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α-Selective Allylation of Isatin Imines Using Metallic Barium

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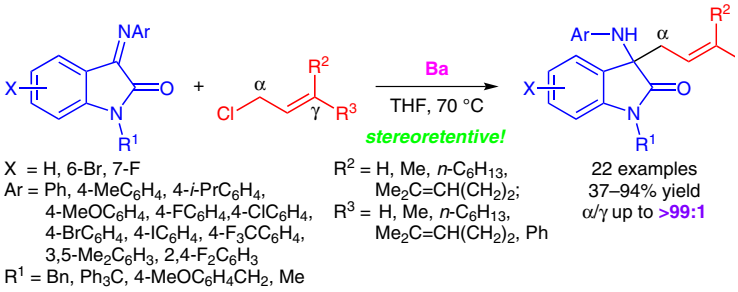

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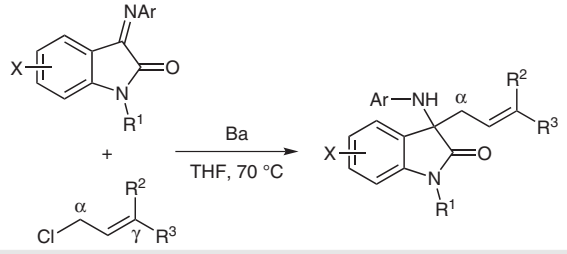
Abstract The Barbier-type allylation of isatin imines with allylic chlorides was achieved by using metallic barium as the promoter. Various α-allylated 3-amino-2-oxindoles were synthesized from the corresponding allylic chlorides and isatin imines. The double-bond geometry of allylic chlorides was retained throughout the reaction. An arylic bromide or iodide functionality of the products was robust to metalation under the optimum reaction conditions.

Key words allylation, allylic chlorides, 3-amino-2-oxindoles, barium, imines



Scheme 1 Barbier-type α-allylation of isatin imines using metallic barium

A 3-amino-2-oxindole structure is often seen in biologically active substances, such as CRTH2 receptor antagonists,[1] antituberculosis agents,[2] and so on.[3] Therefore, the development of useful methods for the synthesis of isatin derivatives possessing a nitrogen atom at the 3-position has attracted considerable interest among researchers of organic synthesis. One of the facile routes to the 3-amino-2-oxindole structure is the allylation of isatin imines.[4,5] Allylic indium reagents[4b] and allylic zinc reagents[4d] have been utilized for the transformation; however, these reagents show γ-regioselectivity and as far as we know, there is no example of the α-regioselective allylation of isatin imines. We report herein a metallic-barium-promoted Barbier-type α-allylation of isatin imines with allylic chlorides (Scheme 1).

Allylic barium reagents, which can be prepared from reactive barium (Rieke barium)[6] and allylic chlorides, are known to react α-regioselectively with diverse electrophiles.[7] We have previously reported that an α-selective allylation of azo compounds with allylic barium reagents occurs smoothly at –78 °C, yielding allylic hydrazines (α products). The double-bond geometry of the allylic barium reagents is retained throughout the reaction at low temperature.[8] A benzylation of azo compounds with benzylic chlorides has been also achieved by employing a Barbier-type method that involves the formation of benzylic barium species in situ in the presence of reactive barium as the low-valent metal, affording benzylic hydrazines.[9] We envisioned that if an allylic barium reagent could be generated from metallic barium[10] and the corresponding allylic halide under mild reaction conditions and displayed α-selectivity in the reaction with an isatin imine, the allylation would provide a practical synthetic procedure for α-allylated 3-amino-2-oxindoles. Thus, we first selected isatin imine **1a** and prenyl chloride (**2a**) as the electrophile and the precursor of allylic barium reagent, respectively, and attempted to carry out a Barbier-type reaction because of the simplicity of the experimental procedure. When a 2:1 mixture of prenyl chloride (**2a**, 2 equiv) and isatin imine **1a** (1 equiv) was exposed to metallic barium (2 equiv) in THF at room temperature for 12 hours, the reaction proceeded sluggishly and targeted prenylated 3-amino-2-oxindole **3aa** (α-adduct) was formed in 43% yield. The corresponding γ-adduct was not observed at all (Table 1, entry 1). The chemical yield was improved when the amounts of prenyl chloride (**2a**) and metallic barium were increased to four equivalents, respectively (Table 1, entry 2). Elevating the reaction

