Polymer-supported selenium reagents for organic synthesis

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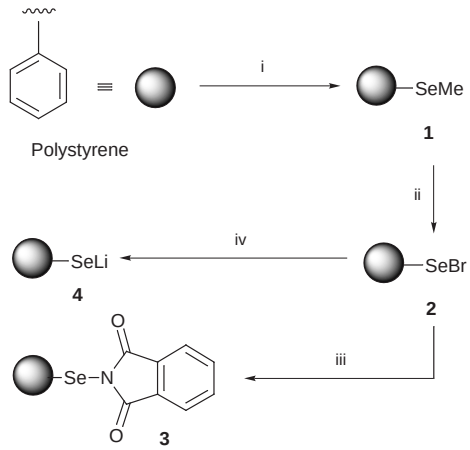
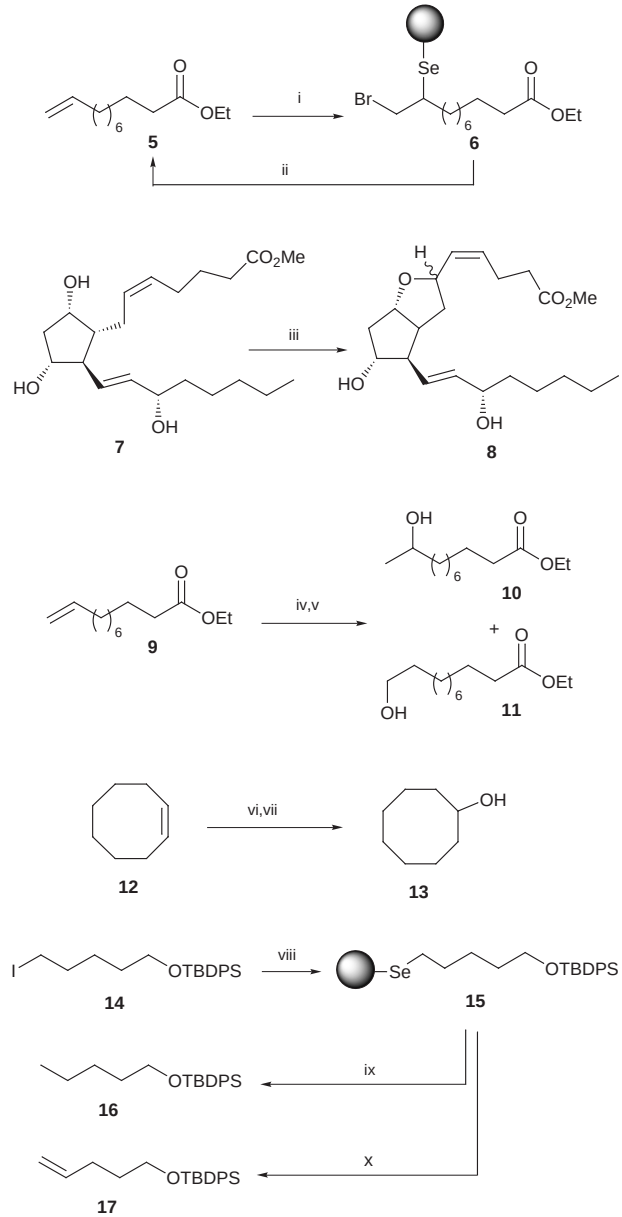
Organoselenium resins 1–4 were prepared from polystyrene *via* lithiation and quenching with MeSeSeMe, and shown to react with a variety of substrates, aiding in useful functionalizations.

Combinatorial chemistry and solid phase synthesis have recently emerged as powerful tools for the drug discovery process.[1] The latter technique is particularly useful for combinatorial library construction due to its adaptability to the powerful and elegant split-pool methods[2] and because of the well recognized purification advantages associated with it. The utilization of polymer-bound reagents,[3] in particular, has gained popularity due to the non-requirement for tethering the substrate to the polymer. Here we describe the preparation of a series of solid-supported selenium resins[4,5] **2–4** (Scheme 1) and their application as linkers and reagents for solid phase synthesis. A distinct advantage of the new reagents is the convenience of handling and their totally odorless nature as compared to the non-bound reagents, whose toxicity and foul smell is often problematic.

Scheme 1 summarizes the preparation of the new resins **2–4** from readily available starting materials. Thus, polystyrene beads suspended in cyclohexane were treated with Bu^{n}Li–TMEDA[6] and the lithiated species was quenched with MeSeSeMe,[7] furnishing selenium reagent **1** as a pale yellow resin (the loading of selenium was controlled by addition of MeSeSeMe in substoichiometric amounts to the lithiated polystyrene). Exposure of **1** to bromine resulted in quantitative conversion[8] to the polymer-supported selenenyl bromide **2**, which was isolated after filtration and washing as a deep red resin. The selenium

