[1] a) M. L. Zapp, S. Stern, M. R. Green, *Cell* **1993**, *74*, 969 – 978; b) B. Clouet-d'Orval, T. K. Stage, O. C. Uhlenbeck, *Biochemistry* **1995**, *34*, 11186 – 11190; c) Y. Tor, T. Hermann, E. Westhof, *Chem. Biol.* **1998**, *5*, R277-R283; d) U. von Ahsen, J. Davies, R. Schroeder, *Nature* **1991**, *353*, 368 – 370; e) Y. Wang, J. Killian, K. Hamasaki, R. Rando, *Biochemistry* **1996**, *35*, 12338 – 12346; f) L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, *Chem. Biol.* **1997**, *4*, 35 – 50.

[2] a) D. Moazed, H. F. Noller, *Nature* **1987**, *327*, 389 – 394; b) P. Purohit, S. Stern, *Nature* **1994**, *370*, 659 – 662; c) D. Formy, M. I. Recht, S. C. Blanchard, J. D. Puglisi, *Science* **1996**, *274*, 1367 – 1371.

[3] a) M. Howard, R. A. Frizzell, D. M. Bedwell, *Nat. Med.* **1996**, *2*, 467 – 469; b) G. Werstuck, M. R. Green, *Science* **1998**, *282*, 296 – 298.

[4] E. Shtivelman, B. Lifshitz, R. P. Gale, E. Canaani, *Nature* **1985**, *315*, 550 – 555.

[5] A. B. Raitano, Y. E. Whang, C. L. Sawyer, *Biochem. Biophys. Acta* **1997**, F201-F216.

[6] a) S. Kharbanda, R. Ren, P. Pandey, T. D. Shafman, S. M. Feller, R. R. Weichselbaum, D. W. Kufe, *Nature* **1995**, *376*, 785 – 788; b) Z. G. Liu, R. Baskaran, E. T. Lea-Chou, L. D. Wood, Y. Chen, M. Karin, J. Y. Wang, *Nature* **1996**, *384*, 273 – 276.

[7] a) T. Skorski, P. Kanakaraj, D. H. Ku, M. Nieborowska-Skorska, E. Canaani, G. Zon, B. Perussia, B. Calabretta, *J. Exp. Med.* **1994**, *179*, 11855 – 11865; b) R. A. Mandanas, D. S. Leibowitz, K. Gharenbaghi, T. Tauchi, G. S. Burgess, K. Miyazawa, H. N. Jayaram, H. S. Boswell, *Blood* **1993**, *82*, 1838 – 1847.

[8] C. Turc-Carel, S. Lizard-Nacol, E. Justrabo, M. Favrot, T. Philip, E. Tabone, *Cancer Genet. Cytogenet.* **1986**, *19*, 361 – 362.

[9] N. Galili, R. J. Davis, W. J. Fredericks, S. Mukhopadhyay, F. J. Rauscher III, B. S. Emanuel, G. Rovera, F. G. Barr, *Nat. Genet.* **1993**, *5*, 230 – 235.

[10] a) C. Szczylik, T. Skorski, N. C. Nicolaides, L. Manzella, L. Malaguarnera, D. Venturelli, A. M. Gewirtz, B. Calabretta, *Science* **1991**, *253*, 562 – 565; b) M. Bernasconi, A. Remppis, W. J. Fredericks, F. J. Rauscher III, B. W. Schaefer, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 13164 – 13169.

[11] M. Hendrix, E. S. Priestly, G. F. Joyce, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 3641 – 3648.

[12] M. Hendrix, P. B. Alper, E. S. Priestly, C.-H. Wong, *Angew. Chem.* **1997**, *109*, 119 – 122; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 95 – 98.

[13] W. A. Greenberg, E. S. Priestly, P. S. Sears, P. B. Alper, C. Rosenbohm, M. Hendrix, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 6527 – 6541.

New Selenium-Based Safety-Catch Linkers: Solid-Phase Semisynthesis of Vancomycin**

