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Improved Synthesis of Prostanoids on a Non-Cross-Linked Polystyrene Soluble Support

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Abstract—Prostaglandins are potent natural products which are involved in many biological processes. Here we report an improved synthesis of prostanoids by a three-component coupling approach using a soluble-polymer supported technique. Access to prostanoids should be valuable in drug discovery programs. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Prostaglandins constitute one of the most physiologically potent families of non-protein molecules found in mammals. These natural products which are of low molecular weight and delicate structure play an important role in the processes of inflammation, tissue repair and in the immunoresponse.[1] Because of their enormous potential with regards to therapeutic benefits, extensive efforts have been made to design and synthesize pharmacologically active analogues.[2] Recently, we reported a soluble-polymer technology using non-cross-linked polystyrene (NCPS) for the preparation of a prostanoid library[3–5] and identified active compounds for the inhibition of cytomegalovirus (CMV),[6] a virus of the herpes family. From this prostanoid library, compound **1** (Fig. 1) showed potent antiviral activity.

CMV infections are a major cause of morbidity and mortality among immunocompromised patients. This is especially true with recipients of bone marrow, solid-organ transplants and patients with AIDS.[7–9] Antiviral agents currently licensed for the treatment of CMV infections include ganciclovir,[10] foscarnet[11] and cidofovir.[12] However, these drugs can produce some undesirable side effects and have limited oral bioavailability. Furthermore, viral strains resistant to each of them are emerging[13] and consequently there is the need for a more selective and potent drug to treat CMV infections. Herein we describe the preparation of a new library, where diversity is focused on the ω-side chain, with the aim of discovering more potent analogues.

Results and Discussion

During the course of our efforts in identifying new prostanoid analogues based on the lead compound **1**, we first focused on solution phase[14] synthesis via a three-component coupling approach starting from 4-(*R*)-(+)-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-one **2**[15] (Schemes 1 and 2). Solution phase synthesis appeared to be the most direct and convenient way to quickly synthesize analogues to be tested.

We decided to prepare two different classes of second-generation compounds. Prostanoids **9a**, **9b** and **9d**, which contained different ω-side chains and the same α-side chain as **1**, belonged to the first class. The second class of prostanoids contained derivatives **10c** and **10d** that possessed a triple bond instead of the typical prostanoid double bond in the α-side chain. Compound **10c** had the same alkenyl residue in the ω-side chain found in lead compound **1**, while **10d** had a *tert*-butyl group in the same position.

We applied the Schwartz reagent $[Cp_2Zr(H)Cl]$[16] to our synthesis since hydrozirconation of terminal alkynes is

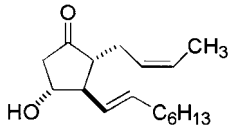

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Figure 1.

Keywords: silyl enol ethers; prostanoids; soluble polymer-supported reactions; cytomegalovirus.

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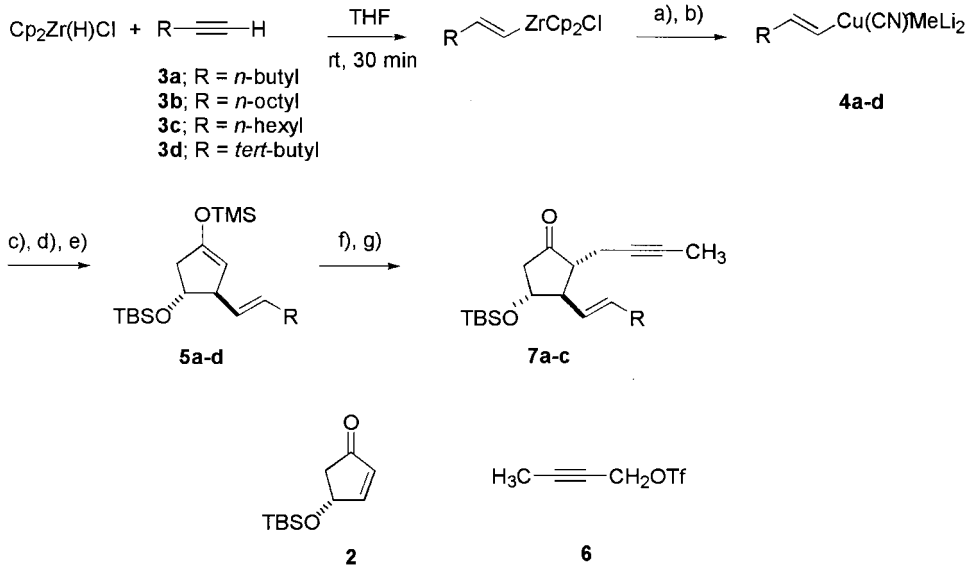


