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Synthesis and Use of a 2-(Trimethylsilyl)ethoxymethyl-Based Linker in Solid-Phase Organic Chemistry

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The synthesis of a linker derived from the 2-(trimethylsilylethoxy)methyl (SEM) protection group is described. This linker is particularly useful for the immobilization of steroids on solid phases, because the linker is robust but allows the substrates to be cleaved from the solid phase by fluoridolysis. The use of the linker is demonstrated by the coupling and cleavage of eight different steroids. Furthermore, two palladium coupling reactions are shown, whereby the steroidal vinyl triflates are attached to the solid phase via this linker.

The linker strategy is an important part in the designing of a library. This is clearly indicated by the various papers about the synthesis and use of new linkers that have appeared over the past few years.[1] As we were particularly interested in the synthesis of steroid libraries, we needed a robust linker that would allow for cleavage under essentially neutral conditions. Because literature contains only few reports of synthetic transformations of polymer-bound steroids[2] and none of the then-known linkers looked suitable to us, we decided to develop a new linker based on a silyl protection group. A number of silicon-based linkers had already been described, but they suffered from (technical) drawbacks, such as a lengthy synthesis[3] or the fact that they have to be attached to the ligand molecule prior to their attachment to the support.[4] During our research several other silicon-based linkers were published but, although useful in their own right, none of them fulfilled our requirements.[5] The linker described in this paper is based on the 2-(trimethylsilyl)ethoxymethyl (SEM) protection group (Figure 1). SEM ethers are more

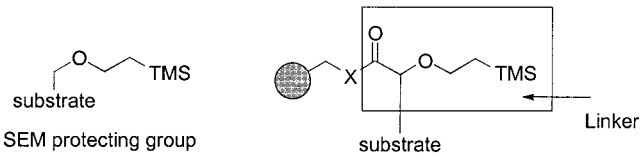
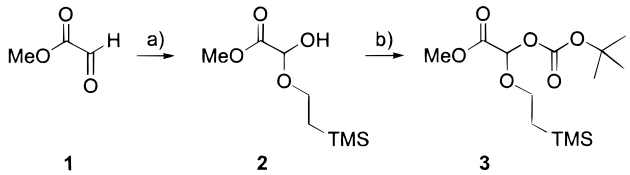


Figure 1.

rugged than trialkylsilyl ethers, but they can still be deprotected using fluoride.[6] Furthermore, they are stable to acidic conditions which cleave THP and TBS ethers. Therefore, we expected that the SEM-linker would be more robust than the other silicon-based linkers and might even show additional stability toward acids due to the electron-withdrawing behavior of the carbonyl.

The synthesis started from methyl glyoxylate (**1**) (Scheme 1).[7] Addition of 2-trimethylsilylethanol yielded the hemiacetal **2**[8] which was converted to acetal **3** under standard conditions. This acetal **3** is the key intermediate for our linker. Starting from acetal **3**, two routes were followed

Scheme 1[a]



[a] Reagents and conditions: (a) 2-trimethylsilylethanol, CH_2Cl_2, 20 h, 73%; (b) $(t\text{-Boc})_2O$, DMAP, CH_2Cl_2, 1 h, 78%.

(Scheme 2). In the first route, acetal **3** was saponified to yield the free acid, which was subsequently coupled to a solid phase under standard esterfication or amidation conditions (route I). Various solid phases were used: hydroxymethyl resin, aminomethyl resin (with NH_2 end groups as well as with NHR end groups), Wang resin, TentaGel (with NH_2 end groups as well as with NHR end groups), and pins (both polystyrene- and MA/DMA-based). On the basis of coloring reagents, gain of mass, and IR, it was concluded that the coupling went virtually quantitatively in all cases. The resulting solid phase **4** is air and moisture stable and can be stored for prolonged period of times. To activate the linker for coupling, the solid phase was treated with hydrogen chloride in diethyl ether at 0 °C for 1 h. This reaction can easily be monitored by IR because of the disappearance of the distinct carbonyl absorption of the *t*-Boc group (1748 cm^{-1}). To our delight, the resulting chloroacetal **5** appeared to be much more stable than its equivalent in solution. In fact, resin **5** could be stored for a few days without losing much of its reactivity. Most likely, this is due to the more shielded and hydrophobic nature of the solid phases. A chloride analysis was carried out with some of the resins to determine the loadings, which confirmed the high loading of the linker to the solid phases. Alternatively, **3** was treated with hydrogen chloride followed by phenylselenol to give selenoacetal **6** (route II). Coupling of **6** under conditions similar to those described for **3** resulted in the formation of **7**. This now opens a second route for coupling of substrates to the solid phase under conditions well known in sugar chemistry.[9] An alternative route for the synthesis of **7** is the consecutive treatment of **4** with hydrogen chloride and phenolselenol to give **7**. We found hardly any difference

