

Solid-phase cleavage by a thermal retro-Diels-Alder reaction: preparation of a small β -substituted α,β -ethylenic aldehydes library

Sébastien Albert, Luis Blanco, and Sandrine Deloisy*

Laboratoire de Synthèse Organique et Méthodologie, I.C.M.M.O. (UMR 8182-CNRS),

Université de Paris-Sud 11, Bât. 420, 91405 Orsay cedex, France

E-mail: sdeloisy@icmo.u-psud.fr

Abstract

Michael addition of heteroatom- and carbon-centered nucleophiles on 7-oxanorborna-2,5-diene-2-carboxaldehyde derivatives followed by a retro-Diels-Alder reaction allowed liquid- and solid-phase synthesis of a small library of α,β -unsaturated aldehydes. Emphasis should be put on the purity of the enals prepared on solid support, a purification step was not necessary.

Keywords: Diels-Alder reaction, retro-Diels-Alder reaction, Michael addition, solid-phase synthesis

Introduction

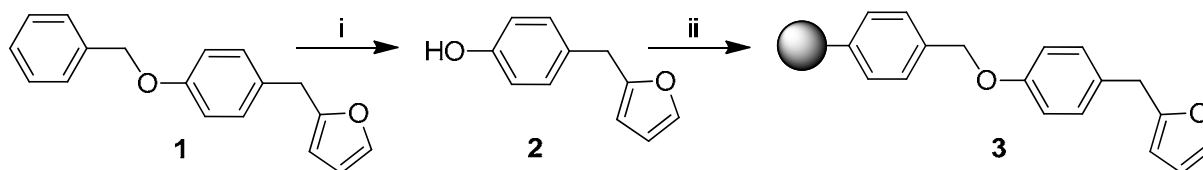
Among the traceless linkers employed in solid-phase organic synthesis, only few of them allow the cleavage of the synthesized product by a retro-Diels-Alder reaction.¹⁻⁶ The use of a resin with a dienic moiety could immobilize an unsaturated compound by Diels-Alder reaction. After chemical transformation of the cycloadduct, a retro-Diels-Alder-based cleavage step would release a modified unsaturated compound and regenerate the starting resin. Survey of Diels-Alder reactions on solid support⁷ shows some examples of furan-functionalized resins which have allowed the attachment of unstable species (benzyne, cyclopentadienone),⁸ Buckminsterfullerene C₆₀^{3b} and methyl acrylate.⁹

We have compared fur-2-ylated and fur-3-ylated resins in a sequence involving a Diels-Alder reaction with an acetylenic dienophile followed by functionalization of the cycloadduct by Michael addition of thiophenol. A subsequent retro-Diels-Alder cleavage step yielded an olefinic product in a traceless strategy. The fur-2-ylated resin appears more interesting in a synthetic aim since only one regioisomer was obtained in the Diels-Alder reaction, a better diastereoselectivity was noticed in the Michael addition and the yield of the olefinic product was higher.¹⁰

This paper is dealing with the preparation of a small library of β -substituted α,β -ethylenic aldehydes using the 4-(fur-2-ylmethyl)phenyloxymethyl crosslinked polystyrene **3**.

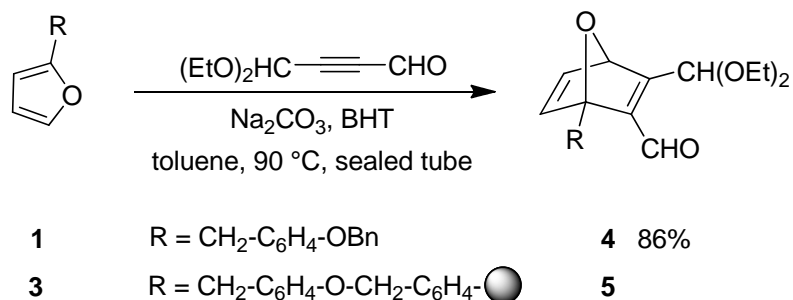
Results and Discussion

The fur-2-ylated resin **3** was prepared by condensation in basic conditions of Merrifield resin with 4-(fur-2-ylmethyl)phenol **2** obtained by hydrogenolysis of the benzylated compound **1** (Scheme 1).¹⁰



Scheme 1. Reagents and conditions: (i) Na, *n*-BuOH, 80 °C, 15 h, 98%. (ii) Merrifield resin (loading 0.74 mmol/g), Cs₂CO₃, NaI, DMF, rt, 27 h.

Diels-Alder reactions of the soluble furan derivative **1** and the furylated resin **3** with 4,4-diethoxybut-2-ynal were performed in degassed toluene at 90 °C in the presence of sodium carbonate and 2,6-di-*tert*-butyl-4-methylphenol (BHT). In each case, only one diastereomer was obtained and structure of the soluble adduct **4** was determined by NOESY experiments. From the analogy of the NMR data of adducts **4** and **5**, the same regioselectivity was assigned to the solid-phase Diels-Alder reaction (Scheme 2).¹⁰

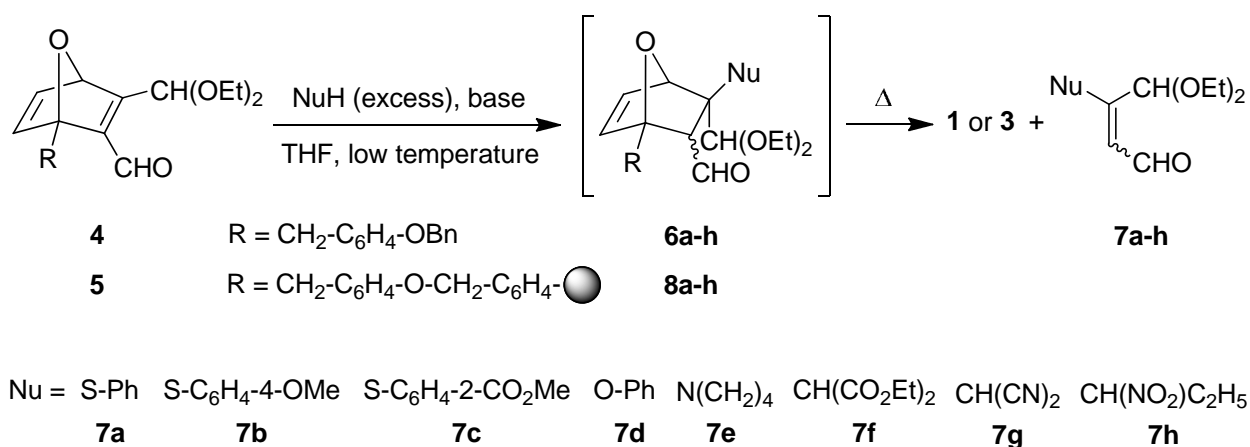


Scheme 2

The soluble Diels-Alder reaction product **4**, a mimic of the cycloadduct-spacer appendage of the resin **5**, was used to optimize the experimental conditions of the solid-phase sequence.

Reactions in solution-phase

Treatments of the Diels-Alder adduct **4** with various nucleophiles (3 equivalents of NuH and generally 0.3 equivalent of base) were performed at low temperature. Retro-Diels-Alder reaction in a higher temperature yielded in most cases the 3-substituted 4,4-diethoxybut-2-enals **7** with regeneration of the furan derivative **1**. Generally, the Michael addition product **6** was not isolated (Scheme 3). Different reaction conditions were tested and the best results are collected in Table 1.

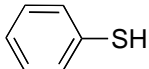
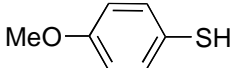
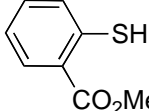
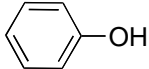
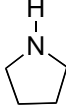
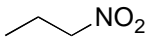


Scheme 3

In each case, the ratio of *Z*- to *E*-aldehyde **7** has been determined on the crude reaction product by ¹H NMR spectroscopy and after silica gel chromatography (from the mass of pure isolated compounds and/or from the mass of mixed isomers fractions). The *Z* and *E* configurations were assigned by NOESY experiments.

