Natural Products Synthesis

Synthesis of the Furanosteroidal Antibiotic Viridin**

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Among the natural products that modulate protein function with high selectivity,[1] there is a group of reactive molecules that alkylate nucleophilic residues in the active sites of important enzymes. Lipstatin,[2] fumagillin,[3] and microcystin[4] embody the chemistry of the carbonyl group, the epoxide, and the electron-deficient alkene, respectively, and are prominent examples of protein-reactive natural products. These and related secondary metabolites are important because they have yielded insight into the cellular functions of key enzymes and will likely prove invaluable as molecular probes in protein-activity-profiling experiments.[5]

Our interest in research opportunities provided by natural products that covalently inhibit protein function[6] induced us to address the chemical problem posed by viridin (**1**)[7] (Scheme 1), a potent antifungal metabolite of *Gliocladium virens* and the parent member of a family of furanosteroids that includes wortmannin (**2**), viridiol, and demethoxyviridin.[8] These natural products are biosynthesized from the triterpene lanosterol and are distinguished by an unusual structural feature: an electron-deficient furan ring fused between C4 and C6 of the steroid framework. The doubly activated carbon atom of this heterocycle predisposes these compounds to react efficiently with a range of amines,[9] including the active-site lysine of phosphatidylinositol 3-kinase (PI_3-kinase).[10] Wortmannin (**2**) and demethoxyviridin are potent and relatively selective covalent inhibitors of PI_3-kinase[11] and have served as valuable molecular tools for deciphering the role of PI_3-kinase in signal-transduction pathways.

With potential as therapeutic agents for the treatment of neoplasms and other diseases,[12] viridin and its relatives provide prime targets for research in organic synthesis.

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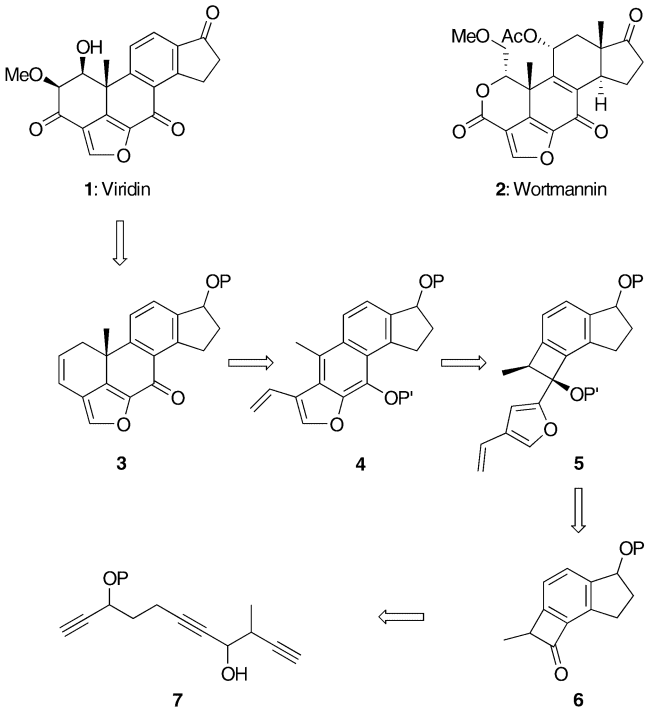
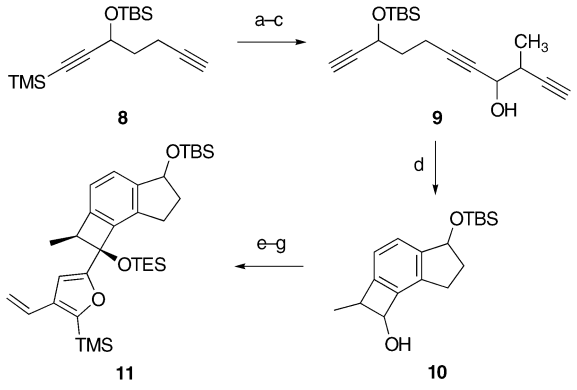
Although a total synthesis of viridin has not yet been reported, Shibasaki and co-workers reported an impressive synthesis of the complex furanosteroid wortmannin (**2**)[13] and Souza and Rodrigo described a creative route to the pentacyclic core of viridin (**1**).[14] Herein we report the first total synthesis of racemic viridin (**1**; Scheme 1).