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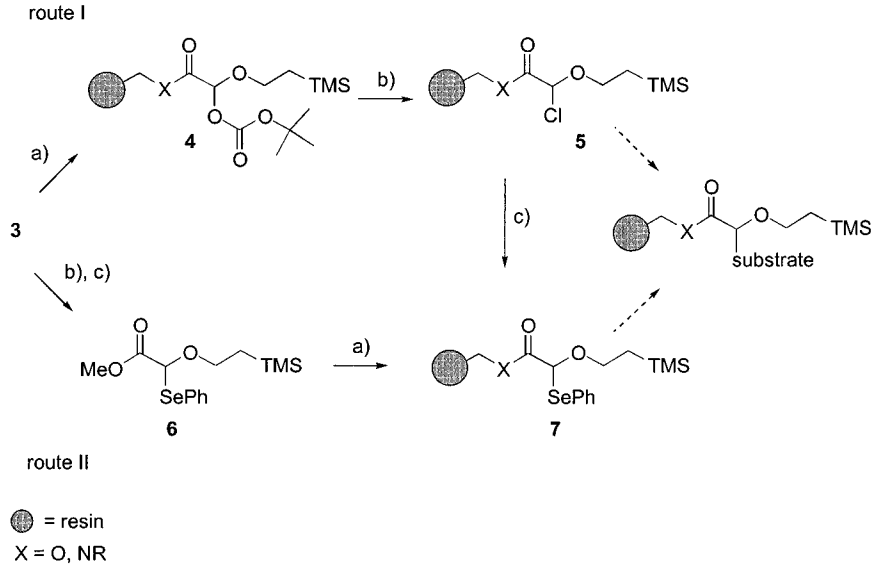
Scheme 2[a]



[a] Reagents and conditions: (a) (1) KOH, H_2O/MeOH, 3 h, (2) TBTU, DIPEA, resin-CH_2-XH, DMF or CH_2Cl_2, 18 h; (b) HCl, Et_2O, 0 °C, 1 h; (c) PhSeH, KO-*t*-Bu, *t*-BuOH/DMF, 3 h.

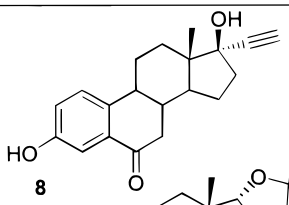
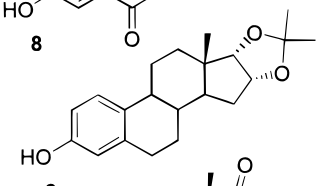
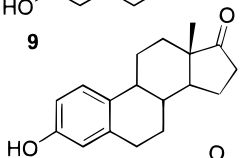
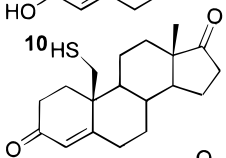
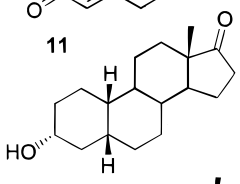
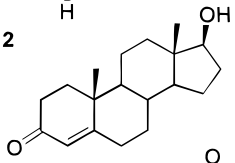
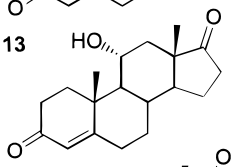
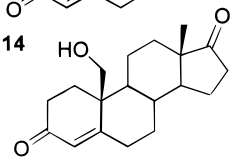
between the solid phases obtained via either route. Just like **4**, resin-bound selenoacetal **7** is air and moisture stable and can be stored for prolonged period of times.

Because the synthesis of steroid libraries is our ultimate goal, we tried to couple various steroids to resins **5** and **7**. Our resin of choice was N-benzylated aminomethyl resin.[10] As shown in Table 1, the coupling of the steroids to the resin proceeded in satisfactory to good yields. Although being a heterogeneous mixture, coupling to the selenoacetal **7** in the presence of K_2CO_3/AgOTf was successful as well, but the yield was lower (Table 1, entry 6). The yield of the coupling reactions were determined as follows: First, the loading of the linker (**3** or **6**) was determined from the gain of weight of the resin after coupling of the linker. Next, the theoretical loss of weight was calculated due to the removal of the *t*-$BuOCO_2$ or PhSe group. This then was abstracted from the weight of the resin to give the theoretical starting weight. The gain of weight, with respect to this theoretical starting weight, was then measured and divided by the theoretical maximum gain of weight to give the yield mentioned in Table 1. Admittedly, the determination of the yield is somewhat arbitrary, but we think this method gives the best representation of the yield of the coupling reaction.[11] Although in principle most steroids can be coupled to both the chloroacetal **5** and the selenoacetal **7**, we have a preference for the latter because of the shorter reaction times. However, we experienced certain limitations: Coupling of A-aromatic steroids to **7** has not been successful so far and we found that the coupling reaction to **5** is more sensitive to steric hindrance. For instance, although steroid **13** and **14** could be coupled to resin **7** (Table 1, entry 8 and 9), the coupling of steroid **13** to resin **5** went very sluggishly and the coupling of steroid **14** to resin **5** was not successful at all. The stability of the linker has not been tested extensively yet, but we found it to be stable under the following conditions: 0.1 M solution of AcOH/pyridine in MeOH, 0.1 M HCl in MeOH, 5% HCl in EtOH/CH_2Cl_2, 10% TFA in CH_2Cl_2, treatment with BuLi and Grignard reagents. However, considerable loss of substrate was observed when a 0.1 M solution of PPTS in MeOH was used.