After reaction of the adduct **4**, in THF at -78 °C, with benzenethiol (3.0 equiv) and NaH (0.3 equiv), temperature was allowed to increase to 0 °C and the reaction mixture was washed at 0 °C with an aqueous NaOH solution to remove the unreacted benzenethiol. Extraction and concentration of the dried organic phase at 20 °C delivered a mixture of furan **1** and aldehydes *Z*-**7a** and *E*-**7a** in the ratio *Z/E*=75/25.^{10b} Aldehydes **7a** were isolated with a similar ratio (*Z/E*=77/23) after silica gel chromatography in 88% yield for the 2 steps reaction (entry 1). The ratio of isomeric aldehydes **7a** was clearly dependent of the temperature of the various steps of the work-up: performing the concentration at 40 °C instead of 20 °C furnished a 49/51 mixture of *Z*-**7a** and *E*-**7a** while extraction at 0 °C and concentration at 20 °C yielded a 97/3 mixture. Thus, the retro-Diels-Alder reaction of the Michael adduct **6a** should release the aldehyde *Z*-**7a** and isomerization into the more thermodynamic stable *E* isomer occurred during the work-up. The reaction was monitored by TLC, carried out at 20 °C, and information about the temperature dependance of the Michael adduct **6a** stability was not available (*vide infra*). Formation of 4,4-diethoxy-3,3-bis(phenylsulfanyl)butanal, resulting from Michael addition of benzenethiolate to the aldehyde **7a**, was noticed when the basic washing was made at 20 °C.^{10b}

Table 1. Michael addition of various nucleophiles to enal **4** and retro-Diels-Alder reaction

Entry	Nucleophile (3 equiv)	Base (0.3 equiv)	Furan 1 Yield (%) ^a	Olefinic compound			
				N ^o	Crude <i>Z/E</i> ratio ^b	Isolated <i>Z/E</i> ratio ^c	Yield (%) ^a
1		NaH	85	7a	75/25	77/23	88 ^d
2		NaH	84	7b	87/13	85/15	84
3		NaH	83	7c	64/36	65/35	82
4		NaH ^e	38	7d	35/65	22/78	31 ^f
5		–	46	7e	0/100	–	0 ^g
6	CH ₂ (CO ₂ Et) ₂	NaH	87	7f	38/62 ^h	35/65	25 ⁱ
7	CH ₂ (CN) ₂	Triton [®] B ^j	60	7g	–	–	–
8		Triton [®] B ^j	64	7h	100/0	100/0	51

^a Two steps yield after silica gel column chromatography.

^b Ratio determined on the crude reaction product by ¹H NMR.

^c Isolated ratio determined after silica gel column chromatography by ¹H NMR.

^d See Ref. 10b.

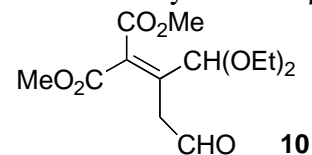
^e Reaction was carried out using 1.0 equiv of NaH.

^f 42% of the starting enal **4** was recovered.

^g Degradation of the *E* olefin on silica gel.

^h Before heating at 55 °C, the *Z/E* ratio was 41/59.

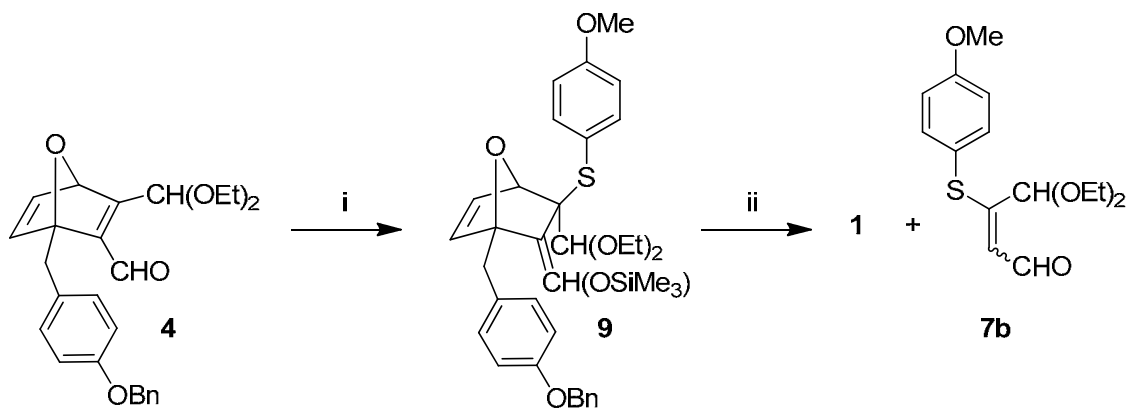
ⁱ Calculated yield. The β,γ-ethylenic aldehyde **10** was also obtained in 12% yield.



^j Benzyltrimethylammonium hydroxide.

Using the optimized reaction conditions described above, *p*-methoxybenzenethiol and methyl 2-sulfanylbenzoate gave the expected aldehydes **7b** and **7c** in good yields (entries 2 and 3). After 2 weeks at 20 °C, the *Z* isomer of the isolated 85/15 mixture of aldehydes *Z*-**7b** and *E*-**7b** was totally isomerized into the more stable *E* isomer.

Trapping at -78 °C by chlorotrimethylsilane (2 equiv) the enolate coming from addition of adduct **4** to sodium *p*-methoxybenzenethiolate (1.5 equiv) in a THF solution yielded the silyl enol ether **9** as a single diastereomer (Scheme 4). The relative configuration of the carbon atom bearing the phenylsulfanyl group was attributed by NOESY experiments, but the configuration of the enolic double bond could not be determined. Cross-peaks appeared between the methynic proton of the acetal group and the ethylenic proton H-5. Examination of Dreiding models of the two possible diastereomers with the acetal group in *endo* and *exo* position shows for the latter a length between the indicated protons too important to allow an interaction. The structure with the acetal group in *endo* position was then attributed to the isolated compound **9**. It should result from an *exo* attack of the *p*-methoxybenzenethiolate on the Diels-Alder adduct **4**, as reported for reactions with other oxabicycloheptadienic compounds.¹¹ The presence of three sp²-carbon atoms on the bicyclic core of the compound **9** increases the activation energy of the retro-Diels-Alder reaction and allows this adduct to be isolated. Treatment of the silyl enol ether **9** with tetrabutylammonium fluoride at 0 °C delivered in 10 minutes the furan **1** and the aldehydes **7b**, but degradation was important. This reaction was not optimized even though it is a new example of a safety-catch process.



Scheme 4. Reagents and conditions: (i) MeO-C₆H₄-SH (1.5 equiv), NaH (1.5 equiv), THF, -78 °C; then TMSCl (2.0 equiv), -78 °C, 2 h, 93%. (ii) NBu₄F (1.0 equiv), THF, 0 °C, 10 min.

Few examples of Michael addition of phenols on α,β -unsaturated aldehydes were reported.¹² Interestingly, reaction of the adduct **4** with phenol (3.0 equiv) and NaH (1.0 equiv) at -25 °C during 15 hours followed by a work-up at 0 °C with an aqueous ammonium chloride solution gave the furan **1** and the expected aldehydes **7d** in 38 and 31% yield, respectively, while 42% of the starting aldehyde **4** was recovered (entry 4). A lower yield of aldehydes **7d** (13%) was obtained using 0.3 equivalent of NaH (62% conversion) although the yield of furan **1** (43%) was

slightly better than previously. No reaction occurred between -78 and 0 °C using quasi stoichiometric conditions (1.1 equiv of phenol and NaH) or benzyltrimethylammonium hydroxide (Triton[®] B, 0.3 equiv, reaction temperature between -40 and -20 °C).

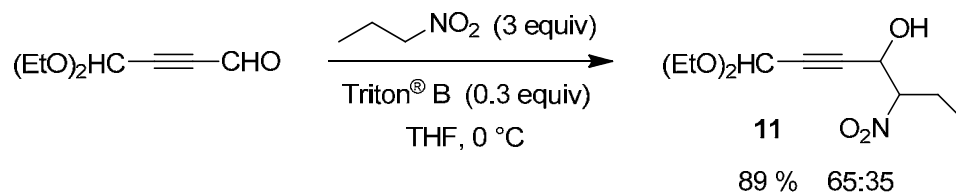
Reaction of the adduct **4** with pyrrolidine (3 equiv) between -40 and -10 °C gave a mixture of furan **1** and enamine *E-7e* (*vide infra*) but this olefinic compound was completely transformed during the chromatography over silica gel (entry 5).

Various reactions were attempted with carbon-centered nucleophiles. Reaction of diethyl malonate with the adduct **4** in the optimized conditions reported for the benzenethiols gave a mixture of furan **1** and a 41/59 mixture of alkenes *Z-7f* and *E-7f*. ¹H NMR spectrum of the crude reaction mixture shows also a signal at 9.68 ppm attributed to the Michael addition product **6f**. After heating this mixture at 55 °C for 15 hours, the Michael addition product was totally transformed and silica gel chromatography allowed to isolate the furan **1** in good yield and an inseparable mixture of alkenes *Z-7f*, *E-7f* and a β,γ -ethylenic aldehyde **10** in 37% overall yield (entry 6).

Reaction of malononitrile with the adduct **4** in the presence of Triton[®] B (0.3 equiv) at 0 °C gave the furan **1** in 60% yield but degradation was noticed. The presence of furan **1** showed the occurrence of the Michael addition and the retro-Diels-Alder reaction, but the probable instability of the expected olefinic compound **7g** prevented its isolation (entry 7).

Treatment of the adduct **4**, between -40 and 10 °C, with 1-nitropropane (3.0 equiv) in the presence of Triton[®] B (0.3 equiv) gave the furan **1**, the nitroaldehyde *Z-7h* in moderate yields (64 and 51%, respectively) and unidentified compounds (entry 8). No reaction has occurred using NaH (0.3 equiv) or triethylamine in the place of Triton[®] B. Using NaH in quasi stoichiometric conditions (1.1 equiv of nitropropane and NaH, reaction temperature between -55 and 40 °C) or sodium methoxide in THF, the furan **1** was obtained (in 35 and 21% yield, respectively) but the expected alkene was not noticed.

