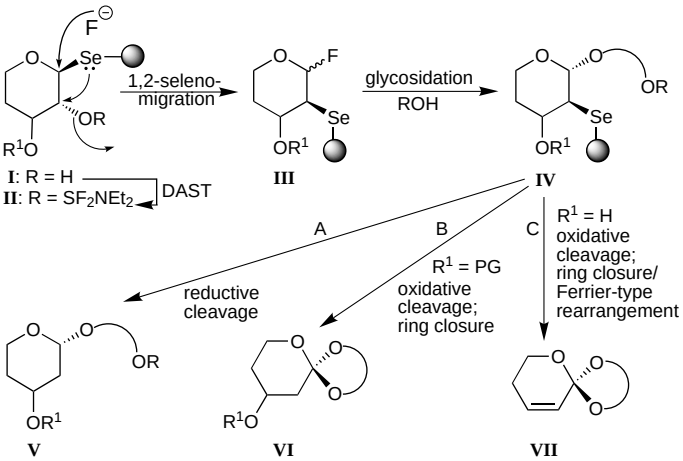
1,2-Seleno Migrations in Carbohydrate Chemistry: Solution and Solid-Phase Synthesis of 2-Deoxy Glycosides, Orthoesters, and Allyl Orthoesters**

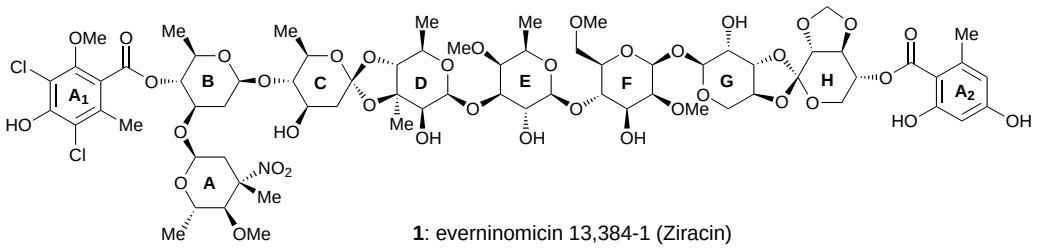
K. C. Nicolaou,* Helen J. Mitchell, Konstantina C. Fylaktakidou, Hideo Suzuki, and Rosa M. Rodríguez

In the field of antibiotics lead compounds derived from natural sources, for example, vancomycin and penicillin, provide a starting point from which a library of analogues can be synthesized and screened for biological activity. The naturally derived everninomicin 13,384-1 (Ziracin, **1**),[1] a potent antibiotic against methicillin-resistant *staphylococci* and vancomycin-resistant *enterococci*, is rapidly advancing through clinical trials as a new weapon against multidrug resistant bacteria. With the total synthesis of this antibiotic now accomplished,[2] the feasibility of constructing semisynthetic analogues for biological investigations through solution and solid-phase combinatorial chemistry can be put to the test. Furthermore, the synthesis of libraries of compounds representing novel regions, such as the 2-deoxy glycoside and orthoester moieties, of this complex molecule for general screening purposes is deemed highly desirable and important. Herein we report a general method for the stereocontrolled construction of 2-deoxy glycosides and orthoesters, both in solution and on a solid support, which is facilitated by a 1,2-selenium migration.

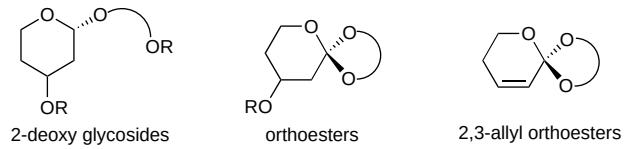
Based on the observation of the 1,2-phenylseleno migration[3] and its application to the synthesis[2] of everninomicin's orthoester moieties in solution together with recognizing the potential use of our previously synthesized polystyrene-based selenium resin,[4] we designed the chemistry shown in Scheme 1. A general method employing this novel 1,2-selenium migration reaction was envisioned for both the solution (● = phenyl) and solid-phase (● = polystyrene) synthesis of 2-deoxy glycosides, 2-deoxy orthoesters, and 2,3-allyl orthoesters from structures of general type **I**. Thus, treatment of the readily available 2-hydroxy-1-seleno glycoside (**I**) with diethylaminosulfur trifluoride (DAST)[5] should result in a stereospecific 1,2-migration of the selenium group, with simultaneous installation of a fluoride group at C-1, to furnish **III**. Exposure of these reactive donors (**III**) to various alcohols in the presence of Lewis acids should then selectively afford the desired α-glycosides **IV** through participation of the seleno group. From **IV**, one of the following three paths may be followed: path A should furnish the 2-deoxy glycosides **V** in high yield, via radical deselenation, facilitated with nBu$_3$SnH; path B would first require removal of the protecting group R, followed by oxidation of the selenium to the selenoxide and heating to promote the *syn*-elimination and cyclization, to furnish 2-deoxy orthoesters (**VI**); and path C would require that both protecting groups (R and R^1) be removed before subsequent oxidation and heating, and should afford the 2,3-