Although cleavage was achieved under a variety of conditions for various resin-bound steroids, it was difficult to find cleavage conditions that could be applied to all resin-bound steroids. In the end, TBAF/tetramethyl urea turned out to be our cleavage system of choice because so far we have been able to cleave all steroids from the resin with this mixture. Agitation of the cleavage mixture with ultrasound accelerated the cleavage considerably. Furthermore, consecutive treatment with four aliquots under agitation with ultrasound gave even better results. Each aliquot resulted in only partial release of the steroid, which might be useful for the testing of libraries. However, TBAF/TMU at 100 °C seems to be the condition of choice in case of steroids that are difficult to cleave from the resin or if one wants to cleave all the steroid at once. The yields mentioned in Table 1 are based on the loadings calculated as described earlier (vide supra). ^{1}H NMR data of the cleaved steroids were in complete agreement with the ^{1}H NMR data of the starting materials **8**−**15**. No indication of the formation of side products was observed. As it might be difficult to compare the yields of the cleaved steroids with results from other resins, the amount of steroid obtained from 50 mg of resin (loaded with the steroid) is also given.

Having established suitable coupling and cleavage conditions, the linker is set for the use in solid-phase organic chemistry. To show its applicability, the linker was used in palladium-mediated coupling reactions of a resin-bound vinyl triflate. Vinyl triflates are excellent starting materials for C−C bond formation.[12] In addition, there are several (solution-phase) examples known in the literature where vinyl triflates have been prepared from keto-steroids and were subsequently used for C−C bond formation.[13] Therefore, steroidal vinyl triflates might be interesting scaffolds for library syntheses. Coupling of vinyl triflate **16** to resin **7** (X = *N*-benzyl) gave resin-bound vinyl triflate **17** (Scheme 3), which was used in a Heck and a Stille coupling reaction.

Table 1. Steroid Loading and Cleavage[a]

entry	steroid	coupling method[b]	yield[c]	cleaving method[d]	yield (weight)[e]
1	 **8**	A	80%	E	72% (4.8 mg)
2	 **9**	A	84%	F	50% (3.7 mg)
3	 **10**	A	n.d.[f]	G	(4.4 mg)
4				H	(2.3 mg)
5	 **11**	B	66%	I	30% (1.5 mg)
6	 **12**	C	[g]	E	(2 mg)[g, h]
7		D	85%	E	71% (3.8 mg)
8	 **13**	D	75%	E	33% (2 mg)
9	 **14**	D	67%	E	51% (2.7 mg)
10	 **15**	D	50%	E	50% (2.5 mg)

[a] Reference 10. [b] A: steroid, **5**, DIPEA, CH_2Cl_2, 18 h. B: steroid, **5**, KOtBu, *t*-BuOH/DMF, 5 h. C: steroid, **7**, AgOTf, K_2CO_3, 3 Å mol. sieves, CH_2Cl_2, 15 h. D: steroid, **7**, NIS, TfOH, CH_2Cl_2/dioxane, 1 h. [c] See text and ref 11. [d] E: TBAF, TMU, sonicate, 4 × 15 min. F: TBAF, TMU, microwave (100 W), 4 × 15 min. G: TBAF, TMU, 100 °C, 1 h. H: TBAF, THF, 50 °C, 20 h. I: TBAF/CsF, DMPU, sonicate, 4 h. [e] See text. In parentheses: amount of purified steroid obtained from 50 mg of loaded resin; >95% purity according to ^{1}H NMR. [f] Not determined. [g] Yield not determined due to contamination with silver salts. [h] ^{1}H NMR of the *crude* product indicated mixture PhSeH:**12** = 1:1.

