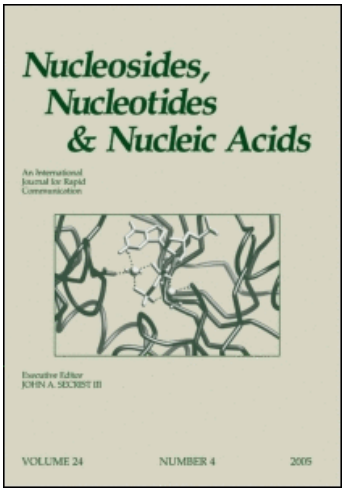

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Yadav, Lal Dhar S. and Rai, Vijai K.(2008) 'An Expeditious Synthesis of Benzoxazine-2-Thione *c*-Nucleosides Via $Cu(OTf)_2$-Mediated Dehydrazinative β-Glycosylation', Nucleosides, Nucleotides and Nucleic Acids, 27: 12, 1227 — 1237
To link to this Article: DOI: 10.1080/15257770802458212
URL: http://dx.doi.org/10.1080/15257770802458212

Nucleosides, Nucleotides and Nucleic Acids, 27:1227–1237, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802458212

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AN EXPEDITIOUS SYNTHESIS OF BENZOXAZINE-2-THIONE *C*-NUCLEOSIDES VIA $Cu(OTf)_2$-MEDIATED DEHYDRAZINATIVE β-GLYCOSYLATION

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□ *A novel expeditious synthetic protocol for 1,3-benzoxazine-2-thione* C*-nucleosides via Cu(OTf)$_2$-mediated dehydrazinative β-glycosylation of 4-hydrazino-2*H*-benz[*e*]-1,3-oxazine-2-thiones with unprotected D-ribose is reported.*

Keywords 1,3-Benzoxazine-2-thione *C*-nucleosides; unprotected D-ribose; non-nucleoside reverse transcriptase inhibitor (NNRTI)

INTRODUCTION

Efavirenz (Sustiva), a benzoxazinone derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been approved by the U.S. Food and Drug administration (FDA) and is presently in clinical use for the treatment of AIDS. The strategy for the fight against HIV by developing more efficacious drugs than Efavirenz has been the prime driving force for ingenious benzoxazinone derivatizations.[1–6] Moreover, our interest in the family of *C*-nucleosides also resides with the naturally occurring antibiotics. Several of these have potent antiviral, anticancer and antitumour activity and, as a result of C-C glycosidic linkage, they are resistant to enzymatic hydrolysis which is the major factor in the degradation of N-nucleosides.[7]

The formation of C-C bond at the anomeric carbon, especially *C*-glycosylation of bioactive heterocycles, is a field of increasing interest in synthetic organic chemistry. The most common methods for the C-C bond formation at the anomeric centre involve nucleophilic attack on the

Received 8 July y2008; accepted 20 August 2008.
We sincerely thank the Sophisticated Analytical Instrument Facility (SAIF), Punjab University, Chandigarh, for providing microanalyses and spectra.
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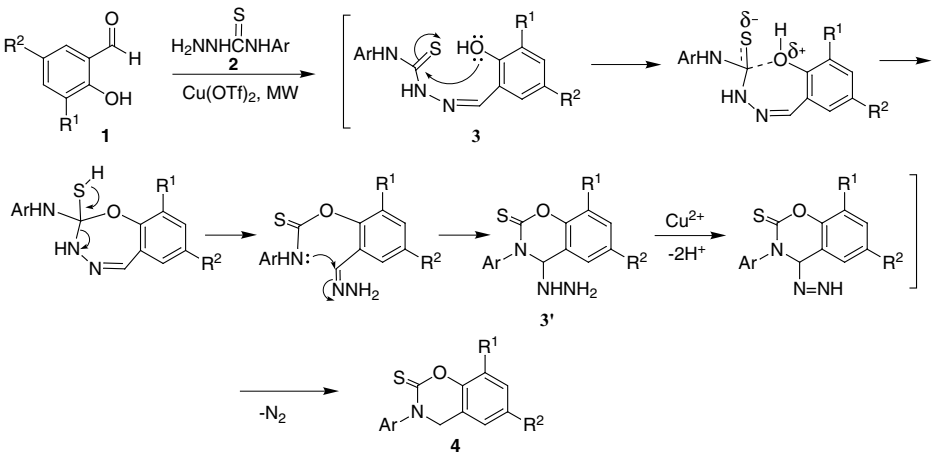
intrinsically electrophilic anomeric carbons.[8–11] In most cases, these procedures require specific, awkward reaction conditions and generally suffer from low yields. Although microwave (MW)-assisted heterocyclisations have gained significant interest for over a decade,[12,13] the first example of MW-assisted solvent-free synthesis of nucleoside analogues was reported very recently.[14]

