

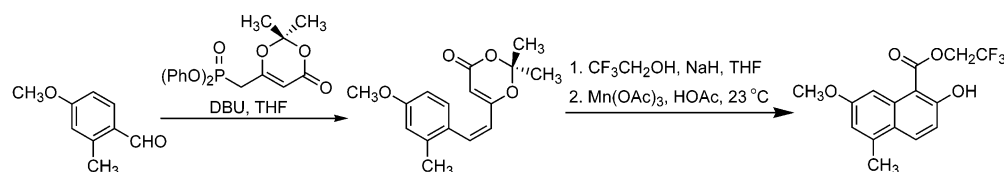
# Method for the Rapid Synthesis of Highly Functionalized 2-Hydroxy-1-naphthoates. Syntheses of the Naphthoic Acid Components of Neocarzinostatin Chromophore and N1999A2

Nan Ji, Brad M. Rosen, and Andrew G. Myers\*

Department of Chemistry and Chemical Biology, Harvard University,  
Cambridge, Massachusetts 02138  
myers@chemistry.harvard.edu

Received September 21, 2004

## 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 ( $\text{Mn}(\text{OAc})_3$ ) of the resultant trifluoroethyl  $\beta$ -keto esters.

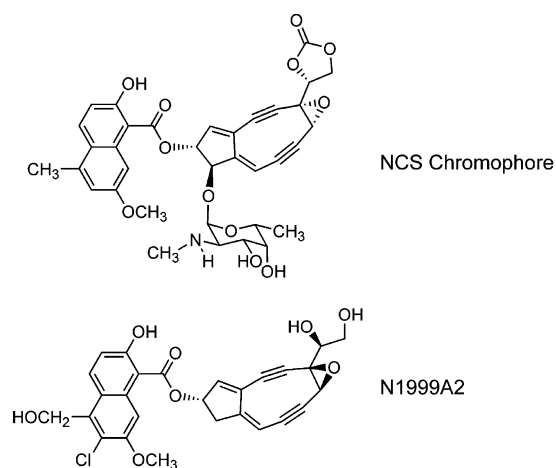
Complex 2-hydroxy-1-naphthoic acid esters figure prominently in the DNA-damaging natural product agents neocarzinostatin chromophore (NCS)<sup>1</sup> and N1999A2<sup>2</sup> and have been proposed to function as intercalating groups in DNA binding.<sup>3</sup> In this work we describe a short and efficient 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

(1) (a) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, 26, 331–334. (b) Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M.; Koide, Y.; Ishida, N. *J. Antibiot.* **1986**, 39, 1615–1619. (c) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, 110, 7212–7214.

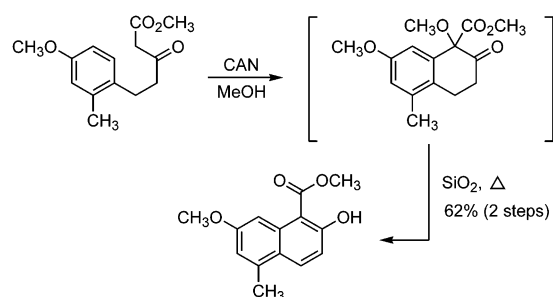
(2) (a) Ando, T.; Ishii, M.; Kajiura, T.; Kameyama, T.; Miwa, K.; Sugiura, Y. *Tetrahedron Lett.* **1998**, 39, 6495–6498. (b) Kobayashi, S.; Ashizawa, S.; Takahashi, Y.; Sugiura, Y.; Nagaoka, M.; Lear, M. J.; Hiram, M. *J. Am. Chem. Soc.* **2001**, 123, 11294–11295.

(3) Povirk, L. F.; Dattagupta, N.; Warf, B. C.; Goldberg, I. H. *Biochemistry* **1981**, 20, 4007–4014.

