Solution- and Soluble-Polymer Supported Asymmetric Syntheses of Six-Membered Ring Prostanoids

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Abstract: An asymmetric synthesis of prostanoids containing a six-membered ring core structure (11a-homoprostaglandins), both in solution and using non-cross-linked polystyrene (NCPS) as a soluble support, was developed. Target molecule **1** was generated in a convergent fashion using a three-component coupling strategy, wherein chiral enone (*R*)-**2** was the precursor of the central ring and the cuprate **3** and triflate **4** were used to introduce the side chains. The chiral center of (*R*)-**2** directed the facial selectivity of the conjugate addition reaction which then dictated the stereochemical outcome of the subsequent α alkylation. Attachment of a six-membered ring scaffold to NCPS facilitated purification without compromising synthetic yields, still allowed ^{1}H-NMR analysis of the intermediates in the synthesis, and provided an avenue for the construction of six-membered ring prostanoid libraries.

Keywords: asymmetric synthesis · cuprates · polymers · prostanoids · six-membered rings

Introduction

Prostaglandins (PGs) are naturally occurring substances biosynthesized in mammals from C_{20} polyunsaturated fatty acids. Since the isolation and characterization of PGs over sixty years ago,[1] extensive synthetic efforts have resulted given their challenging architectures and potent biological activities.[2] However, the therapeutic utility of natural PGs has been impeded principally because of chemical instability, rapid in vivo metabolism and unavoidable side effects.[3] In order to overcome these problems, access to prostaglandin analogues (prostanoids) with improved pharmacological profiles are desirable and remain a focal point in organic and medicinal chemistry.

In the past five years, combinatorial chemistry has proven to be useful for the synthesis of libraries of organic compounds.[4] Significantly, the combinatorial strategy has been largely directed at the drug-discovery process.[5] In the construction of small, organic-molecule libraries, established chemical reactions have been adapted from solution to the solid-phase,[6] liquid-phase[7] or fluorous-phase techniques.[8] The use of soluble polymers in liquid-phase organic synthesis (LPOS) has been particularly advantageous.[7] LPOS has combined the benefits of traditional homogeneous solution-phase synthesis with the ease of purification afforded by solid-phase methods.

Natural PGs and prostanoids were synthesized on soluble- and solid-polymer supports in our laboratory and by other workers that provided a foundation for the preparation of prostanoid libraries.[9] Since molecular diversity is an important objective in the synthesis of all chemical libraries, we reasoned that switching the cyclopentyl core of the PGs to a cyclohexyl ring in prostanoids (11a-homoprostaglandins) would be another avenue toward prostanoid diversity. Surprisingly, only a few examples of the synthesis of six-membered ring prostanoids have appeared in the literature and these have been racemic in nature.[10, 11]

Recently, we screened a library of five-membered ring prostanoids and found a lead compound with antiviral activity against cytomegalovirus.[9d] This result has prompted us to continue development of various prostanoids and prostanoid libraries. The inclusion of a family of six-membered ring compounds would generate an entirely new subset of libraries for potential drug discovery. Herein, we report a methodology for the enantioselective synthesis of six-membered ring prostanoids as well as the adaptation of the solution procedure to LPOS using a soluble-polystyrene support.

Results and Discussion

Solution-phase synthesis: The instability of E-type PGs results from the facile β-elimination of the 11-hydroxyl group (prostaglandin numbering) catalyzed by either acid or base.[3]

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A six-membered ring analogue **1** of the PGE series in which the hydroxyl functionality is placed in a γ position relative to the carbonyl group would circumvent this problem (Figure 1).

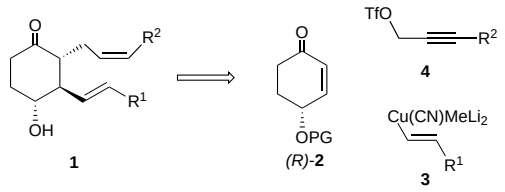
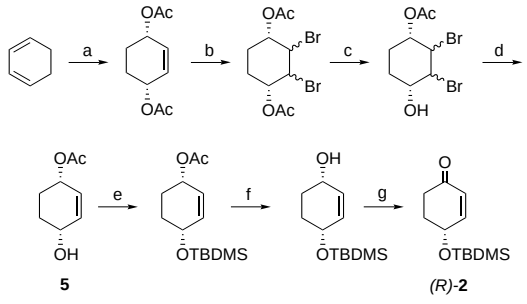


Figure 1. Retrosynthetic analysis for six-membered ring prostanoids.

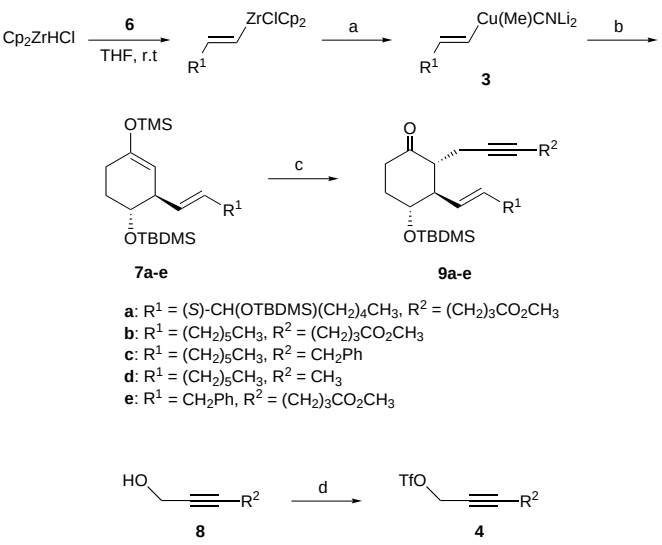
The structure **1** not only precludes a β-elimination decomposition pathway, but also incorporates four contiguous functionalized carbon centers with the same configurations as in the natural PG framework. In this way, biological activity might be retained together with having the benefit of enhanced in vivo stability.