Considering the above points and in pursuing our work on the development of organic syntheses in solvent-free MW-assisted conditions,[15–19] we present herein the first report on $Cu(OTf)_2$-mediated dehydrazinative β-glycosylation yielding benzoxazine-2-thione *C*-nucleosides. The key element in our approach is the novel utilization of salicylaldehyde as a bifunctional building block whose application to the construction of various benzo-fused oxygen heterocycles of chemical and biological interest is well documented.[20–23]

RESULTS AND DISCUSSION

1,3-Oxazine-2-thiones **4** were synthesized in 78–89% yields by MW irradiation of an intimate solvent-free mixture of salicylaldehydes **1**, thiosemicarbazide **2**, and $Cu(OTf)_2$ (0.30 equivalent) in an open vessel under air. The reaction proceeds via domino cycloisomerization of in situ formed *N*-phenylthiosemicarbazones **3** to 4-hydrazino-1,3-oxazine-2-thiones **3′** and dehydrazination of compounds **3′** to target oxazines **4** (Scheme 1). Here, $Cu(OTf)_2$ plays a dual role of Lewis acid and oxidant. Only 0.30 equivalent of $Cu(OTf)_2$ is sufficient to complete the reaction because Cu(I) formed is oxidized to Cu(II) by air under the reaction conditions and a redox cycle is established. A plausible mechanism of dehydrazination of **3′** into **4** using Cu(II) is depicted in Scheme 2. Although the present dehydrazinative cyclization to afford 1,3-oxazine-2-thione **4** is our new finding, similar dehydrazination reactions using Cu(II) have already been reported in the literature.[24–27]

In our initial experiments for the synthesis of compounds **4,** we used $CeCl_3.7H_2O/NaI$ as Lewis acid catalyst but compounds **3′** rather than compounds **4** were isolated in 73–87% yields. Compounds **3′** on further treatment with copper(II) sulfate on alumina support afforded the target oxazines **4** in 55–67% yields. In order to improve the yields and synthesize target 1,3-oxazine-2-thiones **4** expeditiously from salicylaldehydes **1** in a one-pot procedure, we relied upon the significant advantages of $Cu(OTf)_2$, which acts not only as an efficient Lewis acid catalyst for cycloisomerization of compounds **3** to **3′** but also as copper(II) source for the desired dehydrazination of 4-hydrazino-1,3-oxazin-2-thiones **3′** to afford **4**. Other mineral catalysts, viz. $CeCl_3.7H_2O$, K-10 clay, and acidic, neutral, or basic alumina were far less effective resulting in either no reaction (in the case of basic alumina) or relatively moderate (36–50%, in case of $CeCl_3.7H_2O$, K-10