K. C. Nicolaou,* Nicolas Winssinger, Robert Hughes, Christopher Smethurst, and Suk Young Cho

The generation of molecular diversity through solid-phase combinatorial chemistry has become an important component of the drug discovery process.[1] An enduring challenge in the design of solid-phase synthetic sequences is the selection of an appropriate linker[2] that is stable to the proposed chemistry, yet which can be readily and practically cleaved. Solid-phase synthesis of natural products offers a particularly good platform to evaluate linkers because of the multitude of functionality often present. Vancomycin[3] (**1**, Scheme 1), renowned for its activity against methicillin-resistant *Staphylococcus aurus* (MRSA), has been used for the past forty years to treat Gram-positive bacterial infections. The emergence of vancomycin-resistant *enterococci* strains (VRE) has raised serious health concerns and prompted a renewed vigor in the field of glycopetide antibiotics.[3, 4] Researchers from Eli Lilly have demonstrated that modification of the oligosaccharide portion of vancomycin can enhance its activity against VRE to a clinically significant level.[5] However, more in-depth investigations of the role of the oligosaccharide unit in the glycopeptide's biological activity has been hampered by the synthetic inaccessibility of analogues. The completion of the total synthesis of vancomycin in these laboratories[6] encouraged us to investigate a solid-phase approach to the glycosidation of vancomycin's aglycon, which might be applicable to the semisynthesis of vancomycin libraries for biological screening purposes. Herein we report the preparation and scope of a selenium-based safety-catch linker and its application to the solid-phase semisynthesis of vancomycin (**1**).

Vancomycin's carboxylic acid group was identified as the most suitable site for linkage to a solid support since it is the only singularly present functional group on vancomycin and, therefore, does not require some form of regioselective derivatization. The required protected vancomycin **2** was readily prepared in two steps from **1** as shown in Scheme 1. The criteria for the selection of a linker included acid and base

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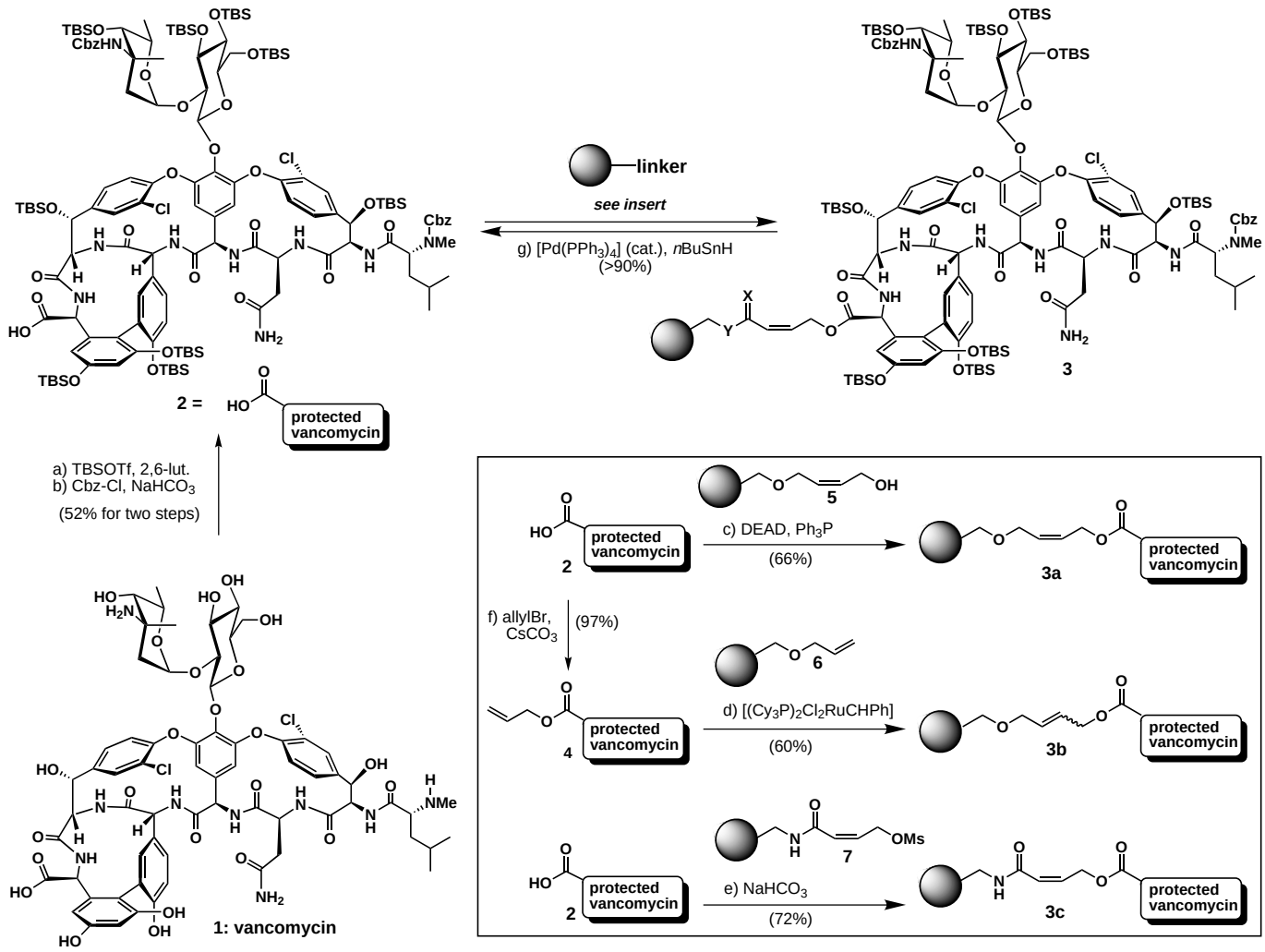