Scheme 1. General concept for the stereoselective synthesis of 2-deoxy glycosides (**V**), orthoesters (**VI**), and allyl orthoesters (**VII**) via 1,2-selenium migrations. PG = protecting group.



1: everninomicin 13,384-1 (Ziracin)



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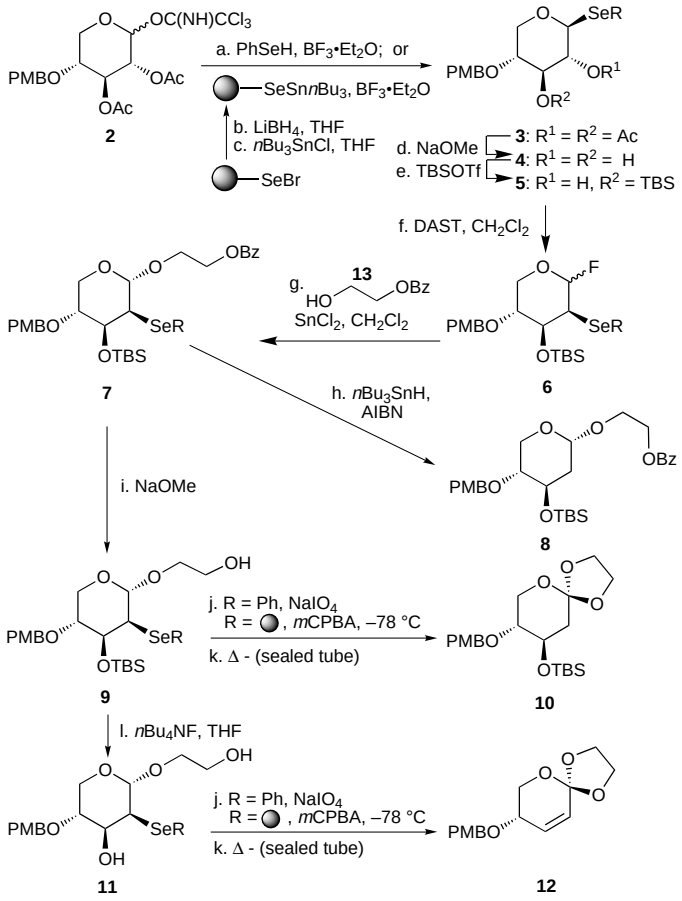
[**] We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. We gratefully thank Nicolas Winssinger for helpful discussions and preparation of the selenium bromide resin. This work was financially supported by the Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), postdoctoral fellowships from M.E.C., Spain (R.M.R., Fullbright), the Japan Society for the Promotion of Science (H.S.), the George Hewitt Foundation (K.C.F.), and grants from Schering Plough, Pfizer, Glaxo, Merck, Hoffmann–La Roche, DuPont, Abbott Laboratories, and Boehringer–Ingelheim.

allyl orthoesters (**VII**) through a Ferrier-type rearrangement.[6]

