JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

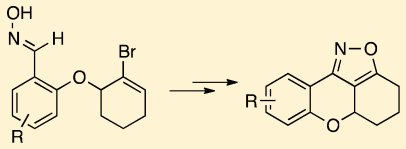
Annulated Isoxazoles via [3 + 2] Cycloaddition of Alkenyl Bromides and Oximoyl Chlorides and Ag(I) Promoted Elimination

Emmanuel B. Castillo-Contreras, Alexander M. Stahl,† and Gregory R. Dake*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, B. C., Canada, V6T 1Z1

Supporting Information

ABSTRACT: Substituted salicylaldehydes are converted to fused tetracyclic isoxazoles through a synthetic sequence incorporating substitution of 2-bromo-2-cyclohexen-1-ol, formation of an oxime function, conversion to an oximoyl chloride, intramolecular [3 + 2] cycloaddition, and elimination of an equivalent of hydrogen bromide using silver(I) carbonate. Six examples of this sequence are presented.



It is well-established that [3 + 2] dipolar cycloaddition reactions provide straightforward access to a variety of functionalized heterocyclic ring systems.[1] Indeed, the effectiveness of this specific strategy has led to its frequent application in the generation of heterocyclic lead compounds for potential treatments in human disease.[2] On a tangent within a broader synthetic project, we became interested in the construction of isoxazole and isoxazoline heterocycles connected to substituted [4.4.0]-bicyclooxacyclodecane ring systems (Figure 1). The

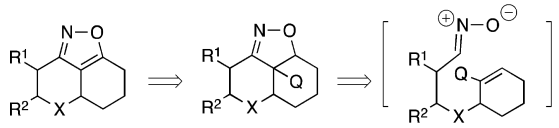
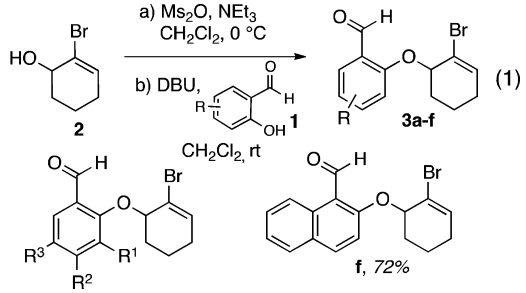


Figure 1. Strategy for annulated isoxazoles.

experimental record suggested that a synthetic approach incorporating a dipolar cycloaddition would be viable. First, dipolar cycloadditions of nitrones and nitrile oxides had been described previously in substrates, where Q = H.[3] In addition, alkenyl halides (e.g., if Q = Cl or Br) had been used as dipolarophiles in [3 + 2] cycloadditions,[4] although not in this specific context. Finally, an example of an elimination of a bromo-substituted isoxazoline to generate an unstrained isoxazole had been carried out some time ago.[5] Consequently, the proposed route seemed to have validity. This report summarizes our brief investigation in this matter.

Substituted salicylaldehydes (**1a**–**f**) were selected as starting materials for the sequence. The alkylation of the phenol function of these salicylaldehydes with an appropriate electrophile was more challenging than anticipated. Extensive experimentation established that 2-bromo-2-cyclohexen-1-ol (**2**) could be reacted with methanesulfonyl anhydride and triethylamine to generate a (putative) methanesulfonate.[6] A direct interception of this intermediate required DBU and salicylaldehyde (**1a**) in dichloromethane to generate **3a** in 72% yield (eq 1). Attempted substitutions using Mitsunobu conditions (side reactions), *p*-toluenesulfonate electrophiles (reagent instability), or chloride electrophiles (low yields) had significant disadvantages. This procedure was used to react **2**

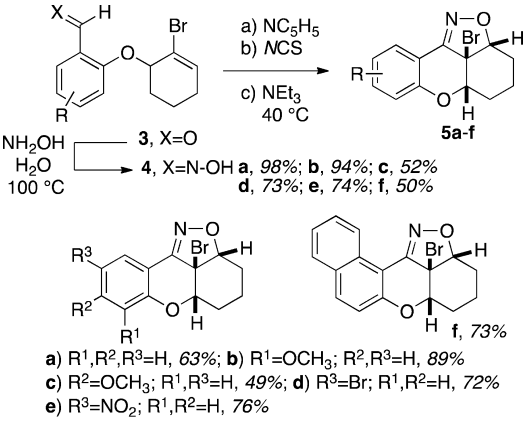


a) R^1,R^2,R^3=H, *72%*; **b**) R^1=OCH_3; R^2,R^3=H, *98%*
c) R^2=OCH_3; R^1,R^3=H, *40%*; **d**) R^3=Br; R^1,R^2=H, *7%*
e) R^3=NO_2; R^1,R^2=H, *30%*

with a small number of substituted salicylaldehydes to produce ethers **3b**–**f**. The reaction of 4-bromosalicylaldehyde was particularly low yielding; extended efforts to improve the reaction yields were not made.

The aldehyde functions in **3a**–**f** were converted to oximes using established reaction conditions (NH_2OH, water, 100 °C, Scheme 1). No unexpected reactivity was noted. The Suzuki

Scheme 1

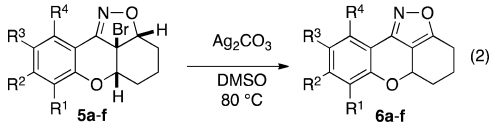


Received: June 19, 2014
Published: July 22, 2014

   dx.doi.org/10.1021/jo501376q | J. Org. Chem. 2014, 79, 7250–7255

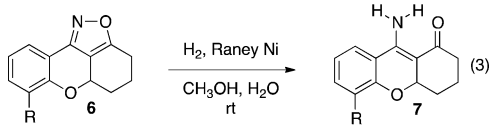
group has disclosed a highly effective method to convert oximes to oximoyl chlorides using *N*-chlorosuccinimide in basic conditions, followed by cycloaddition.[7] In our hands, this procedure was most efficient. Isolation of these intermediates was not required; direct [3 + 2] cycloaddition occurred in the presence of triethylamine to generate the expected heterocyclic adducts in excellent yield.