Our synthetic approach to prostanoid **1** was based on three-component coupling methods used in PG synthesis.[12] To our knowledge, there has been no reported application of this methodology to the synthesis of six-membered ring prostanoids.[13] Hence, we first optimized the reaction conditions for solution-phase syntheses before attempting polymer-supported approaches. The strategy (Figure 1) was analogous to that previously employed in our laboratory for the synthesis of PGs[9a,b] and prostanoids.[9d] Consequently, compound (*R*)-**2** was obtained from 1,3-cyclohexadiene in seven steps in 19% overall yield and 98% enantiomeric excess (^{1}H and ^{19}F NMR of the Mosher ester derivative) according to published procedures (Scheme 1).[14] This route was chosen because both enantiomers of the target compound could be obtained from a common intermediate.[15]



Scheme 1. a) $Pd(OAc)_2$, $LiOAc_2 \cdot H_2O$, MnO_2, *p*-benzoquinone, LiCl (cat.), AcOH/pentane. b) Br_2, CS_2. c) *Candida rugosa* lipase. d) Zn, EtOH. e) TBDMSCl, imidazole, CH_2Cl_2. f) LiOH, $MeOH/H_2O$. g) Dess–Martin periodinane, CH_2Cl_2.

In our retrosynthetic analysis of **1**, it was anticipated that the presence of the chiral center at C-4 in (*R*)-**2** would direct the stepwise addition of the C-3 and C-2 side chains to generate the desired (2*R*,3*R*) configuration of the final product. The attachment of the C-3 moiety to the enone was achieved by 1,4-addition of cuprate **3** (Scheme 2), prepared in situ from terminal alkynes such as **6**.[16] The intermediate enolate was trapped as the silyl-enol ether **7** by quenching



Scheme 2. a) 1) MeLi, $-50\,^\circ$C, THF; 2) CuCN; 3) MeLi. b) 1) (*R*)-**2a**, $-78\,^\circ$C; 2) TMSCl, Et_3N. c) 1) MeLi, $-30\,^\circ$C, THF; 2) **4**. d) 1) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butylpyridine, $-30\,^\circ$C, CH_2Cl_2; 2) $-78\,^\circ$C, hexanes.

with chlorotrimethylsilane (Scheme 2). The compound **7** was not purified and used immediately after workup. Importantly, the ^{1}H NMR of crude **7** indicated the exclusive formation of one diastereomer. The coupling of the C-2 chain was then accomplished by treatment of **7** with MeLi in THF and reaction of the metallic enolate with triflate **4** generated in situ from the corresponding propargylic alcohol **8** (Scheme 2). Purification of the crude reaction mixture afforded the chiral cyclohexanone **9** containing various chains at both the C-2 and C-3 positions (Scheme 2, Table 1). In all cases, only one

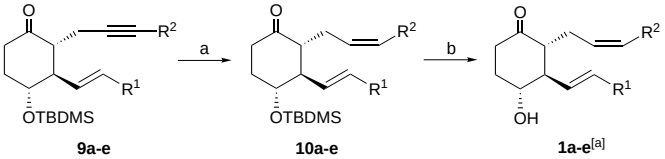
Table 1. Functionalized cyclohexanones **9** obtained by three-component-coupling.

Compound	R^1	R^2	% Yield[a]
9a	(*S*)-CH(OTBDMS)$(CH_2)_4CH_3$	$(CH_2)_3CO_2CH_3$	61
9b	$(CH_2)_5CH_3$	$(CH_2)_3CO_2CH_3$	56
9c	$(CH_2)_5CH_3$	CH_2Ph	53
9d	$(CH_2)_5CH_3$	CH_3	55
9e	CH_2Ph	$(CH_2)_3CO_2CH_3$	49

[a] Yield from cyclohexenone (*R*)-**2**.

diastereomer of **9** could be detected. The yields were comparable to those previously reported for cyclohex-2-enone ring systems.[10b, 17]

In order to obtain PGE-type prostanoids, the C-2 chain of **9** was further modified by reduction of the triple bond to the Z-alkene via hydrogenation in the presence of 5% $Pd/BaSO_4$. Silica gel chromatography afforded **10** in excellent yields (Scheme 3, Table 2). Notably, when $R^2 = CH_3$, extended



Scheme 3. a) H_2, Pd-$BaSO_4$, quinoline, 40 °C benzene/cyclohexane. b) HF/pyridine, CH_3CN. [a] In compound **1a** $R^1 = (S)$-CH(OH)$(CH_2)_4CH_3$.

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Table 2. Reduction products **10** and prostanoids **1** obtained by solution-phase synthesis.

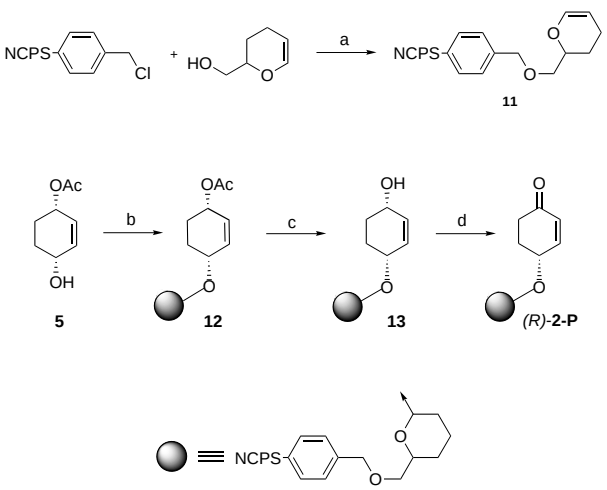
Entry	R^1	R^2	**10** (% yield)	**1** (% yield)
a	(*S*)-CH(OTBDMS)$(CH_2)_4CH_3$	$(CH_2)_3CO_2CH_3$	93	81[a]
b	$(CH_2)_5CH_3$	$(CH_2)_3CO_2CH_3$	89	79
c	$(CH_2)_5CH_3$	CH_2Ph	89	76
d	$(CH_2)_5CH_3$	CH_3	83	88
e	CH_2Ph	$(CH_2)_3CO_2CH_3$	86	85