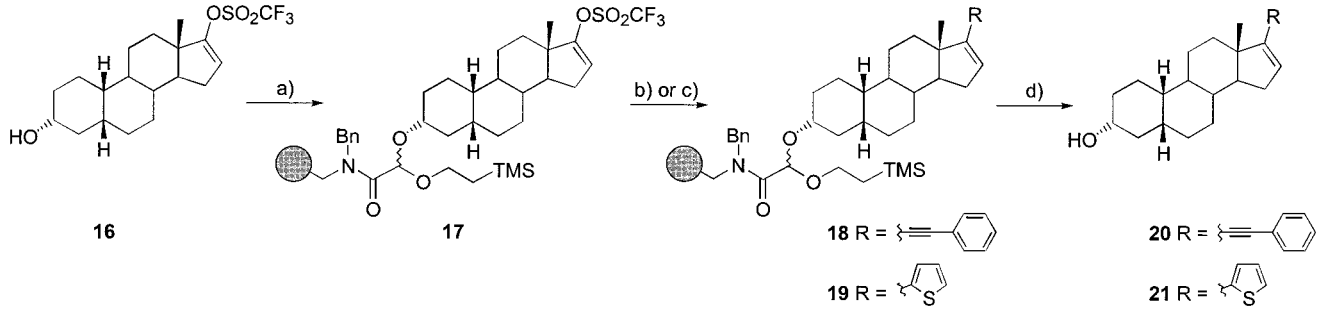
Both the attachment of steroid **16** to the resin and the palladium coupling reactions performed with resin **17** could easily be monitored by IR due to the distinct absorption of the triflate moiety at 1210 cm^{-1}. The resulting resins **18** and **19** were subsequently treated with TBAF/TMU at 100 °C to give steroid **20** and **21** in reasonable amounts and good purities (90−95% according to ^{1}H NMR; 90% according to HPLC).[14]

In conclusion, a facile method for the synthesis of a SEM-based linker has been developed for use in solid-phase organic chemistry. This SEM-linker can be used for the attachment to and detachment from the resin of (sterically very hindered) steroids. The application of this linker has been demonstrated in a Heck and a Stille coupling reaction. Further studies on the use of this SEM-linker for the synthesis of steroid libraries, immobilization of other substrates, and other solid-phase synthesis applications are underway and will be reported in due course.

Experimental Section

Standard reagents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 200 MHz or a Bruker DPX 400 MHz and are reported in ppm (δ). Infrared

Scheme 3[a]



[a] Reagents and conditions: (a) **7**, NIS, TfOH, CH_2Cl_2/dioxane, 1 h, 61%; (b) phenylacetylene, PPh_3, $Pd(OAc)_2$, DMF/Bu_3N, 80 °C, 2 h; (c) thienyl$SnBu_3$, $Pd(PPh_3)_4$, LiCl, DMF, 110 °C, 3 h; (d) TBAF, TMU, 100 °C, 1 h, 46% (**20**)/38% (**21**).

spectra were recorded on a Bruker Vector 22 equipped with a DRP-BR1 Praying Mantis Diffuse Reflection Accessory from Anadis Instruments. Cl analysis was performed on a Unicam Crystal CE system equipped with a Crystal 1000 conductivity detector. A Waters HPLC system equipped with a Waters 486 Tunable Absorbance Detector (set at 218 nm) and a Symmetry C18 column was used to determine the purity of **20** and **21**. Ultrasound-assisted cleavage reactions were carried out with a TranssonicDigital from Elma. Microwave-assisted cleavage reactions were performed using a MSP1000 from CEM.

Methyl Ester of Hydroxy[2-(trimethylsilyl)ethoxy]acetic Acid (2). Freshly distilled methyl glyoxylate (**1**) (7.9 g, 90 mmol) was dissolved in dichloromethane (70 mL), immediately followed by the addition of 2-(trimethylsilyl)-ethanol (16 mL, 112 mmol). The resulting solution was stirred for 20 h. Evaporation in vacuo gave hemiacetal **2** (13.5 g, 65 mmol) in 73% yield (crude) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 0.0 (s, 9 H, $Si(CH_3)_3$), 0.84−1.10 (m, 2 H, CH_2TMS), 3.64 (m, 1 H, *H*CHCH$_2$TMS), 3.81 (s, 3 H, OMe), 3.90 (m, 1 H, HC*H*CH$_2$TMS), 4.93 (s, 1 H, OCHO).