Formally, the nitroaldehyde *7h* is the result of a 1,4-addition to 4,4-diethoxybut-2-ynal. Interestingly, treatment of this aldehyde with nitropropane in the presence of Triton[®] B gave only a mixture of the diastereomeric 1,2-addition products **11** in high yield (Scheme 5).



Scheme 5

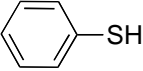
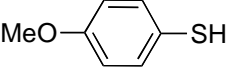
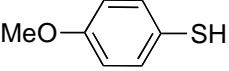
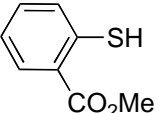
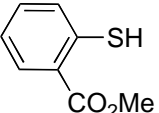
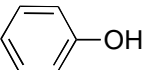
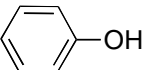
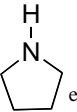
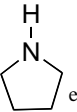
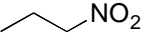
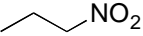
Reactions on solid support

The polymer-bound Diels-Alder reaction adduct **5** was added to a suspension, maintained at -40 °C, of sodium *p*-methoxybenzenethiolate in THF, prepared from *p*-methoxybenzenethiol (5 equiv) and NaH (0.4 equiv). After 15 hours at -35 °C, the resin-bound Michael adduct **8b** was

washed to remove the reagents. THF was added to the washed resin, the temperature was allowed to increase to 20 °C, and the liquid phase was periodically removed and replaced with fresh THF. After 22 hours, the retro-Diels-Alder reaction was over and evaporation of solvent afforded an 83/17 mixture of aldehydes **Z-7b** and **E-7b** in 42% yield (Table 2, entry 3). The yield calculated from the Merrifield resin (4 steps) shows an average yield of 81% *per* step. The first THF withdrawal was done after 45 minutes leaving a 95/5 mixture of **Z-7b** and **E-7b** in 28% yield. In the next separated THF solutions, the ratios **Z-7b/E-7b** were between 66/34 and 53/47 (see experimental part). When the retro-Diels-Alder step was carried out at -2 °C (Table 2, entry 2), 89 hours were necessary to obtain a complete transformation. In these conditions, the overall yield was similar to the previous one (43%) and a lower ratio of **Z-7b** to **E-7b** was noticed (74/26). In another similar experiment, the retro-Diels-Alder reaction was performed at 20 °C and the product was continuously removed from the reaction vessel by a THF stream during 75 minutes. The collected THF solution was stored at -40 °C and protected from light. After evaporation of the solvent under a light shelter, the pure enal **Z-7b** was isolated in 41% overall yield from the starting Merrifield resin. Thus, the retro-Diels-Alder reaction on solid support released the *Z* isomer and the presence of the *E* isomer resulted from a subsequent isomerization. We have a strong evidence of an *exo* attack of the benzenethiolate on the Diels-Alder adduct **4** (*vide supra*). If we assume the same selective attack on the polymer-bound Diels-Alder reaction adduct **5**, it appears that the protonation of the enolate resulting from the Michael addition occurs by the *endo*-face. ¹H NMR MAS spectra of the resins recovered after the first two sequences exhibited the characteristic signals of the polymer-bound furan **3** and the absence of signals of the Diels-Alder adduct **5**. One of these recovered resins **3** was reused in the same sequence Diels-Alder reaction, Michael addition and cycloreversion (2.5 h at 20 °C). A mixture of aldehyde **Z-7b** and unidentified compounds was obtained, and the ¹H NMR MAS spectrum of the resin after this reuse showed signals of the polymer-bound furan **3** and those of unknown compounds.

In Table 2 the results of the addition of various nucleophiles (5 equiv) on the polymer-bound Diels-Alder reaction adduct **5** and a subsequent retro-Diels-Alder reaction are reported. The conditions of the Michael addition were selected from the results obtained in solution-phase. After the Michael addition, the resins were carefully washed at low temperature under argon, then THF was added and the temperature was allowed to increase. As described previously, the THF solution with the released alkenes was removed and replaced with fresh THF time to time, until the retro-Diels-Alder reaction was over. Yields were calculated for the 4 steps reaction sequence starting from Merrifield resin and from the cumulative weight of products. The reported ratios of isomers were calculated from the weight of each fraction and the ratios of products measured by ¹H NMR spectroscopy. A small library of pure α,β -ethylenic aldehydes **7a-f** and **7h** substituted in β position with phenylsulfanyl, phenoxy, pyrrolidinyl, malonate or 1-nitropropyl groups was obtained, without any purification step, in 34 to 49% overall yield.

Table 2. Reaction sequence on the polymer-bound Diels-Alder adduct **5**

Entry	Nucleophile (5 equiv)	Base (0.4 equiv)	Temperature of the Michael addition	Temperature of the retro- Diels-Alder reaction	Olefinic compound		
					N°	Z/E ratio ^a	Yield (%) ^b
1		NaH	-35 °C	-2 °C	7a	100/0	49 ^c
2		NaH	-35 °C	-2 °C	7b	74/26	43
3		NaH	-35 °C	20 °C	7b	83/17	42
4		NaH	-35 °C	-2 °C	7c	23/77	37
5		NaH	-35 °C	20 °C	7c	37/63	40
6		NaH ^d	-20 °C	20 °C	7d	7/93	36
7		NaH ^d	-20 °C	35 °C	7d	8/92	26
8		–	-20 °C	20 °C	7e	0/100	31
9		–	-20 °C	35 °C	7e	0/100	40
10	CH ₂ (CO ₂ Et) ₂	NaH	-40 °C	0, 20, 35 °C	7f	33/67	34 ^f
11	CH ₂ (CN) ₂	Triton [®] B ^g	-40 °C	20 °C	7g	–	–
12		Triton [®] B ^g	-20 °C	20 °C	7h	70/30	30
13		Triton [®] B ^g	-20 °C	35 °C	7h	66/34	38

^a See text. ^b Overall yield based on the Merrifield resin (4 steps). ^c See Ref. 10b. ^d Reaction was carried out using 1.0 equiv of NaH. ^e Reaction was carried out using 3.0 equiv of pyrrolidine. ^f Calculated overall yield. The β,γ-ethylenic aldehyde **10** was also obtained in 15% yield. ^g Benzyltrimethylammonium hydroxide.

As expected, an increase of the temperature in the retro-Diels-Alder reaction allowed the decrease of the reaction time. But the overall yield increased in the sequences starting from methyl 2-sulfanylbenzoate, 1-nitropropane and pyrrolidine, and decreased in other ones.

When the reaction of phenolate was attempted at $-40\text{ }^{\circ}\text{C}$, in the place of $-20\text{ }^{\circ}\text{C}$, alkene **7d** was not detected after the retro-Diels-Alder reaction step. It means that the Michael addition did not occur at this temperature.

Solid-phase synthesis allowed enamine **7e** to be easily isolated (entries 8 and 9) whereas it was, due to its instability on silica gel, totally transformed in our attempted separation from the furan **1** after the solution-phase preparation.

The overall yield (34%) for the solid-phase synthesis of the malonate derivatives **7f** (slightly unstable on silica gel) was higher than the yield obtained in liquid phase (25%), but formation of the β,γ -unsaturated aldehyde **10** could not be prevented (entry 10).

Finally, the sequence with malononitrile gave degraded compounds and the expected alkenes **7g** were not detected (entry 11). The ^1H NMR MAS spectrum of the recovered resin showed mainly the signals of the polymer-bound furan **3**. Thus, the Michael addition and the retro-Diels-Alder reaction should have occurred but the released products were too unstable to be isolated.

Conclusions

7-Oxanorborna-2,5-diene-2-carboxaldehydes prepared by reaction of 4,4-diethoxybut-2-ynal with a furan derivative or a fur-2-ylated resin are masked forms of the acetylenic aldehyde. Michael adducts obtained by reaction of these α,β -ethylenic aldehydes with heteroatom- and carbon-centered nucleophiles were generally unstable at room temperature. They undergo retro-Diels-Alder reaction and deliver β -substituted α,β -ethylenic aldehydes. This sequence Diels-Alder reaction/Michael addition/Cycloreversion with an acetylenic aldehyde allows to drive the reaction of nucleophiles only to the 1,4-addition. On solid support, the thermal retro-Diels-Alder reaction is advantageous since excess of reagents are removed by filtration at low temperature prior to the cycloreversion step, thus eliminating purification of the synthesized α,β -ethylenic aldehydes and avoiding subsequent reactions.