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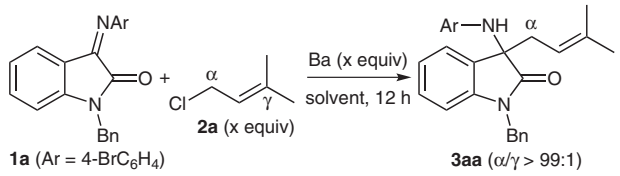
temperature to 70 °C also raised the reactivity (Table 1, entry 5) and the yield of **3aa** exceeded 80% when four equivalents of those chemicals were used in the reaction at 70 °C (Table 1, entry 6). Subsequently, we tested solvents other than THF (Table 1, entries 7–10) and found that THF was the most suitable solvent with regard to chemical yield (Table 1, entry 6). Diethyl ether was also a promising solvent (Table 1, entry 7); in contrast, dichloromethane and toluene gave unsatisfactory results, and the desired adduct **3aa** was not obtained at all in the reaction that used 1,4-dioxane as solvent (Table 1, entries 8–10).

Table 1 Optimization of Metallic-Barium-Promoted Barbier-Type Prenylation of Isatin Imine **1a**[a]



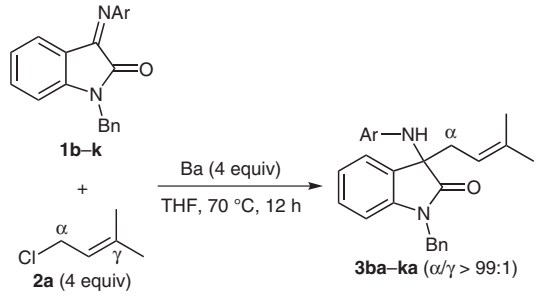
1a (Ar = 4-BrC$_6$H$_4$) **2a** (x equiv) **3aa** (α/γ > 99:1)

Entry	x (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	2	THF	r.t.	43
2	4	THF	r.t.	66
3	6	THF	r.t.	65
4	2	THF	40	55
5	2	THF	70	74
6	4	THF	70	86
7	4	Et_2O	70	56
8	4	CH_2Cl_2	70	4
9	4	toluene	70	8
10	4	1,4-dioxane	70	<1

[a] The Barbier-type reaction was carried out using isatin imine **1a** (1 equiv), metallic barium (x equiv), and prenyl chloride (**2a**, x equiv) in the specified solvent.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard.

With the optimum reaction conditions in hand, we examined the prenylation of isatin imines **1b**–**k** derived from various anilines and *N*-benzyl isatin (Table 2). High reactivities were observed for the reactions of isatin imines **1f** and **1g**, which have an electron-withdrawing group at the 4-position of the *N*-phenyl group (Table 2, entries 5 and 6). In contrast, isatin imines **1c**,**d**,**e**, which have an electron-donating group, afforded products **3ca**,**da**,**ea**, in higher yields than isatin imine **1b** derived from aniline (Table 2, entries 2–4 vs. entry 1). Employment of 4-trifluoromethylaniline-derived isatin imine **1i** caused a significant decrease in the yield (37%) of its product **3ia** probably due to low solubility of isatin imine **1i** in the reaction solvent (THF) and the concomitant reduction of the imine by metallic barium (Table 2, entry 8). Disubstituted aniline-derived isatin imines **1j** and **1k** furnished products in satisfactory yields (Table 2, entries 9 and 10).

Table 2 Metallic-Barium-Promoted Barbier-Type Prenylation of Various Isatin Imines **1b**–**k**[a]



Entry	**1** Ar	Product **3**	Yield (%)[b]
1	**1b** Ph	**3ba**	65
2	**1c** 4-MeC$_6$H$_4$	**3ca**	69
3	**1d** 4-*i*-PrC$_6$H$_4$	**3da**	82
4	**1e** 4-MeOC$_6$H$_4$	**3ea**	69
5	**1f** 4-FC$_6$H$_4$	**3fa**	82
6	**1g** 4-ClC$_6$H$_4$	**3ga**	93
7	**1h** 4-IC$_6$H$_4$	**3ha**	69
8	**1i** 4-F$_3$CC$_6$H$_4$	**3ia**	37
9	**1j** 3,5-Me$_2$C$_6$H$_3$	**3ja**	91
10	**1k** 2,4-F$_2$C$_6$H$_3$	**3ka**	77

[a] The Barbier-type reaction was carried out using isatin imines **1b**–**k** (1 equiv), metallic barium (4 equiv), and prenyl chloride (**2a**, 4 equiv) in dry THF at 70 °C for 12 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard.

