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Diels−Alder and Stille Coupling Approach for the Short Protecting-Group-Free Synthesis of Mycophenolic Acid, Its Phenylsulfenyl and Phenylselenyl Analogues, and Reactive Oxygen Species (ROS) Probing Capacity in Water

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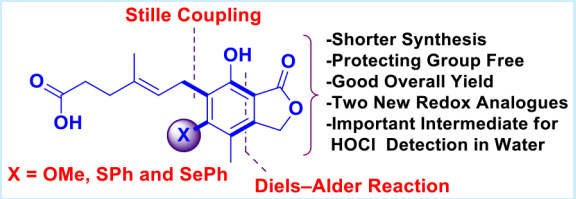
Supporting Information

ABSTRACT: A short, protecting-group-free synthesis is achieved. The synthesis is step-efficient and general. A Diels−Alder and Stille cross-coupling approach includes key transformations, allowing for a competitive synthesis which involves a rare halophenol Stille cross-coupling study. The phenylselenyl and phenylsulfenyl analogues were prepared as novel compounds in good overall yield. The applicability of one of the intermediates as a potential probe for reactive oxygen species (ROS) in water is investigated.



Mycophenolic acid was discovered by Gosio in 1893 in a strain of *Penicillium fungus*; it is recognized as one of the oldest known antibiotics.[1] The potential use of mycophenolic acid as an antitumor agent was described by William and co-workers;[2] mycophenolic acid was found to possess broad biological activity such as antiviral, antifungal, antibacterial, anticancer, and antipsoriasis properties.[3] Mycophenolic acid (MPA) was later found to be an immunosuppressive agent (Figure 1).[4] MPA (in prodrug form) has been successfully used

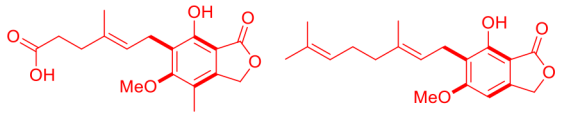


Figure 1. Mycophenolic acid and a closely related lipophilic molecule.

to prevent organ rejection in patients who have undergone a transplantation.[5] It is a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is an important rate-limiting enzyme involved in purine synthesis, which converts inosine monophosphate (IMP) to guanosine monophosphate (GMP).

Aside from its biological activity, MPA has attracted the attention of synthetic organic chemists since 1912. Notably, the central core contains an arene with six substituents which are all different. Nelson and co-workers were the first to address structural features of MPA together with biological activity; for these purposes some resorcylate analogues were synthesized in 1996.[6] Accordingly, the lactone ring and the aromatic methyl were essential for activity; for high potency, a phenolic −OH group with an adjacent hydrogen bond acceptor (e.g., the lactonic carbonyl) was required. One small success in terms of biological activity involved the replacement of the $-OCH_3$ group by $-C_2H_5$; this subtle change in lipophilicity afforded a material that was 2 to 4 times as potent as MPA, both in terms of *in vivo* and *in vitro* measurements.

Organoselenium and organosulfur compounds are interesting and considered because of their potential biological activities. Diaryl sulfide derivatives possess a broad spectrum of therapeutic activity: antidiabetic, antiinflammatory, proposed anti-Alzheimer's disease activity, proposed anti-Parkinson disease activity, anticancer, and anti-HIV activity.[7] On the other hand, organoselenium compounds also possess interesting potential activities, such as antiviral, antihypertensive, antioxidant antimicrobial, and antitumor properties.[8] Organochalcogenides play important roles as constituent parts of intermediates in organic synthesis and have useful applications in materials science.

The first total synthesis of MPA was reported by Birch in 1969.[10a] Since then, several other syntheses have been achieved.[10b−n] These syntheses were generally low yielding, and/or involved sequences of many steps and required protecting groups. Therefore, we sought to devise a shorter and more efficient protecting-group-free total synthesis of the natural product and its analogues.