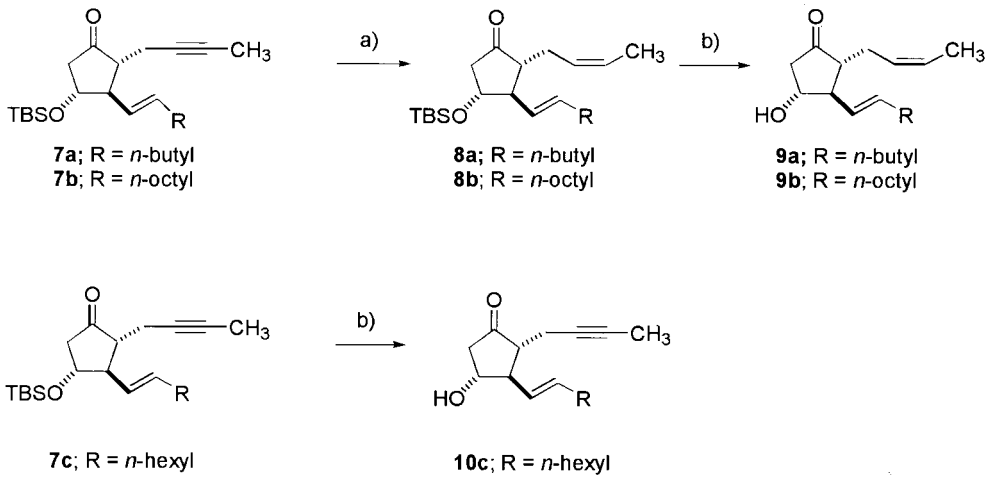
Scheme 1. (a) −50°C, 4 equiv. MeLi, 15 min; (b) −50°C, 2 equiv. CuCN, 15 min, 2 equiv. MeLi, 15 min; (c) **2** in THF, 30 min; (d) 5 equiv. TMSCl, 15 min; (e) 10 equiv. Et_3N, 0°C; (f) 1.5 equiv. MeLi, −25°C, 15 min, then −70°C; (g) 1.7 equiv. of in situ prepared **6**, −70°C, 5 min, −25°C, 10 min.

known to afford excellent stereochemical and regiochemical control for *E*-isomer formation. The required organocyanocuprates **4a–d** could be generated in situ from 1-alkynes **3a–d** via the corresponding vinylzirconocene followed by transmetallation. Afterwards, 1,4-addition of the cyanocuprate to **2** gave the copper enolate intermediate which was directly converted to the corresponding TMS enolates **5a–d**. These could not be purified by silica gel chromatography due to their known instability under these conditions.

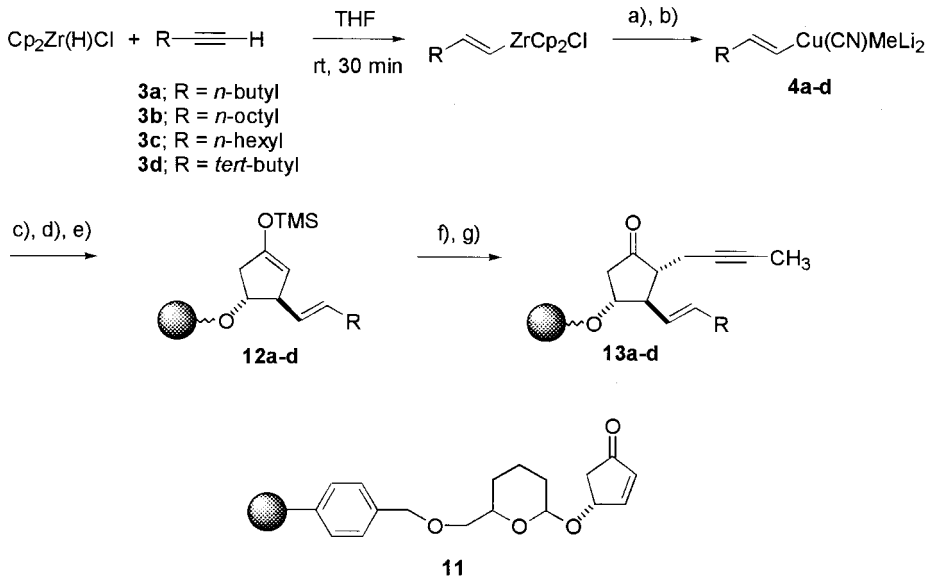
The α chain insertion was accomplished on crude mixtures of silyl enol ethers which also contained side products arising from decomposition of the organocuprate. Derivatives **7a**, **7b** and **7c** were obtained from lithium enolates generated by treatment of the corresponding silyl enol ethers with methyllithium and subsequent trapping by the in situ generated triflate **6**. This step led to the formation of a significant amount of unalkylated ketone besides the desired α-alkylated products. Several attempts to separate these mixtures by chromatography were made, but all were unsuccessful. The ratio of the unalkylated ketone to the α-alkylated ketone was roughly 1:1 in all cases and could be estimated by ^{1}H NMR spectroscopy.

Partial hydrogenation of the triple bond to afford the *Z*-alkene was accomplished using 5% Pd/$BaSO_4$ catalyst on the mixtures of unalkylated and α-alkylated products **7a** and **7b** and yielded derivatives **8a** and **8b** which could now be separated from the corresponding unalkylated ketones by silica gel chromatography. Hydrogenation of **7c** was not carried out as it would produce the previously synthesized lead compound **1**. Finally, cleavage of the TBS ether of **8a**, **8b** and **7c** was obtained in 8.5 h at room temperature by using a 30% HF-pyridine complex leading to final prostanoids **9a**, **9b** and **10c**. In all cases, only a single diastereoisomer was detected by proton NMR spectroscopy. The *trans* orientation of the three contiguous stereocenters was assigned by analogy to prostanoids previously synthesized by the same synthetic strategy in our laboratories.[4]

Surprisingly, prostanoids **9d** and **10d** arising from *tert*-butyl



Scheme 2. (a) H_2, 5% Pd/$BaSO_4$, quinoline, benzene:cyclohexane, 1:1, 45°C, 7.5 h; (b) 30% HF–py complex, rt, 8.5 h.