We performed the metallic-barium-promoted Barbier-type prenylation of isatin imines **1l**–**p** derived from 4-bromoaniline and a diversely substituted isatin (Table 3). The effect of R^1 group at 1-position of isatin imines **1n**–**p** on the chemical yield was worthy of note: an electron-withdrawing group (Ph_3C) enhanced the electrophilicity of **1n** (Table 3, entry 3), whereas an electron-donating group (4-MeOC$_6$H$_4$CH$_2$) reduced the reactivity of **1o** (Table 3, entry 4). The Me group was also a suitable protective group for the amide nitrogen of isatin imine **1p** (Table 3, entry 5).

To investigate the *E*/*Z* stereoselectivity as well as the α-regioselectivity of the present α-allylation, we executed the metallic-barium-promoted Barbier-type reaction between isatin imine **1a** and a diverse range of allylic chlorides **2b**–**i** other than prenyl chloride (**2a**) under the optimum reaction conditions (Table 4). Not only γ-disubstituted allylic chlorides **2b** and **2c**, but also γ-monosubstituted allylic chlorides **2d**–**f** showed exclusive α selectivity (Table 4, entries 1–5). The γ isomer **4ag** was detected as a minor product in the reaction of *trans*-1-chloro-2-butene (**2g**, Table 4,

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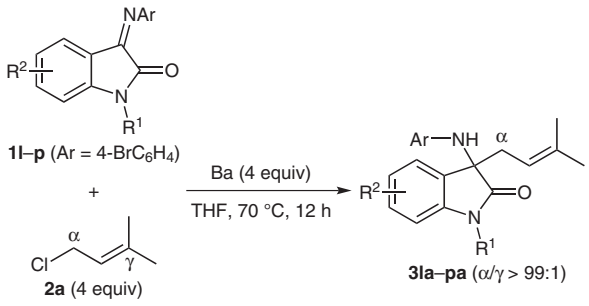
Table 3 Metallic-Barium-Promoted Barbier-Type Prenylation of Various Isatin Imines **1l**–**p**[a]



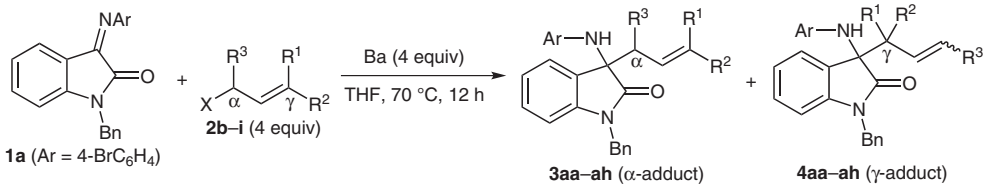
Entry	R^1	**1** R^2	Product **3**	Yield (%)[b]
1	Bn	**1l** 6-Br	**3la**	76
2	Bn	**1m** 7-F	**3ma**	83
3	Ph_3C	**1n** H	**3na**	94
4	4-$MeOC_6H_4CH_2$	**1o** H	**3oa**	76
5	Me	**1p** H	**3pa**	89

[a] The Barbier-type reaction was carried out using isatin imines **1l**–**p** (1 equiv), metallic barium (4 equiv), and prenyl chloride (**2a**, 4 equiv) in dry THF at 70 °C for 12 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard.

entry 6). The geometric purity of α products **3ab**–**ag** shows that the geometric isomerization (*E* to *Z* or *Z* to *E*) of allylic chlorides **2b**–**g** can be suppressed to a large extent during the reaction (Table 4, entries 1–6). Therefore, *E*-enriched α-allylated 3-amino-2-oxindoles **3ab**,**ad**,**af**,**ag** were selectively obtained from *E*-allylic chlorides **2b**,**d**,**f**,**g** (Table 4, entries 1, 3, 5, and 6), whereas *Z*-allylic chlorides **2c** and **2e** provided the *Z* isomers of α products **3ac** and **3ae** predominantly (Table 4, entries 2 and 4). Although the reactivity of a secondary allylic chloride was also tested in the present α-allylation procedure for 3-amino-2-oxindoles, the α/γ ratio given by the reaction of 3-chloro-1-butene (**2h**, Table 4, entry 7) was opposite to that of *trans*-1-chloro-2-butene (**2g**, Table 4, entry 6). This reveals that the in situ generating secondary allylic barium reagent rapidly isomerizes to the corresponding primary allylic barium reagent before its reaction with isatin imine **1a** at 70 °C. Use of prenyl bromide (**2i**) instead of prenyl chloride (**2a**) resulted in a considerable reduction in yield of **3aa** because of the Wurtz coupling (homocoupling) of the allylic bromide (Table 4, entry 8).