The cleavage of the N−O bond of the isoxazoline heterocycles[8] using hydrogen gas and Raney nickel was complicated by the generation of a large number of undesired side products resulting from the reactivity of the C−Br bond. The elimination of an equivalent of hydrogen bromide from each of the compounds **5a−f** could be accomplished using silver carbonate in DMSO at 80 °C (eq 2). A number of annulated isoxazoles **6a−f** was generated. A solid-state molecular structure obtained using X-ray crystallography confirmed the structure of **6a**.



a) R^1,R^2,R^3,R^4=H, *78%*; **b**) R^1=OCH_3; R^2,R^3,R^4=H, *79%*
c) R^2=OCH_3; R^1,R^3,R^4=H, *77%*; **d**) R^3=Br; R^1,R^2,R^4=H, *69%*
e) R^3=NO_2; R^1,R^2,R^4=H, *65%*, **f**) R^3,R^4=$(CH)_4$; R^1,R^2=H, *34%*

An example of the utility of these heterocycles can be demonstrated using a N−O bond cleavage reaction. The reduction of the isoxazole N−O bond was expected to be much simpler due to the increase of ring strain of **6** compared with **5**. Thus, the hydrogenolysis of the N−O bond in **6a** and **6b** using hydrogen gas over Raney nickel readily occurred to generate vinylogous amides **7a** and **7b** in 98% and 92% yields, respectively (eq 3). The structure of **7b** was confirmed by X-ray crystallography.



a, R=H, *98%*
b, R=OCH_3, *92%*

In summary, isoxazole heterocycles appended onto an oxabicyclo[4.4.0]decane ring could be formed through a sequence incorporating a intramolecular dipolar cycloaddition using an alkenyl bromide as a dipolarophile and a silver(I) promoted elimination. These heterocyclic frameworks, and nitrogen-containing versions, could prove to be useful structural motifs for exploratory medicinal chemistry programs.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out in flame-dried glassware under a nitrogen atmosphere. Dichloromethane, pyridine, and triethylamine were distilled from calcium hydride under an argon atmosphere. Dimethyl sulfoxide was distilled from calcium chloride under high vacuum and was stored with molecular sieves under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise specified. Reactions were magnetically stirred and monitored by thin-layer chromatography with 250 μm precoated silica gel plates. Flash column chromatography was performed using silica gel (230−400 mesh). Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform. Chemical shifts are recorded in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.27 ppm ^{1}H NMR; δ 77.2 ppm ^{13}C NMR). High-resolution mass spectra were obtained on a time-of-flight instrument using electrospray ionization.

Representative Procedure of Salicylaldehyde Alkylation Using 2. 2-((2-Bromocyclohex-2-en-1-yl)oxy)benzaldehyde (3a). Triethylamine (1.96 g, 15.2 mmol, 1.5 equiv) was added to a solution of 2-bromo-2-cyclohexene-1-ol (1.77 g, 10 mmol, 1 equiv) in 50 mL of CH_2Cl_2 at 0 °C. A solution of methanesulfonic anhydride (2.72 g, 15.2 mL, 1.5 equiv) in 50 mL of CH_2Cl_2 was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 30 min and then warmed to rt for 1 h. A solution of 3.78 g (30.3 mmol, 3 equiv) of salicylaldehyde and 4.68 g (30.2 mmol, 3 equiv) of DBU in 50 mL of CH_2Cl_2 was then slowly added dropwise over 30 min. The reaction mixture was stirred at rt for 1 h and then heated to reflux for 16 h. After it was cooled to rt, the reaction mixture was poured into a separatory funnel and washed successively with aqueous 2 M HCl solution (twice), aqueous 2 M NaOH solution (twice), and water (twice). Drying over sodium sulfate and concentration by rotary evaporation in vacuo produced a yellowy thick oil that, after purification using chromatography over silica gel (hexanes:ethyl acetate 9:1 to 4:1), yielded 2.0 g (72%) of the title compound as a white solid, mp 78−79 °C. IR (neat): 2932, 1682, 1596, 1229, 653 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.56 (s, 1H), 7.85 (dd, J = 7.7, 1.5 Hz, 1H), 7.54 (td, J = 7.9, 1.4 Hz, 1H), 7.11−7.03 (m, 2H), 6.42 (dd, J = 4.7, 3.1 Hz, 1H), 4.89 (s, 1H), 2.30−2.07 (m, 3H), 2.00−1.90 (m, 1H), 1.84−1.68 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 190.2, 161.0, 135.9, 135.5, 128.4, 126.4, 121.6, 120.2, 114.9, 77.6, 29.6, 27.8, 17.1. MS (ESI$^+$): 305.2 (M + Na)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{13}O_2Na^{79}Br$ (M + Na)$^+$: 302.9997, found: 302.9990.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-3-methoxybenzaldehyde (3b). The reaction was performed with 3.64 g (20.6 mmol) of 2-bromo-2-cyclohexenol, 5.59 g (31.1 mmol) of methanesulfonic anhydride, 3.19 g (31.6 mmol) of triethylamine, 9.54 g (62.1 mmol) of *o*-vanillin, and 9.57 g (61.6 mmol) of DBU. After purification, 6.40 g (98% yield) of the title compound was isolated as an off-white solid, mp 64−65 °C. IR (neat): 2950, 1687, 1243, 572 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 7.37 (dd, J = 7.2, 2.1 Hz, 1H), 7.09−7.00 (m, 2H), 6.29 (dd, J = 4.6, 3.0 Hz, 1H), 4.88 (s, 1H), 3.82 (s, 3H), 2.21−2.14 (m, 2H), 2.04 (d, J = 8.1 Hz, 1H), 1.80 (dd, J = 15.3, 7.3 Hz, 2H), 1.64−1.61 (m, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 190.7, 152.3, 150.7, 135.1, 130.3, 123.7, 120.7, 118.8, 117.9, 79.6, 55.9, 30.1, 27.8, 16.5. MS (ESI$^+$): 333.3 (M + Na)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{15}O_3Na^{79}Br$: 333.0102, found: 333.0099.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-4-methoxybenzaldehyde (3c). The reaction was performed with 1.81 g (10.2 mmol) of 2-bromo-2-cyclohexenol, 2.81 g (15.8 mmol) of methanesulfonic anhydride, 1.60 g (15.8 mmol) of triethylamine, 2.40 g (15.5 mmol) of 2-hydroxy-4-methoxybenzaldehyde, and 2.44 g (15.7 mmol) of DBU. After purification, 1.26 g (40% yield) of the title compound was obtained as a light yellow oil. IR (neat): 2939, 1675, 1596, 1254, 620 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.38 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 6.62−6.56 (m, 2H), 6.43 (dd, J = 5.1, 3.1 Hz, 1H), 4.87−4.85 (m, 1H), 3.88 (s, 3H), 2.25−2.14 (m, 3H), 1.98−1.90 (m, 1H), 1.79−1.72 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 188.8, 166.1, 162.7, 135.6, 130.4, 120.6, 120.1, 107.1, 100.9, 77.6, 55.9, 29.6, 27.8, 17.1. MS (ESI$^+$): 333.3 (M + Na)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{15}O_3Na^{79}Br$: 333.0102, found: 333.0107.