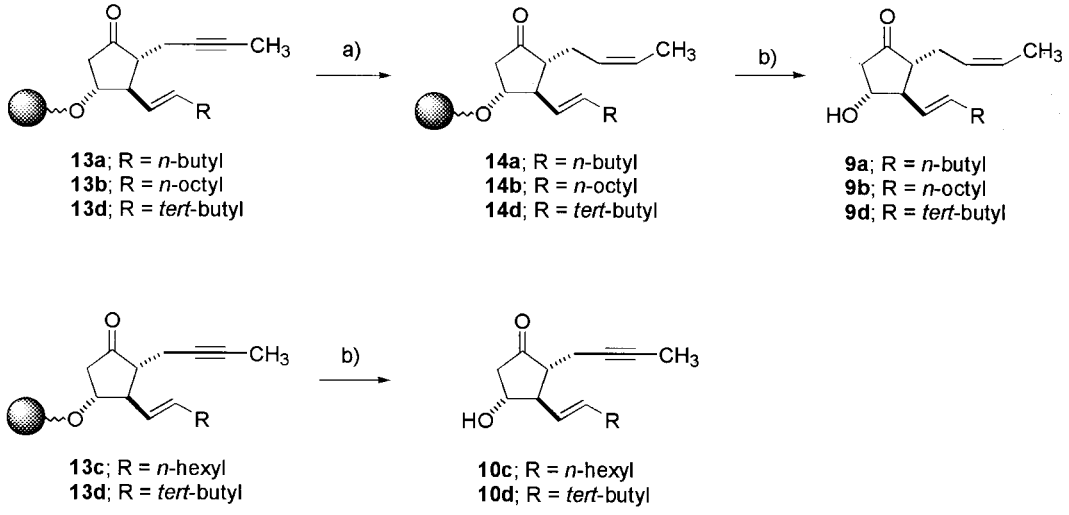


Scheme 3. (a) −50°C, 10 equiv. MeLi, 15 min; (b) −50°C, 5 equiv. CuCN, 15 min, 5 equiv. MeLi, 15 min; (c) **11** in THF, 40 min; (d) 25 equiv. TMSCl, 50 min; (e) 50 equiv. Et_3N, 0°C; (f) 4.5 equiv. MeLi, −25°C, 1 h, then −70°C; (g) 20 equiv. of in situ prepared **6**, −70°C, 10 min, −25°C, 50 min.

acetylene could not be obtained by the classical solution-phase method. Only a trace of intermediate **5d** was detected by ^{1}H NMR spectroscopy and all alkylation attempts using triflate **6** failed. We previously experienced a case in which a prostanoid could be obtained only by our soluble-polymer technique while its synthesis in solution was unsuccessful.[5] Therefore, we decided to attempt the preparation of derivatives **9d** and **10d** through our soluble-polymer technology.

In the polymer-supported approach, NCPS-bound (*R*)-(+)-4-hydroxy-2-cyclopenten-1-one **11** was prepared as previously described.[3] The remarkable solubility properties of this polymer make it amenable to organic synthesis. NCPS is soluble in THF, dichloromethane, chloroform and ethyl acetate even at the low temperatures required during prostanoid synthesis, but insoluble in water and methanol. These features allow for the implementation of solvent extraction techniques used in traditional organic synthesis in conjunction with the polymer crystallization techniques currently used in the polyethyleneglycol (PEG) liquid-phase approach.[17] Finally, because NCPS is a soluble polymer, NMR analysis of all intermediates can be accomplished in a nondestructive manner without the need for any specialized NMR techniques often used in solid-phase synthesis.[18]

The organocyanocuprate **4d**, prepared via hydrozirconation of terminal alkyne **3d** followed by transmetallation, was used in the 1,4-Michael type addition to the polymer supported chiral enone **11**. This reaction was slower compared to its solution phase counterpart and a 5 fold excess of the cuprate was required. Trapping of the enolate was accomplished by adding 25 equiv. of chloromethylsilane and 50 equiv. of triethylamine. In contrast to the solution phase approach, polymer-bound trimethylsilyl enol ether **12d** was easily purified by precipitation of the crude



Scheme 4. (a) H_2, 5% Pd/$BaSO_4$, quinoline, benzene:cyclohexane, 1:1, 45°C, 48 h; (b) 48% aqueous HF, THF, 45°C, 6 h.

Table 1. Comparison between yields of prostanoids obtained by the solution phase approach and by the soluble polymer-supported technology

Prostanoid	Yield (%)[a]	Yield (%)[b]
9a	5	21
9b	9	32
10c	8	31
9d	–	19
10d	–	24

[a] Yields of products obtained by the solution phase approach.
[b] Yields of products obtained by the soluble supported technology.

reaction mixture from cold methanol followed by several washings with cold methanol to remove the large excess of reagents and organometallic side products. In this way, polymer-supported trimethylsilyl enol ether **12d** was obtained in high purity. This product was stable and could be stored for several months for later elaboration if desired.

The lithium enolate of **12d** was generated by treatment with MeLi and the highly reactive in situ generated triflate **6** was then added to afford, after precipitation and washing with cold methanol, polymer-bound derivative **13d**. Compound **14d** was subsequently obtained by hydrogenation of the triple bond to the *Z*-alkene by using 5% $Pd/BaSO_4$ as catalyst. This reaction required 48 h at 45°C to be complete and gave, after filtration of the catalyst and precipitation from cold methanol, **14d**. The ^1H NMR spectrum of this compound showed the expected four olefinic protons whereas precursor **13d** exhibited only two olefinic signals in the same region of the spectrum. Efficient liberation of prostanoid **9d** from the support was accomplished by heating **14d** at 45°C for 6 h in a 48% aqueous HF–THF solution. The polymeric material was removed by precipitation from cold methanol and the crude product was purified by chromatography to yield **9d** in 19% overall yield for the four chemical steps starting from polymer-supported enone **11**. The synthesis of **10d** was similarly accomplished in 24% overall yield from **11**.