Methyl Ester of [[(1,1-Dimethylethoxy)carbonyl]oxy]-[2-(trimethylsilyl)ethoxy]acetic Acid (3). A solution of freshly prepared hemiacetal **2** (13.5 g, 65 mmol), *tert.*-butyl pyrocarbonate (16.5 g, 76 mmol), and *N*,*N*-(dimethylamino)-pyridine (740 mg, 6.06 mmol) in dichloromethane (150 mL) was stirred for 1 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (150 mL), and the water layer was extracted with dichloromethane (2 × 150 mL). The combined organic layers were dried over sodium sulfate. The crude product was purified by flash chromatography (ethyl acetate:heptane = 10:90 → 30:70) giving acetal **3** (15.7 g, 51 mmol) in 78% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.0 (s, 9 H, $Si(CH_3)_3$), 0.97 (ddd, 1 H, J = 5.9, 10.6, 13.7 Hz, *H*CHTMS), 1.03 (ddd, 1 H, J = 5.9, 11, 13.7 Hz, HC*H*TMS), 1.48 (s, 9 H, $C(CH_3)_3$), 3.74 (ddd, 1 H, J = 5.9, 9.8, 10.6 Hz, *H*CHCH$_2$TMS), 3.79 (s, 3 H, OMe), 3.87 (ddd, 1 H, J = 5.9, 9.8, 11 Hz, HC*H*CH$_2$TMS), 5.82 (s, 1 H, OCHO). ^{13}C NMR (50 MHz, $CDCl_3$): −1.4, 18.0, 27.7, 52.8, 68.1, 83.5, 94.4, 152.2, 166.4.

SEM-Resin 4 (X = *N*-benzyl). A 2 M solution of potassium hydroxide in water (11.7 mL, 23.4 mmol) was added to a solution of acetal **3** (3.60 g, 11.7 mmol) in methanol (80 mL). The resulting solution was stirred for 3 h, after which it was cooled to 0 °C. The solution was acidified with a 1 M solution of hydrogen chloride in water (11.7 mL, 11.7 mmol) followed by the addition of *N*,*N*-diisopropylethylamine (2 mL, 11.5 mmol). Water (160 mL) and saturated aqueous sodium chloride (40 mL) were added, and the water layer was extracted with dichloromethane (4 × 160 mL) containing *N*,*N*-diisopropylethylamine (4 × 2 mL). The combined organic layers were dried over sodium sulfate.

The crude product was dissolved in *N*,*N*-dimethylformamide (80 mL) and *N*,*N*-diisopropylethylamine (9 mL, 51.7 mmol), *N*-benzylated aminomethyl resin[10] (3 g, 2.34 mmol), and 2-(1*H*-benzotriazoyl-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (4.0 g, 12.5 mmol) were added consecutively. The resulting suspension was shaken for 18 h. After filtration, resin **4** was washed with *N*,*N*-dimethylformamide (2 × 30 mL), water (2 × 30 mL), ethanol/water (3:1) (2 × 30 mL), ethanol (2 × 30 mL), and dichloromethane (3 × 30 mL), in this order. Total weight: 3.58 g of resin-bound acetal **4** (91% on gain of weight, 0.59 mmol/g). IR: 1748, 1685 cm^{-1}.

SEM-Resin 5 (X = *N*-benzyl). Hydrogen chloride was bubbled through a suspension of resin-bound acetal **4** (500 mg, 0.30 mmol) in diethyl ether (15 mL) at 0 °C for 1 h. The resulting suspension was filtered and washed with diethyl ether (3 × 15 mL). Total weight: 471 mg of resin **5**. Cl analysis: 0.6 mmol/g. IR: 1663 cm^{-1}.

Methyl Ester of (Phenylseleno)[2-(trimethylsilyl)ethoxy]-acetic Acid (6). Hydrogen chloride was bubbled through a solution of acetal **3** (4.17 g, 13.6 mmol) in diethyl ether (50 mL) at 0 °C for 1 h, and the resulting solution was concentrated in vacuo.

A suspension of benzeneselenol (1.5 mL, 14.1 mmol) and potassium *tert*-butoxide (1.65 g, 14.7 mmol) in *tert*-butyl alcohol (11.5 mL) was freshly prepared, and *N*,*N*-dimethylformamide (5.6 mL) was added. This solution was added to the crude chloroacetal, and the resulting mixture was stirred for 3 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (60 mL), and the water layer was extracted with diethyl ether (4 × 60 mL). The combined organic layers were dried over sodium sulfate. Purification over silica (ethyl acetate:heptane = 10:90 → 20:80; 1% triethylamine) gave selenoacetal **6** (2.6 g, 7.5 mmol) in 55% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.0 (s, 9 H, $Si(CH_3)_3$), 0.94 (ddd, 1 H, J = 5.9, 9.8, 13.7 Hz, *H*CHTMS), 0.99 (ddd, 1 H, J = 5.9, 10.6, 13.7 Hz, HC*H*TMS), 3.56 (ddd, 1 H, J = 5.9, 10.6, 11 Hz, *H*CHCH$_2$TMS), 3.65 (s, 3 H, OMe), 3.95 (ddd, 1 H, J = 5.9, 9.8, 11 Hz, HC*H*CH$_2$TMS), 5.45 (s, 1 H, SeCHO), 7.29

(m, 3 H), 7.58 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): −1.3, 17.5, 52.4, 67.4, 80.9, 128.7, 129.2, 136.0.