5-Bromo-2-((2-bromocyclohex-2-en-1-yl)oxy)benzaldehyde (3d). The reaction was performed with 1.77 g (10.0 mmol) of 2-bromo-2-cyclohexenol, 2.81 g (15.8 mmol) of methanesulfonic anhydride, 1.60 g (15.8 mmol) of triethylamine, 3.29 g (16.4 mmol) of 5-bromo-2-hydroxybenzaldehyde, and 2.55 g (16.4 mmol) of DBU. After purification, 0.25 g (7% yield) of the title product was obtained as a light yellow solid, mp 117 °C. IR (neat): 2938, 1678, 1598, 1252, 618 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.39 (s, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.55 (dd, J = 8.9, 2.5 Hz, 1H), 6.97 (d, J = 8.9 Hz, 1H), 6.35 (dd, J = 4.5, 3.3 Hz, 1H), 4.80 (s, 1H), 2.24−2.00 (m, 6H), 1.98−1.87 (m, 2H), 1.71 (dd, J = 15.6, 4.2 Hz, 2H), 1.19 (t, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 188.5, 159.8, 138.2, 135.6, 130.8,

dx.doi.org/10.1021/jo501376q | J. Org. Chem. 2014, 79, 7250−7255

127.5, 119.6, 116.8, 114.2, 77.9, 30.9, 29.5, 27.6, 16.9. MS (ESI^-): 359.1 $(M - H)^-$. HRMS (ESI^+): Calculated for $C_{13}H_{12}O_2Na^{79}Br_2$: 380.9102, found: 380.9103.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-5-nitrobenzaldehyde (3e). The reaction was performed with 1.78 g (10.0 mmol) of 2-bromo-2-cyclohexenol, 2.76 g (15.5 mmol) of methanesulfonic anhydride, 1.52 g (15.1 mmol) of triethylamine, 3.58 g (21.2 mmol) of 2-hydroxy-5-nitrobenzaldehyde, and 3.36 g (21.6 mmol) of DBU. After purification, 0.98 g (30% yield) of the title compound was obtained as a white powder, mp 114−117 °C. IR (neat): 3118, 2953, 1683, 1587, 1342, 1268, 667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.51 (s, 1H), 8.72 (d, J = 2.9 Hz, 1H), 8.42 (dd, J = 9.2, 2.9 Hz, 1H), 7.21 (d, J = 9.3 Hz, 1H), 6.49 (dd, J = 5.0, 3.2 Hz, 1H), 5.06 (t, J = 3.6 Hz, 1H), 2.37−2.16 (m, 3H), 2.15−2.02 (m, 1H), 1.82−178 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 187.9, 173.9, 142.0, 136.6, 130.6, 125.9, 124.9, 118.7, 114.5, 78.3, 29.6, 27.7, 17.1. MS (ESI^-): 324.2 $(M - H)^-$. HRMS (ESI^+): Calculated for $C_{13}H_{11}O_4N^{79}Br$: 323.9871, found: 323.9878.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-1-naphthaldehyde (3f). The reaction was performed with 1.81 g (10.2 mmol) of 2-bromo-2-cyclohexenol, 2.80 g (15.8 mmol) of methanesulfonic anhydride, 1.60 g (15.8 mmol) of triethylamine, 5.40 g (30.7 mmol) of 2-hydroxy-1-naphthaldehyde, and 4.78 g (30.8 mmol) of DBU. After purification, 2.44 g (72% yield) of the title compound was obtained as an off-white solid, mp 88−90 °C. IR (neat): 3084, 2952, 1234, 649 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.97 (s, 1H), 9.31 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.65−7.60 (m, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 6.42 (dd, J = 4.9, 3.1 Hz, 1H), 4.99 (s, 1H), 2.29−2.05 (m, 3H), 1.99−1.68 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 192.6, 163.1, 137.5, 135.6, 131.6, 129.8, 129.1, 128.3, 125.22, 125.10, 119.9, 118.8, 115.7, 78.6, 29.9, 27.7, 16.9. MS (ESI^+): 355.3 $(M + Na)^+$. HRMS (ESI^+): Calculated for $C_{17}H_{16}O_2{}^{79}Br$: 331.0334, found: 331.0337.

