replicon with EC_{50}s of 0.6 and 43 nM. Although the precise stereochemical relationship between these two dimers has not been established, the more potent dimer converts to the weaker dimer when heated at 55 °C in CD_3CN, which is suggestive of either a rotameric or a stereoisomeric relationship. It is hypothesized that the formation of the dimeric species from **3** arises from its susceptibility to form a captodative radical (**11**) in the presence of a radical initiator such as molecular oxygen, which has a diradical ground state. Since **11** is a stabilized radical, it persists such that it can undergo either dimerization to afford **14** or combine with molecular oxygen to afford the peroxy intermediate **12**, which would be susceptible to reduction to alcohol **6** followed by rearrangement to afford thiohydantoin **8** *via* ketoamide **7**.[22] Transfer of the ketoacyl moiety of intermediate **7** to a nucleophilic species in the replicon medium would afford thiourea **9**. Although a simple hydrolysis of ketoamide **7** in assay medium is also possible, the byproduct of such a hydrolytic process, keto acid **10**, was not identified. It is noteworthy that acetate **13**, which can be prepared from **3** in 78% yield by oxidation with $Mn(OAc)_3$–$Cu(OAc)_2$–AcOH, afforded thiohydantoin **8** when treated with MeOH–K_2CO_3, providing supportive evidence for a key step of the proposed mechanism.[23]

Although the identification of the dimeric derivatives represented marked progress for the medicinal chemistry effort, optimizing these architecturally complex leads to a drug candidate appeared to be a challenging task, given that their physical properties fall far outside conventional drug space.[24–26] However, based on insights gleaned from the preliminary SAR investigation, a significant simplification of the dimeric species was achieved when the key pharmacophoric elements were successfully captured in the bibenzyl **15**, which exhibited a G-1b EC_{50} of 30 nM, potency that was improved further with the structurally more rigid stilbene analog **16**, which displayed an EC_{50} of 0.086 nM in the G-1b replicon assay.[20] This new lead molecule was relatively stable when incubated in replicon medium for the length of the assay period and exhibited a resistance profile that mirrored that of **3**, supportive of a similar mode of inhibitory effect and confirming that this molecule contains the key pharmacophore within dimers **14**. With its impressive potency and simplified structure compared with **14**, stilbene **16** served as the starting point for the next phase of the medicinal chemistry campaign. This enterprise focused on expanding genotype coverage, since the EC_{50} of **16** in a G-1a replicon was >10 μM, and optimizing ADME properties. The effort involved significant chemotype evolution based on the application of bioisostere concepts and ultimately culminated in the discovery of the highly potent, first-in-class NS5A replication complex inhibitor daclatasvir (**1**).[1] Daclatasvir inhibits G-1b and G-1a replicons with EC_{50}s of 0.009 and 0.05 nM, respectively. In addition, it inhibits G-2a to G-5a replicons with EC_{50}s ranging from 0.033 to 0.146 nM. This unprecedented *in vitro* potency spectrum established a new benchmark for the HCV field.

A similar cell-based screening of compound libraries conducted by scientists at Arrow Pharmaceuticals (subsequently acquired by AstraZeneca) led to the identification of two distinct hits (**17** and **19**) with HCV inhibitory activity that