As a demonstration of the efficiency and utility of the 1,2-seleno-migration chemistry, we employed three different carbohydrate donors which were coupled with three alcohols of varying complexity, to afford a small library of 2-deoxy glycosides and orthoesters, followed by the formation of three 2,3-allyl orthoesters. Scheme 2 illustrates the method and conditions used for one example, while Tables 1 and 2 provide combined yields for all the examples. Solution-phase β-seleno glycosides such as **3** were prepared by treating the respective trichloroacetimidate donors[7] (**2**, Scheme 2) with freshly prepared PhSeH[8] in the presence of $BF_3 \cdot Et_2O$, using C-2 esters as participating agents to control the anomeric ratio. The sugar was further manipulated to remove the ester groups to afford **4** followed by selective silylation to furnish **5**. Treatment of the 2-hydroxy compound with DAST facilitated the 1,2-selenophenyl migration affording the 2-seleno-1-fluoro donor **6** in excellent yield. The donor was coupled with alcohol **13** in the presence of $SnCl_2$ to selectively form the α-glycoside **7** in 95% yield. Formation of the 2-deoxy glycoside (**8**) was achieved by exposure to nBu$_3$SnH/AIBN via radical cleavage of the Se–C bond. Deprotection of the ester from **7** to afford **9**, followed by oxidation of selenium to the selenoxide, and heating in a sealed tube[9] led to the formation of the 2-deoxy orthoester **10** in 87% yield. On the other hand, removal of the silyl group from **9** to afford diol **11**, followed by oxidation to the selenoxide and heating in a sealed tube as described above, led to elimination of the C-2 hydroxyl group with simultaneous migration of the double bond and formation of the orthoester to afford the 2,3-allyl orthoester **12** in good yield (79%). Table 1 provides the combined yields (66–95%) for the formation of the glycosides from the glycosylation of the donors **16**, **17**, and **6** with alcohols **13**, **14**, and **15**, as well as the formation of the corresponding 2-deoxy glycosides. Table 2 provides yields for the formation of the orthoester for each glycoside as well as for the examples of 2,3-allyl orthoesters. In order to compare the stereochemistry of the 2-deoxy orthoester and the 2,3-allyl orthoester (**42** and **43**, Table 2, see Table 3 for spectroscopic data), **42** was transformed into its respective 2,3-allyl orthoester by first removal of the TBS group (TBAF, THF, 95%) followed by dehydration (Martin sulfurane, $CHCl_3$, 50 °C, 1 h, 80%). Examination of the NMR spectrum of each orthoester revealed that the allyl orthoester derived from **42** (three step procedure) had the opposite configuration of **43** (one-pot procedure). Thus, while the stereochemistry during 2-deoxy orthoester formation (**42**) is reported to be controlled by the anomeric effect (the alcohol approaches the ketene acetal from an axial direction so as to maximize the anomeric effect), in the case of the 2,3-allyl orthoester (**43**), the incoming alcohol must come from the top face or same side as the leaving hydroxyl group. A more detailed investigation of this stereochemical effect is on-going.

Satisfied with the results of the solution-phase chemistry, we now proceeded to apply this technology to solid-phase



Scheme 2. Solution and solid-phase synthesis of 2-deoxy glycosides (**8**), 2-deoxy orthoesters (**10**), and 2,3-allyl orthoesters (**12**). Reagents and conditions: R = Ph: a) 2.0 equiv of PhSeH (0.5 M solution in CH_2Cl_2), 1.5 equiv of $BF_3 \cdot Et_2O$ CH_2Cl_2, –78 °C, 2 h, 90%; d) 2.5 equiv of NaOMe, MeOH, 25 °C, 3 h, 95%; e) 1.1 equiv of TBSOTf, 1.3 equiv of 2,6-lutidine, CH_2Cl_2, –78 °C, 1 h, 90%; f) 1.5 equiv of DAST, CH_2Cl_2, 0 °C, 0.5 h, 100%; g) 1.5 equiv of $HOCH_2CH_2OBz$, 1.5 equiv of $SnCl_2$, CH_2Cl_2, 0 °C, 3 h, 95%; h) 10 equiv of nBu$_3$SnH, 0.1 equiv of AIBN, benzene, 80 °C, 1 h, 90%; i) 1.5 equiv of NaOMe, MeOH, 25 °C, 3 h, 95%; j) 10 equiv of $NaIO_4$, MeOH:CH_2Cl_2:H_2O (7:3:1), 25 °C, 1 h; k) vinyl acetate:toluene:diisopropylamine (2:2:1), sealed tube, 140 °C, 12 h, 82%; l) 1.5 equiv of nBu$_4$NF, THF, 25 °C, 1 h, 95%. R = polystyrene: a) 3.0 equiv of **2**, 1.5 equiv of $BF_3 \cdot Et_2O$ CH_2Cl_2, –78 °C, 2 h, >90%; b) 1.5 equiv of $LiBH_4$, THF, 25 °C, 2 h, 100%; c) 20 equiv of nBu$_3$SnCl, THF, 25 °C, 2 h, 100%; d) 5.0 equiv of NaOMe, MeOH, 25 °C, 3 h, >95%; e) 1.1 equiv of TBSOTf, 1.3 equiv of 2,6-lutidine, CH_2Cl_2, –78 °C, 1 h, >80%; f) 3.0 equiv of DAST, CH_2Cl_2, 0 °C, 0.5 h, 100%; g) 10 equiv of $HOCH_2CH_2OBz$, 3.0 equiv of $SnCl_2$, CH_2Cl_2, 0 °C, 3 h, >89%; h) 10 equiv of nBu$_3$SnH, 0.1 equiv of AIBN, benzene, 80 °C, 1 h, 95%; i) 5.0 equiv of NaOMe, MeOH, 25 °C, 3 h, >95%; j) 3.0 equiv of mCPBA, CH_2Cl_2, –78 °C, 10 min; k) vinyl acetate:toluene: diisopropylamine (2:2:1), sealed tube, 140 °C, 12 h, >85%; l) 5.0 equiv of nBu$_4$NF, THF, 25 °C, 1 h, >95%. Yields from the solid support reported here represent purity as determined by NMR spectroscopy, see Tables 1 and 2 for overall yields determined by cleavage. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; PMB = *p*-methoxybenzyl; AIBN = 2,2′-azobisisobutyronitrile; DAST = diethylaminosulfur trifluoride; mCPBA = *meta*-chloroperoxybenzoic acid; = polystyrene.