Representative Procedure for Conversion of Substituted Salicylaldehydes to Oximes. Synthesis of 2-((2-Bromocyclohex-2-en-1-yl)oxy)benzaldehyde Oxime (4a). A solution of hydroxylamine (0.75 mL, 12.2 mmol, 50% in water, 1.4 equiv) was added to a cloudy solution of 2.01 g (7.17 mmol, 1 equiv) of aldehyde **3a** in 70 mL of water at 100 °C. The reaction mixture was stirred for 16 h. The reaction mixture was cooled to rt and was extracted three times with ethyl acetate. The combined organic extracts were washed with brine twice and dried over sodium sulfate. The dried extracts were filtered and concentrated using rotary evaporation in vacuo to produce a thick yellow oil. The oil was purified by chromatography on silica gel (hexanes:ethyl acetate 8:2 to 7:3) to yield 2.1 g (98%) of the title compound as a white solid, mp. 119−121 °C. IR (neat): 3272, 2931, 1599, 1451, 1233, 642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.28 (br s, 1H), 7.78 (dd, J = 7.7, 1.8 Hz, 1H), 7.36 (ddd, J = 8.5, 7.3, 1.7 Hz, 1H), 7.04−6.97 (m, 2H), 6.40 (dd, J = 5.1, 3.1 Hz, 1H), 4.81 (d, J = 3.7 Hz, 1H), 2.32−2.05 (m, 3H), 1.93−1.65 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 156.5, 146.9, 135.2, 131.4, 126.7, 122.5, 121.8, 120.7, 114.7, 77.4, 29.5, 27.9, 17.0. MS (ESI^+): 320.3 $(M + Na)^+$; HRMS (ESI^+): Calculated for $C_{13}H_{15}NO_2{}^{79}Br$: 296.0286, found: 296.0282.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-3-methoxybenzaldehyde Oxime (4b). The reaction was performed with 3.88 g (12.5 mmol) of aldehyde **3b** and 1.10 mL (17.8 mmol) of hydroxylamine. After purification, 3.79 g (94% yield) of the title compound was obtained as a light yellow thick oil, which solidified upon standing, mp 159−164 °C (decomposed). IR (neat): 3284, 2937, 1475, 1438, 1266 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.36 (dd, J = 4.8, 2.9 Hz, 1H), 4.83 (s, 1H), 3.86 (s, 3H), 2.30−2.22 (s, 1H), 2.18−2.09 (m, 3H), 1.96−1.83 (m, 1H), 1.68−1.25 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.7, 147.3, 145.9, 135.2, 126.9, 124.2, 121.3 118.1, 113.9, 79.3, 56.0, 29.9, 28.1, 16.8. MS (ESI^+): 350.3 $(M + Na)^+$. HRMS (ESI^+): Calculated for $C_{14}H_{17}NO_3{}^{79}Br$: 326.0392, found: 326.0396.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-4-methoxybenzaldehyde Oxime (4c). The reaction was performed with 0.57 g (1.8 mmol) of aldehyde **3c** and 0.23 mL (3.8 mmol) of hydroxylamine. After purification, 0.31 g (52% yield) of the title compound was obtained as a light yellow oil, which solidified upon standing, mp 97−115 °C (decomposed). IR (neat): 3240, 2933, 1608, 1265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.55 (s, 1H), 7.72 (d, J = 9.3 Hz, 1H), 6.56−6.54 (m, 2H), 6.36 (dd, J = 5.1, 3.0 Hz, 1H), 4.76 (s, 1H), 3.80 (s, 3H), 2.22−2.15 (m, 1H), 2.14−2.01 (m, 2H), 1.90−1.70 (m, 2H), 1.68−1.60 (m, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 162.4, 157.6, 146.4, 135.2, 127.6, 120.4, 115.2, 106.8, 101.2, 77.3, 55.6, 29.3, 27.7, 16.9. MS (ESI^+): 328.2 $(M + H)^+$. HRMS (ESI^+): Calculated for $C_{14}H_{17}NO_3{}^{79}Br$: 326.0392, found: 326.0389.

5-Bromo-2-((2-bromocyclohex-2-en-1-yl)oxy)benzaldehyde Oxime (4d). The reaction was performed with 0.25 g (0.70 mmol) of aldehyde **3d** and 0.09 mL (1.5 mmol) of hydroxylamine. After purification, 0.19 g (73% yield) of the title compound was obtained as a light yellow thick oil, which solidified upon standing, mp 105−110 °C (decomposed). IR (neat): 3280, 2951, 1481, 1268, 663, 634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.09 (br s, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.40 (dd, J = 8.8, 2.3 Hz, 1H), 6.89 (d, J = 8.9 Hz, 1H), 6.36 (dd, J = 4.9, 3.1 Hz, 1H), 4.72 (s, 1H), 2.27−2.09 (m, 3H), 1.90−1.61 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 155.4, 145.5, 135.4, 133.7, 129.2, 124.4, 120.1, 116.4, 114.2, 77.8, 60.8, 29.4, 27.7, 16.9. MS (ESI^+): 398.1 $(M + Na)^+$. HRMS (ESI^+): Calculated for $C_{13}H_{14}NO_2{}^{79}Br_2$: 373.9391, found: 373.9389.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-5-nitrobenzaldehyde Oxime (4e). The reaction was performed with 0.96 g (2.9 mmol) of aldehyde **3e** and 0.36 mL (5.9 mmol) of hydroxylamine. After purification, 0.74 g (74% yield) of the title compound was obtained as a light yellow oil, which solidified upon standing, mp 134.5−141 °C (decomposed). IR (neat): 3413, 2929, 1511, 1339, 1269, 674 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.67 (d, J = 2.9 Hz, 1H), 8.54 (s, 1H), 8.24 (dd, J = 9.2, 2.9 Hz, 1H), 7.07 (d, J = 9.4 Hz, 1H), 6.45 (dd, J = 5.1, 3.1 Hz, 1H), 4.96 (m, 1H), 2.29 (m, 4.6 Hz, 1H), 2.21−2.07 (m, 2H), 2.05−1.93 (m, 1H), 1.83−1.70 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 160.7, 145.0, 141.9, 136.2, 126.6, 122.90, 122.8, 119.2, 113.4, 77.8, 29.5, 27.7, 17.0. MS (ESI^-): 339.2 $(M - H)^-$. HRMS (ESI^+): Calculated for $C_{13}H_{13}N_2O_4Na^{79}Br$: 362.9956, found: 362.9962.

2-((2-Bromocyclohex-2-en-1-yl)oxy)-1-naphthaldehyde Oxime (4f). The reaction was performed with 2.44 g (7.4 mmol) of aldehyde **3f** and 0.72 mL (11.1 mmol) of hydroxylamine. After purification, 1.26 g (50% yield) of the title compound was obtained as a light yellow thick oil. IR (neat): 3312, 2935, 1588, 1509, 1234, 637 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ 9.00 (s, 1H), 8.93 (s, 1H), 8.86 (dd, J = 8.7, 0.9 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.82 (dt, J = 8.0, 0.6 Hz, 1H), 7.58 (ddd, J = 8.6, 6.9, 1.5 Hz, 1H), 7.44 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.41 (dd, J = 5.1, 3.0 Hz, 1H), 4.90 (d, J = 3.5 Hz, 1H), 2.23−2.20 (m, 1H), 2.15−2.08 (m, 2H), 1.90−1.82 (m, 2H), 1.70−1.66 (m, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 155.8, 148.0, 135.3, 132.1, 131.7, 129.8, 128.4, 128.0, 125.8, 124.7, 120.6, 116.4, 116.3, 78.8, 29.7, 27.8, 16.9. MS (ESI^+): 348.3 $(M + H)^+$. HRMS (ESI^+): Calculated for $C_{17}H_{17}NO_2{}^{79}Br$: 346.0443, found: 346.0446.