To demonstrate the superiority and the generality of our polymer-supported technology over the classical solution phase approach, prostanoids **9a**, **9b** and **10c** were resynthesized on the polymer. In all cases, the final prostanoids were obtained with excellent reproducibility and in higher yields and purities. Significantly, the polymer mass balance for each step in the synthesis was ≥93% and only a single polymer-bound species was detected by NMR in each case (Schemes 3 and 4) (Table 1).

The success in the preparation of **9d** and **10d** as well as the improved yields of prostanoids **9a**, **9b** and **10c** on the polymer could result from linker and/or solvent-like microenvironment effects, although the sterically more demanding TBS protecting group of the alcohol in the solution phase approach might adversely effect the efficiency of the process. Another possible explanation might be the higher purity of all polymer-supported intermediates **12a–d** that were achieved. Notably, this seemed to be of great importance for the success of the α-alkylation step. In the solution-phase approach, the alkylation of derivatives **5a–d** with the in situ generated triflate **6** was accomplished with crude TMS–enolate mixtures that contained side products due to decomposition of the cuprate.[14] The instability of these intermediates on silica gel precluded any purification by column chromatography. We found that the alkylation was the most crucial step of the entire synthesis and that in the traditional solution approach the reaction in all aspects was extremely poor. When the synthesis was performed on the polymer, however, it was possible to obtain a clean polymer-bound product free of any organometallic by-products by simple precipitation from cold methanol followed by several washings with cold methanol.

Conclusions

Despite the different conditions used in our soluble-polymer approach, such as large excess of reagents and longer reaction times, we have shown that the three-component coupling strategy applied here provides novel prostanoids with yields not otherwise obtainable by the conventional solution phase method. Thus, the soluble-supported technology represents a valuable tool to access a variety of prostanoids and could find broad application in the synthesis of many new analogues and for the potential discovery of new drugs. Biological screening of the obtained prostanoids is currently in progress. Additionally, studies aimed at further improvement of the chemical yields and in the preparation of new interesting prostanoids are under investigation in our laboratories.

Experimental

General methods

^1H and ^{13}C spectra were recorded on Bruker AC 250, AMX 400 and DRX 500 spectrometers in $CDCl_3$ at 25°C. The assignments of signals were confirmed by 2D-NMR experiments. High resolution mass spectra were obtained on Micromass LCT by using atmospheric pressure chemical ionization orthogonal-acceleration time-of-flight MS. Unless otherwise noted, reagents were purchased from commercial suppliers and used without any further purification. Tetrahydrofuran (THF) was distilled under nitrogen atmosphere from sodium-benzophenone. Dichloromethane (DCM) was distilled under nitrogen atmosphere from calcium hydride. All reactions were carried out under an argon atmosphere in flame-dried glassware with dry reagents and solvents. Column chromatography was performed using Merck 60 230–400 Mesh silica gel. Methyllithium (MeLi) was purchased from Aldrich as a 1.4 M solution in ether.

General procedure for the synthesis of trimethylsilylenol ethers 5a–c

To a flame-dried 10 mL round bottom flask equipped with a stir bar and septum, was added $Cp_2Zr(H)Cl$ (135 mg, 0.49 mmol), followed by THF (0.7 mL) and 1-hexyne (56 μL, 0.47 mmol). The suspension was shielded from light by wrapping in aluminum foil and allowed to stir for 30 min, after which time the reaction was judged to be complete as evidenced by a clear, homogeneous solution.

This mixture was then cooled to −50°C, MeLi (0.68 mL, 0.94 mmol) was added, and the reaction mixture was stirred for 15 min. At the same time, to another 10 mL round bottom flask was added CuCN (42.2 mg, 0.47 mmol) and the temperature brought to −50°C. The solution containing the methyl vinyl zirconocene was transferred via cannula into the flask containing the copper cyanide and the resulting mixture was stirred for 15 min. After this time, MeLi (0.34 mL, 0.48 mmol) was added dropwise and the mixture was allowed to stir for 15 min before a solution of enone **2** (50 mg, 0.23 mmol) in THF (0.7 mL) was added dropwise over 2 min. After 30 min, chlorotrimethylsilane (128 mg, 1.18 mmol) was added dropwise, stirring was continued for 15 min, and triethylamine (238 mg, 2.35 mmol) was added. The mixture was allowed to warm to 0°C and was then poured into a solution of deionized water (12 mL) and hexanes (24 mL). The aqueous layer was extracted with hexanes (3×25 mL) and the combined organic solutions were dried over magnesium sulfate. Filtration and concentration gave a colorless oil which was taken into 25 mL of toluene and concentrated under high vacuum to give 190 mg of **5a** as a clear oil. In addition to the desired silyl enol ether **5a** this material contained side products due to decomposition of the cuprate. Compounds **5d** and **5c** were obtained in a similar manner from 1-decyne and 1-octyne, respectively.

5a. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (s, 6H, $SiMe_2$), 0.25 (s, 9H, $SiMe_3$), 0.9 (s, 12H, CH_3+CMe_3), 1.26–1.32 (m, 4H, 2×CH_2), 2.00 (m, 2H, CH_2), 2.26 (dd, ^1J=15.1 Hz, ^2J=5.5 Hz, 1H, CH(H)CO), 2.50 (dd, ^1J=15.4 Hz, ^2J=7.0 Hz, 1H, C(H)HCO), 3.04 (bs, 1H, CH), 4.00 (m, 1H, CHOTBS), 4.45 (bs, 1H, CH), 5.32 (dd, ^1J=15.1 Hz, ^2J=7.5 Hz, 1H, olefinic H), 5.44 (m, 1H, olefinic H).

