

# Concise Total Synthesis of (–)-Auxofuran by a Click Diels–Alder Strategy

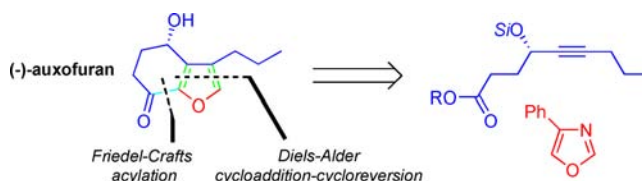
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## ABSTRACT



The first synthesis of auxofuran, a newly discovered auxin-like signaling molecule of streptomycetes, has been achieved in seven steps and 59% overall yield from commercial starting materials. Central to the synthetic route is a click–unclick Diels–Alder cycloaddition/cycloreversion regimen enabling rapid access to an advanced intermediate from an unactivated alkyne.

Soil-dwelling bacteria of the genus *Streptomyces* produce a cornucopia of natural products of clinical, agricultural, and biotechnological value.<sup>1</sup> These include over 70% of commercial antibiotics,<sup>2</sup> antibiotic production inducers,<sup>3</sup> and some little known signaling molecules whose role can be surprisingly subtle.<sup>4</sup> The first such compound, auxofuran, was reported in 2006 by Tarkka, Fiedler, and co-workers as the dominant fungal-growth promoter produced by the mycorrhiza helper bacterium *Streptomyces* strain AcH 505.<sup>5a</sup> Remarkably, auxofuran facilitates the mutually beneficial colonization of spruce roots by the fungus *Amanita muscaria* (fly agaric), a process vital to forest ecosystems whereby plants provide carbohydrates to fungi and in return fungi provide phosphates to plants.<sup>6,7</sup> Because

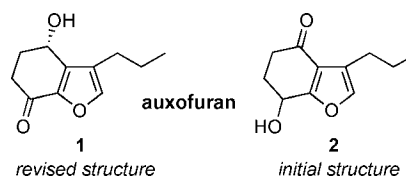


Figure 1. Structure of auxofuran.

streptomycetes, produce signaling molecules only in tiny amounts, it is often difficult to obtain sufficient material for proper characterization and testing. Initially, the structure of auxofuran was disclosed as **2**<sup>5a</sup> but was soon revised to **1** by Süßmuth<sup>5b</sup> who also determined its absolute configuration as *S* by modified Mosher ester analysis (Figure 1).

Intrigued by the exquisite 4-hydroxy-7-keto-4,5,6,7-tetrahydrobenzofuran motif of **1** and the need for meaningful quantities for biological studies, we were led to undertake its total synthesis. Reported herein is the first synthesis of auxofuran, which demonstrates the scaffolding power of click Diels–Alder chemistry and certifies the revised structure assignment.

Retrosynthetically, we envisioned assembly of **1** from chiral carboxylic acid **3** through intramolecular Friedel–Crafts acylation (Scheme 1). Among possible approaches to **3**, the most expedient entailed

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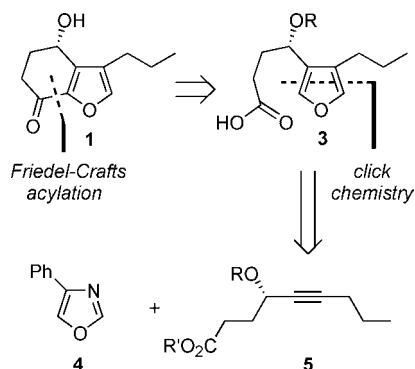
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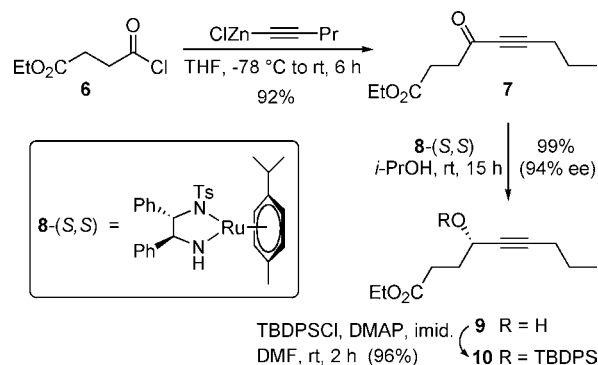
### Scheme 1. Synthesis Strategy for Auxofuran (1)



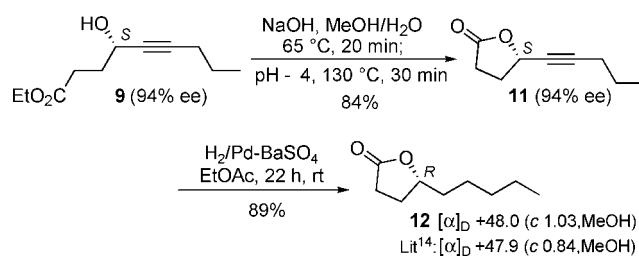
a “click–unclick” cycloaddition/cycloreversion reaction of oxazole **4** with chiral dienophile **5**. Although variants of this chemistry have found several applications in natural product synthesis,<sup>8–10</sup> the use of unactivated alkynes as external dienophiles is rare.<sup>11</sup> Moreover, the few known examples pertain to the preparation of fairly simple, achiral furan reagents.<sup>11</sup> Hence, the serviceability of this process in the context of total synthesis had yet to be investigated.