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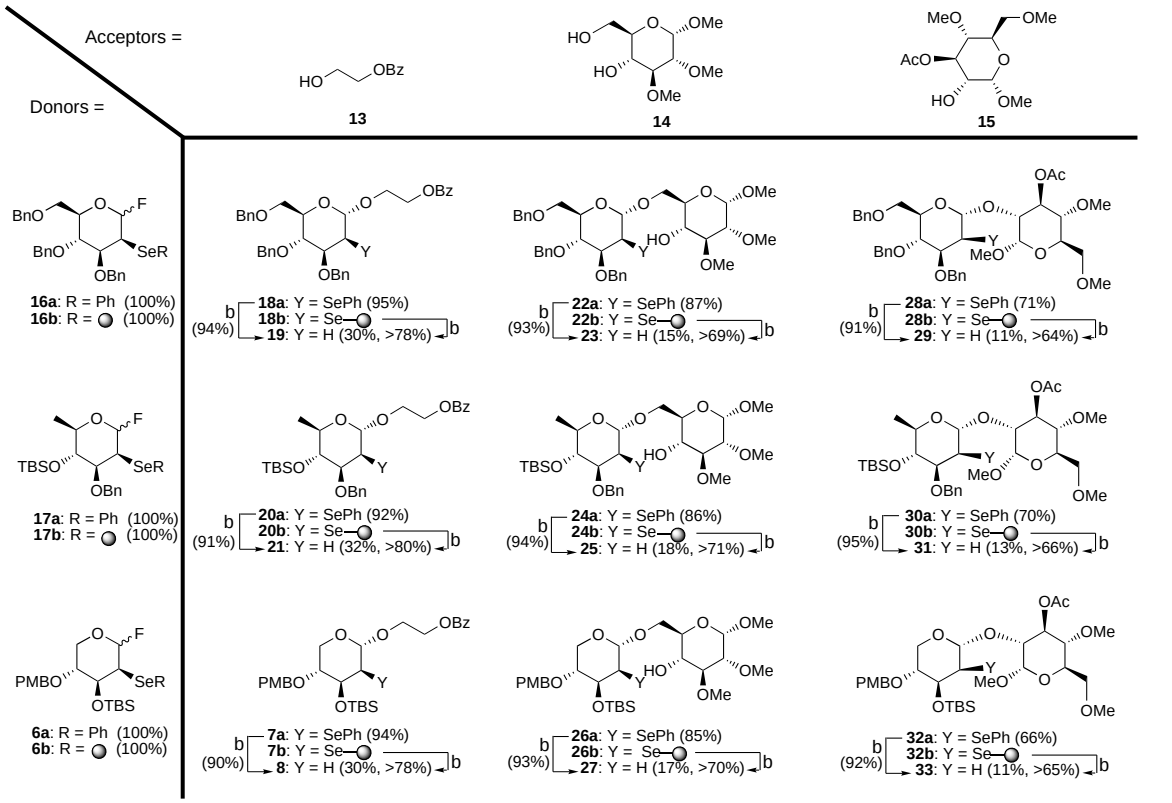
Table 1. Solution and solid-phase synthesis of 2-seleno glycosides and 2-deoxy glycosides.[a]