5b. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (s, 6H, $SiMe_2$), 0.21 (s, 9H, $SiMe_3$), 0.88 (s, 12H, CH_3+CMe_3), 1.2–1.4 (m, 12H, 6×CH_2), 2.0 (m, 2H, CH_2), 2.2 (dd, 1H, ^1J=15.1 Hz, ^2J=5.7 Hz, 1H, CH(H)CO), 2.50 (dd, ^1J=15.8 Hz, ^2J=7.6 Hz, 1H, C(H)HCO), 3.01 (bs, 1H, CH), 4.00 (m, 1H, CHOTBS), 4.40 (bs, 1H, CH), 5.32 (dd, ^1J=15.3 Hz, ^2J=7.3 Hz, 1H, olefinic H), 5.45 (m, 1H, olefinic H).

5c. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 6H, $SiMe_2$), 0.21 (s, 9H, $SiMe_3$), 0.88 (s, 12H, CH_3+CMe_3), 1.2–1.4 (m, 8H, 4×CH_2), 1.9–2.0 (m, 2H, CH_2), 2.3 (dd, ^1J=15.4 Hz, ^2J=5.9 Hz, 1H, C(H)HCO), 2.5 (dd, ^1J=15.7 Hz, ^2J=7.3 Hz, 1H, CH(H)CO), 3.05 (bs, 1H, CH), 4.0 (m, 1H, CHOTBS), 4.45 (bs, 1H, CH), 5.34 (dd, ^1J=15.4 Hz, ^2J=7.7 Hz, 1H, olefinic H), 5.46 (m, 1H, olefinic CH).

General procedure for the synthesis of 7a–c

For reproducible results, it was crucial that the synthesis of propargyl triflate **6** (Reaction A) and the preparation of the lithium enolates of **5a–c** (Reaction B) were conducted simultaneously in separate dry apparatus.

Reaction A: A flame-dried 10-mL round bottom flask equipped with an efficient stir bar and septum was brought to −25°C. Trifluoromethanesulfonic anhydride (118 mg, 0.42 mmol) was added followed by the dropwise addition of a mixture of 2-butyn-1-ol (28 mg, 0.40 mmol) and di-*tert*-butylpyridine (80.8 mg, 0.42 mmol) in 0.3 mL of dichloromethane over 3 min. Stirring was continued for 5 min.

Reaction B: During this 5 min period, a 15 mL round bottom flask containing the silyl enol ether **5a** (190 mg, 0.23 mmol, based on a hypothetical 100% yield of **5a**) in 2 mL of THF was vacuum purged with argon and placed in a cooling bath at −25°C.

Reaction A: Hexanes (0.5 mL) was added dropwise to the mixture which was then placed in a −70°C bath and stirred vigorously for 10 min.

Reaction B: During this 10 min period, the solution was treated with MeLi (0.26 mL, 0.362 mmol) in one portion and stirring was continued for 15 min.

Reaction A: The thick, white suspension was filtered through a pad of anhydrous magnesium sulfate under argon into a pre-cooled pear-shaped 15 mL flask and the filtrate was rinsed with hexanes (0.1 mL). The filtrate was quickly concentrated at T<0°C, then cooled to −70°C and THF (0.5 mL) was added to the flask. The solution was purged with argon and kept at −70°C until needed.

Reaction B: The yellow anion solution was brought to −70°C and the contents of the flask from reaction A were rapidly added via cannula. After 5 min at −70°C and 10 min at −25°C the mixture was quenched with saturated aqueous ammonium chloride (0.5 mL). Upon warming to room temperature the mixture was poured into saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo to provide 40 mg of a pale yellow oil **7a** which also contained unalkylated ketone. Since attempts to separate these products by chromatography were unsuccessful, the mixture was used directly in the next step. Compounds **7b** and **7c** were obtained in similar manner from **5b** and **5c**, respectively.

General procedure for the synthesis of 8a–b

The mixture of crude oil **7a** (40 mg), benzene (3.6 mL), cyclohexane (3.6 mL), 5% palladium on barium sulfate (108 mg), and synthetic quinoline (108 mg) was stirred at room temperature for 3 h and at 40°C for 4.5 h under hydrogen (1 atm). The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography (diethyl ether:hexanes, 1:10) to give **8a** (6 mg, 7% from **2**) as a colorless oil. Compound **8b** was prepared in a similar manner from **7b**.

8a. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6H, $SiMe_2$), 0.87 (s, 12H, CH_3+CMe_3), 1.2–1.4 (m, 4H, 2×CH_2), 1.6 (d, ^3J=7.3 Hz, 3H, CH_3), 2.0–2.2 (m, 4H, CH+CH_2+CH), 2.3–2.4 (m, 3H, CH+CH_2), 2.6 (dd, ^1J=14.0 Hz, ^2J=7.0 Hz, 1H CH(H)CO), 4.0 (m, 1H, CHOTBS), 5.2–5.6 (m, 4H, olefinic H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6 ($SiMe_2$), 13.0 (CH_3), 15.4 (CH_3), 18.0 (CMe_3), 22.7 (CH_2), 24.4 (CH_2), 25.5 (CMe_3), 32.0 (CH_2), 32.5 (CH_2),

46.7 ($COCH_2$), 53.0 (CH), 54.0 (CH), 72.0 (CHOTBS), 126.2 (olefinic CH), 126.5 (olefinic CH), 129.9 (olefinic CH), 131.4 (olefinic CH), 214.7 (CO). ESMS; *m/z* (%); 373 [M+Na^+] (85), 389 [M+K^+] (80).