Experimental Section

General. Solvents were dried according to standard procedures and all reactions requiring anhydrous conditions were performed under argon. In solution-phase, reactions were monitored by TLC on silica gel 60 F₂₅₄ 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). ^1H and ^{13}C NMR spectra were recorded on Bruker

AC200 (200 and 50.3 MHz, respectively), Bruker AC250 (250 and 62.9 MHz, respectively) or Bruker DRX400 (400 MHz) spectrometers. Chemical shifts (δ) are given in parts per million using solvent (CDCl_3) signals as internal standards (CHCl_3 $\delta=7.27$ ppm; CDCl_3 $\delta=77.14$ 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). Infrared (IR) spectra of products and resins were recorded using an FT-IR Perkin-Elmer spectrophotometer (Spectrum One). For solid-phase reactions, the reported yields are overall yields (4 steps) calculated with respect to the Merrifield resin (loading 0.74 mmol/g, styrene-1%DVB, 200-400 mesh purchased from Noviochem[®]). For MAS NMR experiments, the resins were swollen with the minimal volume of deuterated solvent (CDCl_3) after introducing them into the rotor. ^1H 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. Proofs of purity of aldehydes **7a-f** and **7h** released from the resins were provided by their ^1H NMR spectrum (>95% pure).

4,4-Diethoxy-3-[(4-methoxyphenyl)sulfanyl]but-2-enal **7b**

From Diels-Alder adduct 4. To a mixture of a 60% dispersion of sodium hydride in mineral oil (7.0 mg, 0.175 mmol) and anhydrous THF (2.5 mL) under argon was added dropwise *para*-methoxybenzenethiol (215 μL , 1.748 mmol) at room temperature. A gas release was observed and the suspension was then stirred for an additional 30 min. After cooling at -78 $^\circ\text{C}$, a solution of adduct **4** (246 mg, 0.586 mmol) in THF (1.5 mL) was added. The reaction mixture was maintained for 1 h at -78 $^\circ\text{C}$ and the temperature was allowed to increase to 0 $^\circ\text{C}$ over 4 h. A 2.5 M sodium hydroxide aqueous solution was then added at 0 $^\circ\text{C}$ 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). ^1H NMR spectrum of the crude residue shows the enals **Z-7b** and **E-7b** in a ratio **Z-7b/E-7b**=87/13. Chromatography on silica gel (pentane/ Et_2O : 90/10, then 70/30) afforded furan **1** (130 mg, 84%) and a mixture of enals **7b** (145 mg, 84%) in the ratio **Z-7b/E-7b**=85/15. Under these chromatographic conditions, partial separation of the enals **Z-7b** and **E-7b** was observed and pure samples of each isomer could be obtained.

From Diels-Alder adduct 5. In a three-necked round-bottomed flask fitted with a bent solid addition bulb, a paper coated filtering cannula, an argon inlet and a small magnetic stirring bar were placed a 60% dispersion of sodium hydride in mineral oil (1.0 mg, 0.026 mmol) and anhydrous THF (1 mL). *Para*-methoxybenzenethiol (40 μL , 0.329 mmol) was then added dropwise and the suspension was stirred for 30 min at room temperature. The reaction mixture

was cooled at $-40\text{ }^{\circ}\text{C}$ and resin **5** (100 mg, 0.066 mmol) previously placed in the solid addition bulb was added. After gentle stirring for 15 h at $-35\text{ }^{\circ}\text{C}$, the liquid phase was removed through the filtering cannula under argon and the resin maintained at $-35\text{ }^{\circ}\text{C}$ was extensively washed with THF, mixtures of THF/MeOH (increasing then decreasing MeOH ratios) and THF (the solvents being removed each time through the cannula under argon). Analysis by TLC and ^1H NMR spectrum of the residue obtained by concentration *in vacuo* of the combined filtrates show exclusively the presence of *para*-methoxybenzenethiol. After addition of distilled THF (2 mL) at $-35\text{ }^{\circ}\text{C}$, the heterogeneous reaction mixture was allowed to warm slowly to $20\text{ }^{\circ}\text{C}$ and was gently stirred for 45 min at this temperature. The liquid phase was then removed through the filtering cannula under argon and the resin was washed with distilled THF at $20\text{ }^{\circ}\text{C}$. Concentration *in vacuo* (water bath at room temperature) of the combined filtrates gave enal **7b** (5.5 mg, **Z-7b/E-7b**=95/5 determined from ^1H NMR spectrum). The resulting resin was once again suspended in distilled THF (2 mL) and stirred for an additional 2 h 15 min at $20\text{ }^{\circ}\text{C}$. After filtering and washings of the resin with THF, enal **7b** (0.6 mg, **Z-7b/E-7b**=66/34) was isolated. Stirring at $20\text{ }^{\circ}\text{C}$ of the recovered resin in THF (2 mL) for an additional 2 h allowed enal **7b** (0.8 mg, **Z-7b/E-7b**=53/47) to be isolated. More release of enal **7b** was noticed after stirring the remaining resin in THF (2 mL) for an additional 17 h at $20\text{ }^{\circ}\text{C}$ (1.4 mg, **Z-7b/E-7b**=60/40). The complete experiment furnished enal **7b** (8.3 mg, 42% overall yield, **Z-7b/E-7b**=83/17). After drying under reduced pressure and standing *in vacuo* in the presence of P_2O_5 , the recovered resin (109 mg) was identified by IR spectroscopy as resin **3**.

Under the same conditions for the Michael addition and after slowly warming of the resin from $-35\text{ }^{\circ}\text{C}$ to $-2\text{ }^{\circ}\text{C}$, enal **7b** (8.4 mg, 43% overall yield, **Z-7b/E-7b**=74/26) was isolated after concentration *in vacuo* of the combined filtrates obtained by periodical washings of the resin at $-2\text{ }^{\circ}\text{C}$ for 89 h (19 h, 5.5 mg, **Z-7b/E-7b**=90/10; + 5.5 h, 1.0 mg, **Z-7b/E-7b**=65/35; + 64.5 h, 1.9 mg, **Z-7b/E-7b**=33/67).

(Z)-4,4-Diethoxy-3-[(4-methoxyphenyl)sulfanyl]but-2-enal Z-7b. Yellow oil. ^1H NMR (200 MHz, CDCl_3) δ 1.13 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 3.20-3.31 (m, 2H, OCH_2CH_3), 3.44-3.52 (m, 2H, OCH_2CH_3), 3.81 (s, 3H, OMe), 4.63 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.53 (d, $J=7.0$ Hz, 1H, $\text{C}=\text{CH}$), 6.88 (d, $J=8.7$ Hz, 2H, H_{Ar}), 7.45 (d, $J=8.7$ Hz, 2H, H_{Ar}), 10.15 (d, $J=7.0$ Hz, 1H, CHO). ^{13}C NMR (50.3 MHz, CDCl_3) δ 15.0 (OCH_2CH_3), 55.4 (OMe), 62.2 (OCH_2CH_3), 99.0 ($\text{CH}(\text{OEt})_2$), 114.9 (CH_{Ar}), 119.9 (C_{Ar}), 125.7 ($\text{C}=\text{CH}$), 136.5 (CH_{Ar}), 158.1 (C_{Ar}), 160.8 ($\text{C}=\text{CH}$), 190.4 (CHO). MS (ES^+) m/z (%): 615 (24) [$2\text{M}+\text{Na}$] $^+$, 351 (16) [$\text{M}+\text{MeOH}+\text{Na}$] $^+$, 319 (100) [$\text{M}+\text{Na}$] $^+$. HRMS (IE): calcd mass for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{S}$: 296.1082. Found: 296.1076.

(E)-4,4-Diethoxy-3-[(4-methoxyphenyl)sulfanyl]but-2-enal E-7b. Yellow oil. ^1H NMR (250 MHz, CDCl_3) δ 1.29 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 3.64-3.90 (m, OCH_2CH_3) and 3.83 (s, OMe) (7H), 5.35 (d, $J=7.5$ Hz, 1H, $\text{C}=\text{CH}$), 5.67 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.95 (d, $J=9.1$ Hz, 2H, H_{Ar}), 7.38 (d, $J=9.1$ Hz, 2H, H_{Ar}), 9.97 (d, $J=7.5$ Hz, 1H, CHO). ^{13}C NMR (50.3 MHz, CDCl_3) δ 15.1 (OCH_2CH_3), 55.4 (OMe), 62.7 (OCH_2CH_3), 99.0 ($\text{CH}(\text{OEt})_2$), 115.7 (CH_{Ar}), 118.8 (C_{Ar}), 123.3 ($\text{C}=\text{CH}$), 137.1 (CH_{Ar}), 161.3 (C_{Ar}), 167.2 ($\text{C}=\text{CH}$), 188.1 (CHO). MS (ES^+) m/z (%): 319 (100) [$\text{M}+\text{Na}$] $^+$. HRMS (ES^+): calcd mass for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{SNa}$: 319.0980. Found: 319.0980.

