Substitution Alters the Mode of Molecular Iodine-Mediated Intramolecular Cyclization: Syntheses of Benzoxepine and Benzo-2*H*-pyran Derivatives

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Abstract: The synthesis of benzoxepine and benzo-2*H*-pyran derivatives by the implementation of an inexpensive and easy to handle molecular iodine-mediated intramolecular electrophilic cyclization strategy is described. Simple substitution at the terminus of the propargyl group alters the course of the iodocyclization.

Key words: iodine, intramolecular cyclization, benzoxepine, benzo-2*H*-pyrans

Substituted heterocyclic compounds are frequently found as key structural components in a vast number of biologically active natural and non-natural compounds. Five- and six-membered heterocyclic rings are important structural subunits in numerous natural products, such as polyacetylenic esters,[2] phytane-type diterpenedilactones,[3] cylindriline C, and lepadiformine.[4] The 2*H*-benzopyran Daurichromenic acid is known to have anti-HIV properties[5] as well as antidiabetic activity.[6] They are also useful for the treatment of proliferative skin disorders, microbial infections,[7] and show potent antifungal activity.[8] It was found that compound **A** is a selective rat 5-hydroxytryptamine1B (r5-HT1B) receptor antagonist.[9] Ishizuka et al. reported that 2-(benzo[1,3]dioxol-5-yl)-2*H*-chromene-3-carboxylic acid (**B**), was found by modifications of their own angiotensin II antagonist.[10] On the other hand, medium-ring oxygen heterocycles, especially oxepines and oxocines, are important structural units that are present in numerous biologically active molecules belonging to a class of medicinally important compounds. These exhibit antianaphylactic, oral hypotensive, and antiulcer activities.[11] The fungal metabolites pterulone (**C**) and its analogue **D**,[12] which inhibit the eukaryotic respiratory chain at the NADH site of the ubiquinone oxidoreductase, possess potent antifungal activity, and are only weakly cytotoxic. Similarly, pterulinic acid (**E**) exhibits significant antifungal and either weak or no cytotoxic activity, and is an effective inhibitor of eukaryotic respiration (Figure 1).[13]

For these and other reasons, the synthesis of various heterocycles, both regular- and medium-ring heterocycles, has been a research objective for many groups for over a century, and a search of the literature reveals that a variety of well-established methodologies are available for the construction of complex heterocyclic compounds.[14] The development of new and efficient approaches for their syntheses, employing mild, economical, and high-yielding routes, is an area of current research interest.[15] Recently, the electrophilic cyclization of heteroatomic nucleophiles, such as oxygen, nitrogen, and sulfur, with alkynes has proven to be an effective method for the synthesis of these types of heterocyclic compounds.[16] Due to the excellent alkynophilicity of molecular iodine, recently, much attention has been paid to iodine-based alkyne activation for developing new and efficient iodocyclizations.[17,18] Moreover, transition-metal-catalyzed cyclizations of polyunsaturated systems to give various heterocyclic compounds containing seven-membered rings have been developed,[19] however, only a few successful examples[20] are found in the literature for the effective construction of medium-sized ring systems by iodine-mediated reaction, possibly because of the disadvantageous influence of both entropic and enthalpic factors, as well as because of electronic and steric effects. Thus, the development of a novel method for the annulation of medium-ring heterocycles, ideally including metal-free, mild, environmentally friendly, and atom-economic conditions, is necessary. Larock et al.[21] reported that an aryl propargylic ether with the terminal of the propargylic group protected, undergoes iodocyclization reaction to give benzopyran derivatives **F**. Surprisingly, we recently reported[20] the syntheses of different benzoxepine deriva-

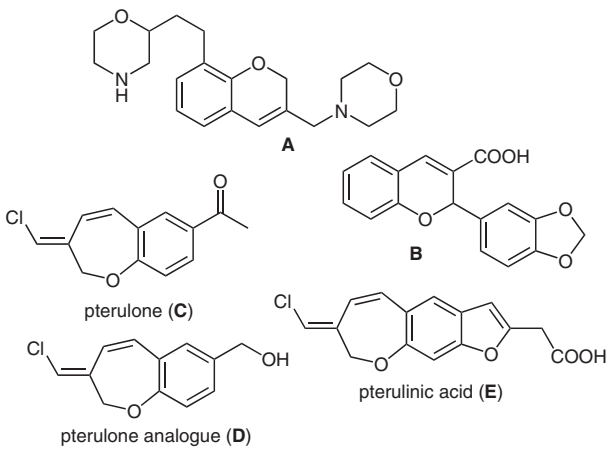

Figure 1

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tives **G** by a 7-*exo* mode of cyclization without the formation of any benzopyran derivatives (Figure 2).

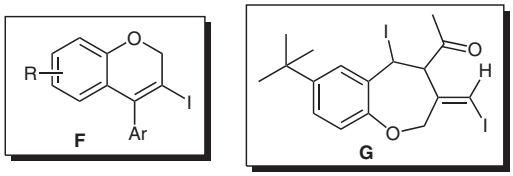
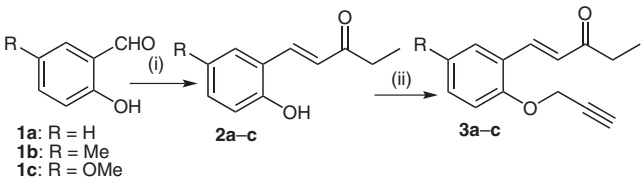


Figure 2

These conflicting findings encouraged us to undertake a thorough study on the effect of substituents upon the mode of cyclization of our previously reported systems. For this purpose, a number of substrates with either a protected or unprotected propargylic group were submitted to the iodocyclization reaction conditions; herein, we report the results.

The required precursors for our present study **3a–c** were synthesized in 68–78% yields by heating compounds **2a–c** to reflux with propargyl bromide in acetone in the presence of anhydrous K_2CO_3 and a catalytic amount of NaI. Compounds **2a–c** were, in turn, prepared by heating salicylaldehydes **1a–c** to reflux in ethyl methyl ketone in the presence of anhydrous K_2CO_3. The hydroxy aldehydes **1a–c** were prepared according to our earlier published procedure (Scheme 1).[22]

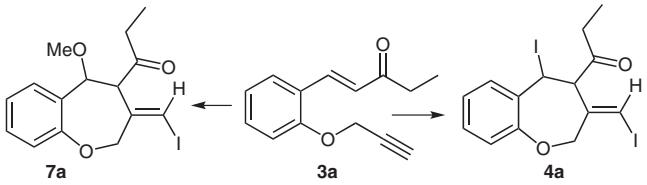


Scheme 1 *Reagents and conditions*: (i) anhyd K_2CO_3, ethyl methyl ketone, reflux, 10–12 h; (ii) propargyl bromide, anhyd K_2CO_3, anhyd acetone, NaI, reflux, 5–6 h.