8b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H, $SiMe_2$), 0.89 (bs, 12H, CH_3+CMe_3), 1.2–1.4 (m, 4H, 2×CH_2), 1.58 (d, ^3J=7.6 Hz, 3H, CH_3), 2.0 (m, 4H, 2×CH_2), 2.2 (dd ^1J=16.7 Hz, ^2J=7.3 Hz, 1H C(H)HCO), 2.3–2.4 (m, 2H, 2×CH), 2.6 (dd, ^1J=16.7 Hz, ^2J=7.1 Hz, 1H CH(H)CO), 4.1 (m, 1H, CHOTBS), 5.2–5.3 (m, 2H, olefinic H), 5.4–5.6 (m, 2H, olefinic H).^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7 ($SiMe_2$), 12.9 (CH_3), 15.3 (CH_3), 18.0 (CMe_3), 22.7 (CH_2), 24.4 (CH_2), 25.7 (CCH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 32.7 (CH_2), 47.7 ($COCH_2$), 53.4 (CH), 54.3 (CH_2), 73.1 (CHOTBS), 126.0 (olefinic CH), 126.5 (olefinic CH), 129.7 (olefinic CH), 131.1 (olefinic CH), 215.7 (CO). ESMS; *m/z* (%); 429 [M+Na^+] (80), 445 [M+K^+] (75).

General procedure for the synthesis of 9a,b and 10c

To a solution of **8a** (6 mg, 0.017 mmol) in acetonitrile (1.8 mL) was added a 30% hydrogen fluoride-pyridine complex (150 μL) at 0°C. The mixture was stirred at room temperature and monitored by TLC (chloroform: methanol, 9:1) and after 4.5 h additional 30% hydrogen fluoride–pyridine complex (150 μL) was added. After 4 h, the reaction was complete and poured into saturated aqueous sodium hydrogen carbonate solution (7 mL). After extraction with chloroform (3×15 mL), the material was purified by silica gel chromatography (ethyl acetate: hexanes, 1:3) to give **9a** (3 mg, 5% from **2**) as a colorless oil. Compounds **9b** and **10c** were obtained in a similar manner from **8b** and **7c**, respectively.

9a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=6.7 Hz, 3H, CH_3), 1.25–1.36 (m, 4H, 2×CH_2), 1.59 (d, ^2J=5.3 Hz, 3H, CH_3), 2.1 (m, 3H, CH_2+CH), 2.2 (dd, ^1J=14.4 Hz, ^2J=7.6 Hz, 1H, CH(H)CO), 2.4 (m, 3H, CH_2+CH), 2.74 (dd, ^1J=11.4 Hz, ^2J=5.4 Hz, 1H, COC(H)H), 4.05 (m, 1H, C*H*OH), 5.3–5.35 (m, 2H, olefinic CH), 5.52 (dd, ^1J=10.6 Hz, ^2J=6.6 Hz, 1H, olefinic CH), 5.65 (dd, ^1J=13.6 Hz, ^2J=6.9 Hz, 1H, olefinic CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9 (CH_3), 13.9 (CH_3), 22.2 (CH_2), 24.2 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 46.2 ($COCH_2$), 53.8 (CH), 54.8 (CH), 72.2 (CHOH), 126.1 (olefinic CH), 126.2 (olefinic CH), 128.9 (olefinic CH), 135.4 (olefinic CH), 214.5 (CO). HR*APCI*MS calcd ([M+H]$^+$ 237.1854, found 237.1833: calcd ([M+H]$^+$−H_2O) 219.1749, found 219.1737.

9b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, ^2J=6.7 Hz, 3H, CH_3), 1.2–1.3 (m, 12H, 6×CH_2), 1.58 (d, ^2J=6.7 Hz, 3H, CH_3), 2.00–2.11 (m, 3H, CH+CH_2), 2.18 (dd, ^1J=18.5 Hz, ^2J=9.7 Hz, 1H, C(H)HCO), 2.35 (m, 3H, CH_2+CH), 2.75 (dd ^1J=18.2 Hz, ^2J=7.3 Hz, 1H, CH(H)CO), 4.04 (m, 1H, C(H)OH), 5.3 (m, 2H, olefinic CH), 5.52 (m, 1H, olefinic CH), 5.67 (m, 1H, olefinic CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2 (CH_3), 14.3 (CH_3), 22.9 (CH_2), 24.5 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.1 (CH_2), 32.9 (CH_2), 46.5 ($COCH_2$), 54.1 (CH), 55.1 (CH), 72.5 (CHOH), 126.4 (olefinic CH), 126.5 (olefinic CH), 129.2, (olefinic CH) 135.7 (olefinic CH), 214.7 (CO). HR*APCI*MS calcd ([M+H]$^+$ 293.2480, found 293.2481: calcd ([M+H]$^+$−H_2O) 275.2375, found 275.2358.

10c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, ^2J=5.1 Hz, 3H, CH_3), 1.25 (m, 8H, 4×CH_2), 1.75 (t, ^2J=2.6 Hz, 3H CH_3), 2.1 (m, 4H, 2×CH_2), 2.2–2.3 (m, 2H, CH+C(H)HCO), 2.6 (m, 1H, CH), 2.76 (dd, ^1J=17.5 Hz, ^2J=7.5 Hz, 1H, CH(H)CO), 4.1 (m, 1H, C(H)OH), 5.34 (dd, ^1J=15.0 Hz, ^2J=7.5 Hz, 1H, olefinic CH), 5.75 (m, 1H, olefinic CH).^{13}C NMR (125 MHz, $CDCl_3$) δ 3.5 (CH_3), 14.1 (CH_3), 16.5 (CH_2) 22.6 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 32.7 (CH_2) 46.3 (CH_2CO), 53.0 (CH), 53.7 (CH), 72.2 (CHOH), 75.2 (C alkyne) 77.7 (C alkyne), 128.2 (olefinic CH), 135.9 (olefinic CH), 213.0 (CO). HR*APCI*MS calcd ([M+H]$^+$ 263.2011, found 263.2008: calcd ([M+H]$^+$−H_2O) 245.1905, found 245.1902.