In continuation of our efforts, directed toward synthesis of phenylselenyl functionalized molecular probes for biological applications,[9] we planned to synthesize phenylselenide and phenylsulfide analogues of the natural product and a possible fluorescence application could be investigated. To the best of

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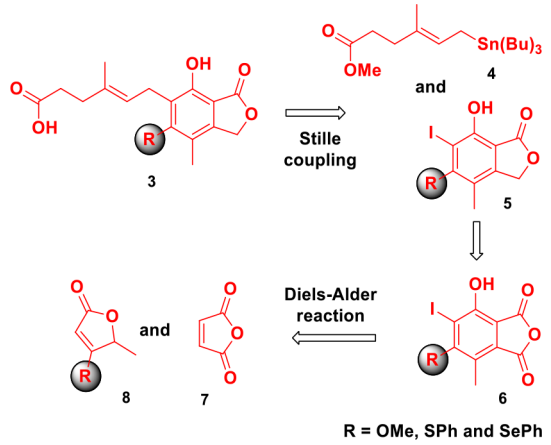
our knowledge, no protecting-group-free total synthesis of this natural product has been reported to date.

As depicted in Scheme 1, the pathway to the natural product could be envisioned via Stille cross-coupling of **5** and stannane

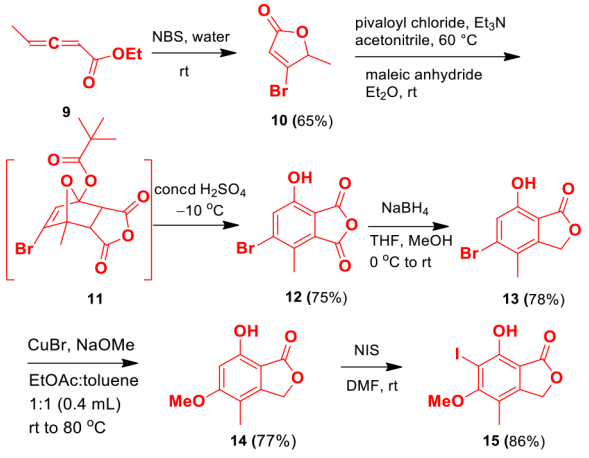
Scheme 1. Retrosynthetic Analysis



4; the stannane (**4**) can be accessed from the geraniol in several synthetic steps. The preparation of the iodolactone was obtained from lactone **8** through a sequence involving enolization, Diels–Alder fusion, reduction, and iodination. Lactone **8** was achieved from commercially available allene.

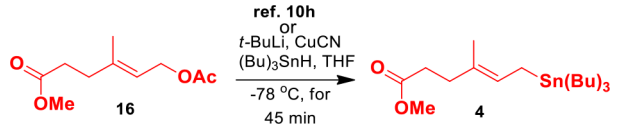
The "forward" synthesis was initiated from commercially available ethyl allenoates **9** which, upon treatment with NBS in water, led to the formation of 4-bromo-furanone (**10**).[11] Enolization of 4-bromo-furanones **10** and subsequent treatment with pivaloyl chloride afforded the diene ester,[12] which without purification was subjected to Diels–Alder reaction conditions with maleic anhydride **7** in diethyl ether. The highly functionalized aromatic anhydride **12** was accessed through intermediate **11**. $NaBH_4$ reduction of the anhydride **12** gave **13** in good yield (Scheme 2).[13] The lactone was further converted

Scheme 2. Synthesis of Iodolactone 15



to **14** upon treatment of NaOMe in the presence of a catalytic amount of CuBr.[14] Iodination of **14** gave **15**.[15] The acetate **16** required for the synthesis of stannane **4** was accessed from geraniol by a known literature method.[10h] Acetate **16** was converted to stannane through Pd cross-coupling chemistry[10h] or base-mediated nucleophilic displacement with $(Bu)_3SnH$ (Scheme 3).[16]

Scheme 3. Synthesis of Stannane 4



With the synthetic building blocks **4**, **15**, and **16** in hand, we then investigated suitable cross-coupling conditions for the most efficient access to mycophenolic acid. Different catalytic systems were evaluated (Table 1). A brief summary of preliminary studies of catalysts and conditions for the coupling of **4** and **15** is documented in the main text of this manuscript (Table 1). Initially, we employed a general protocol for the coupling of haloarenes with allylic acetates; we attempted lithiation and nucleophilic displacement in the presence of Lewis acid, but no product was observed. Of these instances, **14** was observed as a sole product. We also attempted Ni-based catalysts, but failed to obtain the desired compound.[17] We allowed for reactions similar conditions in subsequent trials but could observe the same results (see Supporting Information (SI) Table 1).