SEM-Resin 7 (X = *N*-benzyl). A 2 M solution of potassium hydroxide in water (11.7 mL, 23.4 mmol) was added to a solution of selenoacetal **6** (4.04 g, 11.7 mmol) in methanol (80 mL). The resulting solution was stirred for 3 h, after which it was cooled to 0 °C. The solution was acidified with a 1 M solution of hydrogen chloride in water (11.7 mL, 11.7 mmol) followed by the addition of *N*,*N*-diisopropylethylamine (2 mL, 11.5 mmol). Water (160 mL) and saturated aqueous sodium chloride (40 mL) were added, and the water layer was extracted with dichloromethane (4 × 160 mL) containing *N*,*N*-diisopropylethylamine (4 × 2 mL). The combined organic layers were dried over sodium sulfate.

The crude product was dissolved in *N*,*N*-dimethylformamide (80 mL) and *N*,*N*-diisopropylethylamine (9 mL, 51.7 mmol), *N*-benzylated aminomethyl resin[10] (3 g, 2.34 mmol), and 2-(1*H*-benzotriazoyl-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (4.0 g, 12.5 mmol) were added consecutively. The resulting suspension was shaken for 18 h. After filtration, resin **7** was washed with *N*,*N*-dimethylformamide (2 × 30 mL), water (2 × 30 mL), ethanol/water (3:1) (2 × 30 mL), ethanol (2 × 30 mL), and dichloromethane (3 × 30 mL), in this order. Total weight: 3.63 g of resin-bound selenoacetal **7** (86% on gain of weight, 0.55 mmol/g). IR: 1652 cm^{-1}.

General Procedure for Coupling to Resin 5 (Steroid 8, 9, 10). A suspension of resin-bound chloroacetal **5** (235 mg, 0.15 mmol), the steroid (1.00 mmol), and *N*,*N*-diisopropylethylamine (250 μL, 1.43 mmol) in dichloromethane (3 mL) was shaken for 18 h. The resulting suspension was filtered, and the resulting resin was washed with dichloromethane (2 × 5 mL), saturated aqueous sodium hydrogencarbonate (5 mL), water (2 × 5 mL), ethanol/water (3:1) (2 × 5 mL), ethanol (2 × 5 mL), and dichloromethane (3 × 5 mL), in this order.

Coupling of Steroid 11 to Resin 5. Resin-bound chloroacetal **5** (200 mg, 0.12 mmol) was added to a solution of steroid **11** (145 mg, 0.45 mmol) and *t*-BuOK (50 mg, 0.44 mmol) in *tert*-butanol/*N*,*N*-dimethylformamide (0.7 mL/0.9 mL), and the resulting suspension was shaken for 5 h. The resulting suspension was filtered, and the resulting resin was washed with *N*,*N*-dimethylformamide (2 × 5 mL), saturated aqueous sodium hydrogencarbonate (5 mL), water (2 × 5 mL), ethanol/water (3:1) (2 × 5 mL), ethanol (2 × 5 mL), and dichloromethane (3 × 5 mL), in this order. Yield: 218 mg of resin-bound steroid was obtained (66%).

General Procedure for Coupling to Resin 7 (Steroid 12, 13, 14, 15). A solution of *N*-iodosuccinimide (68 mg, 0.30 mmol) and trifluoromethanesulfonic acid (5 μL, 0.06 mmol) in dichloromethane/dioxane (1.5 mL/1.5 mL) was freshly prepared. Part of this solution (1.3 mL) was added to a suspension of resin-bound selenoacetal **7** (200 mg, 0.12 mmol) and the steroid (0.47 mmol) in dichloromethane (2.5 mL) at 0 °C. The ice bath was removed, and the resulting suspension was shaken for 1 h. The dark brown suspension was filtered, and the resulting resin was washed with dichloromethane (2 × 10 mL), 10% aqueous sodium thiosulfate (10 mL), water (2 × 10 mL), ethanol/water (3:1) (2 × 10 mL), ethanol (2 × 10 mL), and dichloromethane (3 × 10 mL), in this order.

Coupling of Steroid 12 to Resin 7 Using AgOTf. Silver triflate (45 mg, 0.18 mmol) was added to a suspension of resin-bound selenoacetal **7** (100 mg, 0.055 mmol), steroid **12** (65 mg, 0.24 mmol), potassium carbonate (10 mg, 0.072 mmol), and 4 Å molecular sieves (4 beads) in dichloromethane (2 mL), and the resulting suspension was shaken for 15 h, excluded from light. The resulting suspension was filtered, and the resulting resin was washed with dichloromethane (2 × 5 mL), 0.04 M aqueous hydrogen chloride (5 mL), water (2 × 5 mL), 10% aqueous sodium thiosulfate (5 mL), water (2 × 5 mL), ethanol/water (3:1) (2 × 5 mL), *N*,*N*-dimethylformamide (2 × 5 mL), and dichloromethane (3 × 5 mL), in this order.