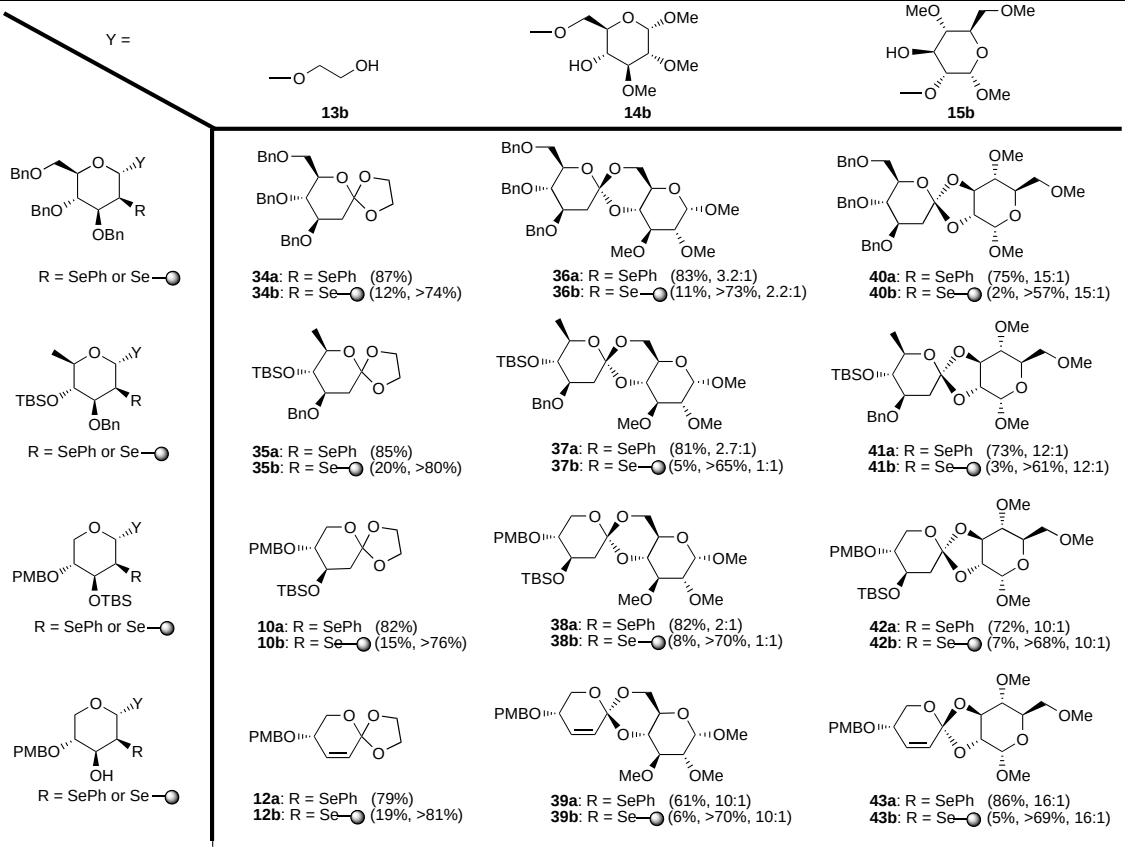


[a] Yields of solid-phase glycosylations reported as the overall yield of 2-deoxy glycoside released from the resin (overall yield, average yield for each step ($0.78^5 = 0.30$)). [b] nBu$_3$SnH, AIBN, benzene, 80 °C, 1 h; ● = polystyrene.