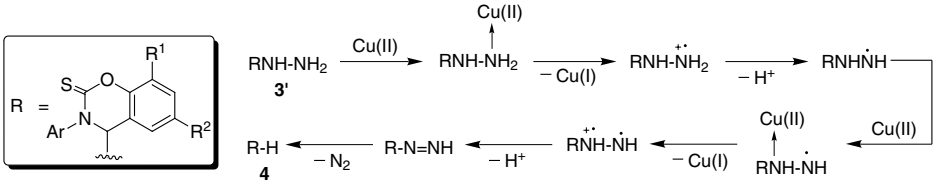


SCHEME 1 Tentative mechanism for the formation of 1,3-benzoxazine-2-thione**4**

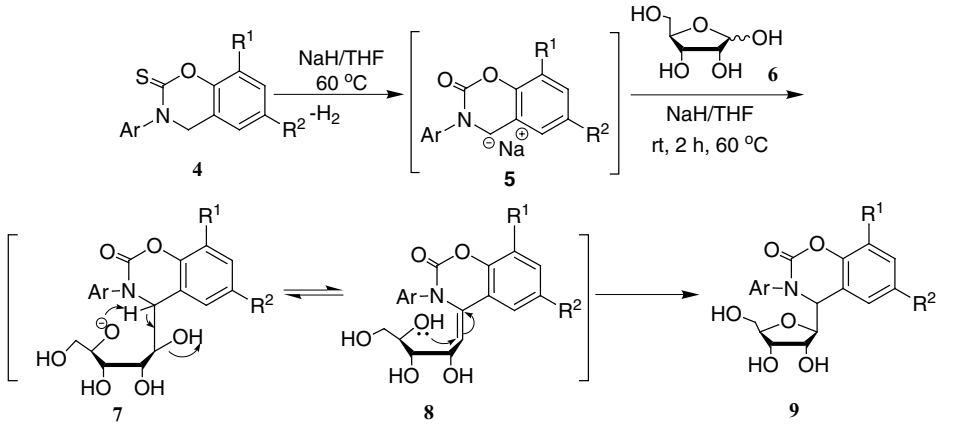
clay) to low yields (12–21%, in case of silica gel, neutral and acidic alumina) of compounds **3′**.

After considerable experimentation, it was found that the envisaged β-glycosylation of **4** was successful with the unprotected D-ribose **6** in the presence of NaH/THF at 60°C to give 4-β-D-ribofuranosyl-2*H*-benz[*e*]-1,3-oxazine-2-thiones **9** in 75–87% yield. The formation of *C*-nucleosides **9** probably results with the initial generation of a carbanion **5** at the activated benzylic carbon and its nucleophilic attack on the electrophilic anomeric carbon of D-ribose **6** followed by cyclization as outlined in Scheme 3.

It has been shown that α,β-*C*-glycofuranoside analogues having an activated methylene group adjacent to the anomeric carbon underwent anomeric equilibration via an acyclic intermediate upon prolonged reaction under basic conditions leading ultimately to one predominant thermodynamically stable anomer.[28] The exclusive formation of the β-ribofuranosyl stereoisomer **9** at 60°C could be perceived from thermodynamic control driven largely by steric interactions because of the bulky benzoxazinone moiety. The critical structural assignments of the configurations at the ribofuranosyl anomeric center of *C*-nucleosides **9** were made on the basis of detailed analysis of ^{1}H NMR spectra, NOE experiments,[29] and comparison



SCHEME 2 Plausible mechanism for dehydrazination of **3′** into **4**



4,9	R^1	R^2	Ar	4,9	R^1	R^2	Ar
a	H	H	4-ClC_6H_4	**f**	H	H	4-$MeOC_6H_4$
b	H	Br	4-ClC_6H_4	**g**	H	Br	4-$MeOC_6H_4$
c	Br	Br	4-ClC_6H_4	**h**	Br	Br	4-$MeOC_6H_4$
d	H	Cl	4-ClC_6H_4	**i**	H	Cl	4-$MeOC_6H_4$
e	Cl	Cl	4-ClC_6H_4	**j**	Cl	Cl	4-$MeOC_6H_4$

SCHEME 3 Tentative mechanism for β-glycosylation of 1,3-benzoxzine-2-thione**4**

with appropriate reference data.[30–32] In fact, selective irradiation of the H-1′ signal of **9** significantly increased the intensity of the H-4′ signal (2.0–2.8%), while no intensity enhancement of the H-3′ signal was observed; this is consistent with the β-glycosidic linkage. Furthermore, the comparison of $J_{1',2'}$ values of **9** ($J_{1',2'}$ = 5.4–5.8 Hz) with those of similar systems in the literature ($J_{1',2'}$ = 5.4–5.9 Hz) also supported a β-glycosidic linkage.[30–32] These analyses permit assignment of compounds **9** as the β-D-ribofuranoside anomer.

In summary, we have developed a novel expeditious synthetic protocol for benzoxazine-2-thione *C*-nucleosides via dehydrazinative β-glycosylation. Furthermore, the Knoevenagel-type condensation presented in this paper represents a very convenient method for the preparation of pure β-*C*-glycosides in one step directly from the unprotected sugar and a compound containing an activated methylene group.

EXPERIMENTAL

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6 and TMS was used as internal reference. Mass (EI) spectra

were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50, 230 volt, 50 Hz power input) was used for all experiments. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

3-Aryl-2*H*-benz[*e*]-1,3-oxazine-2-thiones 4; General Procedure

Thoroughly mixed salicylaldehyde **1** (when $R^1 = R^2 = H$; 0.12 g, 1.00 mmol), *N*-arylthiosemicarbazide **2** (when Ar = 4-ClC_6H_4; 0.20 g, 1.00 mmol) and $Cu(OTf)_2$ (0.11 g, 0.30 mmol) were taken in a 20 mL open vial and subjected to MW irradiation for 7–12 minutes at 90°C under air. After completion of the reaction as indicated by TLC (hexane-AcOEt, 8:2, v/v), the product was extracted with dichloromethane (3 × 25 mL), the extract was filtered and the filtrate was evaporated under reduced pressure to leave the crude product, which was recrystallized from ethanol to obtain an analytically pure sample of **4** as yellowish needles.