Methyl 2-[[1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]sulfanyl]benzoate 7c

From Diels-Alder adduct 4. Following the procedure described for compound **7b**, a solution of cycloadduct **4** (175 mg, 0.416 mmol) in anhydrous THF (2 mL) was added at $-78\text{ }^{\circ}\text{C}$ to a suspension of sodium 2-methoxycarbonylbenzenethiolate in THF (2 mL) prepared from methyl 2-sulfanylbenzoate (170 μL , 1.248 mmol) and a 60% dispersion of sodium hydride in mineral oil (5.0 mg, 0.125 mmol). The reaction mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$ and the temperature was allowed to increase to $0\text{ }^{\circ}\text{C}$ over 4 h. After treatment with a 2.5 M sodium hydroxide aqueous solution at $0\text{ }^{\circ}\text{C}$ and concentration under reduced pressure (water bath at room temperature), a crude mixture of enals **Z-7c** and **E-7c** in a ratio **Z-7c/E-7c**=64/36 was observed by ^1H NMR spectroscopy. Purification by silica gel column chromatography (pentane/Et₂O: 90/10, then 80/20) afforded furan **1** (91 mg, 83%), enal **Z-7c** (71 mg, 53%) and enal **E-7c** (39 mg, 29%).

From Diels-Alder adduct 5. Following the procedure described for compound **7b**, resin **5** (141 mg, 0.093 mmol) was added at $-40\text{ }^{\circ}\text{C}$ to a suspension of sodium 2-methoxycarbonylbenzenethiolate in THF (1 mL) prepared from methyl 2-sulfanylbenzoate (62 μL , 0.455 mmol) and a 60% dispersion of sodium hydride in mineral oil (1.5 mg, 0.036 mmol). After gentle stirring for 15 h at $-35\text{ }^{\circ}\text{C}$, the liquid phase was removed and the resin was extensively washed at $-35\text{ }^{\circ}\text{C}$ as previously described. After addition of distilled THF (2 mL) at $-35\text{ }^{\circ}\text{C}$, the heterogeneous reaction mixture was allowed to warm slowly to $20\text{ }^{\circ}\text{C}$ and was gently stirred at this temperature. The liquid phase was then periodically removed during 22 hours at $20\text{ }^{\circ}\text{C}$ and replaced with distilled THF. Enal **7c** (12.2 mg, 40% overall yield, **Z-7c/E-7c**=37/63) was isolated after concentration *in vacuo* of the combined filtrates obtained by the periodical washings of the resin (45 min, 4.9 mg, **Z-7c/E-7c**=45/55; + 2h15, 6.7 mg, **Z-7c/E-7c**=31/69; + 2 h, 0.3 mg, **Z-7c/E-7c**=34/66; + 17 h, 0.3 mg, **Z-7c/E-7c**=39/61). After drying under reduced pressure and standing *in vacuo* in the presence of P₂O₅, resin **3** (125 mg) was recovered.

Under the same conditions for the Michael addition and after slowly warming of the resin from $-35\text{ }^{\circ}\text{C}$ to $-2\text{ }^{\circ}\text{C}$, enal **7c** (11.2 mg, 37% overall yield, **Z-7c/E-7c**=23/77) was isolated after concentration *in vacuo* of the combined filtrates obtained by periodical washings of the resin at $-2\text{ }^{\circ}\text{C}$ for 122 h (21 h, 3.4 mg, **Z-7c/E-7c**=48/52; + 7 h, 2.4 mg, **Z-7c/E-7c**=23/77; + 20 h, 2.7 mg, **Z-7c/E-7c**=16/84; + 74 h, 2.7 mg, **Z-7c/E-7c**=0/100).

Methyl 2-[[1-(Z)-1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]sulfanyl]benzoate Z-7c. Pale yellow oil. ^1H NMR (200 MHz, CDCl₃) δ 1.16 (t, J =6.8 Hz, 6H, OCH₂CH₃), 3.31-3.41 (m, 2H, OCH₂CH₃), 3.43-3.58 (m, 2H, OCH₂CH₃), 3.92 (s, 3H, CO₂Me), 4.81 (s, 1H, CH(OEt)₂), 6.80 (d, J =7.1 Hz, 1H, C=CH), 7.27-7.45 (m, 3H, H_{Ar}), 7.93 (d, J =7.8 Hz, 1H, H_{Ar}), 10.18 (d, J =7.1 Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl₃) δ 15.0 (OCH₂CH₃), 52.4 (CO₂Me), 62.3 (OCH₂CH₃), 100.0 (CH(OEt)₂), 127.2 (CH_{Ar}), 130.0 (C_{Ar}), 131.0 (CH_{Ar}), 132.1 (CH_{Ar}), 132.2 (CH_{Ar}), 132.5 (C=CH), 134.9 (C_{Ar}), 154.9 (C=CH), 166.5 (CO₂Me), 191.7 (CHO). MS (ES⁺) m/z (%): 379 (94) [M+MeOH+Na]⁺, 347 (75) [M+Na]⁺, 167 (100). HRMS (ES⁺): calcd mass for C₁₆H₂₀O₅SNa: 347.0929. Found: 347.0931.

Methyl 2-[(*E*)-1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]sulfanyl]benzoate *E*-7c. Pale yellow oil. ^1H NMR (200 MHz, CDCl_3) δ 1.26 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 3.62-3.83 (m, 4H, OCH_2CH_3), 3.93 (s, 3H, CO_2Me), 5.35 (d, $J=7.8$ Hz, 1H, $\text{C}=\text{CH}$), 5.64 (s, 1H, $\text{CH}(\text{OEt})_2$), 7.50-7.60 (m, 3H, H_{Ar}), 7.91 (m, 1H, H_{Ar}), 10.00 (d, $J=7.8$ Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl_3) δ 15.1 (OCH_2CH_3), 52.4 (CO_2Me), 62.7 (OCH_2CH_3), 99.2 ($\text{CH}(\text{OEt})_2$), 124.6 ($\text{C}=\text{CH}$), 129.2 (C_{Ar}), 130.1 (CH_{Ar}), 131.2 (CH_{Ar}), 132.6 (CH_{Ar}), 137.5 (CH_{Ar}), 135.8 (C_{Ar}), 165.1 ($\text{C}=\text{CH}$), 166.4 (CO_2Me), 188.3 (CHO). MS (ES^+) m/z (%): 379 (5) [$\text{M}+\text{MeOH}+\text{Na}$] $^+$, 347 (91) [$\text{M}+\text{Na}$] $^+$, 167 (100). HRMS (ES^+): calcd mass for $\text{C}_{16}\text{H}_{20}\text{O}_5\text{SNa}$: 347.0929. Found: 347.0926.

4,4-Diethoxy-3-phenoxybut-2-enal **7d**

From Diels-Alder adduct 4. To a mixture of a 60% dispersion of sodium hydride in mineral oil (9.5 mg, 0.238 mmol) and anhydrous THF (0.5 mL) under argon was added dropwise a solution of phenol (67 mg, 0.712 mmol) in anhydrous THF (0.5 mL). The suspension was then stirred for an additional 15 min at room temperature. After cooling at -25 $^\circ\text{C}$, a solution of adduct **4** (100 mg, 0.238 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was maintained for 15 h at -25 $^\circ\text{C}$ before hydrolysis at 0 $^\circ\text{C}$ with a saturated aqueous solution of ammonium chloride. After three extractions with Et_2O , the combined organic extracts were dried over sodium sulfate and the solvents were evaporated under reduced pressure (water bath at room temperature). ^1H NMR spectrum of the crude residue shows a mixture of **Z-7d** and **E-7d** isomers in a 35/65 ratio. Chromatography on silica gel (pentane/ Et_2O : 90/10, then 70/30) afforded furan **1** (24 mg, 38%), enal **Z-7d** (4 mg, 7%), enal **E-7d** (14.5 mg, 24%) and starting cycloadduct **4** (42 mg, 42%) was also recovered.

From Diels-Alder adduct 5. Following the procedure described for compound **7b**, resin **5** (145 mg, 0.096 mmol) was added at -20 $^\circ\text{C}$ to a suspension of sodium phenolate in THF (1.5 mL) prepared from phenol (46.0 mg, 0.495 mmol) and a 60% dispersion of sodium hydride in mineral oil (4.0 mg, 0.099 mmol). After gentle stirring for 24 h at -20 $^\circ\text{C}$, the liquid phase was removed and the resin was extensively washed at -20 $^\circ\text{C}$ as previously described. After addition of distilled THF (2 mL) at -20 $^\circ\text{C}$, the heterogeneous reaction mixture was allowed to warm slowly to 20 $^\circ\text{C}$ and was gently stirred at this temperature. The liquid phase was then periodically removed during 136 hours at 20 $^\circ\text{C}$ and replaced with distilled THF. Enal **7d** (8.6 mg, 36% overall yield, **Z-7d/E-7d** = 7/93) was isolated after concentration *in vacuo* of the combined filtrates obtained by the periodical washings of the resin (47 h, 2.1 mg, **Z-7d/E-7d** = 14/86; + 20 h, 4.1 mg, **Z-7d/E-7d** = 0/100; + 69 h, 2.4 mg, **Z-7d/E-7d** = 12/88). After drying under reduced pressure and standing *in vacuo* in the presence of P_2O_5 , resin **3** (132 mg) was recovered.