Toward this end, chiral dienophiles **9–11** were prepared from commercially available ethyl malonyl chloride **6** as outlined in Schemes 2–3. Alkynylation<sup>12</sup> of **6** with 1-pentynylzinc chloride afforded ynone **7** (92%), which cleanly underwent Noyori asymmetric transfer hydrogenation<sup>13</sup> to deliver propargyl alcohol **9** (99%) with high enantiomeric purity (>94% ee). Subsequent TBDPS protection provided silyl ether **10** with an overall efficiency of 87% (3 steps, Scheme 2). To ensure that the absolute stereochemistry of **9–10** was indeed as we had expected from the Noyori reduction, **9** was subjected to careful lactonization to (S)-alkynyllactone **11** (ee 94%) followed by hydrogenation

### Scheme 2. Synthesis of Chiral Dienophiles 9–10



### Scheme 3. Conversion of Alcohol 9 to (R)-Nonalactone (12)



of the alkyne linkage to provide the known (R)-nonalactone **12** (Scheme 3). Interestingly, the latter is an aroma component of Australian wines<sup>14</sup> and a worthy target in its own right, recently synthesized in five steps from L-glutamic acid<sup>14</sup> and by optical resolution of (±)-**12**.<sup>15</sup>

At this point, the cycloaddition/cycloreversion reaction of commercially available 4-phenyloxazole **4** with ynone **7** and unactivated alkynes **9–11** was explored (Table 1).

Counterintuitively, the *unactivated* alkyne **11** turned out to be more effective than its ynone counterpart **7**, affording furan **14** in essentially quantitative yield (entry 2 vs 1, Table 1).<sup>16</sup> Furthermore, enantiopure **14** could be obtained in excellent yield directly from hydroxy ester **9** via in situ lactonization (95%, entry 3). Even though the bulkier alkyne **10** was less reactive under the same conditions (ca. 40–45% conversion), a slight modification of the procedure enabled access to **15** with high efficiency (260–270 °C, 20 h, 84%, entry 4). It is worthy of note that none of the Diels–Alder adducts could be observed in these experiments, presumably

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**Table 1.** Assembly of Disubstituted Furans from Alkynes

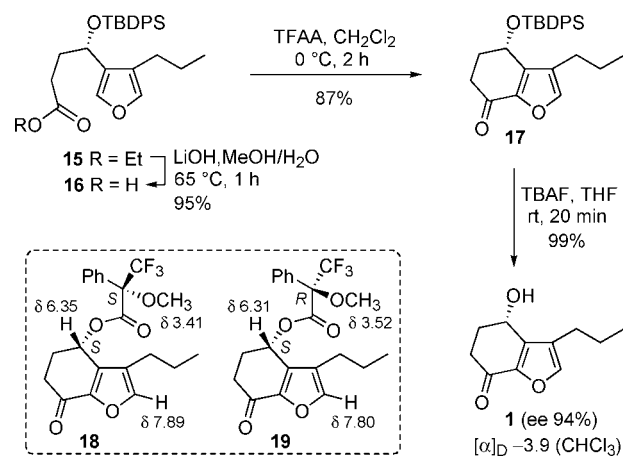
entry	alkyne	product	% yield <sup>a</sup>
1	 7	 13	61
2	 11	 14	97
3 <sup>b</sup>	 9	 14	95
4 <sup>c</sup>	 10	 15	84

<sup>a</sup>Yields refer to chromatographically isolated products.

<sup>b</sup>Lactone **14** had an ee of 94%, as did the sm. <sup>c</sup>Reaction carried out by heating **10** with 6 equiv of **4** for 20 h at 260–270 °C.

due to rapid collapse into furans under the reaction conditions ( $\geq 220$  °C).<sup>17,18</sup>

While auxofuran could ultimately be reached from either **14** or **15**, the latter represented a superior starting point for completing the synthesis. Hydrolysis of the ester group in **15** provided acid **16** thereby setting the stage for intramolecular Friedel–Crafts acylation to ketone **17** (Scheme 4). Initial attempts at generating the acid chloride of **16** proved utterly unrewarding.<sup>19,20</sup> A typical outcome was the formation of lactone **14**, even under essentially

**Scheme 4.** Synthesis of (–)-Auxofuran

HCl-free conditions.<sup>19</sup> Pleasingly, we were able to quell lactonization almost completely by adaptation of the exceptionally mild method of Tedder and Tatlow.<sup>21</sup> Thus, treatment of acid **16** with 1.2 equiv of trifluoroacetic anhydride in dichloromethane at 0 °C for 2 h smoothly promoted cyclization affording **17** in 87% yield (Scheme 4). Finally, TBAF desilylation furnished (–)-auxofuran **1** whose NMR spectra were identical to those of the natural product.<sup>5b</sup> Although no optical data were reported for auxofuran, its absolute configuration could be firmly established as *S* by conversion of synthetic **1** to Mosher esters **18** and **19** and NMR comparison with those derived from a natural sample.<sup>5b,22</sup>

In conclusion, the first synthesis of auxofuran has been achieved in seven steps and 59% overall yield from commercially available starting materials. Central to the success of this route is a tandem Diels–Alder/retro-Diels–Alder process enabling rapid assemblage of advanced intermediate **15** from an unactivated homochiral alkyne. The wider scope of such “click–unclick” regimens in the context of natural product synthesis is currently under investigation.

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**Supporting Information Available.** Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(22) See Table 1 in the Supporting Information for details.

The authors declare no competing financial interest.

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