4a: yellowish needles; m.p. 170–172°C. IR (KBr): ν 3011, 1595, 1585, 1450 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.56 (d, 1H, J = 13 Hz, axial H of CH_2), 6.63 (d, 1H, J = 13 Hz, equatorial H of CH_2), 6.71–7.09 (m, $6H_{arom}$), 7.28–7.35 (m, $2H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.5, 113.1, 114.5, 118.2, 120.5, 122.7, 128.5, 129.6, 130.5, 150.2, 166.2, 192.3. EIMS m/z = 275, 277 (M^+, $M^+ + 2$). Anal. calcd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found: C, 60.67; H, 3.91; N, 5.26.

4b: yellowish needles; m.p. 159–161°C. IR (KBr): ν 3010, 1600, 1585, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.53 (d, 1H, J = 13 Hz, axial H of CH_2), 6.65 (d, 1H, J = 13 Hz, equatorial H of CH_2), 6.69–7.13 (m, $3H_{arom}$), 7.19–7.41 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.2, 113.5, 114.7, 118.8, 120.6, 122.5, 128.1, 129.7, 130.2, 150.1, 166.4, 192.5. EIMS m/z = 355 (M^+). Anal. calcd for $C_{14}H_9BrClNOS$: C, 47.41; H, 2.56; N, 3.59. Found: C, 47.68; H, 2.71; N, 3.45.

4c: yellowish needles; m.p. 143–145°C. IR (KBr): ν 3012, 1601, 1581, 1456 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.55 (d, 1H, J = 13 Hz, axial H of CH_2), 6.64 (d, 1H, J = 13 Hz, equatorial H of CH_2), 6.68–7.05 (m, $2H_{arom}$), 7.21–7.48 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.2, 113.2, 114.1, 118.5, 120.2, 121.9, 128.2, 129.5, 130.3, 150.3, 166.2, 192.1. EIMS m/z = 435 (M^+). Anal. calcd for $C_{14}H_8Br_2ClNOS$: C, 38.78; H, 1.86; N, 3.23. Found: C, 38.44; H, 2.07; N, 2.91.

4d. yellowish needles; m.p. 149–151°C. IR (KBr): ν 3011, 1598, 1580, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.54 (d, 1H, J = 13 Hz, axial H of CH_2), 6.66 (d, 1H, J = 13 Hz, equatorial H of CH_2), 6.75–7.11 (m, $3H_{arom}$), 7.19–7.39 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.5, 113.0, 114.2, 118.4, 120.5, 122.2, 128.5, 129.2, 130.1, 150.2, 166.0, 192.2.

EIMS $m/z = 309, 311$ (M^+, M^++2). Anal. calcd for $C_{14}H_9Cl_2NOS$: C, 54.21; H, 2.92; N, 4.52. Found: C, 54.49; H, 2.78; N, 4.35.

4e. yellowish needles; m.p. 183–185°C. IR (KBr): ν 3010, 1605, 1581, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.59 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.67 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.75–7.12 (m, $2H_{arom}$), 7.31–7.39 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.3, 113.0, 114.4, 118.8, 120.2, 122.9, 129.0, 130.3, 135.5, 151.1, 166.5, 192.1. EIMS $m/z = 343, 345$ (M^+, M^++2). Anal. calcd for $C_{14}H_8Cl_3NOS$: C, 48.79; H, 2.34; N, 4.06. Found: C, 49.03; H, 2.49; N, 4.31.

4f: yellowish needles; m.p. 170–180°C. IR (KBr): ν 3010, 1603, 1587, 1450 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H, OMe), 6.52 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.68 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.70–7.11 (m, $6H_{arom}$), 7.18–7.35 (m, $2H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.5, 64.0, 113.2, 114.7, 118.5, 120.2, 122.7, 128.3, 129.5, 130.3, 150.5, 166.3, 192.3. EIMS $m/z = 273$ (M^+). Anal. calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.69; H, 4.58; N, 5.27.