Under the same conditions for the Michael addition and after warming of the resin from -20 $^\circ\text{C}$ to 35 $^\circ\text{C}$, enal **7d** (6.2 mg, 26% overall yield with respect to Merrifield resin, **Z-7d/E-7d** = 8/92) was isolated after concentration *in vacuo* of the combined filtrates obtained by periodical washings of the resin at 35 $^\circ\text{C}$ for 5.5 h (0.5 h, 1.9 mg, **Z-7d/E-7d** = 24/76; + 5 h, 4.3 mg, **Z-7d/E-7d** = 0/100).

(Z)-4,4-Diethoxy-3-phenoxybut-2-enal Z-7d. Yellow oil. ^1H NMR (250 MHz, CDCl_3) δ 1.20 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 3.41-3.53 (m, 2H, OCH_2CH_3), 3.59-3.71 (m, 2H, OCH_2CH_3), 5.00 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.09 (d, $J=7.8$ Hz, 1H, $\text{C}=\text{CH}$), 7.07-7.40 (m, 5H, Ph), 10.00 (d, $J=7.8$ Hz, 1H, CHO). ^{13}C NMR (50.3 MHz, CDCl_3) δ 15.0 (OCH_2CH_3), 62.2 (OCH_2CH_3), 96.6 ($\text{CH}(\text{OEt})_2$), 115.5 ($\text{C}=\text{CH}$), 118.5 (CH_{Ar}), 124.6 (CH_{Ar}), 130.0 (CH_{Ar}), 155.9 (C_{Ar}), 166.4 ($\text{C}=\text{CH}$), 190.7 (CHO). MS (EI) m/z (%): 250 (4) [M^+], 221 (21), 204 (23), 175 (100), 147 (23), 103 (39), 77 (27), 75 (34). HRMS (EI): calcd mass for $\text{C}_{14}\text{H}_{18}\text{O}_4$: 250.1204. Found: 250.1210.

(E)-4,4-Diethoxy-3-phenoxybut-2-enal E-7d. Yellow oil. ^1H NMR (250 MHz, CDCl_3) δ 1.33 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 3.69-3.90 (m, 4H, OCH_2CH_3), 5.19 (d, $J=7.6$ Hz, 1H, $\text{C}=\text{CH}$), 5.45 (s, 1H, $\text{CH}(\text{OEt})_2$), 7.02-7.44 (m, 5H, Ph), 10.20 (d, $J=7.6$ Hz, 1H, CHO). ^{13}C NMR (50.3 MHz, CDCl_3) δ 15.2 (OCH_2CH_3), 63.4 (OCH_2CH_3), 100.0 ($\text{CH}(\text{OEt})_2$), 109.5 ($\text{C}=\text{CH}$), 121.2 (CH_{Ar}), 127.5 (CH_{Ar}), 130.2 (CH_{Ar}), 152.7 (C_{Ar}), 172.8 ($\text{C}=\text{CH}$), 191.5 (CHO). IR (neat): 2977, 2896, 1663, 1624, 1588, 1489, 1260, 1214, 1152, 1110, 1063, 814. MS (ES^+) m/z (%): 273 (100) [$\text{M}+\text{Na}$] $^+$. HRMS (ES^+): calcd mass for $\text{C}_{14}\text{H}_{18}\text{O}_4\text{Na}$: 273.1103. Found: 273.1104.

(E)-4,4-Diethoxy-3-(pyrrolidin-1-yl)but-2-enal 7e

From Diels-Alder adduct 5. In the same apparatus as described for compound **7b**, were introduced resin **5** (137 mg, 0.090 mmol) and anhydrous THF (1 mL). At -20 °C, pyrrolidine (23 μL , 0.273 mmol) was then added dropwise to the resin. After gentle stirring for 15 h at -20 °C, the liquid phase was removed and the resin was extensively washed at -20 °C as previously described. After addition of distilled THF (2 mL) at -20 °C, the heterogeneous reaction mixture was allowed to warm slowly to 20 °C and was gently stirred at 35 °C. The liquid phase was then periodically removed during 22 hours at 35 °C and replaced with distilled THF. Enal **E-7e** (8.2 mg, 40% overall yield with respect to Merrifield resin) was isolated after concentration *in vacuo* of the combined filtrates obtained by the periodical washings of the resin (40 min, 2.9 mg, 14% overall yield; + 3 h, 3.9 mg, 19% overall yield; + 18 h, 1.4 mg, 7% overall yield). After drying under reduced pressure and standing *in vacuo* in the presence of P_2O_5 , resin **3** (128 mg) was recovered.

Under the same conditions for the Michael addition and after warming of the resin from -20 °C to 20 °C, enal **E-7e** (6.3 mg, 31% overall yield with respect to Merrifield resin) was isolated after concentration *in vacuo* of the combined filtrates obtained by periodical washings of the resin at 20 °C for 18 h (5 h, 2.6 mg, 13% overall yield; + 13 h, 3.7 mg, 18% overall yield).

(E)-4,4-Diethoxy-3-(pyrrolidin-1-yl)but-2-enal E-7e. Brown oil. ^1H NMR (200 MHz, CDCl_3) δ 1.21 (t, $J=7.1$ Hz, 6H, OCH_2CH_3), 1.88 (m, 4H, NCH_2CH_2), 3.20 (m, 2H, NCH_2CH_2), 3.40-3.91 (m, 6H, OCH_2CH_3 , NCH_2CH_2), 5.06 (d, $J=8.0$ Hz, 1H, $\text{C}=\text{CH}$), 5.86 (s, 1H, $\text{CH}(\text{OEt})_2$), 9.62 (d, $J=8.0$ Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl_3) δ 15.0 (OCH_2CH_3), 23.9 (NCH_2CH_2), 25.9 (NCH_2CH_2), 49.1 (NCH_2CH_2), 49.5 (NCH_2CH_2), 63.9 (OCH_2CH_3), 97.7 ($\text{CH}(\text{OEt})_2$), 102.1 ($\text{C}=\text{CH}$), 158.3 ($\text{C}=\text{CH}$), 185.2 (CHO). MS (ES^+) m/z (%): 477 (34) [$2\text{M}+\text{Na}$] $^+$, 281 (100) [$\text{M}+\text{MeOH}+\text{Na}$] $^+$, 250 (92) [$\text{M}+\text{Na}$] $^+$. HRMS (ES^+): calcd mass for $\text{C}_{12}\text{H}_{21}\text{NO}_3\text{Na}$: 250.1419. Found: 250.1424.

Diethyl [1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]malonate 7f and diethyl [1-(diethoxymethyl)-3-oxopropylidene]malonate 10

From Diels-Alder adduct 4. Diethyl malonate (119 μL , 0.783 mmol) was added dropwise to a mixture of a 60% dispersion of sodium hydride in mineral oil (3.1 mg, 0.078 mmol) and anhydrous THF (2 mL) under argon. After stirring for an additional 15 min at room temperature and cooling at $-78\text{ }^\circ\text{C}$, a solution of adduct **4** (110 mg, 0.261 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was stirred for 1 h at $-78\text{ }^\circ\text{C}$ and the temperature was allowed to increase to $0\text{ }^\circ\text{C}$ over 4 h. After hydrolysis with a 0.1 M HCl aqueous solution (2 mL) at $0\text{ }^\circ\text{C}$, the aqueous layer was extracted three times with Et_2O and the combined organic fractions were washed with water to neutrality and dried over sodium sulfate. After concentration under reduced pressure (water bath at room temperature), a mixture of enals **Z-7f** and **E-7f** in a ratio **Z-7f/E-7f**=41/59 in addition to the Michael adduct **6f** were observed by ^1H NMR spectroscopy. The residue was dissolved in THF (4 mL) and the reaction mixture was heated under argon for 15 h at $55\text{ }^\circ\text{C}$. After concentration *in vacuo*, ^1H NMR spectrum of the crude residue shows enals **Z-7f** and **E-7f** in a ratio **Z-7f/E-7f**=38/62 and the β,γ -ethylenic aldehyde **10** in a ratio **7f/10**=74/26. Purification by silica gel column chromatography (pentane/ Et_2O : 90/10, then 75/25) gave furan **1** (60 mg, 87%) and an inseparable mixture of enals **Z-7f**, **E-7f** and **10** (31 mg, 37%, **Z-7f/E-7f**=35/65, **7f/10**=68/32) as a brown oil. MS (ES^+) m/z (%): 371 (12) [$\text{M}+\text{MeOH}+\text{Na}$] $^+$, 339 (100) [$\text{M}+\text{Na}$] $^+$. HRMS (ES^+): calcd mass for $\text{C}_{15}\text{H}_{24}\text{O}_7\text{Na}$: 339.1419. Found: 339.1424.

