br s), 5.83 (br s), 5.87 (br s), 6.06 (br s), 6.52–7.12 (m, H_{Ar}-Pm), 7.12–7.73 (m, H_{Ar}-Pm), 10.46 (br s, C*H*O *minor*), 10.50 (br s, C*H*O *major*). ^{13}C MAS NMR (100 MHz, $CDCl_3$) δ 15.2 (s), 34.5 (s), 38.9–46.5 (m, *C*H-Pm), 40.5 (br s, *C*H$_2$-Pm), 61.3 (s), 61.6 (s), 61.8 (s), 62.4 (s), 70.1 (s), 82.4 (s), 84.1 (s), 85.0 (s), 86.6 (s), 97.9 (s), 98.1 (s), 114.9 (s), 115.0 (s), 125.7 (br s, *C*H$_{Ar}$-Pm), 125.9–130.8 (m, *C*H$_{Ar}$-Pm), 129.5 (s), 130.0 (s), 133.3 (s), 135.4 (s), 144.9–146.4 (m, C_{Ar}-Pm), 152.4 (s), 157.9 (s), 186.9 (s). IR (KBr): 1943, 1873, 1801, 1721, 1657, 1600, 1585, 1508, 1491, 1451, 1239, 1173, 1044, 1013 cm^{-1}.

4.9.4. Michael addition of benzenethiol on resin 27 and retro-Diels–Alder reaction. In a three-necked round-bottomed flask (equipped with the same apparatus as previously used in Section 4.9.2) were placed a 60% dispersion of sodium hydride (1.6 mg, 0.040 mmol) in mineral oil and anhydrous THF (2 mL). Benzenethiol (50 μL, 0.487 mmol) was added dropwise and the suspension was stirred for 15 min at room temperature. The reaction mixture was then cooled at −40 °C and resin **27** (128 mg, 0.097 mmol) was added. After gentle stirring for 17 h at −25 °C, the resin maintained at −25 °C was filtered off and washed with THF, mixtures of THF/MeOH, and THF (analysis by TLC and ^{1}H NMR spectrum of the residue obtained by concentration in vacuo of the combined filtrates show exclusively the presence of benzenethiol). After addition of distilled THF (2 mL), the heterogeneous reaction mixture was allowed to warm within 1 h to room temperature and was gently stirred for 20 h at this temperature. The liquid phase was then removed through the filtering cannula under argon and the resin was washed with distilled THF at room temperature. Concentration in vacuo (water bath at room temperature) of the combined filtrates gave enal **19** (6.0 mg, 23% overall yield with respect to Merrifield resin, (*Z*)-**19**/(*E*)-**19**=71:29 determined from ^{1}H NMR spectrum). The resulting resin was suspended in distilled THF (2 mL) and was stirred for an additional 3 h at room temperature. After filtering and washings of the resin with THF, no more enal **19** was isolated. The recovered resin was again suspended in THF (2 mL) and warmed to 40 °C. After heating at 40 °C for 20 h, filtering and washings of the resin with THF, filtrates were concentrated under reduced pressure and enal **19** (4.0 mg, 16% overall yield with respect to Merrifield resin, (*Z*)-**19**/(*E*)-**19**=70:30 determined from ^{1}H NMR spectrum) was isolated. No more release of enal **19** was noticed after stirring the remaining resin in THF (2 mL) at 40 °C for an additional 3 h and after shaking at 60 °C for 20 h. The recovered resin was filtered off and washed with THF. After drying under reduced pressure and standing in vacuo in the presence of P_2O_5, resin **9** (105 mg) was isolated (identified by IR spectroscopy).

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34. 4,4-Diethoxy-3,3-bis(phenylsulfanyl)butanal was isolated as a mixture with the aldehyde (*Z*)-**19** and was obtained independently by Michael addition of sodium benzenethiolate on aldehyde **19** at room temperature.
35. The *meso*-bis(phenylsulfanyl)diester **23** and the *dl*-isomer should be formed during the reaction of sodium benzenethiolate with the compound **15** or during the basic aqueous workup since fumarate **22** and, probably, the corresponding maleate were released by retro-Diels–Alder reaction.
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