4g: yellowish needles; m.p. 155–157°C. IR (KBr): ν 3009, 1595, 1583, 1452 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H, OMe), 6.53 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.67 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.75–7.11 (m, $3H_{arom}$), 7.28–7.42 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.1, 64.3, 113.1, 114.0, 118.3, 120.1, 122.3, 128.2, 129.2, 130.5, 150.2, 166.4, 192.5. EIMS $m/z = 351$ (M^+). Anal. calcd for $C_{15}H_{12}BrNO_2S$: C, 51.44; H, 3.45; N, 4.00. Found: C, 51.19; H, 3.61; N, 3.85.

4h: yellowish needles; m.p. 138–140°C. IR (KBr): ν 3012, 1599, 1588, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H, OMe), 6.51 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.65 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.78–7.15 (m, $2H_{arom}$), 7.21–7.33 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.3, 64.2, 113.3, 114.3, 118.2, 120.4, 122.2, 128.5, 129.3, 130.2, 150.5, 166.1, 192.2. EIMS $m/z = 331$ (M^+). Anal. calcd for $C_{15}H_{11}Br_2NO_2S$: C, 41.98; H, 2.58; N, 3.26. Found: C, 42.32; H, 2.89; N, 3.39.

4i: yellowish needles; m.p. 163–165°C. IR (KBr): ν 3010, 1605, 1579, 1449 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H, OMe), 6.52 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.68 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.71–7.09 (m, $3H_{arom}$), 7.15–7.34 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.8, 64.4, 113.5, 114.6, 118.7, 120.2, 122.5, 128.1, 129.2, 130.1, 150.8, 166.7, 192.3. EIMS $m/z = 307$ (M^+). Anal. calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58. Found: C, 58.59; H, 3.67; N, 4.87.

4j: yellowish needles; m.p. 134–136°C. IR (KBr): ν 3010, 1600, 1582, 1452 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 3H, OMe), 6.51 (d, 1H, $J = 13$ Hz, axial H of CH_2), 6.66 (d, 1H, $J = 13$ Hz, equatorial H of CH_2), 6.79–7.11 (m, $2H_{arom}$), 7.28–7.39 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.5, 64.3, 113.2, 114.5, 118.6, 120.4, 122.4, 128.2, 129.5, 130.7, 150.6, 166.3, 192.7. EIMS $m/z = 341$ (M^+). Anal. calcd for $C_{15}H_{11}Cl_2NO_2S$: C, 52.95; H, 3.26; N, 4.12. Found: C, 52.71; H, 3.49; N, 3.95.

3-Aryl-4-β-D-ribofuranosyl-3,4-dihydro-2*H*-benz[*e*]-1,3-oxazine-2-thiones 9; General Procedure

To a suspension of 1,3-benzoxazine-2-thione **4** (when Ar = 4-ClC_6H_4, $R^1 = R^2 = H$; 0.28 g, 1.00 mmol) in THF (10 mL) was added slowly a suspension of sodium hydride (0.12 g, 5.00 mmol) in THF (10 mL) with stirring at room temperature. After the addition was completed and the evolution of hydrogen gas (effervescence) had ceased, the reaction mixture was stirred at 60°C for 45 minutes and then cooled to room temperature. Next, D-ribose (0.30 g, 2.00 mmol) was added to it and further stirred for 4–5 hours at 60°C. After completion of the reaction as indicated by TLC (hexane/AcOEt, 9:1, v/v), glacial acetic acid (2.0 mL) was added followed by water (10 mL) and the product was extracted with dichloromethane (3 × 25 mL). The extract was filtered and the filtrate was evaporated under reduced pressure to leave the crude product, which was recrystallized from ethanol to obtain an analytically pure sample of **9** as yellowish powder.

9a. Yellowish powder; m.p. 229–231°C. $[\alpha]_D^{[27]} + 46.4^o$ (c 1.5, MeOH). IR (KBr): ν 3391, 3013, 1605, 1585, 1456 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.53 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.61 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 4.05 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.37 (dd, 1H, J = 5.6, 6.4 Hz, H-1′), 4.49 (ddd, 1H, J = 4.6, 5.6, 6.8 Hz, H-2′), 4.67 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.15 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.31 (d, 1H, J = 5.2 Hz, OH-3′), 5.58 (d, 1H, J = 5.6 Hz, OH-2′), 6.55 (d, 1H, J = 6.4 Hz, H-4), 6.75–7.05 (m, $6H_{arom}$), 7.21–7.38 (m, $2H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.5, 62.2, 72.8, 73.3, 76.6, 78.3, 83.5, 113.2, 114.5, 119.0, 121.5, 122.9, 130.3, 132.0, 151.8, 166.5, 192.2. MS *m/z* (FAB, NBA) 408 [MH^+]. Anal. calcd for $C_{19}H_{18}ClNO_5S$: C, 55.95; H, 4.45; N, 3.43. Found: C, 56.21; H, 4.69; N, 3.27.