Scheme 1. Protection of vancomycin, as well as loading onto and cleavage from allyl ester resins. Reagents and conditions: a) TBSOTf (excess), 2,6-lutidine (120 equiv), CH_2Cl_2:DMF (10:1), 23 °C, sonication, 8 h; b) CbzCl (5.0 equiv), $NaHCO_3$ (10 equiv), 1,4-dioxane: H_2O (3:1), 23 °C, 3 h, 52% over two steps; c) **5** (7.0 equiv), DEAD (7.0 equiv), Ph_3P (7.0 equiv), THF, −15 °C, 1.5 h, 66%; d) **6** (10.0 equiv), $[(Cy_3P)_2Cl_2RuCHPh]$, (2 × 0.1 equiv), benzene, 65 °C, 15 h, 60%; e) **7** (4.0 equiv), $NaHCO_3$ (10.0 equiv), 4-Å molecular sieves, 23 °C (vacuum), 0.5 h; DMF, 65 °C, 18 h, 72%, f) allylBr (10.0 equiv), $NaHCO_3$ (10.0 equiv), 4-Å molecular sieves, DMF, 23 °C (vacuum), 0.5 h; 8 h, 97%. Cbz = benzyloxycarbonyl, Cy = cyclohexyl, DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, lut. = lutidine, TBS = *tert*-butyldimethylsilyl.

stability, as well as mild loading and cleavage conditions compatible with silyl protecting groups. Our first efforts focused on photolabile[7] linkers because of their mild cleavage; however, an acceptable compromise between loading and cleavage efficiency could not be reached. We then turned our attention to allylic ester linkers.[8] As shown in Scheme 1, protected vancomycin **2** was loaded in good yield using Mitsunobu, cross metathesis, or alkylation techniques. All three linkers were cleaved in excellent yield under the very mild palladium(0)-mediated allyl transfer conditions.[9] However, the cleavage efficiency of the linkers in **3a** and **3b** was dramatically reduced after exposure to the Lewis acidic conditions utilized in the glycosidation, presumably as a result of a [3,3] sigmatropic rearrangement[10] to give a secondary allylic ester. The allylic acrylate linker in **3c**, although stable to the glycosidation conditions, was found to be susceptible to premature cleavage and deactivation, which was assumed to arise from a nucleophilic attack on the acrylate functionality. It soon became clear that despite the attractiveness of their mild and efficient cleavage, the linkers in **3a**–**c** were not suitable for application to the vancomycin problem.

In the search for alternative strategies to solve the problem at hand we turned our attention to our recently reported preparation of polymer-bound selenenyl bromide.[11] We reasoned that the facile oxidation/elimination of the polymer-bound phenylseleno group could be used to mask an allylic functionality (Figure 1), thus serving as a pro-allyl safety-catch linker. Since the presence of residual tin can be detrimental to purification and biological assays we further envisioned the use of polymer-bound tin hydride[12] for the removal of the allyl group. Thus, the proposed strategy retains the critical, but cumbersome elements on the resin, and provides a measure of waste control and disposal. To test the scope of this proposal, we prepared resins **9**–**11** (Scheme 2). Thus, $LiBH_4$ reduction of the polymer-bound phenyl selenenyl bromide **8** afforded the corresponding lithiated selenium species, which was quenched with either 1,3-diiodopropane or 3-iodopropanol to furnish resins **9** or **10**, respectively. Treat-

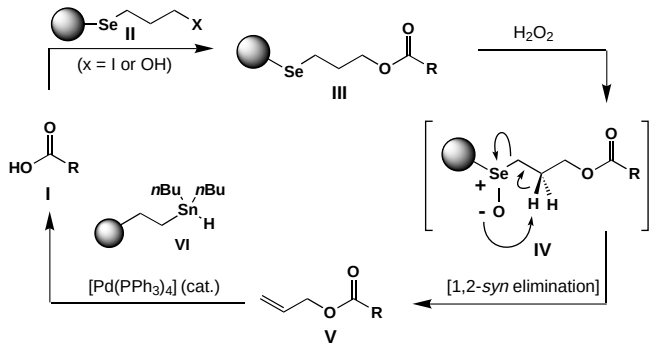
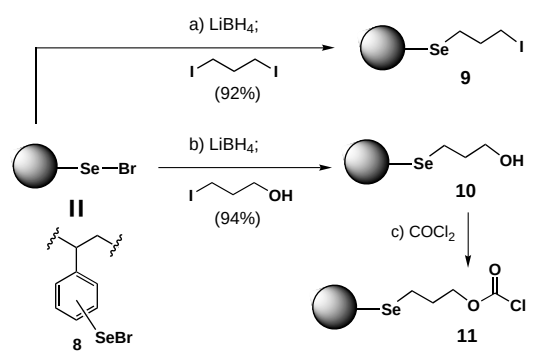
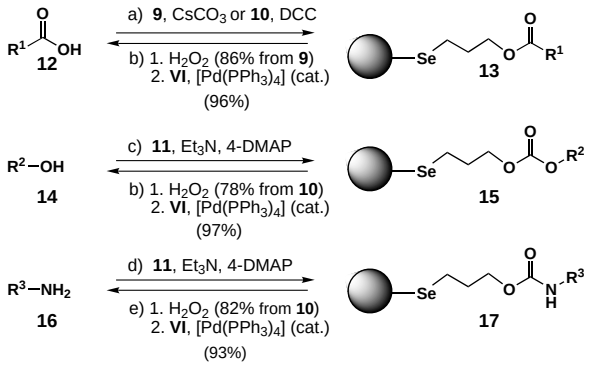