When the iodocyclization reaction was performed with a mixture of compound **3a**, molecular iodine (1 equiv), and $NaHCO_3$ (1 equiv) at room temperature in anhydrous acetonitrile solvent for eight hours, seven-membered benzoxepine derivative **4a** was formed in 55% yield by a 7-*exo* mode of cyclization, accompanied by the formation of some uncyclized iodo-derivative **5a**. The 8-*endo* cyclized product **6a** was not obtained (Scheme 2). The structures of the cyclized products were determined from their spectroscopic and analytical data. The high ^{1}H NMR shift value of the olefinic proton confirms that it is in the deshielding zone of the carbonyl oxygen of the $COCH_3$ group. The proposed seven-membered structure is also supported by the observed resonance of two doublet protons that were observed at δ = 3.43 (J = 1.6 Hz) and 4.49 (J = 1.6 Hz) ppm; in the case of an eight-membered ring, the proton at δ = ~ 4.49 ppm would be expected to split in a more complex manner. The relative stereochemistry of the iodine (methoxy) substituent and the ketone in the benzoxepine moiety was found from an NOE experiment to be in a *syn* configuration.[20]

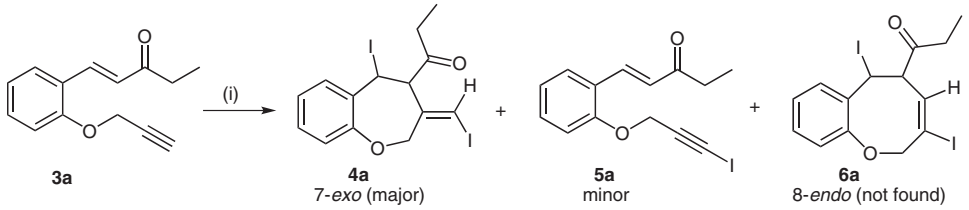
To expand the scope of the iodine-mediated process, the reaction was also carried out using the procedure stated above but adding a small amount of methanol; under these conditions, it was observed that the reaction produced a reduced amount of diiodo product **4a** and a small amount of a new 7-*exo* cyclized product **7a**. The presence of the new product establishes the fact that, in this system, iodine acted as an electrophile and methanol as a nucleophile. Encouraged by this positive result, a thorough investigation was performed to find the optimum reaction conditions. Interestingly, the amount of iodine as well as base ($NaHCO_3$) both played important roles in this reaction. The use of two equivalents of iodine increased the amount of the uncyclized iodo-derivative **5a** at the expense of the desired cyclized product. A similar result was

Table 1 Optimization of I_2-Mediated Reactions



Entry	Electrophile (equiv)	Nucleophile (equiv)	Solvent	Product	Yield (%)[b]
1[a]	I_2 (1)	–	MeCN	**4a**	55
2	I_2 (2)	–	MeCN	**4a**	20
3	I_2 (3)	–	MeCN	**4a**	15
4	I_2 (1)	MeOH (1)	MeCN	**4a** + **7a**	25 + 10
5	I_2 (1)	MeOH (10)	MeCN	**4a** + **7a**	25 + 25
6[a]	I_2 (1)	MeOH (20)	MeCN	**7a**	50
7	I_2 (1)	MeOH	MeOH	**7a**	45

[a] Optimized reaction conditions. In each case, 1 equiv of $NaHCO_3$ was used as base.
[b] Isolated yield.



Scheme 2 *Reagents and conditions*: (i) I_2, $NaHCO_3$, anhyd MeCN, r.t.

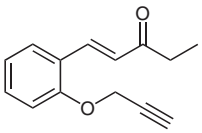
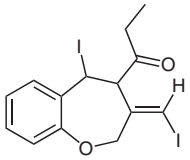
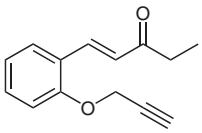
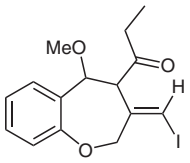
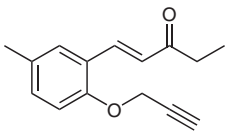
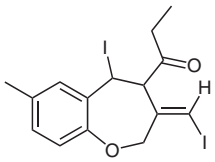
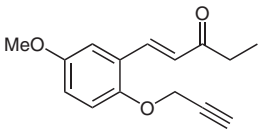
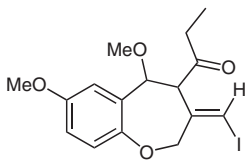
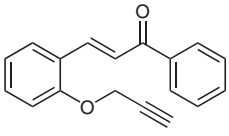
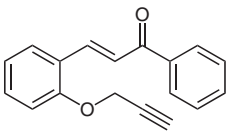
obtained when two equivalents of $NaHCO_3$ was used. Increasing the amount of both I_2 and $NaHCO_3$ drastically reduced the amount of cyclized product, and no improvement was observed when the reaction time was extended. In acetonitrile solvent, iodine acted both as an electrophile and a nucleophile. It was also observed that increasing the amount of methanol increased the amount of **7a** formed. When an excess of methanol was used (20 equiv) the reaction afforded only a mixture of **7a** and uncyclized iodo-derivative **5a**, without any cyclized diiodo product **4a**. The results are summarized in Table 1.

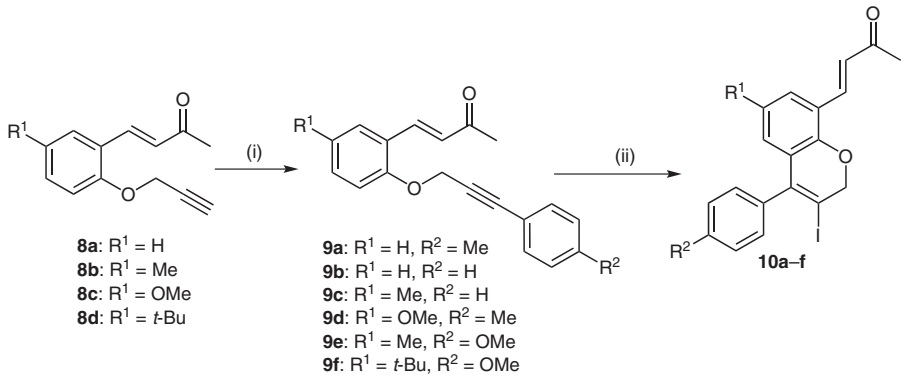
After establishing the optimized reaction conditions, other substrates were similarly treated under the optimized reaction conditions to afford the corresponding *exo*-cyclized benzoxepine derivatives in 48–52% yields; the results are summarized in Table 2.

It is worth noting that we have recently reported[20] the synthesis of some benzoxepine derivatives by an iodine-mediated cyclization reaction. In our present investigation, we have also found that a similar type of reaction occurs when the alkyl group of the keto alkyl moiety is substituted with different alkyl groups. This suggests that the alkyl group has no effect upon the mode of cyclization of this reaction. However, it should be noted that compound **3d**, possessing an aryl group in place of an alkyl group in the keto alkyl moiety, does not undergo the iodocyclization reaction, probably for electronic reasons. We also carried out the reaction of compound **2a** with one equivalent of iodine in acetonitrile, which resulted in the formation of an inseparable mixture of products.

