Method for the Rapid Synthesis of Highly Functionalized 2-Hydroxy-1-naphthoates. Syntheses of the Naphthoic Acid Components of Neocarzinostatin Chromophore and N1999A2

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ABSTRACT

We describe a four-step sequence for the synthesis of complex 2-hydroxy-1-naphthoic acids involving Z-selective olefination of benzaldehyde derivatives with a novel dioxolenone-containing phenyl phosphonate reagent, followed by dioxolenone cleavage with alkaline trifluoroethanol and oxidative cyclization (Mn(OAc)₃) of the resultant trifluoroethyl α-keto esters.

Complex 2-hydroxy-1-naphthoic acid esters figure prominently in the DNA-damaging natural product agents neocarzinostatin chromophore (NCS)¹ and N1999A2² and have been proposed to function as intercalating groups in DNA binding.³ In this work we describe a short and efficient strategy for the synthesis of 2-hydroxy-1-naphthoic acids that is suitable for the preparation of a variety of complex naphthoates, including NCS naphthoic acid (1) and N1999A2 naphthoic acid (2).

Published syntheses of the naphthoic acid component of NCS chromophore (1) have involved 6–19 steps from commercially available starting materials,⁴ while only one route to naphthoic acid 2 has been described, this involving a linear sequence of 11 steps (8% yield).⁵ One of the shorter and more efficient published routes to compound 1 employs the oxidative cyclization shown in Scheme 1 as a key step.
transformation. This transformation did not prove to be general, however, for only electron-rich aromatic substrates were found to undergo efficient oxidative cyclization by this method. In our own published route to compound 1 (seven steps, 33% yield), we employed the photochemical cyclization of eq 1 as a key step. In subsequent studies, we have found that this sequence, too, is not general, for when we attempted a closely analogous cyclization in an effort to synthesize naphthoic acid 2 (eq 2), the desired product 3 was formed in no more than 30% yield; the dechlorination product 4 was identified as one of several byproducts.

In a new strategy for 2-hydroxy-1-naphthoic acid synthesis, we have developed a four-step sequence that appears to offer both greater generality and efficiency than any prior route. The new protocol is illustrated first with the synthesis of 1, shown in Scheme 2, and later (Table 1) for the preparation of a number of different 2-hydroxy-1-naphthoic acid esters of different substitution patterns. In the first step of the sequence, an aromatic aldehyde is subjected to Z-selective olefination using the novel phenyl phosphonate ester 6 (Scheme 2). Phenyl phosphonate esters have been widely used as reagents for Z-selective olefin synthesis. Optimal Z-selectivity (4:1) in coupling with aromatic aldehydes was achieved using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in the absence of any other additive. The inclusion of sodium iodide, recommended for a different stabilized phenyl phosphonate ester system, was found to lead to reduced Z-selectivity in the case of reagent 6.

In the next step of the sequence, the 1,3-dioxolenone group of the coupling products was transformed into the corresponding beta-keto trifluoroethyl ester, without detectable isomerization of the adjacent (Z)-olefin, by subjecting the coupling products to sodium trifluoroethoxide in trifluoroethanol. The trifluoroethyl group was chosen because it is more easily saponified than the more common methyl or ethyl esters. The beta-keto trifluoroethyl ester products, which existed as a nearly equal mixture of keto and enol tautomeric forms (CDCl₃, ~0.10 M), underwent smooth cyclization to the corresponding trifluoroethyl 2-hydroxy-1-naphthoic acid esters in the presence of manganese triacetate in acetic acid (23 or 40 °C, depending upon the substrate; see Table 1).

Finally, saponification of the trifluoroethyl ester group of the cyclized products was readily achieved, in essentially quantitative yield, using lithium hydroxide in aqueous tetrahydrofuran at 40 °C.


As shown by the examples of Table 1, this new protocol has been successfully employed for the transformation of both electron-rich and electron-poor ortho-substituted aromatic aldehydes into the corresponding trifluoroethyl 2-hydroxy-1-naphthoic acid esters. The final example of Table 1, 3-triisopropylsilyloxy benzaldehyde, shows that it is possible to achieve regioselective cyclization without ortho substitution, in this case almost certainly a consequence of steric shielding by the triisopropylsilyloxy substituent.

In a final illustration of the new method, we have synthesized the 2-hydroxy-1-naphthoic acid component of N1999A2 in protected form (12), as shown in Scheme 3. The overall yield for the four-step sequence in this case was 69% (eight steps and 35% yield from 3-methoxybenzyl alcohol). This protocol has successfully provided more than 2 g of compound 12 in our largest-scale implementation of the procedure. In addition to the utility of the method we describe for the synthesis of 2-hydroxy-1-naphthoic acids, the phenyl phosphonate 6 provides an interesting and potentially more broadly useful reagent for carbon-carbon bond formation in synthetic organic chemistry.

**Table 1.** Synthesis of Differently Substituted Trifluoroethyl 2-Hydroxy-1-naphthoic Acid Esters from Benzaldehyde Derivatives by the Sequence of Scheme 2

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
</tr>
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<tbody>
<tr>
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<td><img src="" alt="image" /></td>
<td>78</td>
</tr>
<tr>
<td>2b</td>
<td><img src="" alt="image" /></td>
<td><img src="" alt="image" /></td>
<td>70</td>
</tr>
<tr>
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</tr>
<tr>
<td>5c</td>
<td><img src="" alt="image" /></td>
<td><img src="" alt="image" /></td>
<td>62</td>
</tr>
</tbody>
</table>

* Isolated yield after three steps. 

**Scheme 3.** Synthesis of N1999A2 Naphtho Acid in Protected Form

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(6) Phenyl phosphonate ester 6 was synthesized in two steps from 2,2,6-trimethyl-4H-1,3-dioxane-4-one (see Supporting Information). The corresponding ethyl phosphonate ester is known and has been employed in E-selective olefination reactions: Boeckman, R.; Thomas, A. J. Org. Chem. 1982, 47, 2823–2824.


(9) Aromatic aldehyde used as starting material (9) was prepared in four steps and 51% yield from commercially available 3-methoxybenzyl alcohol (See Supporting Information).

(10) Trifluoroethyl group is not necessary for successful cyclization. The product of methanolysis of the dioxolenone 10 (Scheme 3) also cyclizes to give the corresponding methyl 2-hydroxy-1-naphthoic acid ester (Mn(OAc)₃, HOAc, 40 °C, 93% over two steps); (d) LiOH, THF, H₂O, 40 °C, 100%.

In a final illustration of the new method, we have synthesized the 2-hydroxy-1-naphthoic acid component of N1999A2 in protected form (12), as shown in Scheme 3. The overall yield for the four-step sequence in this case was 69% (eight steps and 35% yield from 3-methoxybenzyl alcohol). This protocol has successfully provided more than 2 g of compound 12 in our largest-scale implementation of the procedure. In addition to the utility of the method we describe for the synthesis of 2-hydroxy-1-naphthoic acids, the phenyl phosphonate 6 provides an interesting and potentially more broadly useful reagent for carbon-carbon bond formation in synthetic organic chemistry.

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