Representative Procedure of Conversion to Oximoyl Chlorides and in Situ Cycloaddition. Synthesis of 2a1-Bromo-2a,2a1,3,4,5,5a-hexahydroxantheno[9,1-*cd*]isoxazole (5a). Pyridine (0.14 mL, 1.7 mmol 0.2 equiv) was added to a solution of oxime **4a** (2.48 g, 8.4 mmol, 1 equiv) in 85 mL of chloroform. The reaction mixture was heated to 40 °C. *N*-Chlorosuccinimide (1.28 g, 9.4 mmol, 1.1 equiv) was added in small portions over a period of 30 min. The reaction mixture was further stirred at 40 °C for 3 h. Triethylamine (1.2 mL, 8.6 mmol, 1 equiv) was added, converting the yellow-orange solution to a dark red fuming one. The reaction mixture was stirred at 40 °C for 2 h. The mixture was diluted with 100 mL of CH_2Cl_2. The organic layer was washed with aqueous 1 M hydrochloric acid (once) and water (twice) and dried over sodium sulfate. Concentration by rotary evaporation in vacuo yielded an orange solid. Purification using column chromatography on silica gel (hexanes:ethyl acetate 8:2 to 7:3) yielded 1.54 g (63%) the title compound as a white solid, mp 170−173 °C. IR (neat): 2933, 1611, 1462, 1209, 665 cm^{-1}.

dx.doi.org/10.1021/jo501376q | J. Org. Chem. 2014, 79, 7250−7255

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.41 (ddd, J = 8.3, 7.4, 1.6 Hz, 1H), 7.08−7.02 (m, 2H), 5.13 (t, J = 8.5 Hz, 1H), 4.90 (dd, J = 11.6, 6.0 Hz, 1H), 2.28−2.20 (m, 1H), 2.14−2.05 (m, 1H), 1.70−1.65 (m, 1H), 1.39−1.20 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.3, 151.5, 133.4, 125.9, 122.3, 118.4, 110.5, 89.6, 81.6, 67.1, 30.6, 29.0, 16.9; MS (ESI$^+$): 294.3 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{13}NO_2{}^{79}Br$: 294.0130, found: 294.0135

2a1-Bromo-7-methoxy-2a,2a1,3,4,5,5a-hexahydroxantheno[9,1-*cd*]isoxazole (5b). The reaction was performed with 4.56 g (14.0 mmol) of oxime **4b**, 0.22 mL of pyridine (2.7 mmol), 2.10 g (15.4 mmol) of *N*-chlorosuccinimide, and 2.0 mL (14.0 mmol) of triethylamine. After purification, 4.04 g (89% yield) of the title compound was obtained as a white solid, mp 170−172 °C. IR (neat): 2941, 1572, 1489, 1211, 626 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.41 (dd, J = 5.6, 3.7 Hz, 1H), 6.95−6.93 (m, 2H), 5.08 (t, J = 8.3 Hz, 1H), 4.97 (dd, J = 11.3, 5.9 Hz, 1H), 3.81 (s, 4H), 2.20−2.07 (m, 2H), 1.60 (dd, J = 7.1, 3.7 Hz, 1H), 1.36−1.09 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 151.2, 149.1, 141.8, 121.8, 117.0, 114.3, 110.8, 89.6, 81.7, 77.7, 77.2, 76.8, 66.7, 56.1, 30.3, 28.7, 16.6. MS (ESI$^+$): 326.3 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{15}NO_3{}^{79}Br$, 324.0235, found: 324.0238.

2a1-Bromo-8-methoxy-2a,2a1,3,4,5,5a-hexahydroxantheno[9,1-*cd*]isoxazole (5c). The reaction was performed with 0.31 g (1.0 mmol) of oxime **4c**, 0.02 mL of pyridine (0.2 mmol), 0.15 g (1.1 mmol) of *N*-chlorosuccinimide, and 0.14 mL (1.0 mmol) of triethylamine. After purification, 0.15 g (49% yield) of the title compound was obtained as a thick clear oil, which solidified upon standing, mp 131−135.5 °C. IR (neat): 2942, 1614, 1591, 1437, 1197, 634 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.75 (d, J = 8.7 Hz, 1H), 6.63 (dd, J = 8.8, 2.5 Hz, 1H), 6.51 (s, 1H), 5.09−5.03 (m, 1H), 4.86 (dd, J = 11.4, 5.9 Hz, 1H), 3.80 (s, 3H), 2.22−2.14 (m, 1H), 2.10−2.02 (m, 1H), 1.68−1.63 (m, 1H), 1.40−1.18 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 163.9, 153.9, 130.1, 127.5, 127.0, 122.0, 110.5, 103.0, 102.0, 89.0, 81.8, 55.6, 30.4, 29.0, 17.0. MS (ESI$^+$): 326.2 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{15}NO_3{}^{79}Br$: 324.0235, found: 324.0241.

2a1,9-Dibromo-2a,2a1,3,4,5,5a-hexahydroxantheno[9,1-*cd*]-isoxazole (5d). The reaction was performed with 0.19 g (0.5 mmol) of oxime **4d**, 0.01 mL of pyridine (0.1 mmol), 0.08 g (0.6 mmol) of *N*-chlorosuccinimide, and 0.07 mL (0.5 mmol) of triethylamine. After purification, 0.14 g (72% yield) of the title compound was obtained as a foamy clear thick oil. IR (neat): 2952, 1459, 1440, 1213, 728, 680 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.99 (d, J = 2.5 Hz, 1H), 7.48 (dd, J = 8.9, 2.5 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.15 (d, J = 8.8 Hz, 1H), 4.90−4.86 (m, 1H), 2.28−2.19 (m, 1H), 2.13−2.04 (m, 1H), 1.68−165 (m, 1H), 1.37−1.14 (m, 4H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 151.2, 150.5, 136.1, 128.2, 120.3, 114.5, 112.2, 89.9, 81.8, 66.2, 30.5, 28.9, 16.7. MS (ESI$^+$): 374.0 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{12}NO_2{}^{79}Br_2$: 371.9235, found: 371.9233.