General Procedure for the Cleavage of Steroid 8, 12, 13, 14, 15. A suspension of resin-bound steroid (ca. 50 mg, 0.020 mmol) in a 0.1 M solution of tetrabutylammonium fluoride in tetramethylurea (0.5 mL) was agitated by ultrasound for 15 min. The resulting suspension was filtered, and the resin was washed with ethyl acetate (3 × 0.5 mL). This procedure was repeated three times (four cycles). The combined tetramethylurea/ethyl acetate fractions were washed with aqueous sodium chloride (3 × 5 mL) and dried over magnesium sulfate. The crude product was purified by solid-phase extraction (silica, ethyl acetate:heptane = 1:1), yielding the steroid.

Cleavage of Steroid 9. A suspension of resin-bound steroid (35 mg, 0.016 mmol) in a 0.1 M solution of tetrabutylammonium fluoride in tetramethylurea (0.5 mL) was agitated by microwaves (100 W) for 15 min. The resulting suspension was filtered, and the resin was washed with ethyl acetate (3 × 0.5 mL). This procedure was repeated three times (four cycles). The combined tetramethylurea/ethyl acetate fractions were washed with aqueous sodium chloride (3 × 5 mL) and dried over magnesium sulfate. The crude product was purified by solid-phase extraction (silica, ethyl acetate:heptane = 1:1) giving steroid **9** in 50% yield (2.6 mg, 0.08 mmol).

Cleavage of Steroid 10 in TMU. A suspension of the resin-bound steroid (50 mg) in a 0.1 M solution of tetrabutylammonium fluoride in tetramethylurea (0.5 mL) was kept at 100 °C for 1 h, and the resulting suspension was filtered. This procedure was repeated three times (four cycles). The combined filtrates were concentrated in vacuo, and the crude product was purified by solid-phase extraction (C18, 15 mL of water then 5 mL of methanol), yielding steroid **10** (4.4 mg, 0.016 mmol).

Cleavage of Steroid 10 in THF. A suspension of the resin-bound steroid (50 mg) in a 0.1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.5 mL) was kept at 50 °C for 20 h, and the resulting suspension was filtered. The resin was washed with ethyl acetate (3 × 1 mL), and the combined filtrates were concentrated in vacuo. The crude product was purified by solid-phase extraction (C18, 15 mL of water then 5 mL of methanol), yielding steroid **10** (2.3 mg, 0.008 mmol).

Cleavage of Steroid 11. A suspension of the resin-bound steroid (65 mg, 0.018 mmol) and CsF (40 mg, 0.26 mmol)

in a 0.06 M solution of tetrabutylammonium fluoride in DMPU (0.5 mL) was agitated by ultrasound for 4 h. The resulting suspension was filtered, and the resin was washed with ether (3 × 5 mL). The combined DMPU/ether fractions were washed with water (15 mL) and dried over sodium sulfate. The crude product was purified by solid-phase extraction (silica, ethyl acetate:heptane = 1:1), giving steroid **11** in 30% yield (1.5 mg, 0.005 mmol).

Resin 17. A solution of *N*-iodosuccinimide (225 mg, 1.00 mmol) and trifluoromethanesulfonic acid (16 μL, 0.18 mmol) in dichloromethane/dioxane (5 mL/5 mL) was freshly prepared. Part of this solution (6.5 mL) was added to a suspension of resin-bound selenoacetal **7** (600 mg, 0.33 mmol) and steroid **16** (565 mg, 1.38 mmol) in dichloromethane (8 mL), and the resulting suspension was shaken for 1 h. The dark brown suspension was filtered, and resin **17** was washed with dichloromethane (2 × 10 mL), 10% aqueous sodium thiosulfate (10 mL), water (2 × 10 mL), ethanol/water (3:1) (2 × 10 mL), ethanol (2 × 10 mL), and dichloromethane (3 × 10 mL), in this order. Yield: 630 mg of resin-bound steroid **17** was obtained (61%). IR: 1660, 1210 cm^{-1}.

Resin 18. A solution of palladium(II)acetate (6 mg, 0.03 mmol) and triphenylphosphine (13 mg, 0.05 mmol) in *N*,*N*-dimethylformamide (2 mL) was added to resin-bound steroid **17** (48 mg, 0.015 mmol). Tributylamine (1.2 mL) and phenylacetylene (140 μL, 1.27 mmol) were added, and the resulting suspension was kept at 80 °C for 2 h. Then, resin **18** was washed with *N*,*N*-dimethylformamide (2 × 2 mL), methanol (2 × 2 mL), and dichloromethane (3 × 2 mL). Yield: 47 mg of resin-bound steroid **18** was obtained.