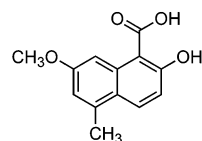


commercially available starting materials,<sup>4</sup> while only one route to naphthoic acid **2** has been described, this involving a linear sequence of 11 steps (8% yield).<sup>5</sup> One of the shorter and more efficient published routes to compound **1** employs the oxidative cyclization shown in Scheme 1 as a key

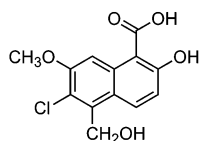
**Scheme 1.** Synthesis of the Naphthoic Acid Component of NCS Chromophore by Oxidative Cyclization of an Electron-Rich  $\delta$ -Aryl  $\beta$ -Keto Ester<sup>4c</sup>



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.<sup>4c</sup> In our own published route to compound **1** (seven steps, 33% yield), we employed the photochemical cyclization of eq 1 as a key step.<sup>4c</sup> 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.



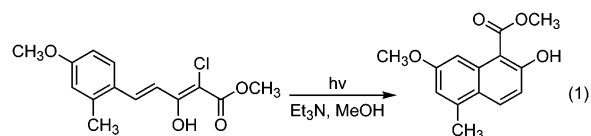
NCS Naphthoic Acid (**1**)



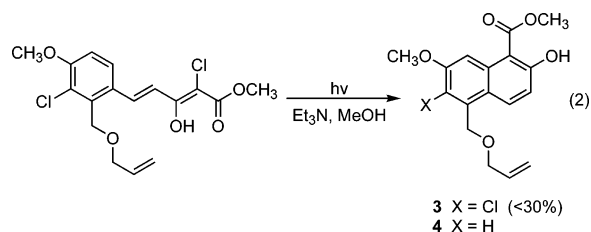
N1999A2 Naphthoic Acid (**2**)

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).<sup>6</sup> Phenyl phosphonate esters have been widely used as reagents for *Z*-selective olefin synthesis.<sup>7</sup> In the case of reagent **6**, optimal *Z*-selectivity ( $\sim$ 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,<sup>7c</sup> was found to lead to reduced *Z*-selectivity in the case of reagent **6**.

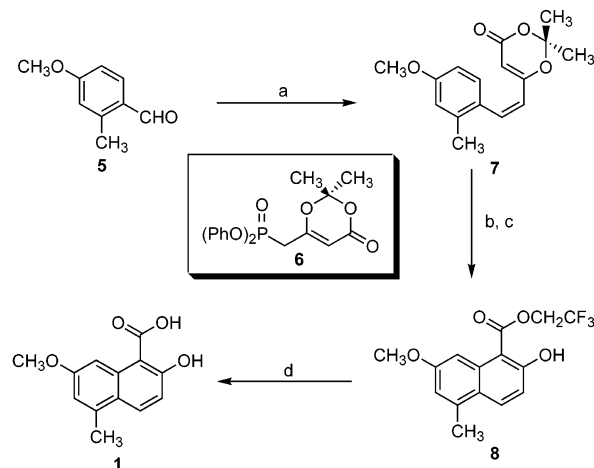


In the next step of the sequence, the 1,3-dioxolenone group of the coupling products was transformed into the corresponding  $\beta$ -keto trifluoroethyl ester, without detectable isomerization of the adjacent (*Z*)-olefin, by subjecting the coupling products to sodium trifluoroethoxide in trifluoroethanol. 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 ( $\text{CDCl}_3$ ,  $\sim$ 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).<sup>8</sup>



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.

**Scheme 2.** Synthesis of Complex 2-Hydroxy-1-naphthoic Acids from Benzaldehyde Derivatives<sup>a</sup>


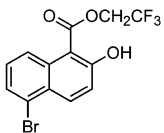
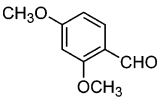
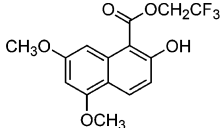

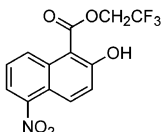

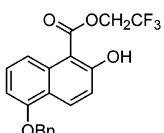
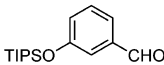
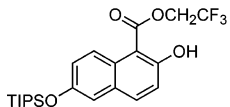


(4) (a) Shibuya, M.; Toyooka, K.; Kubota, S. *Tetrahedron Lett.* **1984**, 25, 1171–1174. (b) Shishido, K.; Yamashita, A.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1989**, 30, 111–112. (c) Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis* **1990**, 142–144. (d) Takahashi, K.; Suzuki, T.; Hiram, M. *Tetrahedron Lett.* **1992**, 33, 4603–4604. (e) Myers, A. G.; Subramanian, V.; Hammond, M. *Tetrahedron Lett.* **1996**, 37, 587–590. (f) Göth, F. C.; Rucker, M.; Eckhardt, M.; Brückner, R. *Eur. J. Org. Chem.* **2000**, 14, 2605–2611.