chemistry. Before attempting the coupling between the resin and sugars, we required a resin-bound selenol in a form that could be manipulated in air (PhSeH rapidly oxidatively dimerizes in air, and must be kept under argon at all times). It was found that the nBu$_3$Sn ether of the resin-bound selenol was easy to prepare, fairly stable to air, and quite reactive in couplings. This reagent was readily prepared from the previously reported selenium bromide resin[4] (Scheme 2) by lithiation ($LiBH_4$, THF) followed by quenching with excess nBu$_3$SnCl to form a colorless, odorless resin, which could be quickly filtered in air. Treatment of this resin with three equivalents of the trichloroacetimidate donors in the presence of $BF_3 \cdot Et_2O$ led to excellent loading of the sugar (as determined by IR spectroscopy and cleavage with nBu$_3$SnH). Of particular interest was the obervation that cleavage of the resin-bound 1- or 2-seleno glycosides with nBu$_3$SnH/AIBN regenerated the nBu$_3$SnSe resin, which could be filtered off and re-used in subsequent coupling reactions. As in the solution-phase chemistry, the C-2 esters were removed under basic hydrolysis (NaOMe, THF/MeOH), followed by exposure to DAST to precipitate the 1,2-migration of the seleno resin and yield the resin-bound 1-fluoro-2-seleno donors (**16b**, **17b**, and **6b**, Table 1). The filtrate from the DAST reaction was monitored for products of elimination; surprisingly, very little, if any, was observed. The fluoro donors were exposed to 10 equivalents of alcohols **13**, **14**, and **15** in the presence of $SnCl_2$ to afford the primary alcohols (**18b**, **22b**, **20b**, **24b**, **7b**, **26b**, >70%, Table 1) and secondary alcohols (**28b**, **30b**, **32b**, >60%, Table 1). The 2-deoxy glycosides were prepared as described above by cleavage with nBu$_3$SnH/AIBN (Table 1).[10] Deprotection of the esters was smoothly effected by basic hydrolysis (NaOMe, THF/MeOH), setting the stage for formation of the orthoester. Several methods for oxidizing the selenium to the selenoxide were investigated, including mCPBA in CH_2Cl_2 at −78 °C, H_2O_2 in THF/H_2O at 0 °C, and O_3 in toluene at −78 °C. Unlike the solution-phase selenoxides, it was observed that the resin-bound selenoxide was more prone to eliminate at room temperature and therefore necessitated the use of lower temperatures in the oxidation step. Thus, treatment with mCPBA in CH_2Cl_2 at −78 °C followed by rapid filtration and transfer to a sealed tube was found to give the cleanest results. The selectivity in the stereochemistry of the orthoester formed on a solid support paralleled that observed in the solution-phase chemistry. Furthermore, the 2,3-allyl orthoesters were again prepared by first removal of the silyl group followed by oxidation and orthoester formation.[10]

In conclusion, we have investigated the scope of the 1,2-selenium migration in carbohydrates and have found that 2-deoxy glycosides, orthoesters, and allyl orthoesters[11] can be readily prepared with good selectivities and in high yield. We have also described a novel solid-phase construction of carbohydrate orthoesters employing a selenium-based linking strategy, where the selenium atom serves to link, couple, and facilitate orthoester formation in an efficient and traceless manner. The described technology can now be expanded to

Table 2. Solution and solid-phase synthesis of 2-deoxy orthoesters and 2,3-allyl orthoesters.[a]



[a] Yields of orthoesters derived from solution: (combined yield for deprotection, oxidation, and orthoester formation, as well as the ratio of the orthoester diastereoisomers). Yields of orthoesters derived from solid support (overall yield for the sequence from the selenium bromide resin was determined by the weight of released product, average yield for each step ($0.74^6 = 0.12$), ratio of orthoester diastereoisomers. (● = polystyrene).

Table 3. Selected physical properties of compounds **42** and **43**.