2a1-Bromo-9-nitro-2a,2a1,3,4,5,5a-hexahydroxantheno[9,1-*cd*]isoxazole (5e). The reaction was performed with 0.74 g (2.2 mmol) of oxime **4e**, 0.04 mL of pyridine (0.4 mmol), 0.33 g (0.6 mmol) of *N*-chlorosuccinimide, and 0.3 mL (2.2 mmol) of triethylamine. After purification, 0.56 g (76% yield) of the title compound was obtained as a white powder, mp 166−167.5 °C. IR (neat): 3107, 2944, 1617, 1460, 1338, 1229, 685 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.82 (d, J = 2.8 Hz, 1H), 8.28 (dd, J = 9.2, 2.8 Hz, 1H), 7.17 (d, J = 9.2 Hz, 1H), 5.22 (t, J = 8.5 Hz, 1H), 5.07−5.01 (m, 1H), 2.35−2.26 (m, 1H), 2.23−2.16 (m, 1H), 1.78−1.71 (m, 1H), 1.35−1.20 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 156.7, 150.1, 134.9, 128.1, 122.4, 119.3, 110.9, 90.5, 82.8, 64.9, 30.6, 29.4, 16.6. MS (ESI$^+$): 341.1 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{12}N_2O_4{}^{79}Br$: 338.9980, found: 338.9977.

2a1-Bromo-2a,2a1,3,4,5,5a-hexahydrobenzo[7,8]xantheno-[9,1-*cd*]isoxazole (5f). The reaction was performed with 0.37 g (2.2 mmol) of oxime **4f**, 0.02 mL of pyridine (0.2 mmol), 0.16 g (1.2 mmol) of *N*-chlorosuccinimide, and 0.15 mL (1.1 mmol) of triethylamine. After purification, 0.27 g (73% yield) of the title compound was obtained as a very thick yellow oil. IR (neat): 3058, 2951, 1620, 1442, 1226, 726 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.13 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.80 (dt, J = 8.0, 0.6 Hz, 1H), 7.65 (td, J = 7.8, 1.5 Hz, 1H), 7.49−7.44 (m, 1H), 7.19 (d, J = 9.0 Hz, 1H), 5.15−5.10 (m, 1H), 4.99 (dd, J = 11.7, 5.9 Hz, 1H), 2.29−2.21 (m, 1H), 2.15−2.06 (m, 1H), 1.68−1.62 (m, 1H), 1.50−1.23 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.8, 152.3, 134.5, 130.8, 129.6, 128.9, 128.7, 127.0, 125.1, 118.9, 103.7, 88.3, 81.4, 68.7, 30.5, 28.7, 16.6. MS (ESI$^+$): 346.2 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{17}H_{15}NO_2{}^{79}Br$: 344.0286, found: 344.0291.

Representative Procedure of Elimination to Form 6. Synthesis of 3,4,5,5a-Tetrahydroxantheno[9,1-*cd*]isoxazole (6a). To a solution of 0.30 g (1.0 mmol, 1 equiv) of **5a** in 10 mL of DMSO at 100 °C was added 0.32 g (1.1 mmol, 1.1 equiv) of silver carbonate. The reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to rt and filtered through Celite. The filter cake was washed with water. The solution was extracted with ethyl acetate (three times). The combined organic extracts were washed with brine (twice), dried over sodium sulfate, and concentrated using rotary evaporation in vacuo to yield a brown solid. Purification using chromatography on silica gel (hexanes:ethyl acetate 8:2 to 7:3) yielded 0.17 g (78%) of the title compound as a white solid, mp 94.5 °C. IR (neat): 2943, 1685, 1498, 1200 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.78 (dd, J = 7.6, 1.4 Hz, 1H), 7.33 (td, J = 7.8, 1.3 Hz, 1H), 7.04 (dd, J = 14.2, 7.8 Hz, 2H), 5.11−5.07 (m, 1H), 2.81 (ddt, J = 17.8, 6.4, 1.8 Hz, 1H), 2.69 (dddd, J = 17.5, 11.1, 6.2, 2.3 Hz, 1H), 2.49−2.43 (m, 1H), 2.26−2.22 (m, 1H), 1.87 (ddddd, J = 17.0, 14.1, 11.2, 6.0, 2.9 Hz, 1H), 1.68−1.59 (m, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.2, 156.1, 153.2, 132.1, 125.0, 122.4, 118.6, 115.7, 113.1, 70.0, 29.3, 22.4, 20.7. MS (ESI$^+$): 214.4 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{12}NO_2$: 214.0868, found: 214.0876.

7-Methoxy-3,4,5,5a-tetrahydroxantheno[9,1-*cd*]isoxazole (6b). The reaction was performed with 1.63 g (5.0 mmol) of bromoisoxazoline **5b** and 1.55 g (5.6 mmol) of silver carbonate. After purification, 0.97 g (79% yield) of the title compound was obtained as a white powder, mp 142−143 °C. IR (neat): 2961, 1684, 1575, 1263 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.42 (dd, J = 7.5, 1.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.98 (dd, J = 8.2, 1.7 Hz, 1H), 5.19−5.14 (m, 1H), 3.91 (s, 3H), 2.85 (ddt, J = 17.7, 6.3, 1.7 Hz, 1H), 2.72 (dddd, J = 17.5, 11.1, 6.2, 2.6 Hz, 1H), 2.60 (dddd, J = 12.1, 5.8, 3.7, 2.4 Hz, 1H), 2.32−2.24 (m, 1H), 1.90 (tddd, J = 14.0, 11.0, 6.3, 2.8 Hz, 1H), 1.72 (dddd, J = 14.1, 12.2, 9.5, 2.8 Hz, 1H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 166.3, 149.5, 145.3, 122.1, 116.7, 116.2, 114.2, 112.9, 70.3, 56.1, 29.3, 22.3, 20.6. MS (ESI$^+$): 244.5 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{14}NO_3$: 244.0974, found: 244.0977.