Scheme 1. An approach to a synthesis of viridin (**1**) featuring an alkyne cyclotrimerization and domino electrocyclic reactions. P and P′ are unspecified protecting groups.

Mindful of the electrophilic nature of the doubly activated furan, we favored a design that would introduce this reactive element and the readily epimerizable methoxy-bearing stereocenter at a late stage of the synthesis. By delaying the oxidative functionalization of the steroid A-ring to an advanced phase, we could focus on the problem of building the pentacyclic framework of compound **3**. We envisioned that suitable substrates for annulating the A-ring of viridin (**1**) could be constructed from a naphthalenofuran of type **4**, which in turn could arise in the course of a thermal rearrangement of a benzocyclobutenol derivative **5**. This concept would require an electrocyclic ring opening of the benzocyclobutene substructure of **5** and a subsequent 6π electrocyclization with participation by the furan ring.[15] To contend with the somewhat unusual architecture of compound **5**, we hoped to transmute the simple, substituted acyclic triyne **7** to the tricyclic framework of **6** through a transition-metal-mediated alkyne cyclotrimerization.[16] The attack of an appropriate furanyl lithium reagent on the keto group of **6** would then yield key intermediate **5**.

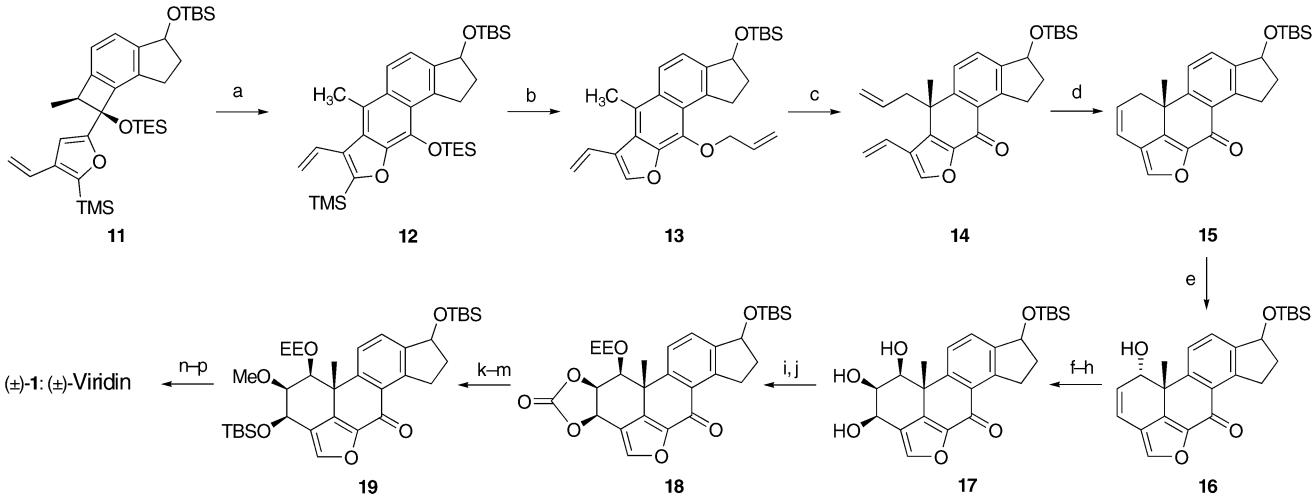
Our synthesis of a benzocyclobutenol of type **5** commenced with diyne **8** (Scheme 2).[17] Formylation of the lithium acetylide produced from **8** with *N*,*N*-dimethylformamide[18] produced an ynal, which was alkylated by a propargylic zinc reagent to yield the triyne **9** as an inconsequential mixture of four diastereoisomers following cleavage of the alkynyl TMS protecting group. Treatment of this triyne with [RhCl(PPh$_3$)$_3$] (3 mol%) in ethanol at 80°C effected cyclotrimerization to the tetrasubstituted aryl cyclobutenol **10** (88%).[16c,d] The pioneering studies of Vollhardt and co-workers demonstrated the power of alkyne cyclotrimerization in steroid synthesis, with impressive constructions of A-ring[16f] and B-ring aromatic steroids.[16g] The work presented herein offers a complementary, efficient approach to the formation of the aromatic C-ring of an eventual steroid.