42: $R_f = 0.35$ (silica, 50 % Et_2O in hexanes); $\alpha_D^{22} = +15.3$ ($c = 1.30$, $CHCl_3$); IR (thin film) $\tilde{\nu}_{max} = 2931, 2856, 1613, 1514, 1468, 1383, 1320, 1250, 1203, 1104, 963, 920, 838, 778\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$, 10:1): $\delta = 7.24$ (d, $J = 8.5$ Hz, 2H, PMB), 6.85 (d, $J = 8.5$ Hz, 2H, PMB), 5.07 (d, $J = 3.0$ Hz, 1H, H-1′), 4.65 and 4.51 (AB, $J = 11.4$ Hz, 2H, CH_2Ar), 4.03 (t, $J = 9.6$ Hz, 1H, H-3′), 3.98–3.92 (m, 1H, H-3), 3.82 (dd, $J = 10.1$, 3.1 Hz, 1H, H-2′), 3.78 (s, 3H, OMe), 3.77 (dd, $J = 11.2$, 4.8 Hz, 1H, H-5), 3.61 (br s, 2H, H-6′), 3.55 (t, $J = 11.4$ Hz, 1H, H-5), 3.52–3.48 (m, 2H, H-4′, H-5′), 3.49 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.33 (ddd, $J = 9.1$, 9.1, 4.1 Hz, 1H, H-4), 2.13 (dd, $J = 13.0$, 5.0 Hz, 1H, H-2), 1.91 (dd, $J = 13.0$, 10.0 Hz, 1H, H-2), 0.86 (s, 9H, *t*BuSi), 0.08 (s, 3H, MeSi), 0.07 (s, 3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.2$, 130.6, 129.4, 120.3, 113.7, 97.2, 78.7, 78.5, 75.2, 72.9, 71.4, 70.7, 70.6, 62.9, 59.3, 58.7, 55.5, 55.2, 40.5, 30.3, 25.7, 18.0, −4.6, −4.8; HR-MS (MALDI): calcd for $C_{28}H_{46}O_{10}SiNa$ [M+Na^+]: 593.2758; found: 593.2755.

43: $R_f = 0.32$ (silica, 100 % Et_2O); $\alpha_D^{22} = +70.0$ ($c = 0.17$, $CHCl_3$); IR (thin film) $\tilde{\nu}_{max} = 2983, 2922, 2862, 1617, 1512, 1451, 1384, 1248, 1182, 1077, 1017, 918, 819\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 10:1): $\delta = 7.25$ (d, $J = 8.6$ Hz, 2H, PMB), 6.86 (d, $J = 8.6$ Hz, 2H, PMB), 6.15 (dd, $J = 10.0$, 4.1 Hz, 1H, H-3), 5.77 (dd, $J = 10.0$, 1.1 Hz, 1H, H-2), 5.06 (d, $J = 3.0$ Hz, 1H, H-1′), 4.59 and 4.51 (AB, $J = 11.7$ Hz, 2H, CH_2Ar), 4.31 (t, $J = 9.5$ Hz, 1H, H-3′), 4.14–4.11 (m, 2H, H-3, H-5), 3.88–3.85 (m, 1H, H-4), 3.81 (s, 3H, OMe), 3.65–3.63 (m, 2H, H-6′), 3.59 (dd, $J = 10.1$, 3.0 Hz, 1H, H-2′), 3.61–3.53 (m, 2H, H-4′, H-5′), 3.50 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.41 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.2$, 130.5, 130.2, 129.3, 128.4, 125.5, 116.6, 113.8, 97.4, 77.7, 76.2, 71.3, 70.7, 69.9, 66.8, 65.7, 59.3, 58.8, 55.7, 55.2, 30.3; HR-MS (MALDI): calcd for $C_{22}H_{30}O_9Na$ [M+Na^+]: 461.1787; found: 461.1789.

the combinatorial synthesis of novel semisynthetic everninomicins and other carbohydrate libraries for biological screening.

Received: October 25, 1999 [Z 14185]

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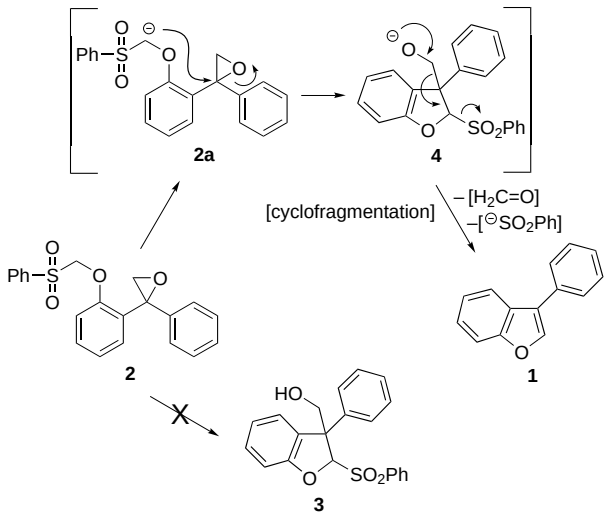
[10] Yields from the solid-support synthesis were determined from the weight of cleaved product and are reported as an overall yield for the sequence based upon the initial loading of the selenium bromide resin (see ref. [4]).
[11] All new compounds exhibited satisfactory spectral and exact mass data.