Figure 1. General concept of the selenium-based resin as a pro-allyl or pro-alloc safety-catch linker.



Scheme 2. Synthesis of pro-allyl and pro-alloc selenium linkers. Reagents and conditions: a) $LiBH_4$ (1.5 equiv), THF, 0 °C, 0.5 h, wash, 1,3-diiodopropane (4.0 equiv), THF:DMF (1:1), 23 °C, 5 h, 92 %; b) $LiBH_4$ (1.5 equiv), THF, 0 °C, 0.5 h, wash, 3-iodopropanol (4.0 equiv), THF:DMF (1:1), 23 °C, 5 h, 94 %; c) $COCl_2$ (4.0 equiv), THF, 23 °C, 5 h. Yields are calculated on the basis of the mass gain of the polymer. Alloc = allyloxycarbonyl.

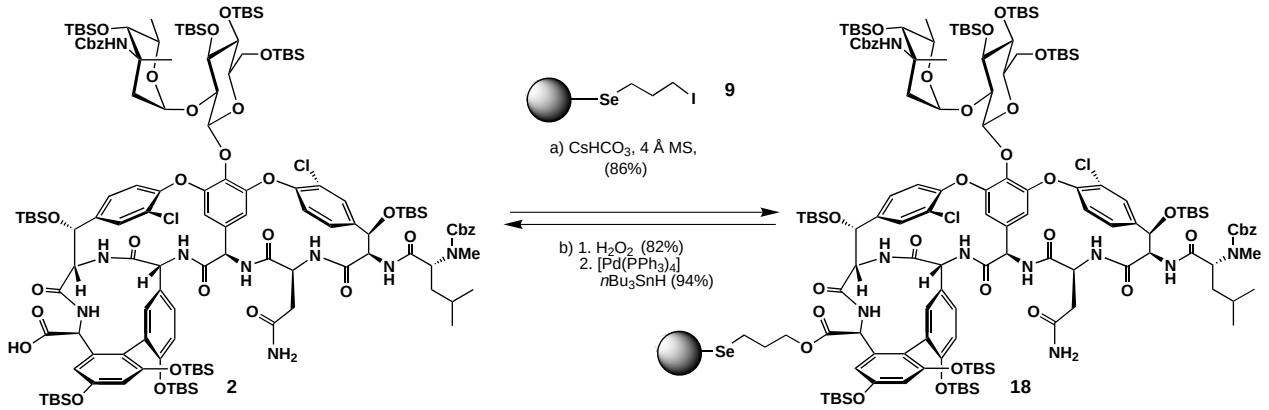
ment of resin **10** with phosgene afforded polymer-bound chloroformate **11**. We were gratified to find that the pro-allyl ester **13** (Scheme 3) was formed smoothly by either alkylation or esterification of resins **9** and **10**, respectively. Furthermore, formation of pro-alloc derivatives **15** and **17** also proceeded smoothly (Scheme 3). Treatment of polymer-bound pro-allyl derivative **13** as well as pro-alloc compounds **15** and **17** with H_2O_2, followed by exposure to catalytic amounts of [Pd(PPh$_3$)$_4$] and polymer-bound tin hydride **VI** (Figure 1)