9b. Yellowish powder; m.p. 205–207°C. $[\alpha]_D^{[27]} + 46.8^o$ (c 1.5, MeOH). IR (KBr): ν 3390, 3009, 1602, 1581, 1450 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.55 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.60 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 4.08 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.34 (dd, 1H, J = 5.6, 6.4 Hz, H-1′), 4.47 (ddd, 1H, J = 4.6, 5.6, 6.8 Hz, H-2′), 4.68 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.18 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.30 (d, 1H, J = 5.2 Hz, OH-3′), 5.55 (d, 1H, J = 5.6 Hz, OH-2′), 6.56 (d, 1H, J = 6.4 Hz, H-4), 6.69–7.08 (m, $3H_{arom}$), 7.18–7.35 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.2, 62.5, 72.8, 73.5, 76.6, 78.7, 83.8, 113.2, 114.9, 119.9, 121.2, 122.5, 130.1, 131.5, 152.0, 166.5, 192.3. MS *m/z* (FAB, NBA) 486 [MH^+]. Anal. calcd for $C_{19}H_{17}BrClNO_5S$: C, 46.88; H, 3.52; N, 2.88. Found: C, 46.52; H, 3.77; N, 3.02.

9c. Yellowish powder; m.p. 195–197°C. $[\alpha]_D^{[27]} + 43.9^o$ (c 1.5, MeOH). IR (KBr): ν 3390, 3011, 1603, 1586, 1449 cm^{-1}. ^1H NMR (400 MHz,

DMSO-d_6): δ 3.52 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.64 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 4.09 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.33 (dd, 1H, J = 5.6, 6.5 Hz, H-1′), 4.48 (ddd, 1H, J = 4.6, 5.6, 6.8 Hz, H-2′), 4.65 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.21 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.29 (d, 1H, J = 5.2 Hz, OH-3′), 5.56 (d, 1H, J = 5.6 Hz, OH-2′), 6.53 (d, 1H, J = 6.5 Hz, H-4), 6.71–7.05 (m, $2H_{arom}$), 7.21–7.35 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.0, 62.1, 72.5, 73.4, 76.3, 78.5, 83.5, 113.1, 114.5, 119.7, 121.1, 122.2, 130.7, 131.2, 152.9, 166.2, 192.1. MS *m/z* (FAB, NBA) 566 [MH^+]. Anal. calcd for $C_{19}H_{16}Br_2ClNO_5S$: C, 40.34; H, 2.85; N, 2.48. Found: C, 40.59; H, 2.99; N, 2.31.

9d. Yellowish powder; m.p. 211–213°C. $[\alpha]_D$:[27] + 44.4 º (c 1.5, MeOH). IR (KBr): ν 3389, 3010, 1601, 1583, 1452 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.56 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.62 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 4.07 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.35 (dd, 1H, J = 5.5, 6.4 Hz, H-1′), 4.51 (ddd, 1H, J = 4.6, 5.5, 6.8 Hz, H-2′), 4.67 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.19 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.33 (d, 1H, J = 5.2 Hz, OH-3′), 5.59 (d, 1H, J = 5.6 Hz, OH-2′), 6.55 (d, 1H, J = 6.4 Hz, H-4), 6.70–7.12 (m, $3H_{arom}$), 7.19–7.35 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.5, 62.5, 72.2, 73.1, 76.2, 78.2, 83.7, 113.5, 114.3, 120.2, 121.5, 122.7, 129.9, 131.3, 152.5, 166.1, 192.5. MS *m/z* (FAB, NBA) 444 [MH^+]. Anal. calcd for $C_{19}H_{17}Cl_2NO_5S$: C, 51.59; H, 3.87; N, 3.17. Found: C, 51.32; H, 3.65; N, 3.39.