[a] The alcohol function in the C-3 chain was also deprotected in this step.

reaction times resulted in over-reduction to the corresponding alkane. The final step of the synthesis was the deprotection of the alcohol group(s) (ring or ring and C-3 chain) (Scheme 3). In previous syntheses of PGE and PGE prostanoids, this was not trivial since mild deprotection conditions were required to avoid racemization at C-2 as well as β-elimination of the hydroxyl group. Here, no problems were encountered and the yields of various prostanoids having structure **1** were excellent (Table 2). In the case of **1a**, the alcohol on the C-3 chain was also deprotected in the last step to furnish the six-membered ring analogue of PGE_2 methyl ester. The configuration of **1a**, and by comparison the other prostanoids, was firmly established as (2*R*,3*R*) based on NMR experiments. First, DQF-COSY was used to assign the chemical shifts of all relevant hydrogens of the central six-membered ring of **1a**. Then, the all-axial relationship of H-2, H-3, and H-4 on the α, β, and γ carbons of the ring, respectively, was established using ROESY spectra (see Supporting Information).

Liquid-phase synthesis: We then investigated the adaptation of our solution-phase methodology to soluble-polymer supported substrates. Hence, the structures described above were synthesized using the soluble polymer as a "protecting group" for the C-4 alcohol moiety. Based on our previous experience, we chose non-cross-linked polystyrene (NCPS) as the polymer of choice.[9a, b] NCPS is soluble in THF at low temperatures ($-78\,^\circ C$), a primary requirement of the three-component coupling strategy, while insolubility of NCPS in water and cold MeOH provides a method for removal of inorganic salts and/or the polymer-bound product from excess reagents by precipitation and filtration.

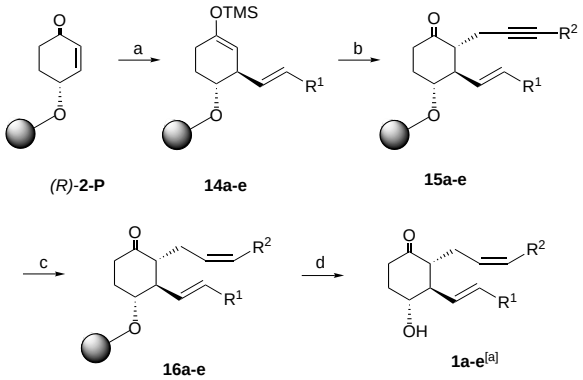
The polymer was synthesized by radical copolymerization of styrene and 4-chloromethylstyrene in a 33:1 molar ratio. The loading level of the polymer was found to be 0.3 mmol per g. Polymer loading was determined using the ^{1}H-NMR integral ratio of the chloromethylene signal to the aromatic and aliphatic signals. To initiate the synthesis, 6-hydroxymethyl-3,4-dihydro-2*H*-pyran was attached to the polymer that provided **11** (Scheme 4).[18] The compound **5**, obtained in the synthesis of (*R*)-**2** (Scheme 1), was used to introduce the six-membered ring scaffold onto polymer **11** (Scheme 4). This strategy was found to be more convenient than the alternative route of deprotection of (*R*)-**2** followed by attachment of the alcohol to **11**. Saponification of **12** was followed by oxidation of the alcohol to form polymer-bound enone (*R*)-**2-P**. The remainder of the polymer-supported synthesis of **1** proved straightforward through utilization of the optimized reaction conditions developed in the solution-phase experiments. In



Scheme 4. a) NaH, DMF. b) **11**, PPTS, CH_2Cl_2, 40 °C. c) LiOH, THF/MeOH/H_2O. d) Dess–Martin periodinane, CH_2Cl_2.

fact, the results were reproduced closely in most cases once an excess of the required reagent was employed together with some minor modifications in reaction conditions (see Experimental Section).

Enone (*R*)-**2-P** was treated with the corresponding cuprate **3** and quenched with chlorotrimethylsilane to afford silyl-enol ether **14** as the only polymer-bound compound as determined by ^{1}H-NMR spectroscopy (Scheme 5). While removal of the excess organometallic reagent proved to be problematic due



Scheme 5. a) 1) **3**, $-78\,^\circ C$, THF; 2) TMSCl, Et_3N. b) 1) MeLi, $-30\,^\circ C$, THF; 2) **4**. c) H_2, Pd/$BaSO_4$, quinoline, 40 °C benzene/cyclohexane. d) HF (aq.), 45 °C, THF. [a] In compound **1a** $R^1 = (S)$-CH(OH)$(CH_2)_4CH_3$.

to its low solubility in cold methanol, using back-to-back precipitation/filtration cycles produced **14** in a pure state. Highly pure **14** was found to be critical in obtaining reproducible results in the formation of **15**. Selective reduction of the alkyne in **15** was not as facile as it was for the solution reaction of **9**. Thus, heating at 40 °C with longer reaction times (2 d) were required for completion. Finally, the prostanoid **1** was released from the polymer support using aqueous HF cleavage followed by silica gel chromatography purification. Comparable yields to the solution-phase syntheses were observed (Table 3)[19] and the spectroscopic data for **1** obtained from the two methods were identical.

Table 3. Comparison of the yields of six-membered ring PGE-type prostanoids obtained from solution-phase and soluble-polymer supported syntheses.

Compound	Solution-phase yields[a]	Liquid-phase yields[b]
1a	46	40
1b	39	38
1c	36	43
1d	40	46
1e	36	31

[a] Total yields from (*R*)-**2**. [b] Total yields from (*R*)-**2-P**. For the method used to calculate these yields see ref. [9a].