We then turned our attention to extending the scope of this methodology to the construction of oxygen heterocycles by protecting the terminal position of the propargylic triple bond with aryl groups. For this purpose, a number of starting materials **9a–f** were synthesized in moderate to good yields by the Sonogashira coupling reaction of **8a–d** and iodobenzene derivatives in the presence of

Table 2 Synthesis of Benzoxepine Derivatives

Entry	Starting	Product	Time (h)	Yield (%)
1	 **3a**	 **4a**	8	55
2	 **3a**	 **7a**	8	50
3	 **3b**	 **4b**	6	52
4	 **3c**	 **7b**	7	48
5	 **3d**	**4c**	12	NR
6	 **3d**	**7c**	12	NR



Scheme 3 *Reagents and conditions*: (i) *para*-substituted iodobenzene, $[Pd(PPh_3)_2Cl_2]$, CuI, DMF–Et_3N, r.t.; (ii) I_2, $NaHCO_3$, MeCN, r.t.

$[Pd(PPh_3)_2Cl_2]$ as catalyst and copper(I) iodide as co-catalyst in anhydrous triethylamine and *N*,*N*-dimethylformamide (DMF) (1:4) as mixed solvent at room temperature for five hours. When **9a** was subjected to the intramolecular iodocyclization reaction under the optimized reaction conditions (Table 1), benzo-2*H*-pyran derivative **10a** was formed in only 25% yield, leaving the rest of the starting material unchanged in the reaction mixture (Scheme 3). The expected benzoxepine derivative was not obtained at all. The product **10a** was characterized from its spectroscopic data and the configuration as well as the mode of cyclization was confirmed by a single crystal X-ray diffraction analysis (Figure 3).[23]

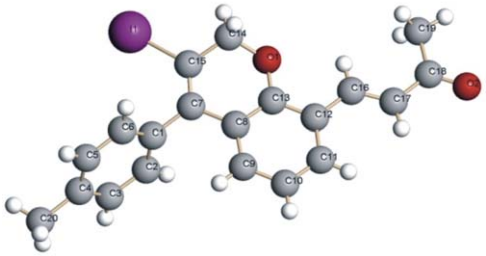


Figure 3 ORTEP diagram of compound **10a**

The formation of **10a** indicates that, in the presence of a terminal protecting group, the reaction does not occur between the α,β-unsaturated double bond and the O-propargylated counterpart, whereas the double bond of the benzene ring participates in the reaction to afford the product. Therefore, a further optimization study was needed to increase the yield of the new reaction. It was observed that two equivalents of iodine, together with two equivalents of $NaHCO_3$ gave a better result (60% yield). By varying the amounts of both iodine and base it was found that use of three equivalents each of iodine and $NaHCO_3$ was optimum; under these conditions the yield was dramatically increased to 90%. Of the bases tested, $NaHCO_3$ found to be most effective for bringing the reaction to completion. It is interesting to note that methanol does not participate in the reaction. On the basis of our observation, the optimized conditions for the reaction were established [I_2 (3 equiv), $NaHCO_3$ (3 equiv), MeCN, r.t.]; the results are summarized in Table 3. With the optimized reaction conditions, the other substrates **9b–f** were treated similarly to afford the benzo-2*H*-pyran derivatives **10b–f** in 85–93% yields (Table 4).

Table 3 Optimization of I_2-Mediated Reactions

Entry	Electrophile (equiv)	Base (equiv)	Solvent	Product	Yield (%)[b]
1	I_2 (1)	$NaHCO_3$ (1)	MeCN	**10a**	25
2	I_2 (2)	$NaHCO_3$ (2)	MeCN	**10a**	60
3[a]	I_2 (3)	$NaHCO_3$ (3)	MeCN	**10a**	90
4	I_2 (3)	K_2CO_3 (3)	MeCN	**10a**	35
5	I_2 (3)	$NaHCO_3$ (3)	CH_2Cl_2	**10a**	25
6	I_2 (3)	Na_2CO_3 (3)	MeCN	**10a**	50
7	I_2 (3)	$NaHCO_3$ (3)	MeOH	**10a**	45

[a] Optimized reaction conditions.
[b] Isolated yield.

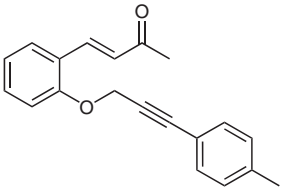
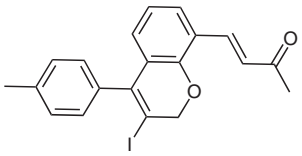
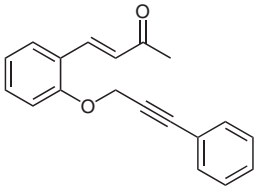
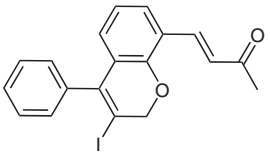
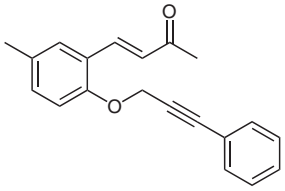
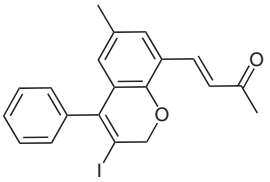
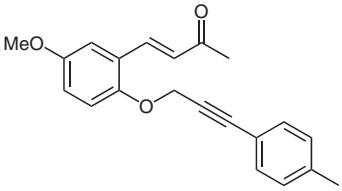
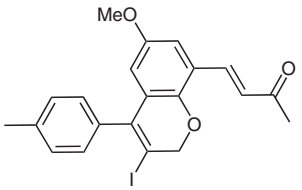
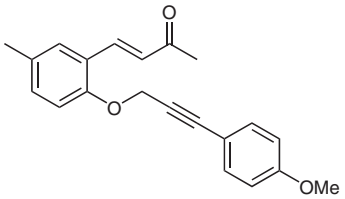
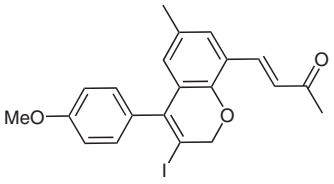
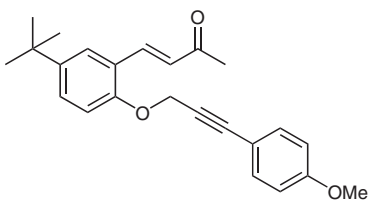
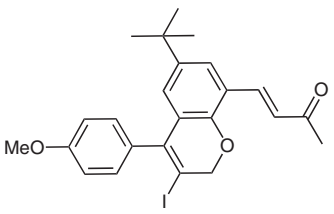
The mechanism of the iodocyclization is assumed to proceed through initial formation of iodonium complex **11** (Scheme 4). When R^1 = H, the remaining I^- ion may attack the double bond of **11** in a Michael fashion to form carbanion **13**. Subsequent attack of the carbanion at the iodonium moiety in a 7-*exo* mode may afford the seven-membered oxepine derivatives **4**. However, when R^1 = aryl, the reaction sequence becomes completely different because the intermediate **13** formed suffers steric hindrance between the more bulky aryl group and the carbonyl group of the α,β-unsaturated counterpart. It is assumed that the initially formed iodonium intermediate **11** undergoes electrophilic attack by electron clouds of the aromatic ring, followed by the loss of a proton through the action of the base, giving the benzo-2*H*-pyran derivatives **10**. The formation of **7a** may be explained by the attack of MeOH nucleophile at the β-carbon of the α,β-unsaturated carbonyl part of the initially formed iodonium intermediate **11** in a Michael fashion, followed by abstraction of a proton by the base ($NaHCO_3$) to form the intermediate **17**. Finally, the benzoxepine derivative **7a** is formed by the at-