9e. Yellowish powder; m.p. 256–258°C. $[\alpha]_D$:[27] + 46.9 º (c 1.5, MeOH). IR (KBr): ν 3393, 3010, 1588, 1455 cm^{-1}. δ 3.48 (ddd, 1H, J = 3.7, 5.4, 11.6 Hz, H_a-5′), 3.65 (ddd, 1H, J = 3.7, 5.8, 11.6 Hz, H_b-5′), 4.08 (ddd, 1H, J = 4.1, 3.7, 3.7 Hz, H-4′), 4.49 (dd, 1H, J = 5.5, 6.4 Hz, H-1′), 4.56 (ddd, 1H, J = 4.5, 5.5, 6.9 Hz, H-2′), 4.74 (ddd, 1H, J = 4.1, 5.1, 6.9 Hz, H-3′), 5.16 (dd, 1H, J = 5.4, 5.8 Hz, OH-5′), 5.32 (d, 1H, J = 5.1 Hz, OH-3′), 5.61 (d, 1H, J = 5.5 Hz, OH-2′), 6.58 (d, 1H, J = 6.4 Hz, H-4), 6.82–7.01 (m, $2H_{arom}$), 7.29–7.43 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.1, 62.5, 72.5, 73.8, 76.5, 78.4, 83.7, 113.5, 114.8, 119.8, 120.6, 122.7, 130.1, 131.6, 152.5, 166.7, 192.5. MS *m/z* (FAB, NBA) 475 [MH^+]. Anal. calcd for $C_{19}H_{16}Cl_3NO_5S$: C, 47.87; H, 3.38; N, 2.94. Found: C, 47.58; H, 3.53; N, 3.09.

9f. Yellowish powder; m.p. 221–223°C. $[\alpha]_D$:[27] + 47.8 º (c 1.5, MeOH). IR (KBr): ν 3391, 3012, 1607, 1580, 1457 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.61 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 3.75 (s, 3H, OMe), 4.06 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.34 (dd, 1H, J = 5.8, 6.4 Hz, H-1′), 4.53 (ddd, 1H, J = 4.6, 5.8, 6.8 Hz, H-2′), 4.63 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.24 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.32 (d, 1H, J = 5.2 Hz, OH-3′), 5.54 (d, 1H, J = 5.6 Hz, OH-2′), 6.57 (d, 1H, J = 6.4 Hz, H-4), 6.68–7.13 (m, $6H_{arom}$), 7.22–7.41 (m, $2H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.1, 53.5, 62.2, 72.6, 73.6, 76.5, 78.3, 83.5, 113.2, 114.5, 120.1, 121.3, 122.5, 130.3, 131.0, 152.3, 166.7, 192.2.

MS *m/z* (FAB, NBA) 404 [MH^+]. Anal. calcd for $C_{20}H_{21}NO_6S$: C, 59.54; H, 5.25; N, 3.47. Found: C, 59.79; H, 5.58; N, 3.31.

9g. Yellowish powder; m.p. 238–240°C. $[\alpha]_D$:[27] + 42.3 º (c 1.5, MeOH). IR (KBr): ν 3390, 3011, 1601, 1583, 1449 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.63 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 3.74 (s, 3H, OMe), 4.05 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.31 (dd, 1H, J = 5.4, 6.3 Hz, H-1′), 4.50 (ddd, 1H, J = 4.6, 5.4, 6.8 Hz, H-2′), 4.62 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.17 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.31 (d, 1H, J = 5.2 Hz, OH-3′), 5.52 (d, 1H, J = 5.6 Hz, OH-2′), 6.51 (d, 1H, J = 6.3 Hz, H-4), 6.62–7.11 (m, $3H_{arom}$), 7.21–7.41 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.3, 53.9, 62.4, 72.5, 73.3, 76.1, 78.6, 83.3, 113.6, 114.2, 120.3, 121.2, 123.2, 130.2, 131.5, 152.9, 166.5, 192.4. MS *m/z* (FAB, NBA) 482 [MH^+]. Anal. calcd for $C_{20}H_{20}BrNO_6S$: C, 49.80; H, 4.18; N, 2.90. Found: C, 49.61; H, 4.05; N, 3.17.