(5) Takahashi, K.; Hagiwara, M.; Ashizawa, S.; Hiram, M. *Synlett* **1999**, 1, 71–72.

<sup>a</sup> Reagents and conditions: (a) **6**, DBU, THF, 0–23 °C, 82%; (b)  $\text{CF}_3\text{CH}_2\text{OH}$ , NaH, THF, 23 °C; (c)  $\text{Mn}(\text{OAc})_3$ , HOAc, 23 °C, 93% (two steps); (d) LiOH, THF,  $\text{H}_2\text{O}$ , 40 °C, 100%.

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

entry	substrate	product	yield (%) <sup>a</sup>
1 <sup>b</sup>			78
2 <sup>b</sup>			70
3 <sup>c</sup>			78
4 <sup>c</sup>			75
5 <sup>c</sup>			62

<sup>a</sup> Isolated yield after three steps. <sup>b</sup> Mn(OAc)<sub>3</sub> oxidative cyclization reaction conducted at 23 °C. <sup>c</sup> Mn(OAc)<sub>3</sub> oxidative cyclization reaction conducted at 40 °C.

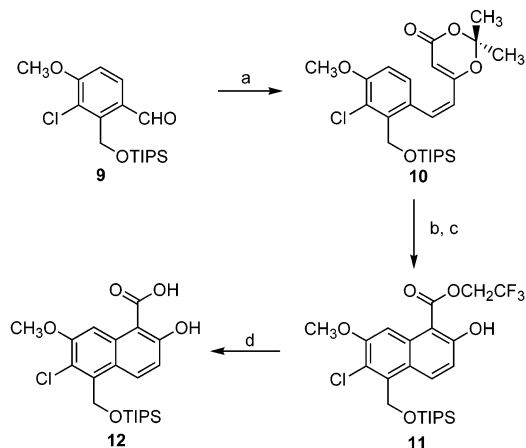
As shown by the examples of Table 1, this new protocol has been successfully employed for the transformation of both electron-rich and electron-poor ortho-substituted aromatic aldehydes into the corresponding trifluoroethyl 2-hydroxy-1-naphthoic acid esters. The final example of Table 1, 3-triisopropylsilyloxy 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.

(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.

(7) (a) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411–8416. (b) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408. (c) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

(8) Manganese(III) acetate was introduced as a reagent for the oxidative cyclization of unsaturated 1,3-dicarbonyl compounds (dihydrofuran products: Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456–3457) and has been shown to be useful for the formation of carbocyclic products from unsaturated  $\beta$ -keto acids (Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384–5385) and  $\beta$ -keto esters (Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659–3661). Review: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.

**Scheme 3.** Synthesis of N1999A2 Naphthoic Acid in Protected Form<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) **6**, DBU, THF, 0–23 °C, 74%; (b) CF<sub>3</sub>CH<sub>2</sub>OH, NaH, THF, 23 °C; (c) Mn(OAc)<sub>3</sub>, HOAc, 40 °C, 93% (two steps); (d) LiOH, THF, H<sub>2</sub>O, 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).<sup>9,10</sup> 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.

**Acknowledgment.** Financial support from the National Institutes of Health and Pfizer, Inc., is gratefully acknowledged. B.M.R. acknowledges funding for a summer fellowship from the Henry and Camille Dreyfus Foundation.

**Supporting Information Available:** Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048075L

(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 dioxolane **10** (Scheme 3) also cyclizes to give the corresponding methyl 2-hydroxy-1-naphthoic acid ester (Mn(OAc)<sub>3</sub>, HOAc, 40 °C, 93% over two steps). Significantly, neither the corresponding *E*-isomeric  $\beta$ -keto methyl ester (**13**) nor the saturated  $\beta$ -keto methyl ester (**14**, cf. Scheme 1) was observed to cyclize under these or other conditions examined.