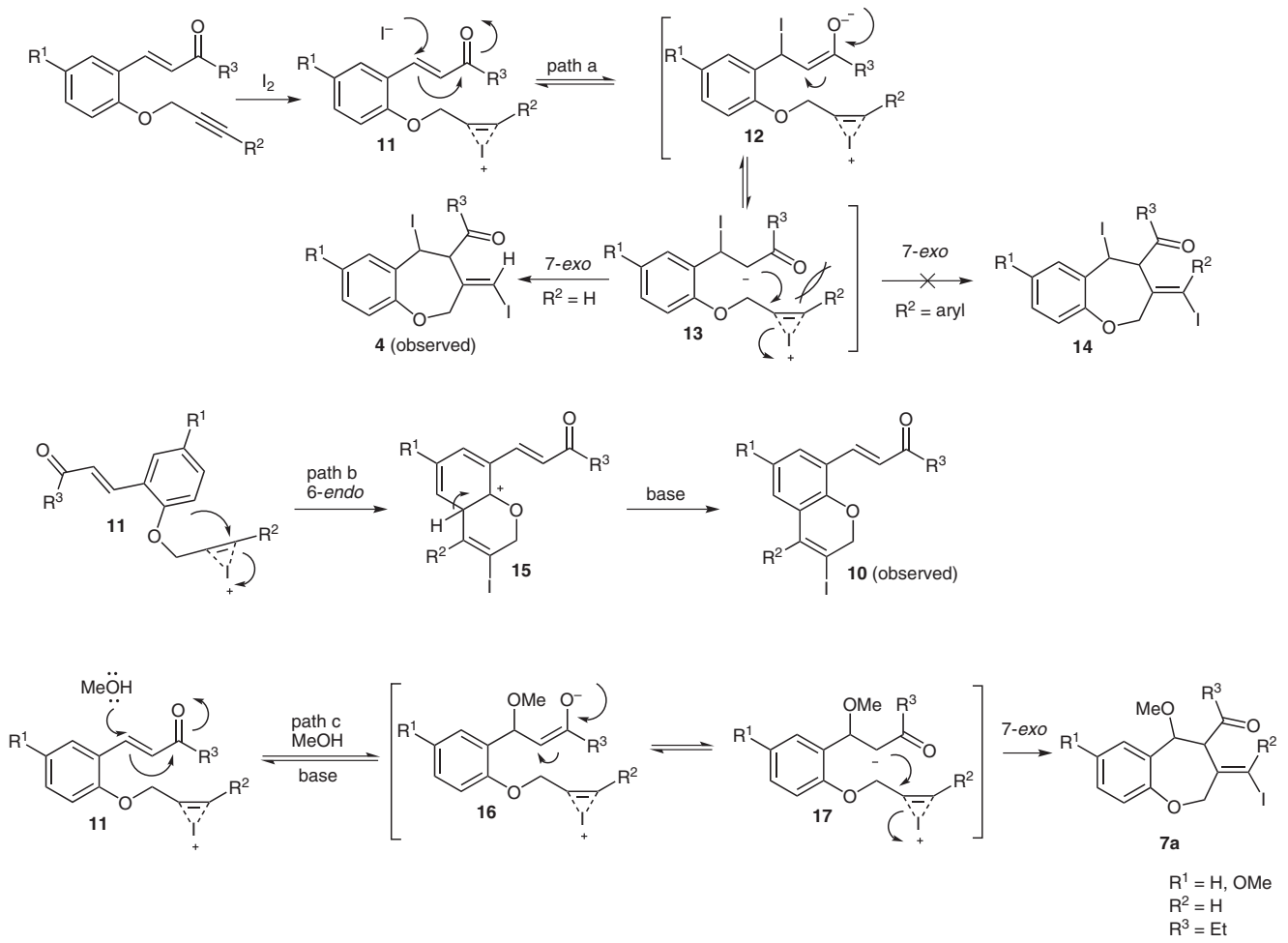
tack of the carbanion on the iodonium moiety of intermediate **17**.

From the above discussion it is clear that the iodine-mediated cyclization protocol is very useful for the construction of a range of heterocycles in a straightforward way. Furthermore, the presence of a halogen functionality on the heterocyclic products makes them useful substrates for derivatization, usually through metal-catalyzed C–C bond formation.[24] It is also important to note that we have selectively synthesized both six- and seven-membered heterocycles, i.e., both benzoxepine- and benzo-2*H*-pyran derivatives, with good to excellent yields under similar reaction conditions, simply by modifying the terminal of the triple bond.

In summary, we have developed an inexpensive, mild, and easy to handle approach to the synthesis, from similar substrates, of both benzoxepine- and 2*H*-pyrans, which are more difficult to prepare using conventional methods. The procedure reported here is more economical than other methods and avoids difficulties associated with product

Table 4 Synthesis of Benzo-2*H*-pyran Derivatives

Entry	Starting	Product	Time (h)	Yield (%)
1	 **9a**	 **10a**	8	90
2	 **9b**	 **10b**	8	85
3	 **9c**	 **10c**	7	93
4	 **9d**	 **10d**	7	88
5	 **9e**	 **10e**	6	92
6	 **9f**	 **10f**	6	87



Scheme 4 Proposed mechanism

isolation. This methodology is tolerant toward a variety of functional groups, including carbonyl groups, and provides a handle for further organic transformations. Further investigations into the scope and limitations of this electrophilic cyclization are underway.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded with a Perkin–Elmer L 120–000A spectrometer (cm^{-1}) on KBr disks. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded with a Qtof-Micro instrument. CHN was recorded with a 2400 series II CHN Perkin–Elmer analyzer. Silica gel [60–120 mesh and 230–400 mesh; Spectrochem, India] were used for chromatographic separation. Silica gel G and silica gel GF-254 (Spectrochem, India) were used for TLC. Petroleum ether (PE) refers to the fraction boiling between 60–80 °C.