8-Methoxy-3,4,5,5a-tetrahydroxantheno[9,1-*cd*]isoxazole (6c). The reaction was performed with 0.15 g (0.5 mmol) of bromoisoxazoline **5c** and 0.26 g (1.0 mmol) of silver carbonate. After purification, 0.087 g (77% yield) of the title compound was obtained as a white powder, mp 151.5−155.0 °C. IR (neat): 2935, 1687, 1616, 1254 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.69 (d, J = 8.5 Hz, 1H), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.11−5.04 (m, 1H), 3.80 (s, 3H), 2.80 (ddt, J = 17.7, 6.4, 1.6 Hz, 1H), 2.67 (dddd, J = 17.4, 11.0, 6.1, 2.4 Hz, 1H), 2.45 (dddd, J = 12.0, 5.7, 3.6, 2.4 Hz, 1H), 2.27−2.22 (m, 1H), 1.95−1.79 (m, 1H), 1.70−1.57 (m, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 165.8, 162.9, 157.6, 130.1, 126.0, 122.1, 109.1, 108.4, 103.6, 77.2, 70.4, 55.5, 29.3, 22.4, 20.8. MS (ESI$^+$): 244.4 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{14}NO_3$: 244.0974, found: 244.0978.

8-Bromo-3,4,5,5a-tetrahydroxantheno[9,1-*cd*]isoxazole (6d). The reaction was performed with 0.14 g (0.4 mmol) of bromoisoxazoline **5d** and 0.21 g (0.8 mmol) of silver carbonate. After purification, 0.073 g (69% yield) of the title compound was obtained as a white powder, mp 124−125 °C. IR (neat): 3060, 2937, 1684, 1496, 1202 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.88 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 8.8, 2.5 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.08 (ddt, J = 9.7, 5.6, 2.2 Hz, 1H), 2.83 (ddt, J = 17.8, 6.4, 1.7 Hz, 1H), 2.69 (dddd, J = 17.5, 11.0, 6.1, 2.5 Hz, 1H), 2.50−2.42 (m, 1H), 2.31−2.21 (m, 1H), 1.96−1.80 (m, 1H), 1.62 (dddd, J = 14.0, 12.2, 9.5, 2.8 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 166.7, 155.1, 152.4, 134.8, 127.6, 120.4, 117.4, 114.6, 112.8, 70.4, 29.3, 22.5, 20.7. MS (ESI$^+$): 294.2 (M

dx.doi.org/10.1021/jo501376q | J. Org. Chem. 2014, 79, 7250−7255

+ H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{11}NO_2{}^{79}Br$: 291.9973, found: 291.9960.

9-Nitro-3,4,5,5a-tetrahydroxantheno[9,1-*cd*]isoxazole (6e). The reaction was performed with 0.35 g (1.0 mmol) of bromoisoxazoline **5e** and 0.58 g (2.1 mmol) of silver carbonate. After purification, 0.17 g (65% yield) of the title compound was obtained as a white powder, mp 195−196 °C. IR (neat): 2968, 1684, 1619, 1499, 1265 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.53 (d, J = 2.8 Hz, 1H), 8.09 (dd, J = 9.1, 2.8 Hz, 1H), 7.03 (d, J = 9.1 Hz, 1H), 5.16 (ddt, J = 9.7, 5.5, 2.1 Hz, 1H), 2.79 (ddt, J = 18.0, 6.5, 1.6 Hz, 1H), 2.64 (dddd, J = 17.6, 11.0, 6.3, 2.4 Hz, 1H), 2.42 (tdd, J = 7.9, 4.2, 2.0 Hz, 1H), 2.27−2.17 (m, 1H), 1.84 (ddd, J = 10.7, 6.4, 2.8 Hz, 1H), 1.57 (dddd, J = 13.9, 12.2, 9.6, 2.8 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 167.5, 160.7, 151.4, 142.0, 127.0, 120.6, 119.1, 116.5, 116.4, 116.4, 115.5, 112.0, 71.3, 28.9, 22.1, 20.3. MS (ESI$^+$): 259.3 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{11}N_2O_4$: 259.0719, found: 259.0723.

3,4,5,5a-Tetrahydrobenzo[7,8]xantheno[9,1-*cd*]isoxazole (6f). The reaction was performed with 0.27 g (0.8 mmol) of bromoisoxazoline **5f** and 0.44 g (1.6 mmol) of silver carbonate. After purification, 0.069 g (34% yield) of the title compound was obtained as a white powder, mp 186−187 °C. IR (neat): 2940, 1617, 1592, 1526, 1209 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.82 (dd, J = 8.4, 0.6 Hz, 1H), 7.79 (dd, J = 8.5, 3.8 Hz, 2H), 7.63 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.44 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 5.19−5.13 (m, 1H), 2.83 (ddt, J = 17.6, 6.3, 1.7 Hz, 1H), 2.70 (dddd, J = 17.3, 10.8, 6.1, 2.5 Hz, 1H), 2.49 (dddd, J = 11.7, 5.7, 3.7, 2.1 Hz, 1H), 2.29−2.20 (m, 1H), 1.85 (tddd, J = 14.0, 10.5, 6.3, 2.4 Hz, 1H), 1.70 (dddd, J = 14.1, 11.7, 9.3, 2.5 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 165.0, 155.4, 153.7, 132.5, 130.3, 129.6, 128.2(0), 128.1(8), 126.5, 124.9, 119.3, 113.1, 109.8, 70.3, 29.3, 22.3, 20.7. MS (ESI$^+$): 264.4 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{17}H_{14}NO_2$: 264.1025, found: 264.1024.

Sample Procedure for the Preparation of 9-Amino-2,3,4,4a-tetrahydro-1*H*-xanthen-1-ones. 9-Amino-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (7a). Raney nickel (30 mg, 30% by weight in water) was added to isoxazole **6a** (0.12 g, 0.6 mmol, 1 equiv). After removal of water in vacuo, 10 mL of methanol was added under a hydrogen atmosphere (using a balloon filled with hydrogen gas). The reaction mixture was stirred at rt for 24 h. The solvent was removed using rotary evaporation in vacuo. Purification using chromatography over silica gel yielded 0.12 g (98% yield) of the title product as a yellow powder, mp 164.5−165.5 °C. IR (neat): 3304, 3154, 2942, 1614, 1598 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.25 (br s, 1H), 7.45 (dd, J = 7.9, 1.5 Hz, 1H), 7.28 (td, J = 7.8, 1.2 Hz, 1H), 6.95 (td, J = 7.6, 1.0 Hz, 1H), 6.89 (dd, J = 8.2, 1.0 Hz, 1H), 5.86 (br s, 1H), 4.77 (dd, J = 9.5, 5.8 Hz, 1H), 2.35−2.25 (m, 3H), 1.92−1.79 (m, 2H), 1.64−1.53 (m, 1H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 196.2, 157.9, 152.1, 132.8, 123.5, 121.6, 119.3, 117.4, 100.1, 75.3, 37.8, 29.8, 18.6. MS (ESI$^+$) (m/z): 216.3 (M + H)$^+$. HRMS (ESI$^+$): Calculated for $C_{13}H_{14}NO_2$: 216.1025, found: 216.1021.