General procedure for the synthesis of polymers 12a–d

To a flame-dried 10 mL round bottom flask equipped with a stir bar and septa was added Cp_2Zr(H)Cl (122 mg, 0.45 mmol) followed by THF (1.8 mL) and 1-hexyne (53 μl, 0.45 mmol). The suspension was shielded from light by wrapping in aluminum foil and allowed to stir for 30 min at room temperature. The clear, homogeneous solution was cooled to −50°C, treated with MeLi (0.64 mL, 0.90 mmol) and stirred at −50°C for 15 min. The mixture was transferred via cannula to a pre-cooled (−50°C) 25 mL round bottom flask containing CuCN (40 mg, 0.45 mmol) and stirred for 15 min at −50°C after which MeLi (0.32 mL, 0.45 mmol) was added. After 15 min, a solution of polymer **11** (300 mg, 0.09 mmol) in THF (3.6 mL) was added over a 20 min period and the resulting thick mixture was allowed to stir for 40 min at −50°C. Chloromethylsilane (245 mg, 2.25 mmol) was added dropwise to afford a clear solution and stirring was continued for 50 min before triethylamine (455 mg, 4.50 mmol) was added. The mixture was allowed to warm to 0°C and then poured into a 1:1 mixture of deionized water and ethyl acetate and filtered through a pad of Celite. The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic solutions were washed with brine, filtered through Celite, and dried over magnesium sulfate. Filtration and concentration gave a thick, colorless oil that was dissolved in a small amount of THF (2 mL). The polymer-bound product was precipitated from cold methanol (−30°C). The polymer was filtered, washed several times with cold methanol, and dried under high vacuum to give **12a** (340 mg, 98% polymer recovery) as white powder. Compounds **12b**, **12c** and **12d** were obtained in a similar manner from 1-decyne, 1-octyne and *tert*-butylacetylene, respectively.

12a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H, $SiMe_3$), 0.88 (m, 3H, CH_3), 1.0–2.2 (broad signal due to the polymer resonance), 2.64 (m, 1H, CH(H)CO), 4.48 (m, 2H, ArCH_2O), 4.54 (bs, 1H, CH), 4.91 (m, 1H, OCHO), 5.4–5.5 (m, 2H, olefinic H), 6.2–7.3 (broad signal due to the polymer resonance). Each polymer supported compound showed the same resonances in the same spectroscopic regions.

12b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9H, $SiMe_3$), 0.89 (m, 3H, CH_3), 2.7 (m, 1H, CH(H)CO), 4.46 (m, 2H, $ArCH_2O$), 4.53 (bs, 1H, CH), 4.91 (m, 1H, OCHO), 5.4–5.5 (m, 2H, olefinic H).

12c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H, $SiMe_3$), 0.88 (m, 3H, CH_3), 2.68 (m, 1H, CH(H)CO), 4.47 (m, 2H, $ArCH_2O$), 4.53 (bs, 1H, CH), 4.92 (m, 1H, OCHO), 5.4–5.7 (m, 2H, olefinic H).

12d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H $SiMe_3$), 0.98 (m, 9H, 3×CH_3), 2.69 (m, 1H, CH(H)CO), 4.46 (m, 2H, $ArCH_2O$), 4.55 (bs, 1H, CH), 4.92 (m, 1H, OCHO), 5.3–5.4 (m, 1H, olefinic H), 5.48–5.54 (d, ^3J=13.2 Hz, 1H, olefinic H).

General procedure for the synthesis of polymers 13a–d

For reproducible results, it was crucial that the synthesis of propargyl triflate **6** (Reaction A) and the preparation of the lithium enolates of polymers **12a–d** (Reaction B) were conducted simultaneously in separate dry apparatus.

Reaction A: A flame-dried 25 mL round bottom flask equipped with an efficient stir bar and septum was brought to −25°C. Trifluoromethanesulfonic anhydride (633 mg, 2.24 mmol) was added followed by the dropwise addition of a mixture of 2-butyn-1-ol (143 mg, 2.04 mmol) and 2,6-di-*tert*-butylpyridine (468 mg, 2.45 mmol) in 1.5 mL of dichloromethane over 3 min. Stirring was continued for 10 min.

Reaction B: A flame-dried 25 mL round bottom flask containing a solution of polymer **12a** (340 mg, 0.102 mmol) in of THF (8 mL) was cooled to −25°C and treated with MeLi (0.33 mL, 0.46 mmol) in one portion. Stirring was continued at −25°C for 1 h.

Reaction A: Hexanes (5 mL) was added dropwise to the mixture that was then cooled to −70°C and stirred vigorously for 10 min. The thick, white suspension was filtered through a pad of anhydrous magnesium sulfate under argon into a pre-cooled (−70°C) pear-shaped 25 mL flask and the filtrate was rinsed with hexanes (1 mL). The filtrate was quickly concentrated at $T<0$°C, then cooled to −70°C, and THF (1 mL) was added to the flask. The solution was purged with argon and kept at −70°C until it was needed.

Reaction B: The yellow anion solution was brought to −70°C and the freshly prepared triflate **6** was added via cannula. The resulting solution was stirred for 10 min at −70°C, for 50 min at −25°C, quenched with saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The mixture was then poured into saturated aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic solutions were washed with brine, filtered through Celite, dried over magnesium sulfate and concentrated. The polymer-supported product **13a** (313 mg, 93% polymer recovery) was obtained as a white powder using the standard precipitation procedure described above. Polymers **13b–d** were obtained in a similar manner from **12a–d**, respectively.