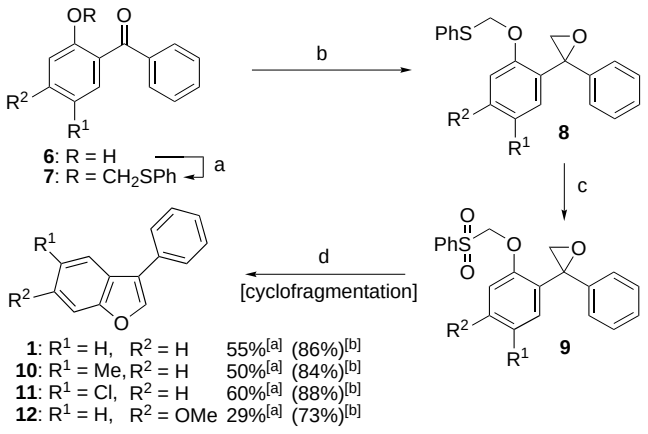
Scheme 1. The cyclofragmentation pathway to 3-arylbenzofurans (**1**).

Solution and Solid-Phase Synthesis of Functionalized 3-Arylbenzofurans by a Novel Cyclofragmentation – Release Pathway**

K. C. Nicolaou,* Scott A. Snyder, Antony Bigot, and Jeffrey A. Pfefferkorn

The 3-arylbenzofuran nucleus is a central component of a diverse class of heterocyclic natural and synthetic products that possess a broad range of biological activities.[1] During the course of recent synthetic investigations we discovered a novel reaction cascade leading to 3-phenylbenzofuran (**1**, Scheme 1), the core structure of the 3-arylbenzofuran class. This serendipitous observation occurred as a result of attempts to convert epoxide **2** (see Scheme 2 for its preparation) into **3** by deprotonation of the methylene group adjacent to the sulfone followed by selective opening of the epoxide ring.[2] Surprisingly, rather than providing the desired system **3**, the only product observed was benzofuran **1**. The proposed mechanism for this transformation, a novel cyclofragmentation pathway, is outlined in Scheme 1, in which after the initial generation of the alkoxide intermediate **4** from a 5-*exo*-trig cyclization, collapse to **1** occurs by the concomitant expulsion of both formaldehyde and a phenylsulfinate anion.[3, 4] Given the importance of 3-arylbenzofurans in biology and medicine, we sought to test the generality of this reaction cascade for the preparation of more highly functionalized systems. Herein, we report the exploration of the scope of this technology, both in solution and on solid support, which led to the generation of a diverse family of 3-arylbenzofurans and the streamlining of the method for use in combinatorial chemistry.

We initially alkylated three commercially available 2-hydroxybenzophenones (**6**) with chloromethylphenyl sulfide to generate **7** (Scheme 2). Subsequent epoxidation with trimethylsulfonium iodide[5] followed by *m*CPBA-mediated oxidation of the sulfide gave **9** in high overall yields. Gratifyingly, treatment of these sulfones with either KO*t*Bu in DMF (−57 °C or 0 °C) or LDA in THF (−78 °C) resulted in the exclusive formation of the desired 3-arylbenzofurans **10** – **12**,[6] thereby establishing the potential of this reaction to generate substituted benzofurans.



Scheme 2. Synthesis of 3-arylbenzofurans (**1**, **10** – **12**) from 2-hydroxybenzophenones. a) $ClCH_2SPh$ (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 50 °C, 5 h; b) trimethylsulfonium iodide (1.5 equiv), KO*t*Bu (1.0 M in THF, 1.5 equiv), DMSO, 0 °C, 10 min; c) *m*CPBA (2.5 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2, 25 °C, 2 h; d) KO*t*Bu (1.0 M in THF, 2.5 equiv), DMF, 0 °C, 5 min. *m*CPBA = *meta*-chloroperbenzoic acid. [a] Overall yield after four steps. [b] Average yield per step.

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[**] Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), doctoral fellowships from the National Science Foundation (S.A.S.) and the Department of Defense (J.A.P.), and grants from Abbott, Amgen, Boehringer – Ingelheim, Glaxo, Hoffmann – La Roche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

  0570-0833/00/3906-1093 $ 17.50+.50/0