Due to the pronounced effect of the phenolic −OH on the lability of the Stille coupling reaction under normal protocol conditions, minimal attention was focused toward establishing a cross-coupling strategy free from the use of protecting groups. Herein, we focused on neutral coupling conditions with the expectation that catalyst chelation plays a crucial role in the outcome of the reaction.[18] We hypothesized that the formation of the desired product could be favored due to a six-membered chelated transition state imparted by the presence of both the hydroxyl and carbonyl group available in the fused ring system (**15**). Along these lines, we explored various experimental conditions to effect the desired reaction and the desired product formation. A variety of conditions were attempted with both **4** and **15**. The main challenge was to identify a Pd(0)- or Pd(II)-based catalyst that would be compatible for the present transformation. DMF and toluene were selected based on the literature precedent with these solvents.[19] Selected optimization results are summarized in Table 1. We used several palladium precatalysts in these trials involving Pd(0) or Pd(II) for the initial screening, but all were unsuccessful (entries 1–4). Interestingly, when we changed the reaction process with nitrogen purging for 30 min using the same reaction conditions, we were able to obtain the desired compound (**17**) in reasonably good yield. We explored the ligand effect as well. After this successful attempt, we screened various Pd catalysts and various ligands for this transformation. We found that $Pd(PPh_3)_4$ in conjuction with the addition of monodentate PPh_3 was found to be most suitable (entry 7); it afforded the desired product in 58% yield, which is good, compared to previous reports in which the authors could obtain a phenolic OH protected version of the compound in moderate yield. However, this added an additional step to the synthesis. We also added CuI and LiCl to the cross-coupling conditions (entry 14);[19] some positive effect on the reaction was observed, but these additions were deemed futile. The final step in the synthesis of mycophenolic acid was the hydrolysis of the methyl ester in **17**, which was performed in good yield using LiOH/H_2O in THF/water (Scheme 4). The spectroscopic data of the

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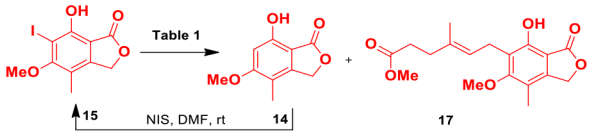
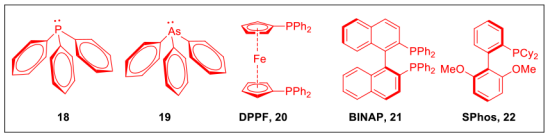
Table 1. Optimization of Reaction Conditions for Stille Coupling



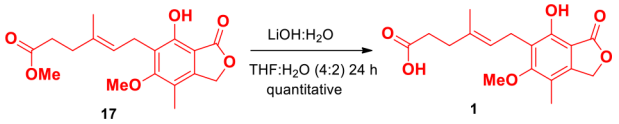


Sr. No.	conditions (additives)	ligand	solvent	temp (°C)	time (h)	yield (%) 14	yield (%) 17
1[a]	$Pd(OAc)_2$	PPh_3	DMF	100	12	80	–
2	$Pd(PPh_3)_4$	PPh_3	toluene	100	16	70	–
3	$Pd(dba)_2$	none	toluene	100	16	65	–
4	$Pd_2(dba)_3$, CuCl, NaOAc	dppf	dioxane	110	16	65	–
5[b]	$Pd(PPh_3)_4$	PPh_3	DMF	100	16	30	30
6	$Pd(PPh_3)_4$	PPh_3	DMF	100	16	10	50
7[c]	$Pd(PPh_3)_4$	PPh_3	DMF	100	16	trace	58
8	$Pd(PPh_3)_4$	BINAP	DMF	100	18	40	5
9	$Pd(PPh_3)_4$	SPhos	DMF	100	16	40	10
10	$Pd(PPh_3)_4$	$AsPPh_3$	DMF	100	18	trace	45
11	$Pd(OAc)_2$	$AsPPh_3$	DMF	100	18	70	5
12[d]	$Pd(PPh_3)_4$	PPh_3	DMF	100	16	trace	56
13	$Pd(OAc)_2$	PPh_3	DMF	100	24	70	10
14	$Pd(PPh_3)_4$, LiCl and CuI	PPh_3	DMF	100	36	50	trace
15	$Pd(OAc)_2$	PPh_3	DMF	100	24	65	–
16[e]	$Pd(PPh_3)_2Cl_2$	PPh_3	DMF	100	24	70	–

[a]Entries 1–4; reaction was attempted with 15 mol % catalyst without N_2 purging. [b]Entries 5–15; reaction was carried out with 15 mol % catalyst and 30 mol % ligand and N_2 purging. [c]2 equiv of **4**. [d]3 equiv of **4**. [e]10 mol % catalyst was used (see Table SI-S1).

synthetic molecule were in complete agreement with those for the natural compound.