Scheme 3. Loading onto and cleavage from pro-allyl and pro-alloc selenium resins. Reagents and conditions: a) **12** (4.0 equiv), $CsCO_3$ (4.0 equiv), DMF, 50 °C, 5 h or **12** (4.0 equiv), DCC (4.0 equiv), DMF, 23 °C, 15 h; b) 1. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 60 °C, 10 h, 86 % from **9** and 78 % from **10**; 2. **VI** (3.0 equiv), [Pd(PPh$_3$)$_4$] (0.1 equiv), CH_2Cl_2, 23 °C, 0.5 h, 96 % for **12** and 97 % for **14**; c) **11** (4.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), 23 °C, 6 h; d) **11** (4.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), 23 °C, 3 h; e) 1. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 60 °C, 10 h, 82 % from **10**; 2. **VI** (3.0 equiv), [Pd(PPh$_3$)$_4$] (0.1 equiv), AcOH (4.0 equiv), CH_2Cl_2, 23 °C, 0.5 h, 93 %. R^1 = 4-bromophenyl, R^2 = 4-iodobenzyl, R^3NH_2 = methoxyvaline, DCC = *N*,*N*′-dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylaminopyridine.

furnished carboxylic acid **12**, alcohol **14**, and amine **16** in yields of 86, 78, and 82 %, respectively. More importantly, loading and cleavage of protected vancomycin derivative **2** proceeded smoothly via intermediate **18** (Scheme 4) and without the previously discussed limitations of the allyl linkers shown in Scheme 1.

The now readily available polymer-bound vancomycin derivative **2** was utilized to demonstrate an efficient sequence of deglycosidation and re-glycosidation reactions leading to vancomycin (**1**, Scheme 5). Thus, the disaccharide moiety was hydrolyzed from **2** under acidic conditions to provide polymer-bound phenol **19**, which was glycosylated with the imidate **20**[6a] ($BF_3 \cdot Et_2O$) to afford glycoside **21**. Deprotection of the C-2 alloc group using palladium(0)-mediated allyl transfer conditions afforded compound **22** (see Table 1) in excellent yield. The polymer-bound monosaccharide **22** was then subjected to a second glycosidation reaction with



Scheme 4. Loading and cleavage of the vancomycin scaffold using a pro-allyl safety-catch linker. Reagents and conditions: a) **9** (8.0 equiv), $CsHCO_3$ (5.0 equiv), DMF, 23 °C (vacuum), 0.5 h, 50 °C, 5 h, 86 %; b) 1. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 23 °C, 48 h, 82 %; 2. [Pd(PPh$_3$)$_4$] (0.1 equiv), *n*$BuSn_3H$ (4.0 equiv), CH_2Cl_2, 0.5 h, 94 %. The loading yield is based on the mass gain of the polymer.

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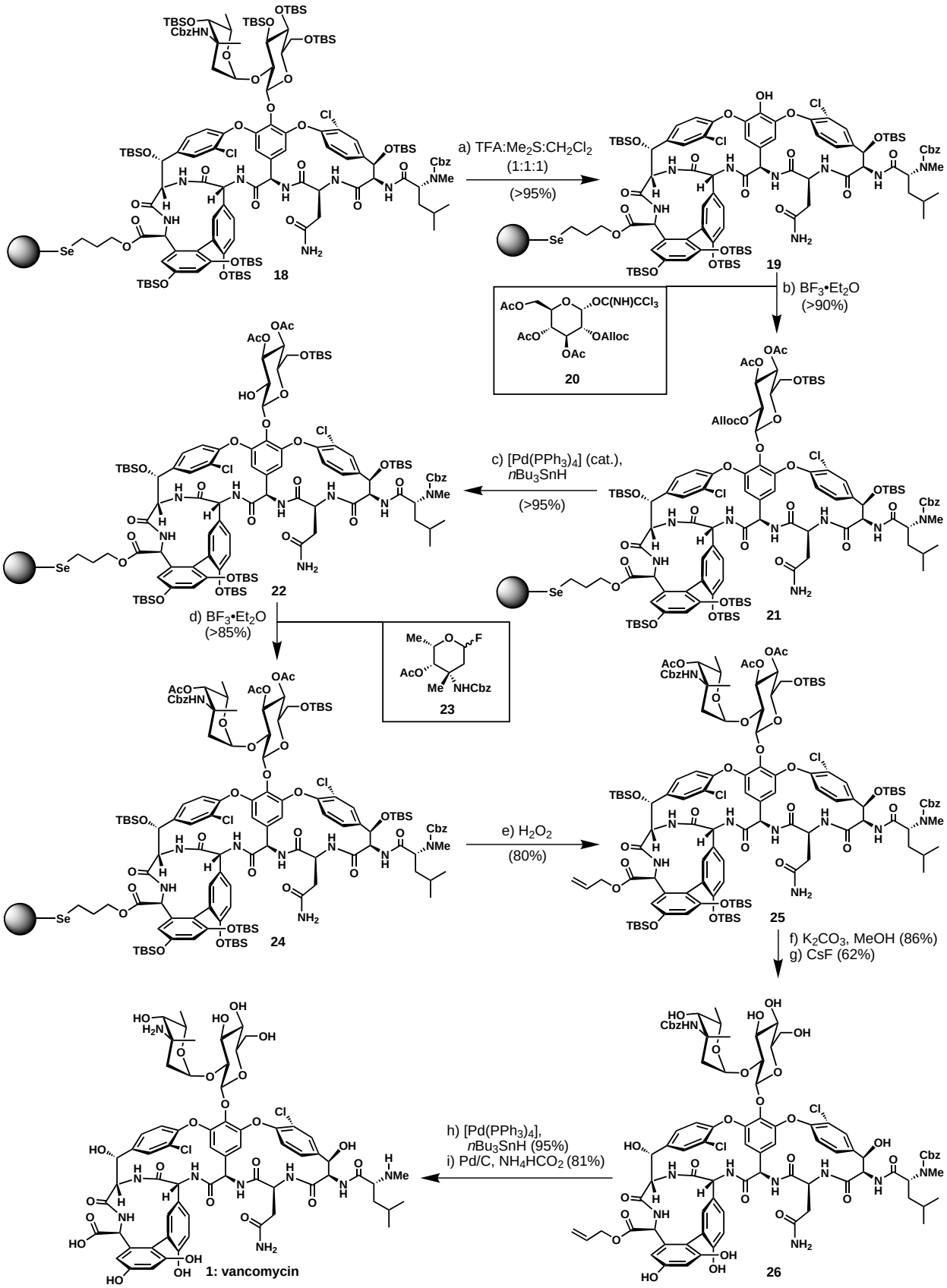

