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# 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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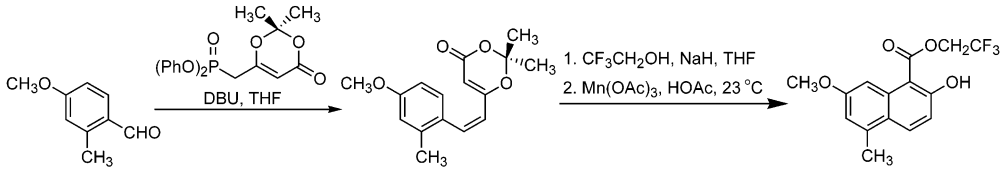
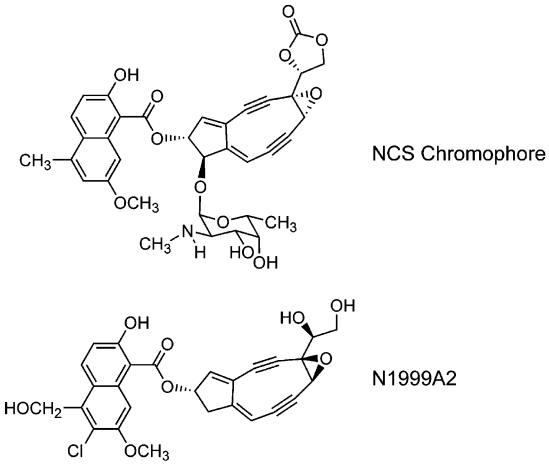
## ABSTRACT




**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 *β*-keto esters.**

Complex 2-hydroxy-1-naphthoic acid esters figure prominently in the DNA-damaging natural product agents neocarzinostatin chromophore (NCS)[1] and N1999A2[2] 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




(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.; Hirama, 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.

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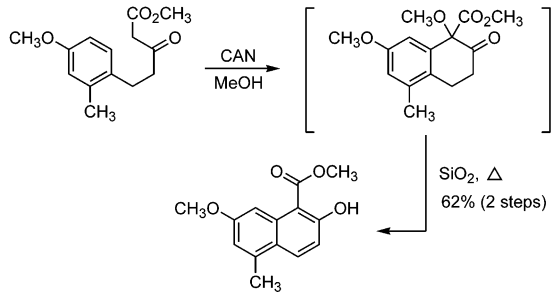
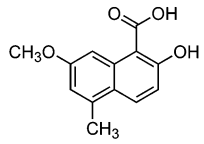
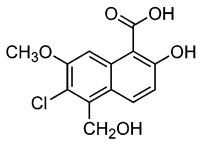
**Scheme 1.** Synthesis of the Naphthoic Acid Component of NCS Chromophore by Oxidative Cyclization of an Electron-Rich $\delta$-Aryl $\beta$-Keto Ester[4c]




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

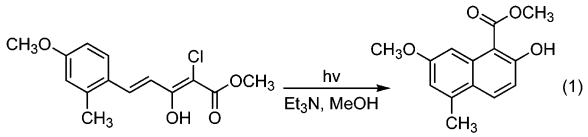



NCS Naphthoic Acid (**1**)

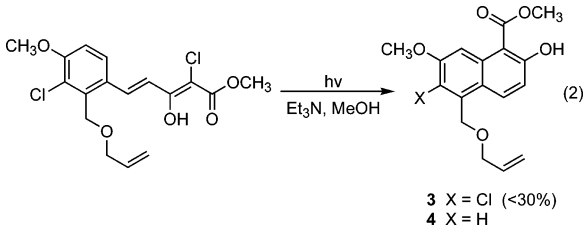



N1999A2 Naphthoic Acid (**2**)

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).[6] Phenyl phosphonate esters have been widely used as reagents for *Z*-selective olefin synthesis.[7] In the case of reagent **6**, 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,[7c] was found to lead to reduced *Z*-selectivity in the case of reagent **6**.