9h. Yellowish powder; m.p. 248–250°C. $[\alpha]_D$:[27] + 45.1 º (c 1.5, MeOH). IR (KBr): ν 3392, 3013, 1599, 1581, 1450 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.54 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.61 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 3.79 (s, 3H, OMe), 4.01 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.32 (dd, 1H, J = 5.6, 6.4 Hz, H-1′), 4.49 (ddd, 1H, J = 4.6, 5.6, 6.8 Hz, H-2′), 4.60 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.21 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.34 (d, 1H, J = 5.2 Hz, OH-3′), 5.51 (d, 1H, J = 5.6 Hz, OH-2′), 6.50 (d, 1H, J = 6.4 Hz, H-4), 6.67–7.15 (m, $2H_{arom}$), 7.18–7.39 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.2, 53.1, 62.3, 72.4, 73.5, 76.7, 78.1, 83.6, 113.4, 114.6, 119.5, 121.6, 123.3, 130.1, 131.8, 151.8, 166.3, 192.2. MS *m/z* (FAB, NBA) 562 [MH^+]. Anal. calcd for $C_{20}H_{19}Br_2NO_6S$: C, 42.80; H, 3.41; N, 2.50. Found: C, 42.55; H, 3.63; N, 2.72.

9i. Yellowish powder; m.p. 224–226°C. $[\alpha]_D$:[27] + 46.8 º (c 1.5, MeOH). IR (KBr): ν 3389, 3013, 1602, 1585, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.63 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 3.72 (s, 3H, OMe), 4.03 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.29 (dd, 1H, J = 5.4, 6.4 Hz, H-1′), 4.47 (ddd, 1H, J = 4.6, 5.4, 6.8 Hz, H-2′), 4.61 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.18 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.29 (d, 1H, J = 5.2 Hz, OH-3′), 5.50 (d, 1H, J = 5.6 Hz, OH-2′), 6.53 (d, 1H, J = 6.4 Hz, H-4), 6.63–7.09 (m, $3H_{arom}$), 7.21–7.38 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.4, 53.3, 62.0, 72.3, 73.1, 76.8, 78.5, 83.8, 113.2, 114.0, 119.9, 121.4, 122.9, 130.3, 131.3, 152.5, 166.8, 192.5. MS *m/z* (FAB, NBA) 438 [MH^+]. Anal. calcd for $C_{20}H_{20}ClNO_6S$: C, 54.86; H, 4.60; N, 3.20. Found: C, 55.02; H, 4.39; N, 2.93.

9j. Yellowish powder; m.p. 260–262°C. $[\alpha]_D$:[27] + 48.5 º (c 1.5, MeOH). IR (KBr): ν 3391, 3012, 1605, 1580, 1453 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.56 (ddd, 1H, J = 3.4, 5.3, 11.6 Hz, H_a-5′), 3.65 (ddd, 1H, J = 3.4, 5.7, 11.6 Hz, H_b-5′), 3.77 (s, 3H, OMe), 4.02 (ddd, 1H, J = 4.2, 3.5, 3.4 Hz, H-4′), 4.34 (dd, 1H, J = 5.8, 6.4 Hz, H-1′), 4.50 (ddd, 1H, J

TABLE 1 Synthesis of products **4** and **9**

Product	Time (minutes)[a]	Yield(%)[b,c]	product	Time (hours)[d]	Yield(%)[b,c]
4a	7	78	9a	3	75
4b	8	87	9b	5	87
4c	8	89	9c	3	85
4d	10	79	9d	4	76
4e	12	88	9e	4	86
4f	10	85	9f	5	85
4g	9	80	9g	5	81
4h	7	86	9h	3	87
4i	11	85	9i	4	87
4j	10	79	9j	5	77

[a]Microwave irradiation time at 90°C.
[b]Yield of isolated and purified products.
[c]All compound gave C, H, and N analyses within ± 0.34% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.
[d]Time for oil-bath heating at 60°C.

= 4.6, 5.8, 6.8 Hz, H-2′), 4.63 (ddd, 1H, J = 4.6, 5.2, 6.8 Hz, H-3′), 5.22 (dd, 1H, J = 5.3, 5.7 Hz, OH-5′), 5.32 (d, 1H, J = 5.2 Hz, OH-3′), 5.51 (d, 1H, J = 5.6 Hz, OH-2′), 6.56 (d, 1H, J = 6.4 Hz, H-4), 6.68–7.12 (m, $2H_{arom}$), 7.19–7.42 (m, $4H_{arom}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.0, 53.4, 62.4, 72.8, 73.7, 76.3, 78.8, 83.5, 113.1, 114.3, 120.2, 121.0, 122.8, 129.8, 131.6, 152.4, 166.5, 192.3. MS *m/z* (FAB, NBA) 472 [MH^+]. Anal. calcd for $C_{20}H_{19}Cl_2NO_6S$: C, 50.86; H, 4.05; N, 2.97. Found: C, 50.63; H, 4.26; N, 3.17 (Table 1).

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