Scheme 5. Solid-phase semisynthesis of vancomycin **1**. Reagents and conditions. a) TFA:Me_2S:CH_2Cl_2 (1:1:1), 23 °C, 3 h, >95%; b) **20** (6.0 equiv), $BF_3 \cdot Et_2O$ (9.0 equiv), 4-Å molecular sieves, −40 →0 °C, 12 h, >90%; c) $[Pd(PPh_3)_4]$ (0.1 equiv), nBu_3SnH (10.0 equiv), CH_2Cl_2, 23 °C, 2 h, >95%; d) **23** (4.0 equiv), $BF_3 \cdot Et_2O$ (6.0 equiv), −40 →0 °C, 4 h, >85%; e) H_2O_2, THF, 23 °C, 48 h, 80%; f) K_2CO_3, MeOH, 23 °C, 6 h, 86%; g) CsF, DMF, 23 °C, 15 h, 62%; h) $[Pd(PPh_3)_4]$, nBu_3SnH, DMF, 23 °C, 1 h, 95%; i) 10% Pd/C, NH_4HCO_2, H_2O:AcOH (1:1), 23 °C, 4 h, 81%. Ac = acetyl, TFA = trifluoroacetic acid. Yields for the reactions carried out on a solid phase are estimates based on ^1H NMR, MS, and TLC analysis of the crude cleavage product.

Table 1. Selected physical data for compounds **22** and **25**.

22 (oxidative cleavage product): $R_f = 0.39$ (silica gel, 5% MeOH in CH_2Cl_2); ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.53-7.48$ (m, 2H), 7.43–7.38 (m, 2H), 7.38–7.27 (m, 7H), 7.27 (s, 1H), 7.08 (d, $J = 2.0$ Hz, 1H), 7.01 (dd, $J = 9.5$, 2.0 Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.41 (d, $J =$ 1.5 Hz, 1H), 6.39 (d, $J = 1.5$ Hz, 1H), 5.98–5.90 (m, 1H), 5.90–5.87 (m, 1H), 5.79 (s, 1H), 5.56–5.17 (m, 9H), 5.01–4.84 (m, 6H), 4.73–4.50 (m, 6H), 4.25–4.18 (m, 1H), 4.11 (s, 1H), 3.89–3.84 (m, 1H), 3.74–3.68 (m, 1H), 3.78–3.70 (m, 1H), 3.60 (dd, $J = 11.0$, 3.2 Hz, 1H), 2.93 (s, 3H, NCH_3), 2.55–2.40 (m, 2H), 2.03 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 1.78–1.75 (m, 1H), 1.53–1.49 (m, 2H), 1.01 (s, 9H, *t*BuSi), 0.94 (s, 9H, *t*BuSi), 0.93–0.91 (m, 6H), 0.89 (s, 9H, *t*BuSi), 0.77(s, 9H, *t*BuSi), 0.73 (s, 9H, *t*BuSi), 0.63 (s, 9H, *t*BuSi), 0.23 (s, 6H, CH_3Si), 0.18 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si), −0.08 (s, 3H, CH_3Si), −0.09 (s, 3H, CH_3Si); MS (ES^+): calcd for $C_{110}H_{160}Cl_2N_8O_{26}Si_6$ [$M+H^+$]: 2247; found: 2247.