Conclusion

We have presented the first general method for the asymmetric three-component coupling synthesis of six-membered ring prostanoids of the general structure **1**. The syntheses described have been accomplished using both solution- and liquid-phase methodologies with similar results. This is notable since the use of organometallic reagents often give poor results when insoluble polymers are employed as supports. Of further note, all chiral centers present in the final product were efficiently generated by transmission of the chiral information present in the enone (*R*)-**2**. The excellent results obtained with NCPS along with the facile access to both enantiomers of the key intermediate **2** should allow the construction of diverse six-membered ring prostanoid libraries for use in drug discovery.

Experimental Section

General: All commercially available chemicals were purchased from Aldrich and were used without further purification. NCPS and compound **11** were prepared according to reference [9a]. Methyl 7-hydroxyhept-5-ynoate,[20] (*S*)-1-octyn-3-ol[21] and Dess–Martin periodinane[22] were prepared following methods described in the literature. All moisture- and air-sensitive reactions were carried out under an inert atmosphere with dry reagents and solvents in flame-dried glassware. Methylene chloride and tetrahydrofuran were distilled from calcium hydride and sodium, respectively. Flash chromatography was carried out with Merck silica gel 60 (230–400 mesh) and analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel coated Kieselgel 60 F_{254} plates. Compounds were visualized with UV light, followed by heat staining with an aqueous cerium-molybdate solution. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ using either a Bruker AMX-400 or AMX-500 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale using residual solvent peaks as a reference. DQF-COSY and ROESY experiments were recorded in $CDCl_3$ using a DRX-600 spectrometer. Optical rotations were determined at 589 nm in a conventional 10 cm cell using a Perkin–Elmer 241 MC polarimeter.

General procedure for the preparation of silyl-enol ether 7: Alkyne **6** (1 mmol) was added dropwise into a round-bottomed flask containing a stirred solution of Cp_2ZrHCl (273 mg, 1.05 mmol) in THF (3 mL). The flask was wrapped with aluminum foil to shield the solution from ambient light. After 30 min the flask was cooled to $-50\,^\circ$C and MeLi (1.43 mL, 1.4 M, 2 mmol) was slowly added to the vessel and stirred for an additional 15 min. This mixture was transferred via cannula to another flask, also cooled to $-50\,^\circ$C, containing a suspension of CuCN (91 mg, 1 mmol) in THF (2 mL). The mixture was stirred for 15 min and then treated with MeLi (0.73 mL, 1.4 M, 1 mmol), stirred for an additional 15 min and cooled to $-78\,^\circ$C. A solution of enone (*R*)-**2** (114 mg, 0.5 mmol) in THF (1 mL) was then added over 30 min and the mixture was stirred for an additional 30 min. Me_3SiCl (0.32 mL, 2.5 mmol) was then added and after 15 min, this was followed by triethylamine (0.7 mL, 5 mmol). The solution was allowed to warm to room temperature and was then poured into a mixture of water (20 mL) and ethyl acetate (25 mL). The aqueous layer was extracted with additional ethyl acetate (3×25 mL) and the combined organic layers were washed with brine (25 mL) and dried over magnesium sulfate. This solution was filtered through Celite and concentrated in vacuo. If the concentrated solution of the crude silyl-enol ether obtained was cloudy, the washing and filtering processes were repeated. This precaution was essential to obtain consistent results. Complete removal of the solvents afforded silyl-enol ether **7** as a yellow oil that was used directly in the next step without further purification. The complete conversion of the starting material to **7** was confirmed by ^{1}H NMR.

General procedure for the preparation of 9: The propargyl alcohol **8** (3 mmol) was placed in a round-bottomed flask and dissolved in methylene chloride (3 mL), cooled to $-30\,^\circ$C and treated with trifluoromethanesulfonic anhydride (0.53 mL, 3.1 mmol) and 2,6-di-*tert*-butylpiridine (0.72 mL, 3.2 mmol). After 15 min dry hexane (15 mL) was added and the flask was cooled to $-78\,^\circ$C and stirred at this temperature for 30 min. A white solid precipitated and the suspension thus obtained was filtered through a pad of magnesium sulfate. The clear solution was concentrated until most of the hexanes were removed while keeping the temperature below $-20\,^\circ$C. Dry THF (5 mL) was added and the solution was stored under an inert atmosphere at $-78\,^\circ$C until the lithium enolate was ready. During the concentration of the hexane solution, a stirred solution of silyl-enol ether **7** (0.5 mmol) in THF (2 mL) was cooled to $-30\,^\circ$C and treated with MeLi (0.53 mL, 1.4 M, 0.75 mmol). After 20 min the solution of the freshly generated triflate in THF was transferred via cannula to the flask containing the stirred enolate solution. After 30 min the reaction was quenched with an aqueous phosphate buffer (15 mL, 0.1 M, pH 7.00) and allowed to warm to room temperature. Extraction of the aqueous layer with ethyl acetate (3×25 mL) was followed by washing of the combined organic layers with brine (25 mL). The organic layer was dried over magnesium sulfate and filtered. Concentration in vacuo afforded an oil. Flash chromatography (hexanes/ethyl acetate 20:1) afforded pure **9**.

Compound 9a: Obtained as a colorless oil following the general procedure in 61% yield; R_f (hexanes/ethyl acetate 8:1) = 0.20; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.87 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.15–1.40 (m, 6H), 1.50 (m, 2H), 1.80 (m, 3H), 2.16 (m, 3H), 2.25–2.50 (m, 8H), 3.65 (s, 3H), 3.83 (dt, ^3J (H,H) = 9.0, 4.1 Hz, 1H), 4.12 (m, 1H), 5.30 (dd, ^3J(H,H) = 15.4, 8.3 Hz, 1H), 5.52 (dd, ^3J(H,H) = 15.4, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, −4.4, −4.2, 14.3, 17.6, 18.0, 18.4, 22.8, 24.1, 26.0, 26.4, 28.9, 29.3, 32.0, 32.7, 32.9, 35.0, 38.2, 51.4, 52.0, 53.8, 70.6, 72.3, 77.6, 79.9, 129.2, 136.5, 170.8, 210.9; HR-MS: FAB $[M+Na]^+$: calcd for $C_{34}H_{62}Si_2O_5Na$ 629.4033, found 629.4040.