From Diels-Alder adduct 5. As described for compound **7b**, resin **5** (141 mg, 0.093 mmol) was added at $-40\text{ }^\circ\text{C}$ to a reaction mixture prepared from diethyl malonate (75 μL , 0.455 mmol) and a 60% dispersion of sodium hydride in mineral oil (1.5 mg, 0.036 mmol) in THF (1.5 mL). After gentle stirring for 24 h at $-40\text{ }^\circ\text{C}$, the liquid phase was removed and the resin was extensively washed at $-40\text{ }^\circ\text{C}$ as previously described. After addition of distilled THF (2 mL) at $-40\text{ }^\circ\text{C}$, the heterogeneous reaction mixture was allowed to warm slowly to $0\text{ }^\circ\text{C}$ and was gently stirred for 24 h at this temperature. Filtration and washings of the resin at $0\text{ }^\circ\text{C}$ could release a mixture of enal **7f** with the β,γ -ethylenic aldehyde **10** (5.8 mg, **Z-7f/E-7f**=31/69, **7f/10**=65/35). No aldehyde **7f** or **10** was recovered after stirring the resin in THF (2 mL) for an additional 24 h at $0\text{ }^\circ\text{C}$. The temperature of the reaction mixture was then allowed to warm slowly to $20\text{ }^\circ\text{C}$ and the liquid phase was then removed after 105 hours at $20\text{ }^\circ\text{C}$ and replaced with distilled THF. After concentration *in vacuo* of the combined filtrates, mixture of enal **7f** and **10** (5.4 mg, **Z-7f/E-7f**=34/66, **7f/10**=71/29) was isolated. Stirring at $35\text{ }^\circ\text{C}$ of the remaining resin in THF (2 mL) for 8 h allowed enal **7f** and aldehyde **10** (3.1 mg, **Z-7f/E-7f**=36/64, **7f/10**=75/25) to be recovered. The complete experiment furnished a mixture of enals **7f** and **10** (14.3 mg, 49% overall yield, **Z-7f/E-7f**=33/67, **7f/10**=69/31). After drying under reduced pressure and standing *in vacuo* in the presence of P_2O_5 , resin **3** (140 mg) was collected.

Diethyl [(Z)-1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]malonate Z-7f. ^1H NMR (200 MHz, CDCl_3) δ 1.10-1.40 (m, 12H, OCH_2CH_3 , $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.42-3.81 (m, 4H, OCH_2CH_3), 4.09-4.40 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.59 (s, 1H, $\text{CH}(\text{CO}_2\text{Et})_2$), 5.67 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.15 (d, $J=7.1\text{ Hz}$, 1H,

C=CH), 10.23 (d, $J=7.1$ Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl_3) δ 14.1 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 15.2 (OCH_2CH_3), 53.8 ($\text{CH}(\text{CO}_2\text{Et})_2$), 62.3 (OCH_2CH_3 or $\text{CO}_2\text{CH}_2\text{CH}_3$), 62.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$ or OCH_2CH_3), 97.8 ($\text{CH}(\text{OEt})_2$), 131.9 (C=CH), 146.8 (C=CH), 166.9 (CO_2Et), 190.7 (CHO).

Diethyl [(E)-1-(diethoxymethyl)-3-oxoprop-1-en-1-yl]malonate E-7f. ^1H NMR (200 MHz, CDCl_3) δ 1.10-1.40 (m, 12H, OCH_2CH_3 , $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.42-3.81 (m, 4H, OCH_2CH_3), 4.09-4.40 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.81 (s, 1H, $\text{CH}(\text{CO}_2\text{Et})_2$), 4.94 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.32 (d, $J=7.3$ Hz, 1H, C=CH), 9.91 (d, $J=7.3$ Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl_3) δ 13.9 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.9 (OCH_2CH_3), 50.9 ($\text{CH}(\text{CO}_2\text{Et})_2$), 62.4 (OCH_2CH_3 or $\text{CO}_2\text{CH}_2\text{CH}_3$), 63.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$ or OCH_2CH_3), 99.8 ($\text{CH}(\text{OEt})_2$), 131.3 (C=CH), 147.3 (C=CH), 167.2 (CO_2Et), 191.7 (CHO).

Diethyl [1-(diethoxymethyl)-3-oxopropylidene]malonate 10. ^1H NMR (200 MHz, CDCl_3) δ 1.10-1.40 (m, 12H, OCH_2CH_3 , $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.42-3.81 (m, 6H, OCH_2CH_3 , CH_2CHO), 4.09-4.40 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.20 (s, 1H, $\text{CH}(\text{OEt})_2$), 9.56 (t, $J=2.5$ Hz, 1H, CHO).

3-(Diethoxymethyl)-4-nitrohex-2-enal 7h

From Diels-Alder adduct 4. To a solution of 1-nitropropane (63 μL , 0.714 mmol) in THF (1 mL) under argon was added a 40% methanolic solution of benzyltrimethylammonium hydroxide (Triton[®] B, 32 μL , 0.071 mmol). After standing for 15 min at room temperature and cooling at -40 $^\circ\text{C}$, a solution of adduct **4** (100 mg, 0.238 mmol) in THF (1 mL) was added dropwise. The temperature of the reaction mixture was then allowed to increase to 10 $^\circ\text{C}$ over 5 hours. An aqueous saturated ammonium chloride solution was added at 10 $^\circ\text{C}$ and the aqueous layer was extracted three times with Et_2O . The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure (water bath at room temperature). ^1H NMR spectrum of the crude residue only shows the enal **7h** in the *Z* form. Furan **1** (40 mg, 64%) and enal **Z-7h** (30 mg, 51%) were isolated after purification by chromatography on silica gel (pentane/ Et_2O : 90/10, then 70/30).

From Diels-Alder adduct 5. Using the same apparatus as described for compound **7b**, 1-nitropropane (40 μL , 0.455 mmol) was added under argon to a 40% methanolic solution of benzyltrimethylammonium hydroxide (16.5 μL , 0.036 mmol) in THF (1.5 mL). The reaction mixture was stirred 15 min at room temperature and, after cooling at -20 $^\circ\text{C}$, resin **5** (141 mg, 0.093 mmol) was added. The heterogeneous reaction mixture was gently stirring for 19 h at -20 $^\circ\text{C}$ and the liquid phase was removed and the resin was extensively washed at -20 $^\circ\text{C}$ as previously described. After addition of anhydrous THF (2 mL) at -20 $^\circ\text{C}$, the reaction mixture was allowed to warm slowly to 20 $^\circ\text{C}$ and was gently stirred at 35 $^\circ\text{C}$. The liquid phase was then periodically removed during 5 hours at 35 $^\circ\text{C}$ and replaced with distilled THF. After drying under reduced pressure and standing *in vacuo* in the presence of P_2O_5 , resin **3** (130 mg) was recovered. Enals **Z-7h** and **E-7h** (8.7 mg, 38% overall yield, **Z-7h/E-7h**=66/34) were isolated after concentration *in vacuo* of the combined filtrates obtained by the periodical washings of the resin (20 min, 1.4 mg, **Z-7h/E-7h**=75/25; + 55 min, 3.2 mg, **Z-7h/E-7h**=63/37; + 3h45, 4.1 mg, **Z-7h/E-7h**=65/35). No more release of aldehyde **7h** was noticed after stirring the remaining resin in THF (2 mL) at 35 $^\circ\text{C}$ for an additional 62 h.

Under the same conditions for the Michael addition and after warming of the resin from $-20\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$, enals **Z-7h** and **E-7h** (6.8 mg, 30% overall yield, **Z-7h/E-7h**=70/30) were isolated after concentration *in vacuo* of the combined filtrates obtained by periodical washings of the resin at $20\text{ }^{\circ}\text{C}$ for 136 h (67 h, 4.1 mg, **Z-7h/E-7h**=68/32; + 69 h, 2.7 mg, **Z-7h/E-7h**=74/26).

(Z)-3-(Diethoxymethyl)-4-nitrohex-2-enal (Z-7h). Pale brown oil. ^1H NMR (250 MHz, CDCl_3) δ 1.02 (t, $J=7.4$ Hz, 3H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 1.22 (t, $J=7.0$ Hz, OCH_2CH_3) and 1.23 (t, $J=7.0$ Hz, OCH_2CH_3)(6H), 1.97 (ddq, $J=14.6$, $J=5.6$, $J=7.4$ Hz, 1H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 2.24 (ddq, $J=14.6$, $J=9.2$, $J=7.4$ Hz, 1H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 3.40-3.91 (m, 4H, OCH_2CH_3), 5.29 (dd, $J=9.2$ Hz, $J=5.6$ Hz, 1H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 5.63 (s, 1H, $\text{CH}(\text{OEt})_2$), 6.30 (d, $J=6.8$ Hz, 1H, $\text{C}=\text{CH}$), 10.23 (d, $J=6.8$ Hz, 1H, CHO). ^{13}C NMR (62.9 MHz, CDCl_3) δ 10.7 ($\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 14.8 (OCH_2CH_3), 27.0 ($\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 63.0 (OCH_2CH_3), 85.3 ($\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 97.9 ($\text{CH}(\text{OEt})_2$), 130.6 ($\text{C}=\text{CH}$), 149.6 ($\text{C}=\text{CH}$), 190.5 (CHO). IR (neat): 2979, 2937, 2884, 1685, 1555, 1368, 1160, 1118, 1060. MS (ES^+) m/z (%): 545 (19) $[\text{2M}+\text{MeOH}+\text{Na}]^+$, 300 (100) $[\text{M}+\text{MeOH}+\text{Na}]^+$, 268 (20) $[\text{M}+\text{Na}]^+$. HRMS (ES^+): calcd mass for $\text{C}_{11}\text{H}_{19}\text{NO}_5\text{Na}$: 268.1161. Found: 268.1157.