Compounds **2a–c** and **8a–d** were obtained according to our previously published procedure.[20]

Synthesis of Compounds 3a–c; Typical Procedure

A mixture of compound **2a** (1.70 mmol) and propargyl bromide (2.55 mmol) was heated at reflux in anhydrous acetone (30 mL) in the presence of anhydrous K_2CO_3 (8.50 mmol) and a catalytic amount NaI for 6 h. The reaction mixture was then cooled to r.t., filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel (60–120 mesh) column chromatography (EtOAc–PE, 1:19) to give compound **3a** as a colorless viscous gum. Compounds **3b** and **3c** were synthesized accordingly.

Compound 3a

Yield: 75%; colorless viscous gum.

IR (neat): 1665, 2119, 3290 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.54 (t, *J* = 2.4 Hz, 1 H, propargylic CH), 2.73 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.79 (d, *J* = 2.4 Hz, 2 H, OCH_2), 6.78 (d, *J* = 16.4 Hz, 1 H, CH_a=CH_b), 7.02 (d, *J* = 7.6 Hz, 1 H, ArH), 7.06 (d, *J* = 8.0 Hz, 1 H, ArH), 7.35–7.39 (m, 1 H, ArH), 7.58 (d, *J* = 7.6 Hz, 1 H, ArH), 7.92 (d, *J* = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 7.2, 30.9, 56.3, 75.9, 78.3, 112.4, 123.2, 125.3, 127.9, 128.7, 139.1, 144.5, 154.1, 199.3.

MS (ESI): *m*/*z* = 237 $[M + Na]^+$.

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.42; H, 6.55.

Compound 3b

Yield: 78%; colorless viscous gum.

IR (neat): 1669, 2129, 3287 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.31 (s, 3 H, CH_3), 2.53 (t, *J* = 2.0 Hz, 1 H, propargylic CH), 2.72 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.75 (d, *J* = 2.0 Hz, 2 H, OCH_2), 6.76 (d, *J* = 16.4 Hz, 1 H, CH_a=CH_b), 6.95 (d, *J* = 8.4 Hz, 1 H, ArH),

7.17 (d, J = 8.4 Hz, 1 H, ArH), 7.38 (s, 1 H, ArH), 7.89 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.2, 20.6, 30.9, 56.7, 76.0, 78.5, 113.5, 123.6, 124.7, 127.9, 129.0, 139.3, 145.1, 154.7, 199.8.

MS (ESI): m/z = 251 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.68; H, 7.23.

Compound 3c
Yield: 68%; colorless viscous gum.

IR (neat): 1668, 2120, 3269 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.54 (t, J = 2.4 Hz, 1 H, propargylic CH), 2.74 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.79 (s, 3 H, OCH_3), 4.73 (d, J = 2.4 Hz, 2 H, OCH_2), 6.73 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.96 (dd, J = 8.4, 2.8 Hz, 1 H, ArH), 7.06 (d, J = 8.4 Hz, 1 H, ArH), 7.11 (d, J = 2.8 Hz, 1 H, ArH), 7.87 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.2, 29.7, 55.3, 57.1, 76.3, 78.9, 115.4, 123.0, 124.3, 129.6, 132.7, 139.5, 151.5, 155.2, 199.2.

MS (ESI): m/z = 267 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.79; H, 6.39.

Synthesis of Compounds 4a and 4b; Typical Procedure
A mixture of compound **3a** (0.50 mmol), I_2 (0.50 mmol), and anhydrous $NaHCO_3$ (0.50 mmol) was stirred in anhydrous MeCN (5 mL) at r.t. for 8 h. The reaction mixture was diluted to 50 mL with CH_2Cl_2. The organic phase was washed successively with 10% aqueous sodium thiosulfate (20 mL), H_2O (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography (EtOAc–PE, 3:97) to give compound **4a** as a colorless gum. Compound **4b** was synthesized accordingly.

Compound 4a
Yield: 55%; colorless gum.

IR (neat): 1710, 2926, 3065 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.45–2.67 (m, 2 H, CH_2CH_3), 3.43 (d, J = 1.6 Hz, 1 H, CH), 4.49 (d, J = 1.6 Hz, 1 H, CH), 4.71 (s, 2 H, OCH_2), 6.84 (d, J = 7.8 Hz, 1 H, ArH), 7.02 (dd, J = 7.8, 7.6 Hz, 1 H, ArH), 7.21 (m, 2 H, = CHI and 1 × ArH), 7.28–7.32 (m, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.2, 30.9, 54.4, 62.7, 74.5, 82.3, 98.2, 112.1, 121.9, 124.7, 125.3, 129.6, 155.7, 206.7.

MS (ESI): m/z = 507 $[M + K]^+$.

Anal. Calcd for $C_{14}H_{14}I_2O_2$: C, 35.92; H, 3.01. Found: C, 35.75; H, 2.97.

Compound 4b
Yield: 52%; colorless gum.

IR (neat): 1715, 2927, 3068 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.28 (s, 3 H, CH_3), 2.45–2.62 (m, 2 H, CH_2CH_3), 3.43 (d, J = 1.6 Hz, 1 H, CH), 4.47 (d, J = 1.6 Hz, 1 H, CH), 4.68 (s, 2 H, OCH_2), 6.74 (d, J = 8.4 Hz, 1 H, ArH), 6.98 (s, 1 H, ArH), 7.08 (d, J = 8.4 Hz, 1 H, ArH), 7.19 (s, 1 H, =CHI).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.2, 20.6, 30.9, 54.4, 62.7, 74.6, 82.1, 98.5, 112.3, 124.4, 125.8, 129.9, 131.4, 153.7, 206.7.

MS (ESI): m/z = 521 $[M + K]^+$.

Anal. Calcd for $C_{15}H_{16}I_2O_2$: C, 37.37; H, 3.35. Found: C, 37.41; H, 3.47.

Synthesis of Compounds 7a and 7b; Typical Procedure
A mixture of compound **3a** (0.50 mmol), I_2 (0.50 mmol), anhydrous $NaHCO_3$ (0.50 mmol), and anhydrous MeOH (10.00 mmol) was stirred in anhydrous MeCN (5 mL) at r.t. for 8 h. The reaction mixture was diluted to 50 mL with CH_2Cl_2 and the organic phase was washed successively with 10% aqueous sodium thiosulfate (20 mL), H_2O (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography (EtOAc–PE, 3:97) to give compound **7a** as a colorless gum. Compound **7b** was synthesized accordingly.

Compound 7a
Yield: 50%; colorless gum.