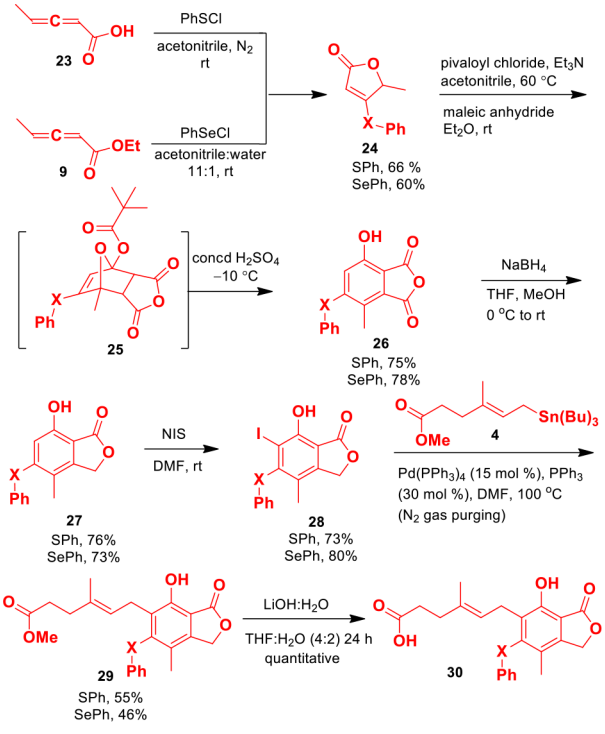
Scheme 4. Synthesis of Mycophenolic Acid



Having synthesized the natural product target, we then turned our attention to –XPh analogues through the similar strategy described for the natural product. The sulfide and selenide are incorporated at the initial stage and followed the same reaction sequence to the analogues of the natural product (Scheme 5).[20] Compound **9**, upon treatment with PhSeCl in acetonitrile/water, led to the formation of γ-lactone. This γ-lactone, through enolization and subsequent treatment with pivaloyl chloride, afforded the diene ester, which without purification was subsequently submitted to Diels–Alder reaction conditions with maleic anhydride in diethyl ether, which delivered the corresponding anhydride through intermediate **25**. $NaBH_4$ reduction and subsequent iodination of **27** allowed for the formation of **28** which facilitated the cross-coupling reaction. The allenoic acid **23** was used for the synthesis of the S-Ph-lactone. We followed the same reaction sequence for the synthesis of the sulfur analogue (SPh–**30**).

Initially, we were concerned with the implications for our choice of reaction conditions for cross-coupling with a substrate

Scheme 5. Synthesis of Phenylselenyl and Phenylsulfenyl Analogues



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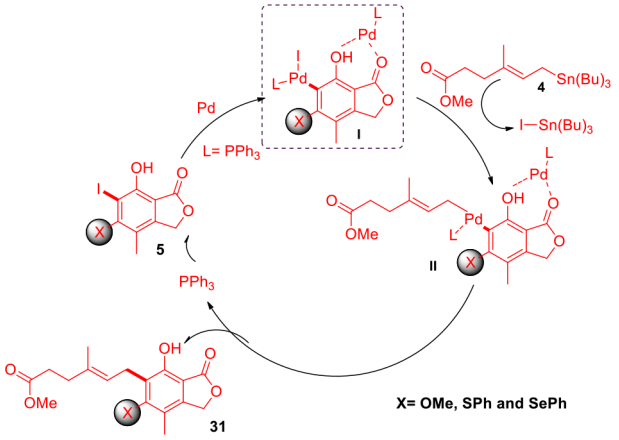
that contains phenylselenyl and phenylsulfenyl groups. The method in which phenylselenide was the coupling partner in the cross-coupling system may compete with the aryl halide position leading to an undesired product or intractable mixture of products.[21] Both lactones were subjected to the adopted Stille coupling reaction conditions for 8 h at 100 °C. To our pleasant surprise, under optimized reaction conditions, we obtained the desired product in 55% and 46% isolated yields, respectively. However, we attempted various conditions for the Stille coupling to attempt to enhance the yields more, but these trials were not fruitful. The hydrolysis of ester **29** afforded the analogues of the natural products (for log *p* value, see SI). While the exact mechanism remains unsupported by evidence for now, we believe that metal (phenolate) chelation during the reaction plays a key role in directing the reaction pathway (Scheme 6). To investigate the proposed mechanism we