Resin 19. A solution of tetrakis(triphenylphosphine)-palladium(0) (5 mg, 4.3 μmol), lithium chloride (15 mg, 0.35 mmol), and 2-(tributylstannyl)thiophene (66 μL, 0.21 mmol) in *N*,*N*-dimethylformamide (2 mL) was added to resin-bound steroid **17** (48 mg, 0.015 mmol), and the resulting suspension was kept at 110 °C for 3 h. Then, resin **19** was washed with *N*,*N*-dimethylformamide (2 × 2 mL), methanol (2 × 2 mL), and dichloromethane (3 × 2 mL). Yield: 46 mg of resin-bound steroid **19** was obtained.

19-Nor-21-phenyl-5β-pregn-16-en-20-yne (20). A 0.1 M solution of tetrabutylammonium fluoride in tetramethylurea (0.5 mL) was added to resin-bound steroid **18** (45 mg), and the resulting suspension was kept at 100 °C for 60 min. The resulting suspension was filtered, and the resin was washed with ethyl acetate (3 × 0.5 mL). The combined filtrates were concentrated in vacuo, and the crude product was purified by solid-phase extraction (ethyl acetate:heptane = 1:1), giving steroid **20** (2.4 mg, 0.007 mmol) in 46% overall yield from **17** as a white solid. MS: ESI *m*/*z* (relative intensity) 361 (20) [MH^+], 343 (100) [$MH^+ - H_2O$]. ^{1}H NMR (200 MHz, $CDCl_3$): 0.89 (m, 1 H), 0.90 (s, 3 H, 18-Me), 1.08−1.98 (m, 18 H), 1.96 (dd, 1 H, J = 2, 11 Hz), 2.06 (dd, 1 H, J = 2, 11 Hz), 2.24 (ddd, 1 H, J = 3, 6.5, 16 Hz), 3.64 (m, 1 H, H-3), 6.09 (dd, 1 H, J = 2, 3.5 Hz), 7.29 (m, 3 H), 7.44 (m, 2 H). HPLC purity of 90%.

17-(2′-Thiophenyl)-5β-estra-16-ene (21). A 0.1 M solution of tetrabutylammonium fluoride in tetramethylurea (0.5 mL) was added to resin-bound steroid **19** (45 mg), and the resulting suspension was kept at 100 °C for 60 min. The resulting suspension was filtered, and the resin was washed with ethyl acetate (3 × 0.5 mL). The combined filtrates were concentrated in vacuo, and the crude product was purified by solid-phase extraction (ethyl acetate:heptane = 1:1), giving steroid **21** (1.8 mg, 0.005 mmol) in 38% overall yield from **17** as a white solid. MS: ESI *m*/*z* (relative intensity) 343 (60) [MH^+], 325 (100) [$MH^+ - H_2O$]. ^{1}H NMR (200 MHz, $CDCl_3$): 0.88 (m, 1 H), 1.00 (s, 3 H, 18-Me), 1.15−1.85 (m, 16 H), 1.94 (m, 2 H), 2.15−2.28 (m, 3 H), 3.63 (m, 1 H, H-3), 5.96 (dd, 1 H, J = 2, 3 Hz), 6.96 (dd, 1 H, J = 3.5, 5 Hz, Th-4) 7.03 (dd, 1 H, J = 1, 4 Hz, Th-3), 7.14 (dd, 1 H, J = 1, 5 Hz, Th-5). HPLC purity of 90%.

Supporting Information Available. ^{1}H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(10) The N-benzylated aminomethyl resin was obtained via Swern oxidation of hydroxymethylene resin followed by a reductive amination with benzylamine.

(11) For example, the coupling of **8** via **5**: The loading of **4** is 0.59 mmol/g. Therefore, 256 mg of **4** equals 0.15 mmol. Treatment with HCl will result in the loss of 0.15 mmol × 117 (molecular weight of *t*-$BuOCO_2$) = 17.6 mg. The theoretical starting weight is 256 − 17.6 = 238.4 mg. Maximum gain of weight will be 0.15 mmol × 310

(molecular weight of **8**) = 46.5 mg. After the reaction, 275.5 mg of resin was recovered. Therefore, 275.5 − 238.4 (theoretical starting weight) = 37.1 mg of **8** was coupled. The yield of the reaction is (37.1/46.5) × 100% = 80%. The loading of the resulting resin is (37.1/310)/0.2755 = 0.43 mmol/g.

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(14) This chemistry has been used for the synthesis of several libraries, which for patenting reasons will be reported in due course.

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