IR (neat): 1713, 2928, 3062 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.79 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.26 (s, 3 H, OCH_3), 4.75 (d, J = 2.2 Hz, 2 H, OCH_2), 4.86 (d, J = 9.2 Hz, 1 H, CH), 5.23 (d, J = 9.2 Hz, 1 H, CH), 6.87 (d, J = 8.0 Hz, 1 H, ArH), 7.06 (dd, J = 7.6, 7.2 Hz, 1 H, ArH), 7.25 (d, J = 2.2 Hz, 1 H, =CHI), 7.32–7.35 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.3, 29.7, 32.9, 33.3, 58.2, 74.8, 82.0, 98.3, 112.3, 121.8, 124.5, 125.1, 129.8, 155.9, 205.9.

MS (ESI): m/z = 395 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{17}IO_3$: C, 48.40; H, 4.60. Found: C, 48.09; H, 4.47.

Compound 7b
Yield: 48%; colorless gum.

IR (neat): 1710, 2933, 3069 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.79 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.27 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.70 (s, 2 H, OCH_2), 4.81 (d, J = 9.0 Hz, 1 H, CH), 5.20 (d, J = 9.0 Hz, 1 H, CH), 6.83–6.89 (m, 3 H, ArH), 7.23 (s, 1 H, =CHI).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.3, 29.7, 32.8, 33.2, 55.7, 58.2, 75.6, 81.8, 98.7, 113.6, 114.1, 114.5, 128.1, 150.1, 154.5, 204.8.

MS (ESI): m/z = 425 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{19}IO_4$: C, 47.78; H, 4.76. Found: C, 47.71; H, 4.77.

Synthesis of Compounds 9a–f: Typical Procedure
A mixture of compound **8a** (1.50 mmol), *p*-methyliodobenzene (1.80 mmol), anhydrous Et_3N (2 mL), $[Pd(PPh_3)_2Cl_2]$ (3 mol%), and CuI (3 mol%) was stirred in anhydrous DMF (8 mL) at r.t. for 5 h. The reaction mixture was diluted to 70 mL with CH_2Cl_2 and the organic phase was washed successively with H_2O (3 × 25 mL), brine (25 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60–120 mesh) column chromatography (EtOAc–PE, 1:19) to give compound **9a** as a white solid. Compounds **9b–f** were synthesized accordingly.

Compound 9a
Yield: 66%; white solid; mp 80–81 °C.

IR (KBr): 1668, 2235, 2927, 3054 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 5.00 (s, 2 H, OCH_2), 6.76 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 7.03 (m, 1 H, ArH), 7.11 (d, J = 7.8 Hz, 2 H, ArH), 7.15 (d, J = 8.0 Hz, 1 H, ArH), 7.31 (d, J = 7.8 Hz, 2 H, ArH), 7.39 (m, 1 H,

ArH), 7.58 (d, J = 8.0 Hz, 1 H, ArH), 7.93 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 27.1, 57.2, 82.7, 87.9, 113.1, 118.9, 121.6, 124.0, 128.0, 128.2, 129.1, 131.7, 138.6, 139.1, 156.5, 199.2.

MS (ESI): m/z = 313 [M + Na]$^+$.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.54; H, 6.17.

Compound 9b
Yield: 68%; colorless gum.

IR (neat): 1664, 2229, 2920, 3056 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.39 (s, 3 H, CH_3), 4.96 (s, 2 H, OCH_2), 6.65 (dd, J = 8.0, 2.0 Hz, 1 H, ArH), 6.74 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.79 (dd, J = 8.0, 7.6 Hz, 1 H, ArH), 7.12 (d, J = 8.0 Hz, 1 H, ArH), 7.21 (d, J = 7.6 Hz, 1 H, ArH), 7.33–37 (m, 3 H, ArH), 7.44 (dd, J = 7.6, 1.8 Hz, 2 H, ArH), 7.92 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.2, 57.5, 82.7, 87.5, 113.2, 121.9, 124.1, 127.8, 128.2, 128.5, 129.0, 131.4, 132.0, 132.5, 137.7, 155.4, 199.5.

MS (ESI): m/z = 299 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.68; H, 5.71.

Compound 9c
Yield: 62%; white solid; mp 71–72 °C.

IR (KBr): 1667, 2239, 2922, 3057 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 4.98 (s, 2 H, OCH_2), 6.74 (d, J = 16.8 Hz, 1 H, CH_a=CH_b), 7.04 (d, J = 8.2 Hz, 1 H, ArH), 7.19 (d, J = 8.2 Hz, 1 H, ArH), 7.30–7.33 (m, 3 H, ArH), 7.39 (s, 1 H, ArH), 7.42 (dd, J = 7.6, 2.0 Hz, 2 H, ArH), 7.91 (d, J = 16.8 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 27.1, 57.4, 83.6, 87.6, 113.2, 122.1, 123.8, 127.8, 128.3, 128.6, 128.8, 131.0, 131.8, 132.3, 138.7, 154.5, 199.2.

MS (ESI): m/z = 313 [M + Na]$^+$.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.48; H, 6.35.

Compound 9d
Yield: 65%; colorless gum.

IR (neat): 1666, 2236, 2923, 3062 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 4.94 (s, 2 H, OCH_2), 6.71 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.95 (dd, J = 8.8, 2.8 Hz, 1 H, ArH), 7.08–7.12 (m, 4 H, ArH), 7.30 (d, J = 8.0 Hz, 2 H, ArH), 7.92 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 27.2, 55.4, 57.4, 83.5, 87.4, 113.3, 113.7, 114.3, 124.0, 128.2, 128.6, 131.0, 132.8, 133.6, 138.9, 154.3, 159.9, 199.8.

MS (ESI): m/z = 343 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.97; H, 6.33.

Compound 9e
Yield: 67%; white solid; mp 90–91 °C.

IR (KBr): 1668, 2227, 2933, 3057 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.31 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 4.96 (s, 2 H, OCH_2), 6.74 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.82 (d, J = 8.8 Hz, 2 H, ArH), 7.04 (d, J = 8.4 Hz, 1 H, ArH), 7.19 (d, J = 8.4 Hz, 1 H, ArH), 7.36 (d, J = 8.4 Hz, 2 H, ArH), 7.38 (s, 1 H, ArH), 7.91 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 27.1, 55.3, 57.5, 82.3, 87.6, 113.3, 113.9, 114.1, 123.8, 127.7, 128.6, 130.9, 132.3, 133.3, 138.8, 154.6, 159.9, 199.2.

MS (ESI): m/z = 343 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.67; H, 6.14.

Compound 9f
Yield: 69%; white solid; mp 81–82 °C.

IR (KBr): 1668, 2223, 2923, 3047 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 [s, 9 H, $C(CH_3)_3$], 2.38 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 4.98 (s, 2 H, OCH_2), 6.72 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.82 (d, J = 8.4 Hz, 2 H, ArH), 6.97 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 7.16 (d, J = 8.4 Hz, 1 H, ArH), 7.32 (d, J = 8.4 Hz, 2 H, ArH), 7.49 (d, J = 2.4 Hz, 1 H, ArH), 7.82 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.1, 31.3, 34.3, 55.2, 57.5, 83.4, 87.5, 113.7, 114.3, 121.8, 123.4, 127.9, 128.2, 131.1, 131.9, 133.0, 138.5, 155.1, 159.5, 198.7.