Compound 9b: Obtained as a colorless oil following the general procedure in 56% yield; R_f (hexanes/ethyl acetate 8:1) = 0.26; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 0.86 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.15–1.40 (m, 9H), 1.72 (m, 3H), 2.03 (m, 2H), 2.11 (m, 1H), 2.18 (m, 2H), 2.20–2.55 (m, 7H), 3.65 (s, 3H), 3.78 (dt, ^3J (H,H) = 9.2, 3.7 Hz, 1H), 5.10 (dd, ^3J(H,H) = 15.1, 8.8 Hz, 1H), 5.50 (dd, ^3J(H,H) = 15.1, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.4, 14.0, 17.3, 18.0, 18.2, 22.6, 24.2, 25.7, 28.9, 29.1, 29.7, 31.7, 32.7, 32.8, 33.5, 38.0, 51.1, 53.5, 72.3, 78.9, 79.6, 129.9, 134.4, 173.8, 208.9; HR-MS: FAB $[M+Na]^+$: calcd for $C_{28}H_{48}SiO_4Na$ 499.3220, found 499.3226.

Compound 9c: Obtained as a colorless oil following the general procedure in 53% yield; R_f (hexanes/ethyl acetate 8:1) = 0.34; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (t, ^3J(H,H) = 7.0 Hz, 3H), 0.86 (s, 9H), 1.15–1.40 (m, 6H), 1.73 (m, 1H), 1.95–2.20 (m, 4H), 2.30–2.60 (m, 7H), 3.54 (s, 2H), 3.79 (dt, ^3J (H,H) = 8.8, 3.9 Hz, 1H), 5.10 (dd, ^3J(H,H) = 14.9, 8.8 Hz, 1H), 5.50 (dd, ^3J(H,H) = 14.9, 6.6 Hz, 1H), 7.15–7.40 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, 14.0, 17.4, 18.0, 18.2, 22.5, 25.1, 25.7, 28.9, 29.1, 31.6, 32.6, 33.5, 38.0, 51.0, 53.5, 72.2, 78.3, 80.3, 126.2, 127.8, 128.2, 129.8, 134.4, 137.5, 208.8; HR-MS: FAB $[M+Na]^+$: calcd for $C_{30}H_{46}SiO_2Na$ 489.3165, found 489.3158.

Compound 9d: Obtained as a colorless oil following the general procedure in 55% yield; R_f (hexanes/ethyl acetate 8:1) = 0.22; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (t, ^3J(H,H) = 6.8 Hz, 3H), 0.87 (s, 9H), 1.15–1.40 (m, 8H), 1.74 (m, 4H), 2.05 (m, 2H), 2.09 (m, 1H), 2.20–2.55 (m, 6H), 3.79 (dt, ^3J (H,H) = 7.2, 4.0 Hz, 1H), 5.12 (dd, ^3J(H,H) = 15.1, 8.9 Hz, 1H), 5.52 (dd, ^3J(H,H) = 15.1, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.4, 3.6, 14.7, 17.2, 22.6, 25.7, 29.0, 29.1, 31.7, 32.6, 33.6, 38.1, 51.1, 53.5, 72.4, 76.2, 88.03, 130.0, 134.3, 209.1; HR-MS: FAB $[M+Na]^+$: calcd for $C_{24}H_{42}SiO_2Na$ 413.2852, found 413.2860.

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Compound 9e: Obtained as a colorless oil following the general procedure in 49% yield; R_f (hexanes/ethyl acetate 8:1) = 0.29; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.65–1.80 (m, 4H), 2.15 (m, 3H), 2.30–2.60 (m, 7H), 3.38 (d, ^3J (H,H) = 6.6 Hz, 2H), 3.63 (s, 3H), 3.80 (dt, ^3J (H,H) = 8.8, 4.0 Hz, 1H), 5.20 (dd, ^3J(H,H) = 15.1, 8.8 Hz, 1H), 5.71 (dd, ^3J(H,H) = 15.1, 6.6 Hz, 1H), 7.10–7.20 (m, 3H, arom.), 5.25–5.40 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.4, 18.3, 25.1, 25.6, 26.2, 32.6, 32.9, 38.5, 38.7, 51.4, 56.8, 72.9, 78.3, 79.3, 126.9, 128.2, 129.8, 130.0, 134.6, 137.5, 174.1, 211.8; HR-MS: FAB $[M+Na]^+$: calcd for $C_{29}H_{42}SiO_4Na$ 505.2750, found 505.2752.

General procedure for the preparation of 10: A round-bottomed flask containing a solution of **9** in a mixture of cyclohexane (2 mL) and benzene (2 mL) was treated with 5% palladium on barium sulfate (450 mg) and quinoline (450 mL). After stirring the mixture at 40 °C under hydrogen (1 atm) for 4 h, the solids were filtered and the solvents were concentrated. The crude oil thus obtained was purified by flash chromatography (hexanes/ethyl acetate 20:1) to afford pure **10**.

Compound 10a: Obtained as a colorless oil following the general procedure in 93% yield; R_f (hexanes/ethyl acetate 8:1) = 0.20; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (t, ^3J(H,H) = 7.1 Hz, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.15–1.35 (m, 6H), 1.40 (m, 2H), 1.63 (m, 2H), 1.75 (m, 1H), 2.04 (m, 3H), 2.25 (m, 6H), 2.39 (m, 1H), 2.42 (m, 1H), 3.65 (s, 3H), 3.79 (dt, ^3J (H,H) = 8.8, 4.0 Hz, 1H), 4.09 (m, 1H), 5.30 (m, 2H), 5.36 (dd, ^3J(H,H) = 15.1, 8.3 Hz, 1H), 5.46 (dd, ^3J(H,H) = 15.1, 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, −4.4, −4.3, 14.0, 18.0, 18.2, 22.6, 24.6, 24.7, 25.8, 25.9, 26.6, 26.7, 31.8, 32.2, 33.5, 36.6, 38.2, 51.4, 52.2, 53.2, 72.0, 72.7, 128.3, 129.7, 136.4, 174.1, 211.1; HR-MS: FAB $[M+Na]^+$: calcd for $C_{34}H_{64}Si_2O_5Na$ 631.4190, found 631.4203.