Scheme 2. Synthesis of benzocyclobutene **11**. a) *n*BuLi, **8**, THF, −40°C; DMF; aqueous KH_2PO_4 (10%), 89%; b) 2-bromobut-3-yne (1.5 equiv), Zn dust (4 equiv), $HgCl_2$ (2 mol%), THF, 60°C, 1 h, 96%; c) K_2CO_3 (0.1 equiv), MeOH, 2 h, 100%; d) [RhCl(PPh$_3$)$_3$] (3 mol%), EtOH, 80°C, 20 min, 88%; e) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; **10**; Et_3N, −78°C→RT, 85%; f) 2-trimethylsilyl-3-vinylfuran (1.3 equiv), *n*BuLi (1.2 equiv), THF, −78→0°C, 2 h; then add to benzocyclobutenone **6** (P = TBS), −78°C, 1 h, 94%; g) TESCl (1.15 equiv), imidazole (2.5 equiv), DMAP (0.1 equiv), DMF, 88%. TMS = $SiMe_3$; TBS = Si*t*-BuMe_2; TES = $SiEt_3$; DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide; DMAP = 4-dimethylaminopyridine.

From tricyclic alcohol **10**, a suitable equivalent of **5** could be synthesized by an efficient three-step reaction sequence. Thus, Swern oxidation of benzocyclobutenol **10** provided the corresponding benzocyclobutenone **6** (P = Si*t*BuMe_2). When the organolithium reagent derived from 2-trimethylsilyl-3-vinylfuran[19] was allowed to react with **6**, a key carbon–carbon bond was formed, with exclusive addition of the heterocyclic nucleophile *anti* to the methyl substituent. Silylation of the newly formed tertiary alcohol then afforded the differentially protected tetracycle **11**.

Tandem conrotatory electrocyclic ring-opening 6π-disrotatory electrocyclizations of alkenyl-substituted benzocyclobutenes are attractive, yet somewhat underutilized, structure-building processes in organic synthesis.[15] In the case of substrate **11**, the silyl ether substituent was expected to confer a high degree of torquoselectivity to the ring-opening process.[20] The predicted inward rotation of the furan would allow a subsequent 6π electrocyclization of the intermediate furanyl quinone dimethide. In the event, heating **11** to 140°C in degassed xylenes containing 2 equivalents of Hünig base, followed by in situ oxidation with DDQ, afforded tetracycle **12** in high yield (83%, Scheme 3). With this key transformation completed, four of the five rings of the viridin