MS (ESI): m/z = 385 [M + Na]$^+$.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.37; H, 6.94.

Synthesis of Compounds 10a–f; Typical Procedure
A mixture of compound **9a** (0.50 mmol), I_2 (1.50 mmol) and anhydrous $NaHCO_3$ (1.50 mmol) was stirred in anhydrous MeCN (5 mL) at r.t. for 8 h. The reaction mixture was diluted to 50 mL with CH_2Cl_2 and the organic phase was washed successively with 10% aqueous sodium thiosulfate (20 mL), H_2O (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography (EtOAc–PE, 1:19) to give compound **10a** as a white solid. Compounds **10b–f** were synthesized accordingly.

Compound 10a
Yield: 90%; white solid; mp 105–106 °C.

IR (KBr): 1667, 2922, 3026 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 5.15 (s, 2 H, OCH_2), 6.69 (d, J = 7.6 Hz, 1 H, ArH), 6.73 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.78 (dd, J = 8.0, 7.6 Hz, 1 H, ArH), 7.08 (d, J = 6.8 Hz, 2 H, ArH), 7.27 (d, J = 6.8 Hz, 2 H, ArH), 7.42 (d, J = 8.0 Hz, 1 H, ArH), 7.82 (d, J = 16.8 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.4, 27.4, 75.1, 91.3, 121.5, 122.4, 124.8, 127.8, 128.1, 128.6, 129.1, 129.4, 136.7, 137.5, 138.1, 141.5, 152.2, 199.0.

MS (ESI): m/z = 439 [M + Na]$^+$.

Anal. Calcd for $C_{20}H_{17}IO_2$: C, 57.71; H, 4.12. Found: C, 57.57; H, 4.11.

Compound 10b
Yield: 85%; white solid; mp 133–134 °C.

IR (KBr): 1668, 2923, 3027 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H, CH_3), 5.16 (s, 2 H, OCH_2), 6.67 (dd, J = 7.6, 1.6 Hz, 1 H, ArH), 6.74 (d, J = 16.4 Hz, 1 H, CH_a=CH_b), 6.79 (dd, J = 8.0, 7.6 Hz, 1 H, ArH), 7.19–7.21 (m, 2 H, ArH), 7.42–7.48 (m, 4 H, ArH), 7.82 (d, J = 16.4 Hz, 1 H, CH_a=CH_b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.3, 75.1, 92.4, 122.7, 123.8, 127.9, 128.3, 128.5, 128.6, 128.9, 129.2, 130.4, 138.1, 140.0, 141.3, 150.7, 198.9.

MS (ESI): *m*/*z* = 425 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{15}IO_2$: C, 56.74; H, 3.76. Found: C, 56.51; H, 3.72.

Compound 10c
Yield: 93%; white solid; mp 91–92 °C.

IR (KBr): 1668, 2924, 3024 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 5.11 (s, 2 H, OCH_2), 6.46 (s, 1 H, ArH), 6.73 (d, *J* = 16.8 Hz, 1 H, C*H*$_a$=CH$_b$), 7.20 (dd, *J* = 8.0, 2.0 Hz, 2 H, ArH), 7.24 (s, 1 H, ArH), 7.42–7.49 (m, 3 H, ArH), 7.80 (d, *J* = 16.4 Hz, 1 H, CH$_a$=C*H*$_b$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 27.3, 75.1, 91.6, 122.1, 124.6, 128.0, 128.1, 128.3, 128.6, 129.1, 129.3, 130.8, 137.6, 139.8, 141.7, 150.1, 198.8.

MS (ESI): *m*/*z* = 417 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{17}IO_2$: C, 57.71; H, 4.12. Found: C, 57.45; H, 3.97.

Compound 10d
Yield: 88%; white solid; mp 152–153 °C.

IR (KBr): 1667, 2923, 3030 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 6 H, 2 × CH_3), 3.65 (s, 3 H, OCH_3), 5.08 (s, 2 H, OCH_2), 6.30 (d, *J* = 3.0 Hz, 1 H, ArH), 6.70 (d, *J* = 16.8 Hz, 1 H, C*H*$_a$=CH$_b$), 6.91 (d, *J* = 3.0 Hz, 1 H, ArH), 7.08 (d, *J* = 7.6 Hz, 2 H, ArH), 7.25 (d, *J* = 7.6 Hz, 2 H, ArH), 7.81 (d, *J* = 16.4 Hz, 1 H, CH$_a$=C*H*$_b$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.4, 27.3, 55.7, 75.2, 92.6, 110.4, 116.0, 122.7, 126.0, 128.1, 129.1, 129.4, 136.5, 137.4, 138.2, 141.5, 146.5, 153.7, 198.9.

MS (ESI): *m*/*z* = 469 $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{19}IO_3$ C, 56.52; H, 4.29. Found: C, 56.47; H, 4.19.

Compound 10e
Yield: 92%; white solid; mp 130–131 °C.

IR (KBr): 1668, 2920, 3032 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.14 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 5.09 (s, 2 H, OCH_2), 6.51 (s, 1 H, ArH), 6.72 (d, *J* = 16.4 Hz, 1 H, C*H*$_a$=CH$_b$), 6.99 (d, *J* = 8.8 Hz, 2 H, ArH), 7.12 (d, *J* = 8.4 Hz, 2 H, ArH), 7.23 (s, 1 H, ArH), 7.80 (d, *J* = 16.4 Hz, 1 H, CH$_a$=C*H*$_b$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 27.3, 55.3, 75.1, 91.8, 113.9, 122.0, 124.9, 127.9, 128.0, 129.3, 130.6, 130.8, 132.0, 137.6, 141.3, 150.2, 159.4, 199.0.

MS (ESI): *m*/*z* = 469 $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{19}IO_3$: C, 56.52; H, 4.29. Found: C, 56.33; H, 4.17.

Compound 10f
Yield: 87%; white solid; mp 123–124 °C.

IR (KBr): 1666, 2927, 3035 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 [s, 9 H, $C(CH_3)_3$], 2.42 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 5.11 (s, 2 H, OCH_2), 6.74 (d, *J* = 2.4 Hz, 1 H, ArH), 6.76 (d, *J* = 16.4 Hz, 1 H, C*H*$_a$=CH$_b$), 6.99 (d, *J* = 8.4 Hz, 2 H, ArH), 7.14 (d, *J* = 8.8 Hz, 2 H, ArH), 7.43 (d, *J* = 2.4 Hz, 1 H, ArH), 7.82 (d, *J* = 16.4 Hz, 1 H, CH$_a$=C*H*$_b$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.2, 31.1, 34.2, 55.3, 75.2, 91.1, 113.8, 121.5, 124.5, 124.6, 126.3, 128.0, 130.6, 131.8, 138.2, 141.5, 144.2, 150.2, 159.3, 199.2.