Compound 10b: Obtained as a colorless oil following the general procedure in 89% yield; R_f (hexanes/ethyl acetate 8:1) = 0.26; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.87 (t, ^3J(H,H) = 6.9 Hz, 3H), 1.10–1.40 (m, 9H), 1.71 (m, 3H), 1.90–2.20 (m, 5H), 2.25–2.50 (m, 7H), 3.65 (s, 3H), 3.76 (m, 1H), 5.12 (dd, ^3J(H,H) = 15.0, 8.9 Hz, 1H), 5.25–5.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.3, 14.3, 17.8, 18.1, 18.2, 22.2, 24.2, 25.1, 28.4, 29.2, 29.7, 31.8, 32.6, 32.8, 33.6, 38.3, 51.4, 53.5, 72.5, 127.8, 128.4, 129.9, 134.9, 174.5, 210.3; HR-MS: FAB $[M+Na]^+$: calcd for $C_{28}H_{50}SiO_4Na$ 501.3376, found 501.3389.

Compound 10c: Obtained as a colorless oil following the general procedure in 89% yield; R_f (hexanes/ethyl acetate 8:1) = 0.32; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.04 (s, 3H), 0.06 (s, 3H), 0.85 (t, ^3J(H,H) = 7.0 Hz, 3H), 0.87 (s, 9H), 1.15–1.30 (m, 6H), 1.52 (m, 2H), 1.73 (m, 1H), 1.90–2.50 (m, 9H), 3.39 (d, ^3J(H,H) = 6.6 Hz, 2H), 3.78 (dt, ^3J (H,H) = 8.0, 4.8 Hz, 1H), 5.14 (dd, ^3J(H,H) = 15.2, 8.3 Hz, 1H), 5.3–5.5 (m, 3H), 7.10–7.20 (m, 3H, arom.), 7.20–7.35 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, 14.6, 17.9, 18.1, 18.6, 23.3, 27.2, 27.5, 28.9, 29.4, 32.6, 32.9, 35.6, 37.8, 51.8, 56.5, 74.0, 126.7, 127.5, 128.6, 129.2, 129.7, 131.0, 131.9, 135.4, 139.5, 210.6; HR-MS: FAB $[M+H]^+$: calcd for $C_{30}H_{49}SiO_2$ 469.3502, found 469.3490.

Compound 10d: Obtained as a colorless oil following the general procedure in 83% yield; R_f (hexanes/ethyl acetate 8:1) = 0.23; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 0.86 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.15–1.30 (m, 7H), 1.46 (m, 1H), 1.60 (m, 2H), 1.71 (m, 1H), 2.01 (m, 2H), 2.12 (d, ^3J (H,H) = 8.1 Hz, 3H), 2.16 (m, 2H), 2.21 (m, 1H), 2.28 (m, 1H), 2.43 (m, 1H), 3.74 (dt, ^3J (H,H) = 7.8, 3.7 Hz, 1H), 5.08 (dd, ^3J(H,H) = 15.0, 8.0 Hz, 1H), 5.30 (m, 2H), 5.40 (dd, ^3J(H,H) = 15.0, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, 14.0, 14.1, 22.6, 22.9, 25.7, 27.6, 29.0, 29.2, 29.5, 31.7, 32.6, 33.5, 37.8, 51.9, 54.3, 72.4, 126.7, 128.7, 130.5, 133.8, 211.7; HR-MS: FAB $[M+Na]^+$: calcd for $C_{24}H_{44}SiO_2Na$ 415.3008, found 415.3001.

Compound 10e: Obtained as a colorless oil following the general procedure in 86% yield; R_f (hexanes/ethyl acetate 8:1) = 0.31; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.03 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.40–1.70 (m, 5H), 1.75–2.00 (m, 2H), 2.10–2.50 (m, 7H), 3.29 (d, ^3J (H,H) = 6.9 Hz, 2H), 3.59 (s, 3H), 3.72 (dt, ^3J (H,H) = 8.6, 4.1 Hz, 1H), 5.00–5.30 (m, 3H), 5.51 (dd, ^3J(H,H) = 15.0, 6.7 Hz, 1H), 7.10–7.40 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = −4.6, −4.5, 17.9, 24.6, 25.3, 25.6, 26.6, 33.4, 33.6, 38.0, 38.9, 51.3, 54.3, 72.2, 126.0, 128.3, 128.5, 129.4, 132.0, 132.4, 137.9, 171.9, 210.3; HR-MS: FAB $[M+H]^+$: calcd for $C_{29}H_{45}SiO_4$ 485.3087, found 485.3099.

General procedure for the preparation of 1: A stirred solution of compound **10** (0.5 mmol) in acetonitrile (6 mL) was placed in a teflon tube and treated with a 15% hydrogen fluoride/pyridine mixture (0.5 mL). The progress of the reaction was followed by TLC and additional HF/pyridine mixture was added if starting material was present after 6 h. When the starting material completely disappeared, the solution was neutralized by addition of a saturated solution of sodium hydrogencarbonate. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate. The crude oil obtained after solvent removal was purified by flash chromatography (hexanes/ethyl acetate 4:1) to afford pure **1**.