Scheme 3. Synthesis of (±)-viridin (**1**). a) iPr$_2$EtN (2 equiv), xylenes (degassed), 140 °C, 3.5 h; then DDQ (1 equiv), room temperature, 15 min, 83 %; b) allyl bromide (10 equiv), CsF (2 equiv), DMF, 67 %; c) mesitylene (degassed), 165 °C, 40 min, 91 %; d) tricyclohexylphosphane[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidene]ruthenium(IV) dichloride (2.5 mol %), CH_2Cl_2, 95 %; e) SeO_2 (5 equiv), dioxane, 100 °C, 6.5 h, 60 % (10 % r.s.m.); f) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, room temperature, 97 %; g) $NaBH_4$ (0.5 equiv), ethanol, 0 °C, 98 %; h) OsO_4 (1.05 equiv), TMEDA (1.1 equiv), CH_2Cl_2, −78 °C, 1 h; then py/H_2O/$NaHSO_3$ (35:30:2), 3 h, 76 %; i) triphosgene (0.5 equiv), py (6 equiv), CH_2Cl_2, −78 °C, 15 min, 95 %; j) PPTS (0.5 equiv), ethyl vinyl ether/CH_2Cl_2 (1.4:1), room temperature, 24 h, 91 %; k) LiOH (1 equiv), THF/H_2O (2:1), 0 °C, 20 min, 97 %; l) TBSOTf (2 equiv), 2,6-lutidine (3 equiv), CH_2Cl_2, −78 °C, 1 h, 95 %; m) NaHMDS (3 equiv), toluene, −78 °C, 10 min; then MeOTf (5 equiv), 75 % (25 % r.s.m.); n) nBu$_4$NF (2.2 equiv), THF, room temperature, 99 %; o) Dess–Martin periodinane (3.0 equiv), CH_2Cl_2, room temperature, 1.5 h, 98 %; p) PPTS (0.5 equiv), methanol, room temperature, 2 h, 84 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; r.s.m. = recovered starting material; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; PPTS = pyridinium *p*-toluenesulfonate; OTf = trifluoromethanesulfonate; EE = 1-ethoxyethyl; NaHMDS = sodium bis(trimethylsilyl)amide.

skeleton had been formed from acyclic triyne **9** in only five steps.

From compound **12**, construction of the A-ring of viridin (**1**) required three transformations. A one-pot desilylation/phenol allylation protocol afforded allyl ether **13**.[21] Allyl migration with concurrent formation of the quaternary methyl-bearing stereocenter was achieved by heating **13** in degassed mesitylene (165 °C, 91 %).[22] A ring-closing metathesis[23] of the resulting diene **14** produced pentacycle **15**, a substance containing the complete carbon skeleton of viridin (**1**), in excellent yield (95 %).

Oxidative functionalization of the viridin A-ring proved challenging. Allylic oxidation of the cyclohexene ring of **15** with SeO_2 provided allylic alcohol **16** in moderate yield (60 %, 10 % recovered starting material), with oxidation occurring exclusively on the less hindered α face. Fortunately, the required β stereochemistry of the alcohol was easily established through an oxidation–reduction sequence. The remaining oxygenation was installed by the powerful hydroxy-directed dihydroxylation method recently described by Donohoe et al.[24] This key oxidation yielded the desired *all-syn* triol **17** in 76 % yield.

The completion of the synthesis began with differentiation of the triol **17** by a selective cyclic carbonate formation using triphosgene,[25] followed by masking of the remaining hydroxy group as the ethoxyethyl ether **18**. A high-yielding hydrolysis of the cyclic carbonate was followed by silylation of the more accessible hydroxy function and methylation of the remaining hydroxy group under the conditions shown to give compound **19**. Fluoride-induced cleavage of the two silyl ethers in **19** set the stage for a twofold oxidation (Dess–Martin periodinane) and a mild deprotection of the ethoxyethyl ether (PPTS, methanol). This efficient reaction sequence yielded viridin (**1**) in racemic form.

In summary, the total synthesis of (±)-viridin (**1**) from pent-4-yn-1-ol in 5.0 % overall yield was based on a strategy featuring an efficient rhodium-catalyzed cyclotrimerization, a high-yielding thermal electrocyclic rearrangement, and a late-stage Donohoe dihydroxylation. We anticipate that the chemistry described herein will facilitate the design and syntheses of manifold viridin-like probes for kinase-activity-profiling experiments.

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