13a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 3H, CH_3), 2.63 (m, 1H, CH(H)CO), 4.46 (m, 2H, $ArCH_2O$), 4.91 (m, 1H, OCHO), 5.3–5.4 (m, 1H, olefinic H), 5.5–5.6 (m, 1H, olefinic H).

13b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (m, 3H, CH_3), 2.7 (m, 1H, CH(H)CO), 4.45 (m, 2H, $ArCH_2O$), 4.92 (m, 1H, OCHO), 5.3–5.7 (m, 2H, olefinic H).

13c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H, CH_3), 2.62 (m, 1H, CH(H)CO), 4.46 (m, 2H, $ArCH_2O$), 4.91 (m, 1H, OCHO), 5.3–5.4 (m, 1H, olefinic H), 5.6–5.7 (m, 1H, olefinic H).

13d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (m, 9H, 3×CH_3), 2.56 (m, 1H, CH(H)CO), 4.45 (m, 2H, $ArCH_2O$), 4.92 (m, 1H, OCHO), 5.2–5.3 (m, 1H, olefinic H), 5.7–5.8 (d, ^3J=16 Hz, 1H, olefinic H).

General procedure for the synthesis of polymers 14a,b and 14d

Polymer **13a** (150 mg, 0.04 mmol) was dissolved in benzene (1.5 mL) and cyclohexane (1.5 mL). Synthetic quinoline (30 mg) and 5% palladium on barium sulfate (30 mg) were added and the mixture was stirred under hydrogen (1 atm) at 45°C for 48 h. The mixture was filtered through a pad of Celite and concentrated. Polymer **14a** (150 mg, 99.6% polymer recovery) was obtained as a white powder using the standard precipitation procedure described above. Polymers **14b** and **14d** were obtained in a similar manner from **13b** and **13d**, respectively.

14a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 3H, CH_3), 2.62 (m, 1H, CH(H)CO), 4.46 (m, 2H, $ArCH_2O$), 4.91 (m, 1H, OCHO), 5.3–5.5 (m, 4H, olefinic H).

14b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (m, 3H, CH_3), 2.62 (m, 1H, CH(H)CO), 4.43 (m, 2H, $ArCH_2O$), 4.91 (m, 1H, OCHO), 5.3–5.6 (m, 4H, olefinic H).

14d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (m, 9H, 3×CH_3), 2.6 (m, 1H, CH(H)CO), 4.49 (m, 2H, $ArCH_2O$), 4.91 (m, 1H, OCHO), 5.3–5.7 (m, 4H, olefinic H).

General procedure for the synthesis of 9a, b, d and 10c, d

A solution of polymer **14a** (150 mg, 0.04 mmol) in THF (1.6 mL) was treated with 48% aqueous hydrofluoric acid (0.2 mL), stirred at 45°C for 6 h, and then neutralized with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate and the organic solution was washed with saturated sodium bicarbonate solution, brine, dried over magnesium sulfate and then concentrated. To the residue was added a small amount of THF and methanol (10 mL).The mixture was cooled to −30°C with vigorous stirring to precipitate the polymer. The polymer was removed by filtration and the filtrate was concentrated to give a crude oil (15 mg) which was then purified by silica gel chromatography (hexanes:ethyl acetate, 3:1) to afford **9a** (2.5 mg, 24% from **14a**, 21% from **11**). The spectroscopic data of **9a** as well as those of **9b** and **10c** were

identical to those previously reported for the solution phase approach.

9d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H, 3×CH_3), 1.58 (d, J=6.75 Hz, 3H, CH_3), 2.1 (m, 1H, COCH), 2.20 (dd, ^1J=18.5 Hz, ^2J=9.7 Hz, 1H, CH(H)CO), 2.3 (m, 3H, CH_2+CH), 2.75 (dd, ^1J=11.5 Hz, ^2J=7.3 Hz, 1H, C(H)HCO), 4.04 (m, 1H, C(H)OH), 5.25 (m, 2H, olefinic CH), 5.55 (m, 1H, olefinic CH), 5.7 (d, J=15.6 Hz, olefin CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9 (CH_3), 24.6 (CH_2), 29.6–29.7 (3×*C*H_3), 33.2 (CMe_3),46.2 (CH_2CO), 53.9 (CH), 54.9 (CH), 72.3 (CHOH), 123.6 (olefinic CH), 126.1 (olefinic CH), 126.3 (olefinic CH), 146.5 (olefinic CH), 214.4 (CO). HR*APCI*MS calcd ($[M+H]^+$ 237.1854, found 237.1844: calcd ($[M+H]^+-H_2O$) 219.1749, found 219.1752.

10d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9H, 3×CH_3), 1.75 (t, ^2J=2.35 Hz, 3H, CH_3), 2.1 (m, 1H, CH), 2.20–2.32 (m, 3H, CH+CH_2), 2.65 (m, 1H, CH), 2.78 (dd, ^1J= 18.5 Hz, ^2J=7.3 Hz, 1H, CH(H)CO), 4.01 (m, 1H, CHOH), 5.25 (dd, ^1J=15.6 Hz, ^2J=8.5 Hz, 1H, olefinic CH), 5.78 (d, J=15.6 Hz, 1H, olefinic CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.9 (CH_3), 17.1 (CH_2), 29.4–29.8 (CMe_3), 33.6 (CMe_3), 46.7 (CH_2CO), 53.6 (CH), 54.2 (CH), 72.6 (CHOH), 75.3 (alkyne C), 77.9 (alkyne C), 123.4 (olefinic CH), 147.1 (olefinic CH), 213.5 (CO). HR*APCI*MS calcd ($[M+H]^+$ 235.1698, found 235.1691: calcd ($[M+H]^+-H_2O$) 217.1592, found 217.1617.

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