(E)-3-(Diethoxymethyl)-4-nitrohex-2-enal E-7h. Attempted separation of the *E* isomer from the *Z* compound by silica gel column chromatography was not successful. The signals attributed to the **E-7h** compound were noted from a spectrum of *Z* and *E* isomers mixture. ^1H NMR (250 MHz, CDCl_3) δ 1.06 (t, $J=7.4$ Hz, 3H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 1.20-1.24 (m, 6H, OCH_2CH_3), 2.40-2.83 (m, 2H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 3.40-3.91 (m, 4H, OCH_2CH_3), 5.00 (s, 1H, $\text{CH}(\text{OEt})_2$), 5.54 (dd, $J=9.1$ Hz, $J=5.6$ Hz, 1H, $\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$), 6.50 (d, $J=6.6$ Hz, 1H, $\text{C}=\text{CH}$), 10.12 (d, $J=6.6$ Hz, 1H, CHO).

[[1-[4-(Benzyloxy)benzyl]-3-(diethoxymethyl)-3-[(4-methoxyphenyl)sulfanyl]-7-

oxabicyclo[2.2.1]hept-5-en-2-ylidene)methyl]oxy]trimethylsilane 9. To a suspension of a 60% dispersion of sodium hydride in mineral oil (7.1 mg, 0.18 mmol) in anhydrous THF (1 mL) under argon was added dropwise *para*-methoxybenzenethiol (22 μL , 0.18 mmol) at room temperature. The mixture was then stirred for 30 min at this temperature. After cooling at $-78\text{ }^{\circ}\text{C}$, a solution of adduct **4** (50 mg, 0.12 mmol) in THF (2 mL) was slowly added, followed by chlorotrimethylsilane (30 μL , 0.24 mmol). The reaction mixture was maintained for 2 h at $-78\text{ }^{\circ}\text{C}$ and was quenched with an ice-cold 0.1 M HCl aqueous solution (9 mL) and extracted with ice-cold pentane (12 mL). The separated organic layer was washed once with a cold aqueous saturated sodium bicarbonate solution and dried over sodium sulfate. Removal of the solvent under reduced pressure gave pure enough silyl enol ether **9** (68 mg, 93%) as a pale brown oil. ^1H NMR (400 MHz, C_6D_6) δ 0.16 (s, 9H, SiMe_3), 1.09 (t, $J=8.0$ Hz, 3H, OCH_2CH_3), 1.26 (t, $J=8.0$ Hz, 3H, OCH_2CH_3), 3.25-3.78 (m, 4H, OCH_2CH_3), 3.39 (s, 3H, OMe), 3.78 (d, $J=15.4$ Hz, 1H) and 4.09 (d, $J=15.4$ Hz, 1H) (AB syst., $\text{CH}_2\text{-C-1}$), 4.13 (s, 1H, $\text{CH}(\text{OEt})_2$), 4.83 (s, 2H, PhCH_2), 5.13 (d, $J=1.6$ Hz, 1H, H-4), 6.21 (dd, $J=5.8$ Hz, $J=1.6$ Hz, 1H, H-5), 6.33 (s, 1H, $\text{CH}(\text{OSiMe}_3)$), 6.50 (d, $J=5.8$ Hz, 1H, H-6), 6.81 (d, $J=9.0$ Hz, 2H, H_{Ar}), 7.08 (d, $J=8.8$ Hz, 2H, H_{Ar}), 7.20-7.39 (m, 5H, Ph), 7.70 (d, $J=8.8$ Hz, 2H, H_{Ar}), 7.93 (d, $J=9.0$ Hz, 2H, H_{Ar}). ^{13}C NMR (50.3 MHz, C_6D_6) δ

-1.1 (SiMe₃), 15.1 (OCH₂CH₃), 36.3 (CH₂-C-1), 54.2 (OMe), 64.0 (OCH₂CH₃), 65.9 (OCH₂CH₃), 66.4 (C-3), 69.5 (PhCH₂), 84.2 (C-4), 91.6 (C-1), 108.5 (CH(OEt)₂), 113.0 (CH_{Ar}), 114.2 (CH_{Ar}), 121.0 (C_{Ar}), 125.1 (C-2), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 130.5 (C_{Ar}), 131.4 (CH_{Ar}), 132.1 (CH_{Ph}), 133.4 (C-5), 136.6 (CH(OSiMe₃)), 137.5 (C_{Ph}), 138.9 (C-6), 140.4 (CH_{Ar}), 157.5 (C_{Ar}), 160.0 (C_{Ar}). MS (ES⁺) *m/z* (%): 671 (23) [M+K]⁺, 655 (100) [M+Na]⁺. HRMS (ES⁺): calcd mass for C₃₆H₄₄O₆SSiNa: 655.2526. Found: 655.2519.

1,1-Diethoxy-5-nitrohept-2-yn-4-ol 11. To a solution of 1-nitropropane (78.5 mg, 0.88 mmol) in THF (1 mL) maintained at 0 °C under argon was added a 40% methanolic solution of benzyltrimethylammonium hydroxide (Triton[®] B, 39 μL, 0.089 mmol). After stirring at 0 °C for 10 min, 4,4-diethoxybut-2-ynal **4** (47 μL, 0.295 mmol) was introduced and the reaction mixture was maintained at 0 °C for 5 hours. After addition of an aqueous saturated ammonium chloride solution, the aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with water, dried over sodium sulfate and concentrated under vacuum. Purification by silica gel column chromatography furnished the major diastereomer **11**_{maj} (33.9 mg, 47%), the minor diastereomer **11**_{min} (14.5 mg, 20%) and a 50/50 mixture of the two isomers (15.7 mg, 22%).

Major diastereomer isomer 11_{maj}. Pale yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 1.01 (t, *J*=7.4 Hz, 3H, CH(NO₂)CH₂CH₃), 1.25 (t, *J*=7.1 Hz, 6H, OCH₂CH₃), 1.97-2.10 (m, 2H, CH(NO₂)CH₂CH₃), 2.64 (d, *J*=7.1 Hz, 1H, OH), 3.52-3.65 (m, 2H, OCH₂CH₃), 3.65-3.79 (m, 2H, OCH₂CH₃), 4.54 (ddd, *J*=8.0 Hz, *J*=7.9 Hz, *J*=6.4 Hz, 1H, CH(NO₂)CH₂CH₃), 4.83 (ddd, *J*=8.0 Hz, *J*=7.1 Hz, *J*=1.2 Hz, 1H, CH(OH)), 5.30 (d, *J*=1.2 Hz, 1H, CH(OEt)₂). ¹³C NMR (62.9 MHz, CDCl₃) δ 9.9 (CH(NO₂)CH₂CH₃), 14.9 (OCH₂CH₃), 23.9 (CH(NO₂)CH₂CH₃), 61.2 (OCH₂CH₃), 63.1 (CHOH), 80.9 (C≡), 83.3 (C≡), 90.9 (CH(NO₂)CH₂CH₃), 93.1 (CH(OEt)₂). IR (neat): 3412, 2978, 2931, 1559, 1459, 1372, 1330, 1151, 1051, 807. MS (CI/NH₃) *m/z* (%): 263 (100) [M+NH₄]⁺, 217 (6), 200 (5), 188 (8), 174 (26), 171 (8).

Minor diastereomer isomer 11_{min}. Pale yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 1.05 (t, *J*=7.4 Hz, 3H, CH(NO₂)CH₂CH₃), 1.24 (t, *J*=7.1 Hz, 6H, OCH₂CH₃), 1.94-2.28 (m, 2H, CH(NO₂)CH₂CH₃), 2.94 (bs, 1H, OH), 3.51-3.65 (m, 2H, OCH₂CH₃), 3.65-3.79 (m, 2H, OCH₂CH₃), 4.53 (ddd, *J*=9.6 Hz, *J*=4.8 Hz, *J*=4.7 Hz, 1H, CH(NO₂)CH₂CH₃), 4.85 (bd, *J*=4.7 Hz, 1H, CH(OH)), 5.29 (d, *J*=1.0 Hz, 1H, CH(OEt)₂). ¹³C NMR (62.9 MHz, CDCl₃) δ 10.4 (CH(NO₂)CH₂CH₃), 15.0 (OCH₂CH₃), 22.4 (CH(NO₂)CH₂CH₃), 61.1 (OCH₂CH₃), 63.0 (CHOH), 80.5 (C≡), 83.2 (C≡), 91.0 (CH(NO₂)CH₂CH₃), 91.9 (CH(OEt)₂). IR (neat): 3407, 2978, 2932, 1555, 1459, 1372, 1330, 1150, 1052, 809. MS (CI/NH₃) *m/z* (%): 263 (100) [M+NH₄]⁺, 217 (21), 200 (12), 188 (24), 174 (19), 171 (46).

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