MS (ESI): *m*/*z* = 511 $[M + Na]^+$.

Anal. Calcd for $C_{24}H_{25}IO_3$: C, 59.03; H, 5.16. Found: C, 58.84; H, 5.07.

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References

(1) Present address: Department of Chemical Science, Tezpur University, Napaam 784028, Assam, India.
(2) Li, C.; Lee, D.; Graf, T. N.; Phifer, S. S.; Nakanishi, Y.; Riswan, S.; Setyowati, F. M.; Saribi, A. M.; Soejarto, D. D.; Farnsworth, N. R.; Falkinham, J. O. III; Kroll, D. J.; Kinghorn, A. D.; Wani, M. C.; Oberlies, N. H. *J. Nat. Prod.* **2009**, *72*, 1949.
(3) Fan, X.; Zi, J.; Zhu, C.; Xu, W.; Cheng, W.; Yang, S.; Guo, Y.; Shi, J. *J. Nat. Prod.* **2009**, *72*, 1184.
(4) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett.* **2008**, *10*, 1871.
(5) (a) Zhendong, J.; Ying, K. PCT Int. Appl. WO 2004058738, **2004**. (b) Iwata, N.; Wang, N.; Yao, X.; Kitanaka, S. *J. Nat. Prod.* **2004**, *67*, 1106. (c) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.
(6) Korec, R.; Sensch, K. H.; Zoukas, T. *Arzneim. Forsch.* **2000**, *50*, 122.
(7) Bonadies, F.; Di Fabio, R.; Bonini, C. *J. Org. Chem.* **1984**, *49*, 1647.
(8) Morandim, A. A.; Bergamo, D. C. B.; Kato, M. J.; Cavalheiro, A. J.; Bolzani, V. S.; Furlan, M. *Phytochem. Anal.* **2005**, *16*, 282.
(9) Stefan, B.; Larsson, L. G.; Rényi, L.; Ross, S. B.; Thorberg, S.-O.; Thorell-Svantesson, G. *J. Med. Chem.* **1998**, *41*, 1934.
(10) Ishizuka, N.; Matsumura, K.; Sakai, K.; Fujimoto, M.; Mihara, S.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041.
(11) (a) TenBrink, R. E.; McCall, J. M.; Johnson, H. G. *J. Med. Chem.* **1980**, *23*, 1058. (b) TenBrink, R. E.; McCall, J. M.; Pals, D. T.; McCall, R. B.; Orley, J.; Humphrey, S. J.; Wendling, M. G. *J. Med. Chem.* **1981**, *24*, 64. (c) O'Shea, D. F.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 515. (d) Tretter, J. R. US Patent 3514449, **1970**; *Chem. Abstr.* **1970**, *73*, 35404u. (e) *Dictionary of Drugs*, 1st ed.; Elks, J.; Ganellin, C. R., Eds.; Chapman and Hall: London, **1990**, 984.
(12) (a) Engler, M.; Anke, T.; Sterner, O.; Brandt, U. *J. Antibiot.* **1997**, *50*, 325. (b) Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swart, H. J.; Frankland, J. C.; Field, J. A. *Tetrahedron Lett.* **1999**, *40*, 5767.
(13) Lin, Y. L.; Kuo, H. S.; Wang, Y. W.; Huang, S. T. *Tetrahedron* **2003**, *59*, 1277.
(14) (a) Di Fabio, R.; Micheli, F.; Baraldi, D.; Bertani, B.; Conti, N.; Dal Forno, G.; Feriani, A.; Donati, D.; Marcchioro, C.; Messeri, T.; Missio, A.; Pasquarello, A.; Pentassuglia, G.;

Pizzi, D. A.; Provera, S.; Quaglia, A. M.; Sabbatini, F. M. *Farmaco* **2003**, *58*, 723. (b) Gibson, S. E.; Jones, J. O.; Kalindjinan, S. B.; Knight, J. D.; Steed, J. W.; Tozer, M. J. *J. Chem. Soc., Chem. Commun.* **2002**, 1938. (c) Alcaide, B.; Polanco, C.; Sierra, M. A. *Eur. J. Org. Chem.* **1998**, 2913. (d) Gibson, S. E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743. (e) Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Tetrahedron Lett.* **2008**, *49*, 1319. (f) Majumdar, K. C.; Chattopadhyay, B. *Synlett* **2008**, 979. (g) Majumdar, K. C.; Chattopadhyay, B. *Curr. Org. Chem.* **2009**, *13*, 731. (h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (i) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (j) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919. (k) Rosillo, M.; Domínguez, G.; Casarrubios, L.; Pérez-Castells, J. *J. Org. Chem.* **2005**, *70*, 10611. (l) Trost, B. M. *Homogeneous Transition Metal Catalyzed Reactions*; Moser, W. R.; Slocum, D. W., Eds.; ACS: Washington/DC, **1992**, Chap. 31, 463.

(15) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

(16) For oxygen heterocycles, see: (a) El-Taeb, G. M. M.; Evans, A. B.; Knight, D. W.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 5945. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. For nitrogen heterocycles, see: (c) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874. (d) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622. (e) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341. (f) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468. (g) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898.

(17) (a) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4764. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62. (c) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (d) He, Z.; Li, H.; Li, Z. *J. Org. Chem.* **2010**, *75*, 4636. (e) Banwell, M. G.; Wills, A. C.; Hamel, E. *Aust. J. Chem.* **1999**, *52*, 767. (f) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (g) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (h) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377. (i) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307. (j) Bui, C. T.; Flynn, B. F. *J. Comb. Chem.* **2006**, *8*, 163.

(18) (a) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (b) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (d) Xie, Y.-X.; Liu, X.-Y.; Wu, L.-Y.; Han, Y.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. *Eur. J. Org. Chem.* **2008**, 1013. (e) Barluenga, J.; Trincado, M.; Rublio, E.; Gonzalez, J. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2406. (f) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (g) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (h) Barluenga, J.; Vazque-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (i) Yue, D.; Della, Ca. N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

(19) (a) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. (b) Hildebrandt, D.; Hüggenberg, H.; Kanthak, M.; Plöger, T.; Müller, I. M.; Dyker, G. *Chem. Commun.* **2006**, 2260. (c) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. (d) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *118*, 3100. (e) Feldman, K. S. *Tetrahedron Lett.* **1983**, *24*, 5585.

(20) Majumdar, K. C.; Sinha, B.; Ansary, I.; Chakravorty, S. *Synlett* **2010**, 1407.

(21) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347.

(22) Majumdar, K. C.; Ansary, I.; Sinha, B.; Chattopadhyay, B. *Synthesis* **2009**, 3593.

(23) CCDC 809665 contains the supplementary crystallographic data for **10a**.

(24) Liu, W.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609.