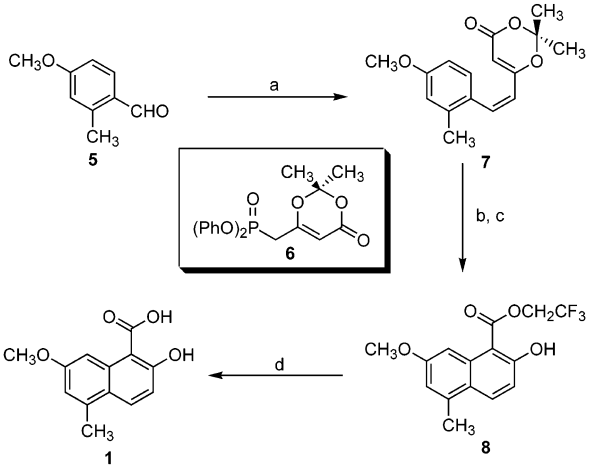



In the next step of the sequence, the 1,3-dioxolenone group of the coupling products was transformed into the corresponding $\beta$-keto trifluoroethyl ester, without detectable isomerization of the adjacent (*Z*)-olefin, by subjecting the coupling products to sodium trifluoroethoxide in trifluoroethanol. 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 ($CDCl_3$, ~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).[8]




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[a]

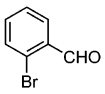
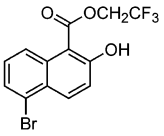
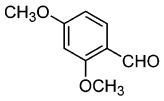
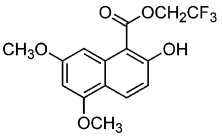
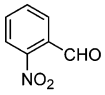
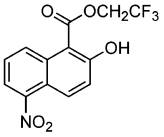
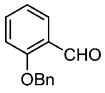
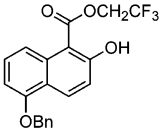
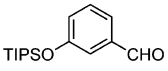
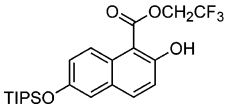



[a] Reagents and conditions: (a) **6**, DBU, THF, 0−23 °C, 82%; (b) $CF_3CH_2OH$, NaH, THF, 23 °C; (c) $Mn(OAc)_3$, HOAc, 23 °C, 93% (two steps); (d) LiOH, THF, $H_2O$, 40 °C, 100%.

(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.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 4603−4604. (e) Myers, A. G.; Subramanian, V.; Hammond, M. *Tetrahedron Lett.* **1996**, *37*, 587−590. (f) Görth, F. C.; Rucker, M.; Eckhardt, M.; Brückner, R. *Eur. J. Org. Chem.* **2000**, *14*, 2605−2611.

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

**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 (%)[a] |
|---|---|---|---|
| 1[b] |  |  | 78 |
| 2[b] |  |  | 70 |
| 3[c] |  |  | 78 |
| 4[c] |  |  | 75 |
| 5[c] |  |  | 62 |

[a] Isolated yield after three steps. [b] $Mn(OAc)_3$ oxidative cyclization reaction conducted at 23 °C. [c] $Mn(OAc)_3$ oxidative cyclization reaction conducted at 40 °C.

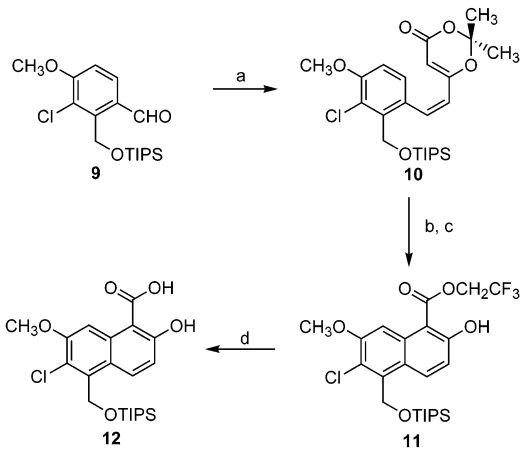
As shown by the examples of Table 1, this new protocol has been successfully employed for the transformation of both electron-rich and electron-poor ortho-substituted aromatic aldehydes into the corresponding trifluoroethyl 2-hydroxy-1-naphthoic acid esters. The final example of Table 1, 3-triisopropylsilyloxy 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-4*H*-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[a]




[a] Reagents and conditions: (a) **6**, DBU, THF, 0−23 °C, 74%; (b) $CF_3CH_2OH$, NaH, THF, 23 °C; (c) $Mn(OAc)_3$, HOAc, 40 °C, 93% (two steps); (d) LiOH, THF, $H_2O$, 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).[9,10] 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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**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.

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(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). 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.