Then, we investigated the tolerance of the arylic halide functionality in the metallic-barium-promoted Barbier-type reaction, in comparison with that in the Rieke barium (Ba*)-promoted reaction (Table 5). In the case of isatin imine **1a** (X = Br), target product **3aa** was formed exclusively and corresponding reduced product **3ba** was not detected at all in the metallic-barium-promoted reaction. In con-

Table 4 Metallic-Barium-Promoted Barbier-Type α-Selective Allylation of Isatin Imine **1a** with Various Allylic Halides **2b**–**i**[a]



Entry	R^1	R^2	R^3	**2** X	Product	Yield (%)[b]	α/γ[c]	*E*/*Z*[c]
1	Me	$Me_2C{=}CH(CH_2)_2$	H	**2b** Cl[d]	**3ab** + **4ab**	80	>99:1	96:4
2	$Me_2C{=}CH(CH_2)_2$	Me	H	**2c** Cl[e]	**3ac** + **4ac**[f]	87	>99:1	3:97
3	H	*n*-C_6H_{13}	H	**2d** Cl[d]	**3ad** + **4ad**	92	>99:1	98:2
4	*n*-C_6H_{13}	H	H	**2e** Cl[e]	**3ae** + **4ae**[g]	79	>99:1	5:95
5	H	Ph	H	**2f** Cl[d]	**3af** + **4af**	61	>99:1	>99:1
6	H	Me	H	**2g** Cl[h]	**3ag** + **4ag**	69	94:6	87:13
7	H	H	Me	**2h** Cl	**3ah** + **4ah**[i]	42	17:83	72:28
8	Me	Me	H	**2i** Br	**3aa** + **4aa**	40	>99:1	–

[a] The Barbier-type reaction was carried out using isatin imine **1a** (1 equiv), metallic barium (4 equiv), and allylic halides **2b**–**i** (4 equiv) in dry THF at 70 °C for 12 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard.
[c] Determined by ^{1}H NMR analysis and HPLC analysis.
[d] *E*/*Z* = >99:1.
[e] *E*/*Z* = <1:99.
[f] **4ac** = **4ab**.
[g] **4ae** = **4ad**.
[h] *E*/*Z* = 85:15; 25% of 3-chloro-1-butene (**2h**) was included.
[i] **3ah** = **4ag**; **4ah** = **3ag**.

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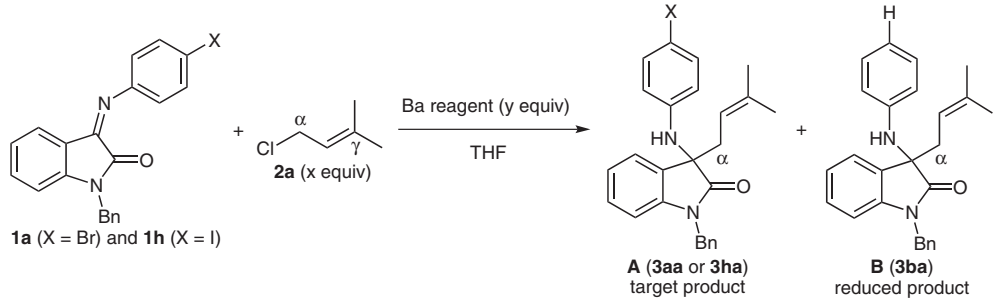
Table 5 Comparison of Metallic Barium with Rieke Barium in the Barbier-Type Prenylation of Isatin Imines **1a** and **1h** Possessing an Arylic Halide (X = Br, I)[a]



Entry	x	Barium reagent	y	**1** X	Temp (°C)	Time (h)	**A**/**B**[b]	Yield (%)[c]
1	4	metallic barium	4	**1a** Br	70	12	>99:1	86
2	2	Ba*	2.2	**1a** Br	−78	2	84:16	33
3	4	metallic barium	4	**1h** I	70	12	94:6	69
4	2	Ba*	2.2	**1h** I	−78	2	50:50	23

[a] The Barbier-type reaction was carried out using isatin imines **1a** and **1h** (1 equiv), metallic barium (4 equiv) or reactive barium (2.2 equiv), and prenyl chloride (**2a**, 4 or 2 equiv) in dry THF.
[b] Determined by ^{1}H NMR analysis.
[c] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard.