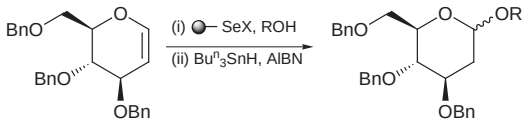


Scheme 1 *Reagents and conditions*: i, Bu^{n}Li (2.5 M in hexanes, 24 equiv.), TMEDA, cyclohexane, 65 °C, 4 h, then filtration and washing with THF, then dimethyl diselenide (2.0 mmol g^{-1} of polystyrene), THF, 0 °C, 30 min, 100%; ii, Br_2 (0.9 equiv.), $CHCl_3$, 0 °C, 10 min, 100% (based on consumption of Br_2), then filtration and washing, then EtOH, 70 °C, 1 h, >95%; iii, potassium phthalimide (1.5 equiv.), 18-crown-6 (1.5 equiv.), benzene, 23 °C, 5 h, >95% yield; iv, $LiBH_4$ (2.0 M in THF, 2.0 equiv.), THF, 23 °C, 1 h, >95%

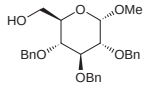
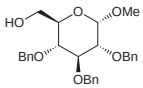
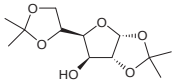


Scheme 2 *Reagents and conditions*: i, **2** (1 equiv.), CH_2Cl_2, 23 °C, 30 min; ii, Bu$^n_3$SnH (4 equiv.), AIBN (0.01 equiv.), PhMe, 110 °C, 6 h, 92% (2 steps); iii, **2** (1.5 equiv), THF, −78 °C, 30 min, then H_2O_2 (30%, 2 equiv.), −78 → 23 °C, 20 h, 94% (2 steps); iv, **3** (0.5 equiv.), H_2O (1 equiv.), CSA (0.05 equiv.), CH_2Cl_2, 24 h; v, Bu$^n_3$SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 82% (2 steps), **10** : **11** = 2 : 1; vi, **3** (0.5 equiv.), H_2O (1 equiv.), CSA (0.05 equiv.), CH_2Cl_2, 24 h; vii, Bu$^n_3$SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 80% (two steps); viii, **4** (0.5 equiv.), THF, 23 °C, 12 h; ix, Bu$^n_3$SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 89% (2 steps); x, H_2O_2 (30%, 1 equiv), THF, 23 °C, 12 h, 78% (2 steps)

Table 1 Polymer-bound selenium promoted synthesis of 2-deoxyglycosides[a]



18 **19**

Entry	ROH	Reagent	Solvent	*t*/h	Yield (%)	Ratio α : β
1	BnOH	**2**	CH_2Cl_2	24	87	2 : 1
2	BnOH	**2**	PhMe	24	96	2 : 1
3	BnOH	**2**	MeCN–CH_2Cl_2 (2 : 1)	24	86	5 : 1
4	BnOH	**3**	CH_2Cl_2	48	68	1 : 5
5	BnOH	**3**	PhMe	48	72	1 : 5
6	BnOH	**3**	MeCN–CH_2Cl_2 (2 : 1)	48	23	1 : 1
7		**2**	MeCN–CH_2Cl_2 (2 : 1)	24	61	8 : 1
8		**3**	PhMe	48	45	1 : 1
9		**2**	MeCN–CH_2Cl_2 (2 : 1)	96	50	20 : 1

[a] All reactions were carried out under an atmosphere of argon in the presence of 4 Å molecular sieves. *Reagents and conditions*: i, (for reagent **2)** ROH (1 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv.), **2** (0.5 equiv.); (for reagent **3)** ROH (1 equiv.), CSA (1 equiv.) and **3** (0.5 equiv.); solvent and time as shown in Table; ii, Bu$^n_3$SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 8 h.

phthalimide reagent **3** was obtained as a yellow resin from **2** by displacement with potassium phthalimide in the presence of 18-crown-6 (> 95% yield),[9] while the lithium selenide **4** (a pale yellow resin) was prepared by $LiBH_4$ reduction of **2** (95% yield). All new reagents appeared to be quite stable in the air at ambient temperature (inert atmosphere is recommended, however, for their storage and use).

Scheme 2 displays chemistry demonstrating the use of resins **2–4** both as solid phase linkers and polymer-bound reagents. Thus, olefin **5** was quantitatively loaded onto the polymer by treatment with the polymer-bound selenium bromide resin **2** and, subsequently, released reductively under the influence of Bu$^n_3$SnH–AIBN (cat.) to recover the starting olefin **5** in 92% overall yield. The polymer-bound selenium bromide **2** was also shown to be as effective as phenylselenium bromide for the known two-step transformation[10] of $PGF_{2\alpha}$ methyl ester **7** to the PGI_2 analogues **8** (94% yield, *ca.* 2 : 1 ratio of C-6 epimers, Scheme 2). Hydration of an olefin was demonstrated to proceed smoothly with the selenium phthalimide resin **3**.[9] Thus, terminal olefin **9** was converted to the regioisomeric alcohols **10** and **11** in 82% overall yield (**10** : **11** *ca.* 2 : 1 ratio) by the action of reagent **3** and CSA in the presence of H_2O, followed by reductive cleavage from the solid support with Bu$^n_3$SnH–AIBN. Furthermore, cyclic olefin **12** was converted to alcohol **13** in 80% overall yield by the same two-step procedure. The use of the resin **4** was demonstrated as follows. Alkyl iodide **14** was efficiently loaded onto the polymer through mild alkylation conditions in THF. The substrate was then released from the polymer (**15**) by either free radical chemistry to obtain the corresponding alkyl compound **16** (89% overall yield) or oxidative conditions leading to olefinic product **17** (78% overall yield).