9-Amino-5-methoxy-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (7b). The reaction was performed with 0.09 g (0.4 mmol) of isoxazole **6b** and ∼25 mg of Raney nickel. After purification, 0.080 g (92% yield) of the title compound was obtained as a light yellow thick oil. IR (neat): 3401, 3233, 2944, 1610, 1572, 1465 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.28 (br s, 1H), 7.05 (t, J = 4.6 Hz, 1H), 6.92 (d, J = 4.5 Hz, 2H), 5.76 (br s, 1H), 4.79 (dd, J = 9.3, 5.9 Hz, 1H), 3.82 (s, 3H), 2.35 (dd, J = 10.6, 5.3 Hz, 3H), 1.95 (ddd, J = 24.0, 11.2, 3.1 Hz, 2H), 1.66−1.55 (m, 1H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 196.3, 152.3, 148.8, 147.6, 121.3, 120.0, 115.0, 114.5, 99.9, 75.8, 56.1, 37.8, 29.8, 18.6. MS (ESI$^+$): 268.4 (M + Na)$^+$. HRMS (ESI$^+$): Calculated for $C_{14}H_{16}NO_3$: 246.1130, found: 246.1126.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra and X-ray data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gdake@chem.ubc.ca.

Present Address

†Undergraduate research student. Department of Orthopedic Surgery, Stanford University, 300 Pasteur Drive, Edwards R163, Stanford, CA 94305.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Brian O. Patrick (U.B.C.) for the solution of solid-state molecular structures in this paper. E.B.C-C. thanks CONACYT of Mexico for a doctoral fellowship (172270). The authors thank the University of British Columbia, the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery and Undergraduate Student Research Assistant programs), and the Canada Foundation for Innovation (CFI) for the financial support of our programs.

■ REFERENCES

(1) (a) Martinez-Ariza, G.; Dietrich, J.; De Moliner, F.; Hulme, C. *Synlett* **2013**, *24*, 1801−1804. (b) Arigela, R. K.; Samala, S.; Mahar, R.; Shukla, S. K.; Kunda, B. *J. Org. Chem.* **2013**, *78*, 10476−10484. (c) Novak, A.; Testen, A.; Bezensek, J.; Groselj, U.; Hrast, M.; Kasunic, M.; Gobec, S.; Stanovnik, B.; Svete, J. *Tetrahedron* **2013**, *69*, 6648−6665. (d) Xiao, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 4662−4665. (e) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2279−2284. (f) Wirtz, L.; Kazmaier, U. *Eur. J. Org. Chem.* **2011**, *2011*, 3467−3473. (g) Zhou, F.; Liu, J.; Ding, K.; Liu, J.; Cai, Q. *J. Org. Chem.* **2011**, *76*, 5346−5353. (h) Cui, P.; Xu, L.; Shi, Z.; Gan, L. *J. Org. Chem.* **2011**, *76*, 4210−4212. (i) Li, R.; Jansen, D. J.; Datta, A. *Org. Biomol. Chem.* **2009**, *7*, 1921−1930.

(2) (a) Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1476−1479. (b) Quinn, J. F.; Gregg, B. T.; Kitchen, D. B.; Lewis, R. M.; Razzano, D. A.; Kayser, L. E.; Schilling, L. J.; Golden, K. C. *Lett. Drug Des. Discovery* **2012**, *9*, 2−7. (c) Pardin, C.; Roy, I.; Lubell, W. D.; Keillor, J. W. *Chem. Biol. Drug Des.* **2008**, *72*, 189−196.

(3) (a) Raihan, M. J.; Kavala, V.; Kuo, C.-W.; Raju, B. R.; Yao, C.-F. *Green Chem.* **2010**, *12*, 1090−1096. (b) Pal, A.; Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **1999**, *55*, 4123−4132. (c) Arai, N.; Iwakoshi, M.; Tanabe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2277−2285. (d) Broggini, G.; Zecchi, G. *Synthesis* **1996**, 1280−1282. (e) Broggini, G.; Folcio, F.; Sardone, N.; Zecchi, G. *Tetrahedron* **1996**, *52*, 11849−11856. (f) Hassner, A.; Lokanatha Rai, K. *Heterocycles* **1990**, *30*, 817−830. (g) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, *11*, 1117−11120.

(4) (a) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113−5123. (b) Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675−678. (c) Jakowiecki, J.; Loska, R.; Makosza, M. *J. Org. Chem.* **2008**, *73*, 5436−5441. (d) Piperno, A.; Rescifina, A.; Corsaro, A.; Chiacchio, M. A.; Procopio, A.; Romeo, R. *Eur. J. Org. Chem.* **2007**, 1517−1521. (e) Hems, W. P.; Tan, C. H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1393−1396. (f) Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans 1* **1991**, 1041−1051.

(5) Hansen, J. F.; Kim, Y. I.; McCrotty, S. E.; Strong, S. A.; Zimmer, D. E. *J. Heterocyclic Chem.* **1980**, *17*, 475−479.

(6) Yagoubi, M.; Cruz, A. C. F.; Nichols, P. L.; Elliott, R. L.; Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 7958−7962.

(7) (a) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391−394. (b) Illescas, B. M.; Martin, N. *J. Org. Chem.* **2000**, *65*, 5986−5995. (c) Sanders, B. C.; Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Arumugam, S.; Guo, J.; Boltje, T. J.; Popik, V. V.; Boons, G.-J. *J. Am. Chem. Soc.* **2011**, *133*, 949−957.
(8) (a) Baldwin, S. W.; Chen, P.; Nikolic, N.; Weinseimer, D. C. *Org. Lett.* **2000**, *2*, 1193−1196. (b) R Nagireddy, J.; Raheem, M.-A.; Haner, J.; Tam, W. *Curr. Org. Synth.* **2011**, *8*, 659−700. (c) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024−4026. (d) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826−5833. (e) Casnati, G.; Ricca, A. *Tetrahedron Lett.* **1967**, *8*, 327−330.

dx.doi.org/10.1021/jo501376q | *J. Org. Chem.* 2014, 79, 7250−7255