Compound 1a: Obtained as a colorless oil following the general procedure in 81% yield; $[\alpha]_D^{20}$ = −37.3 (c = 0.65 in MeOH); R_f (hexanes/ethyl acetate 1:2) = 0.28; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.89 (t, ^3J(H,H) = 7.0 Hz, 3H), 1.25–1.35 (m, 5H),1.43 (m, 1H), 1.60 (m, 6H), 2.05 (m, 4H), 2.35 (m, 6H), 2.41 (m, 2H), 3.67 (s, 3H), 3.74 (dt, ^3J (H,H) = 9.2, 4.0 Hz, 1H), 4.16 (m, 1H), 5.30 (m, 1H), 5.40 (m, 1H), 5.47 (ddd, ^3J(H,H) = 15.2, 9.2, ^4J(H,H) = 1.1 Hz, 1H), 5.71 (dd, ^3J(H,H) = 15.2, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 13.9, 22.5, 24.5, 24.6, 25.2, 26.5, 29.6, 31.6, 32.5, 33.1, 37.3, 38.8, 51.5, 51.6, 54.7, 70.7, 71.9, 128.4, 129.4, 129.5, 139.3, 174.5, 209.2; HR-MS: FAB $[M+Na]^+$: calcd for $C_{22}H_{36}O_5Na$ 403.2460, found 403.2473.

Compound 1b: Obtained as a colorless oil following the general procedure in 79% yield; $[\alpha]_D^{20}$ = −42.5 (c = 0.39 in MeOH); R_f (hexanes/ethyl acetate 2:1) = 0.30; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.86 (t, ^3J(H,H) = 6.8 Hz, 3H), 1.20–1.45 (m, 9H), 1.55–1.70 (m, 4H), 2.00–2.15 (m, 5H), 2.20–2.35 (m, 5H), 2.40–2.50 (m, 2H), 3.66 (s, 3H), 3.70 (m, 1H), 5.20 (dd, ^3J(H,H) = 15.1, 9.4 Hz, 1H), 5.30–5.45 (m, 2H), 5.63 (dd, ^3J(H,H) = 15.1, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.0, 22.6, 24.5, 24.7, 26.7, 28.9, 29.2, 31.6, 32.3, 32.6, 33.5, 38.8, 51.4, 51.5, 55.2, 70.6, 128.2, 129.3, 129.6, 137.2, 174.1, 209.3; HR-MS: FAB $[M+Na]^+$: calcd for $C_{22}H_{36}O_4Na$ 387.2511, found 387.2523.

Compound 1c: Obtained as a colorless oil following the general procedure in 76% yield; $[\alpha]_D^{20}$ = −28.0 (c = 0.73 in MeOH); R_f (hexanes/ethyl acetate 2:1) = 0.30; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.87 (t, ^3J (H,H) = 6.8 Hz, 3H), 1.20–1.40 (m, 8H), 1.69 (m, 1H), 2.00–2.15 (m, 3H), 2.25–2.50 (m, 4H), 3.40 (d, ^3J(H,H) = 7.0 Hz, 2H), 3.64 (s, 3H), 3.70 (dt, ^3J (H,H) = 9.1, 4.1 Hz, 1H), 5.20 (dd, ^3J(H,H) = 15.1, 9.0 Hz, 1H), 5.46 (m, 1H), 5.58 (m, 1H), 5.67 (dd, ^3J(H,H) = 15.1, 7.0 Hz, 1H), 7.10–7.20 (m, 3H, arom.), 7.20–7.35 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.6, 18.5, 18.6, 22.9, 25.1, 26.2, 28.3, 30.0, 31.5, 33.0, 33.5, 38.4, 51.6, 56.5, 76.2, 126.6, 127.5, 128.0, 128.2, 129.7, 130.8, 135.4, 136.9, 209.3; HR-MS: FAB $[M+H]^+$: calcd for $C_{24}H_{35}O_2$ 355.2637, found 355.2634.

Compound 1d: Obtained as a colorless oil following the general procedure in 88% yield; $[\alpha]_D^{20}$ = −31.4 (c = 0.60 in MeOH); R_f (hexanes/ethyl acetate 2:1) = 0.20; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.86 (t, ^3J(H,H) = 7.0 Hz, 3H), 1.11 (m, 1H), 1.15–1.35 (m, 5H), 1.42 (m, 3H), 1.53 (m, 1H), 1.61 (m, 1H), 2.05 (m, 5H), 2.11 (d, ^3J (H,H) = 7.9 Hz, 3H), 2.31 (m, 1H), 2.43 (m, 2H), 3.67 (dt, ^3J (H,H) = 7.7, 4.0 Hz, 1H), 5.17 (dd, ^3J(H,H) = 15.1, 8.6 Hz, 1H), 5.25–5.35 (m, 2H), 5.62 (dd, ^3J(H,H) = 15.1, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.1, 22.6, 22.9, 26.2, 28.8, 29.2, 29.3, 32.2, 32.5, 38.9, 50.9, 55.5, 70.7, 129.6, 130.8, 133.6, 137.0, 210.0; HR-MS: FAB $[M+H]^+$: calcd for $C_{18}H_{31}O_2$ 279.2324, found 279.2337.

Compound 1e: Obtained as a colorless oil following the general procedure in 85% yield; $[\alpha]_D^{20}$ = −23.6 (c = 0.51 in MeOH); R_f (hexanes/ethyl acetate 2:1) = 0.30; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.50–1.80 (m, 4H), 1.95 (m, 3H), 2.15–2.50 (m, 8H), 3.42 (d, ^3J (H,H) = 6.9 Hz, 2H), 3.64 (s, 3H), 3.72 (dt, ^3J (H,H) = 9.3, 4.0 Hz, 1H), 5.20–5.40 (m, 3H), 5.81 (dd, ^3J(H,H) = 15.0, 6.6 Hz, 1H), 7.10–7.40 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 24.6, 26.6, 32.3, 33.4, 38.7, 39.0, 51.3, 51.4, 54.9, 70.2, 126.3, 128.0s, 128.2, 128.4, 128.6, 129.7, 130.9, 135.2, 139.7, 174.0, 209.3; HR-MS: FAB $[M+H]^+$: calcd for $C_{23}H_{31}O_4$ 371.2222, found 371.2220.