Scheme 6. Mechanism of Cross-Coupling Reaction in the Absence of Protecting Group



obtained mass spectrometric data to determine whether the possible intermediate as proposed (**I**) in the aliquot of reaction has present, but attempts were unsuccessful. We propose that intermediate **I** forms through chelation; similar intermediates were proposed in some previous cases.[18] Chelation and the oxidative addition with Pd gives **I** which, upon transmetalation with **4**, gives **II**; subsequent reductive elimination delivers the product (**31**). For the first time, the Stille-cross coupling was studied with halo phenols devoid of protecting groups with encouraging results. The proposed mechanism is shown below (Scheme 6).

Developing water-soluble molecular probes are currently essential in an effort to understand the role and consequences of analytes such as reactive oxygen species (ROS) in biological systems.[9c] During the synthesis, we found molecules **12**, **26a**, and **26b** are water-soluble and possess UV−vis absorbance and emission characteristics (Figure 2). Thus, it is evident from the image that the organoselenium compound is nonfluorescent but can be used as a "turn-on" probe for ROS studies in water (Figure 2). The results of the UV/vis absorption spectra show that molecule **12**, **26a**, and **26b** have a maximum absorption at 403 nm. Upon the addition of $^{-}$OCl to **26b**, the absorbance peak undergoes a red shift (toward red wavelength) at 502 nm, whereas, upon addition of other ROS/RNS, no significant change in the spectra could be observed. The molecule **26b** was found to be selective toward $^{-}$OCl, and there is no increase in

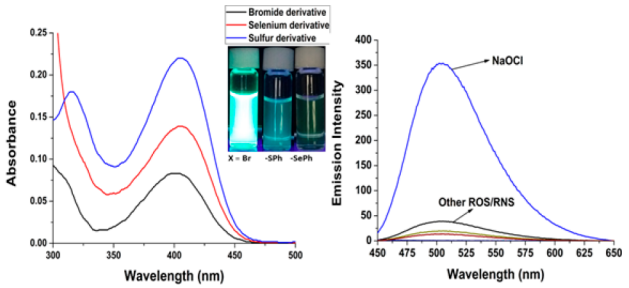


Figure 2. (Left) Absorbance spectra of **12**, **27a**, and **27b**; (right) fluorescence emission spectra of **27b** (15 μM) with ROS/RNS (NaOCl, H_2O_2, ^{t}BuOOH, $O_2^{\bullet-}$, ·OH, ^{t}BuO·, NO, and $ONOO^{-}$) in buffered aqueous solution (10 mM PBS pH 7.4) after incubation for 1.0 min. λ_{ex}: 404 nm, λ_{em}: 502 nm, slit width 3 nm/3 nm.

fluorescence intensity toward other ROS/RNS at higher concentration (20 equiv).

These species are thought to play a very important role in cancer and neurodegenerative disease disorders such as Parkinson's and Alzheimer's disease. An extensive study of these molecular properties will be reported in due course.

In conclusion, we have achieved an economical and protecting-group-free total synthesis for mycophenolic acid and chalcogenide bearing analogues. Diels−Alder reactions and extensive optimization of Stille coupling were key strategies used. The synthesis of mycophenolic acid was completed in 7 steps; 6 steps were required for the phenylsulfenyl and phenylselenyl analogues with 14.6% (MA), 15.1% (−SPh), and 12.6% (−SePh) isolated yields achieved, respectively. We have shown the applicability of **26b** as a potential probing platform for hypochlorous acid in aqueous media. Commercially and inexpensively available materials and efficient synthetic routes, promising for new drug discovery, were explored. Further investigation of this strategy for the synthesis of other related molecules and analogues for biological studies is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01327.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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