25: $R_f = 0.40$ (silica gel, 5% MeOH in CH_2Cl_2); ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.65-7.45$ (m, 3H), 7.40–7.20 (m, 12H), 7.10–7.08 (m, 2H), 7.03 (m, 2H), 6.80 (d, $J = 0.5$ Hz, 1H), 6.78 (d, $J = 0.5$ Hz, 1H), 6.44 (d, $J = 2.0$ Hz, 1H), 6.40 (s, 1H), 5.91 (m, 1H), 5.83–5.78 (m, 2H), 5.64–5.45 (m, 2H), 5.44–5.28 (m, 5H), 5.26–5.10 (m, 5H), 5.01 and 4.88 (AB, $J = 12.5$ Hz, 2H), 4.64 (m, 2H), 4.18–4.07 (m, 2H), 3.85–3.80 (m, 2H), 3.64 (m, 1H), 2.94 (s, 3H, NCH_3), 2.48 (m, 2H), 2.03 (s, 3H), 2.05–1.98 (m, 5H), 1.92 (s, 3H), 1.55 (brs, 3H), 1.29 (s, 3H), 1.09 (m, 3H), 1.02 (s, 9H, *t*BuSi), 0.97 (s, 9H, *t*BuSi), 0.93 (m, 6H), 0.88 (s, 9H, *t*BuSi), 0.82 (s, 9H, *t*BuSi), 0.79 (s, 9H, *t*BuSi), 0.71 (s, 9H, *t*BuSi), 0.24 (s, 3H, CH_3Si), 0.23 (s, 3H, CH_3Si), 0.19 (s, 3H, CH_3Si), 0.18 (s, 3H, CH_3Si), 0.13 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.10 (m, 6H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si), −0.06 (s, 3H, CH_3Si), −0.08 (s, 3H, CH_3Si); MS (ES^+): calcd for $C_{127}H_{181}Cl_2N_9O_{31}Si_6Na$ [$M+Na^+$]: 2592; found: 2592.

glycosyl fluoride **23**[6a] ($BF_3 \cdot Et_2O$) to deliver fully protected polymer-bound vancomycin derivative **24**, which was cleaved with H_2O_2 to release allyl derivative **25** (see Table 1). Finally, vancomycin (**1**) was obtained from **26** through a deprotection sequence involving deacetylation (K_2CO_3/MeOH), desilylation (CsF), deprotection of the carboxylic acid group ($[Pd(PPh_3)_4]$/nBu$_3$SnH[13]), and Cbz cleavage (10% Pd/C, NH_4HCO_2) via intermediate **26**. It is important to note that the four-step deprotection sequence is carried out without work-ups and requires only two purifications (at the stages where **26** and **1** are formed). An interesting solvent effect was observed during the course of studying the desilylation of this series of compounds. Namely, it was found that the phenolic silyl groups could be cleanly removed without affecting the other secondary silyl-protected hydroxyl groups on the core of vancomycin by carrying out the CsF-induced deprotection in CH_3CN rather than DMF.

In conclusion, we have prepared a new set of selenium-based safety-catch linkers for carboxylic acids, alcohols, and amines. The utility of one of these linkers was demonstrated with a solid-phase semisynthesis of vancomycin (**1**). The developed technology and sequence has potential for the construction of vancomycin libraries for biological screening purposes starting from the readily available vancomycin scaffold.

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[1] a) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery* (Eds.: E. M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**, p. 516; b) R. E. Dolle, *Mol. Diversity* **1998**, *3*, 199–233; c) R. E. Dolle, K. H. Nelson, Jr., *J. Comb. Chem.* **1999**, *1*, 235–282.

[2] For a review of linkers, see I. W. James, *Tetrahedron* **1999**, *55*, 4855–4946.

[3] For reviews, see a) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem.* **1999**, *111*, 2230–2287; *Angew. Chem. Int. Ed.* **1999**, *38*, 2097–2152; b) D. H. Williams, B. Bardsley, *Angew. Chem.* **1999**, *111*, 1264–1286; *Angew. Chem. Int. Ed.* **1999**, *38*, 1172–1193.