Compound 11: A solution of (2-hydroxymethyl)-3,4-dihydro-2*H*-pyran[23] (1.02 g, 9 mmol) [this was prepared from (3,4-dihydro-2*H*-puran-2-ylmethyl)-3,4-dihydro-2*H*-pyran-2-carboxylate (Fluka)][18] in dimethylformamide (20 mL) was treated with NaH (0.4 g, 9.9 mmol, 60% suspension in oil) in one portion at rt. After 2 h, a solution of NCPS (10 g, 3 mmol) in dimethylformamide (50 mL) was added to the above reaction mixture. It was then stirred at rt for 24 h and quenched by the addition of water (2 mL). Solvent was then removed and the oil thus obtained was redissolved in CH_2Cl_2 (100 mL) and washed with brine, dried over

magnesium sulfate and concentrated in vacuo. The resulting product bound polymer was purified utilizing the following standard workup procedure: the crude product was dissolved in THF (5 mL) and slowly dripped into a vigorously stirred solution of methanol (300 mL, $-30\,^{\circ}C$). The white precipitated polymer thus obtained was recovered by filtration and dried under high vacuum (10^{-2} atm) at 40 °C for 6 h to afford 10.2 g of polymer **11** (100 % polymer recovered). ^1H NMR ($CDCl_3$, 25 °C): $\delta = 3.5$ (m, 2H), 4.1 (m, 1H), 4.5 (m, 2H), 4.8 (m, 1H). Signals in the 1.2–2.3 and 6.2–7.3 ppm regions overlapped with those of the polymer and hence, assignments in these regions were not possible.

Compound 12: Compound **5** (140 mg, 0.9 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (40 mg, 0.15 mmol) were added to a round-bottomed flask containing a solution of polymer **11** (1 g, 0.3 mmol) in methylene chloride (10 mL). The reaction mixture was stirred for 16 h at 40 °C. The solution was then diluted with methylene chloride (40 mL) and washed with brine (2 × 20 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to yield a thick yellowish oil. The crude product was purified following the standard precipitation procedure described above, yielding 980 mg of polymer **12** (93 % polymer recovered). ^1H NMR ($CDCl_3$, 25 °C): $\delta = 3.4$ (m, 2H), 4.2 (m, 1H), 4.5 (m, 3H), 5.2 (m, 2H), 5.9 (m, 1H), 6.1 (m, 1H).

Compound 13: Polymer **12** (0.8 g, 0.24 mmol) was dissolved in a mixture of THF (3 mL), methanol (3 mL), and water (0.5 mL). LiOH (2 g) was added and the mixture was stirred for 6 h at room temperature. This was then diluted with ethyl acetate (40 mL) and washed with brine (2 × 10 mL). The polymer was purified following the standard precipitation method, affording **13** as a white solid (0.8 g, 100 % polymer recovered). ^1H NMR ($CDCl_3$, 25 °C): $\delta = 3.4$ (m, 2H), 4.1 (m, 1H), 4.4 (m, 3H), 5.0 (m, 1H), 6.0 (m, 2H).

Compound (*R*)-**2-P**: A solution of polymer **12** (0.8 g, 0.24 mmol) in methylene chloride (10 mL) was treated with Dess–Martin reagent (0.5 g, 1.2 mmol) for 4 h. The solution was then diluted with diethyl ether and treated with aqueous $NaHCO_3$ and $Na_2S_2O_3$ until two layers separated. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated in vacuo. Standard precipitation purification afforded polymer (*R*)-**2-P** as a white solid (0.78 g, 97 % polymer recovered). ^1H NMR ($CDCl_3$, 25 °C): $\delta =$ 3.5 (m, 2H), 4.1 (m, 1H), 4.5 (m, 3H), 5.0 (m, 1H), 5.2 (m, 1H), 5.9 (m, 1H).

Compounds 14: Silyl-enol ether **14** was obtained using the standard procedure used to prepare compound **7**. In this case 5 equiv. cuprate **3**, 6 equiv. TMSCl, and 15 equiv. Et_3N gave the best results. The process of filtering through a Celite pad and precipitation was repeated until the concentrated THF solution was completely clear. A cloudy solution did not afford the expected product in the next step. After precipitation, polymer **14** was obtained as a white solid (95 % polymer recovery). The ^1H-NMR characteristic signal at this step was the presence of a trimethylsilyl singlet at $\delta = 0.1$ and a new broad signal from the two new olefinic protons at $\delta = 6.0$.

Compounds 15: Polymer-bound product **15** was obtained with 90 % polymer recovery following the procedure described for compound **9** using 20 equiv. triflate **4**. The disappearance of the trimethylsilyl signal in the ^1H NMR of the product showed the complete conversion of starting material.

Compound 16: The selective reduction described for compound **10** was reproduced with polymer **15** by placing the flask on a bath heated at 40 °C and extending the reaction time to 2 d. ^1H NMR of the product showed the presence of two new protons in the olefinic region. Polymer **16** was recovered as a white powder in 90 % yield.

Cleavage of compound 1 from the polymer: The prostanoid was cleaved form the polymer support using aqueous HF (46 %). Polymer **16** (0.3 g, 0.075 mmol) was dissolved in THF (5 mL) and stirred at 45 °C. Cleavage of **1** could be monitored by TLC and required up to 8 h. The excess HF was slowly neutralized with saturated $NaHCO_3$ and the product was extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The oil obtained upon concentration was redissolved in THF (0.5 mL) and slowly dripped into cold MeOH (30 mL, −30 °C). The white polymer that precipitated was removed by filtration and the solution containing the cleaved prostanoid **1** was concentrated in vacuo. Column chromatography of the crude material afforded compound **1** which was identical to that obtained using solution chemistry. **1a**: 15 mg (52 % from **16a**), **1b**: 13 mg (49 % from **16b**), **1c**: 15 mg (56 % from **16c**), **1d**: 13 mg (60 % from **16d**), **1e**: 11 mg (40 % from **16e**).

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