Table 1 summarizes applications of polymer-bound selenium bromide **2** and selenium phthalimide[11] **3** to the synthesis of 2-deoxyglycosides.[12] Most noteworthy is the inverse glycosidation stereoselectivity obtained under different reaction conditions. Thus, glycosidation of tri-*O*-benzylglucal **18** with BnOH using the polymer-bound selenenyl bromide reagent **2** (X = Br) followed by Bu$^n_3$SnH–AIBN (cat.) cleavage of the newly formed selenium–carbon bond released the 2-deoxy glycosylated product **19** in 86% yield with 5 : 1 selectivity in favor of the α-anomer (entry 3), whereas the same transformation carried out with the polymer-bound selenenyl phthalimide reagent **2** yielded the product in 72% with a 5 : 1 selectivity in favor of the β-anomer (entry 5).

In conclusion, we have successfully prepared a series of polymer-bound selenium reagents/linkers and demonstrated a number of their uses in organic synthesis. These reagents should find useful applications in solid phase and combinatorial synthesis due to their versatility and ease of handling.

We thank Drs Dee H. Huang and Gary Siuzdak for NMR and mass spectroscopic assistance, respectively. This work was financially supported by the Skaggs Institute for Chemical Biology, the National Institutes of Health, USA, and grants from Novartis, Amgen, Pfizer, Merck, DuPont-Merck, Hoffmann LaRoche and Schering-Plough.

Notes and References

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1 For selected reviews, see: F. Balkenhohl, C. von dem Brussche-Hünnefeld, A. Lansky and C. Zechel, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2288; L. A. Thompson and J. A. Ellman, *Chem. Rev.*, 1996, **96**, 555; M. A. Gallop, R. W. Barret, W. J. Dower, S. P. Foder and E. M. Gorden, *J. Med. Chem.*, 1994, **37**, 1233; E. M. Gorden, R. W. Barret, W. J. Dower, S. P. Foder and M. A. Gallop, *J. Med. Chem.*, 1994, **37**, 1385; W. H. Moos, G. D. Green and M. R. Pavia, *Annu. Rep. Med. Chem.*, 1993, **28**, 315.

2 For general references, see: J. J. Baldwin and I. Henderson, in *Synthesis of Encoded Small Molecule Combinatorial Libraries*, ed. J. P. Delvin, Dekker, New York, NY, 1997; A. W. Czarnick, *Curr. Opin. Chem. Biol.*, 1997, **1**, 60; X. Y. Xiao, C. Zhao, H. Potash and M. P. Nova, *Angew. Chem., Int. Ed. Engl.*, 1997, **37**, 780; P. A. Tempest and R. W. Armstrong, *J Am. Chem. Soc.*, 1997, **119**, 7607.

3 S. W. Kaldor and M. G. Siegel, *Curr. Opin. Chem. Biol.*, 1997, **1**, 101.

4 For reviews of the use of organoselenium reagents in organic synthesis see: K. C. Nicolaou and N. A. Petasis, *Selenium in Natural Product Synthesis*, CIS Inc, Philadelphia, PA, 1984; D. Liotta, *Organoselenium Chemistry*, Wiley, NY, 1986.

5 To the best of our knowledge, this constitutes the first report of the polymer-bound reagents presented herein. For previous preparation of polymer bound selenophenol, phenylselenium chloride and diphenyl selenoxide by copolymerization of 4-vinylselenophenol with divinylbenzene, see: R. Michels, M. Kato and W. Heitz, *Makromol. Chem.*, 1976, **177**, 2311.

6 M. J. Farrall and M. J. Fréchet, *J. Org. Chem.*, 1976, **41**, 3877.

7 For an example of a related reaction, see: C. Lambert, M. Hilbert, L. Christiaens and N. Dereu, *Synth. Commun.*, 1991, **21**, 85.

8 L. Laitem, P. Thibaut and L. Christians, *J. Heterocycl. Chem.*, 1976, **13**, 469.

9 K. C. Nicolaou, D. A. Claremon, W. E. Barnette and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3704.

10 K. C. Nicolaou, W. E. Barnette and R. L. Magolda, *J. Am. Chem. Soc.*, 1981, **103**, 3480.

11 To the best of our knowledge, this is the first example of selenium phthalimide promoted glycosidation.

12 For previous examples of selenium mediated glycosidations, see: G. Jaurand, J.-M. Beau and P. Sinay, *Chem. Commun.*, 1981, 572; M. Peres and J.-M. Beau, *Tetrahedron Lett.*, 1989, **30**, 75; F. Calvani, P. Crotti, C. Gardelli and M. Pineschi, *Tetrahedron Lett.*, 1994, **50**, 12 999; W. R. Roush and X.-F. Lin, *J. Am. Chem. Soc.*, 1995, **117**, 2236.

Received in Corvallis, OR, USA, 23rd June 1998; 8/04795B