[4] a) M. Adamczyk, J. A. Moore, S. D. Rege, Z. Yu, *Bioorg. Med. Chem. Lett.* **1999**, *16*, 2437–2440; b) D. Süssmuth, S. Pelzer, G. Nicholson, T. Walk, W. Wohlleben, G. Jung, *Angew. Chem.* **1999**, *111*, 2096–2099; *Angew. Chem. Int. Ed.* **1999**, *38*, 1976–1979; c) T. F. Gale, J. Gorlitzer, S. W. O'Brien, D. H. Williams, *J. Chem. Soc. Perkin Trans. 1* **1999**, *16*, 2267–2270; d) H. Arimoto, K. Nishimura, I. Hayakawa, T. Kinumi, D. Uemura, *Chem. Commun.* **1999**, *15*, 1361–1362; e) J. Rao, L. Yan, J. Lahiri, G. M. Whitesides, R. M. Weis, H. S. Shaw, *Chem. Biol.* **1999**, *6*, 353–359; f) D. P. O'Brien, R. M. H. Entress, M. A. Cooper, S. W. O'Brien, A. Hopkinson, D. H. Williams, *J. Am. Chem. Soc.* **1999**, *121*, 5259–5265; g) R. Xu, G. Greiveldinger, L. Marenus, A. Cooper, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 4898–4899; h) M. Ge, Z. Chen, H. R. Onishi, J. Kohler, L. L. Silver, R. Kerns, S. Fukuzawa, C. Thompson, D. Kahne, *Science* **1999**, *284*, 507–511; i) P. J. Solenberg, P. Matsushima, D. R. Stack, S. C. Wilkie, R. C. Thompson, R. H. Baltz, *Chem. Biol.* **1997**, *4*, 195–199.

[5] R. Nagarajan, *J. Antibiot.* **1993**, *46*, 1181–1195.

[6] a) K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem.* **1999**, *111*, 253–255; *Angew. Chem. Int. Ed.* **1999**, *38*, 240–244; b) K. C. Nicolaou, H. Li, C. N. C. Boddy, J. M. Ramanjulu, T. Y. Yue, S. Natarajan, X.-J. Chu, S. Bräse, R. Rübsam, *Chem. Eur. J.* **1999**, *5*, 2584–2601; K. C. Nicolaou, C. N. C. Boddy, H. Li, A. E. Koumbis, R. Hughes, S. Natarajan, N. F. Jain, J. M. Ramanjulu, S. Bräse, *Chem. Eur. J.* **1999**, *5*, 2602–2621; K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li, R. Hughes, *Chem. Eur. J.* **1999**, *5*, 2622–2647; K. C. Nicolaou, H. J. Mitchell, N. F. Jain, T. Bando, R. Hughes, N. Winssinger, S. Natarajan, A. E. Koumbis, *Chem. Eur. J.* **1999**, *5*, 2648–2667. For a total synthesis of vancomycin's aglycon, see c) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. K. Katz, *Angew. Chem.* **1998**, *110*, 2864–2868; *Angew. Chem. Int. Ed.* **1998**, *37*, 2700–2704; D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2868–2872; *Angew. Chem. Int. Ed.* **1998**, *37*, 2704–270; d) K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *110*, 2872–2878; *Angew. Chem. Int. Ed.* **1998**, *37*, 2708–2714; K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis, T. Bando, *Angew. Chem.* **1998**, *110*, 2879–2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2714–2717; K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando, J. M. Ramanjulu, *Angew. Chem.* **1998**, *110*, 2881–2883; *Angew. Chem. Int. Ed.* **1998**, *37*, 2717–2719; c) D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, O. Loiseleur, S. L. Castle, *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227. For a semisynthesis of vancomycin, see C. Thompson, M. Ge, D. Kahne, *J. Am. Chem. Soc.* **1999**, *121*, 1237–1244.

[7] a) K. C. Nicolaou, N. Watanabe, J. Li, J. Pastor, N. Winssinger, *Angew. Chem.* **1998**, *110*, 1636–1638; *Angew. Chem. Int. Ed.* **1998**, *37*, 1559–1561; b) C. P. Holmes, *J. Org. Chem.* **1997**, *62*, 2370–2380.

[8] a) O. Seitz, H. Kunz, *J. Org. Chem.* **1997**, *62*, 813–826; b) O. Seitz, H. Kunz, *Angew. Chem.* **1995**, *107*, 901–903; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 803–805; c) W. Kosch, J. März, H. Kunz, *React. Polym.* **1994**, *22*, 181.

[9] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385–393.

[10] L. E. Overman, *Angew. Chem.* **1984**, *96*, 565–573; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579–586.

[11] K. C. Nicolaou, J. Pastor, S. Barluenga, N. Winssinger, *Chem. Commun.* **1998**, *18*, 1947–1948. For an alternative synthesis of this resin, see T. Ruhland, K. Anderson, H. Pedersen, *J. Org. Chem.* **1998**, *63*, 9204–9211.

[12] K. C. Nicolaou, N. Winssinger, J. Pastor, F. Murphy, *Angew. Chem.* **1998**, *110*, 2677–2680; *Angew. Chem. Int. Ed.* **1998**, *37*, 2534–2537; b) M. Peterseim, W. P. Neumann, *React. Polym.* **1993**, *20*, 189–205.

[13] The large difference in polarity between nBu$_3$SnH and the reaction product together with the insolubility of nBu$_3$SnH in the HPLC solvent system did not warrant the use of the polymer-bound tin hydride in this instance.

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