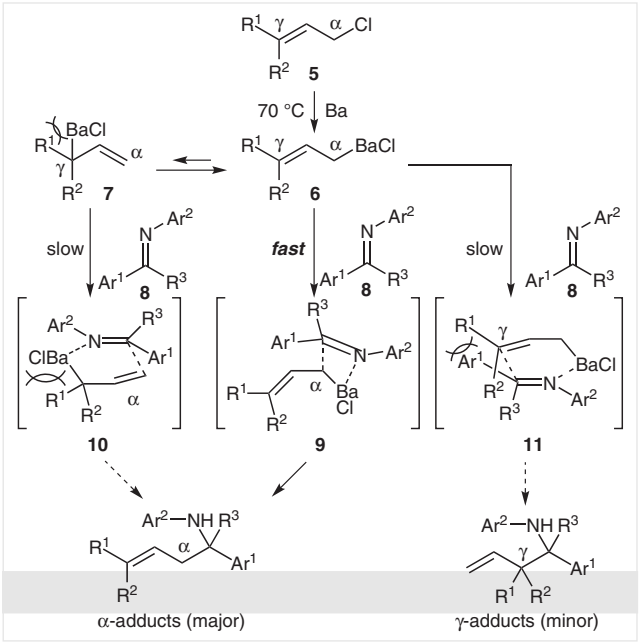
trast, **3ba** was isolated as a minor product in the Rieke barium (Ba*)-promoted reaction (Table 5, compare entry 1 with entry 2). Moreover, a significant difference between the two procedures in their reactivity toward arylic iodide was observed in the reaction of isatin imine **1h**.

A proposed reaction mechanism is illustrated in Scheme 2. Two pathways are possible for α-allylated homoallylic amines (α-adducts). An allylic barium reagent generated from allylic chloride **5** and metallic barium is supposed to be present in equilibrium between α isomer **6** and γ-isomer **7**. Thus, α-adducts are accessible from both isomers **6** and **7** by treating them with imine **8** via transition-state model **9** or **10**, although the latter structure **10** is less favorable due to steric bulkiness of allylic barium species **7**. Meanwhile, γ-allylated homoallylic amines (γ-adducts) can be formed from **6** by an S_E2'-type reaction of **6** with imine **8** through six-membered cyclic transition state **11**. However, **11** is unstable due to steric repulsion between an allylic alkyl group of the barium reagent and an aryl group of the imine. As a consequence, allylic barium species **6** is anticipated to react preferentially at the α carbon with imine **8** via four-membered cyclic transition state **9**,[7b,c,11] yielding the α-adduct without *E*/*Z* stereoisomerization of starting chloride **5**.

In conclusion, we have achieved a novel Barbier-type α-allylation of isatin imines with allylic barium reagents that are prepared from allylic chlorides and metallic barium. The employment of metallic barium as the source of allylic barium reagents has enabled the synthesis of various α-allylated 3-amino-2-oxindoles in a regio- and stereoselective manner.[12] Further studies of related reactions promoted by metallic barium are under way.

Acknowledgment

We gratefully acknowledge the financial support from the Iodine Research Project in Chiba University headed by Professor Hideo Togo.



Scheme 2 Proposed reaction pathways to α- and γ-adducts

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561450.

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(11) Exactly what causes allylic barium reagent **6** to react selectively at the α-carbon with imine **8** is not clear; however, the unusually long barium–carbon bond (2.76–2.88 Å) might prevent the formation of a six-membered cyclic transition-state model **11** leading to the γ-adduct, see: Kaupp, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1992**, *114*, 491.

(12) **Typical Experimental Procedure for α-Selective Allylation: Synthesis of 1-Benzyl-3-[(4-bromophenyl)amino]-3-(3-methylbut-2-en-1-yl)indolin-2-one (3aa, Table 1, Entry 6; Table 4, Entry 8; Table 5, Entry 1)**

Freshly cut barium (small pieces, 137.3 mg, 1.0 mmol) was placed in a Schlenk tube (50 mL) under an argon atmosphere and covered with dry THF (1 mL). The mixture was ultrasonicated for 30 min, and THF was removed through a cannula under an argon stream. The resulting barium pieces were vigorously stirred under reduced pressure until they were pulverized. Then, a solution of prenyl chloride (**2a**, 0.112 mL, 1.0 mmol) and isatin imine **1a** (97.8 mg, 0.25 mmol) in THF (4 mL) was added to the resulting barium powder at room temperature under an argon atmosphere. After being heated to 70 °C, the mixture was stirred for 12 h at this temperature and concentrated in vacuo after filtration through a Celite pad. The residual crude product was purified by column chromatography on silica gel (hexane–EtOAc, 9:1) to afford 3-prenylated 3-amino-2-oxindole **3aa**; mp 136–137 °C. The chemical yield (86%) was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as the internal standard.

Spectral Data of the Product

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.31 (m, 7 H, ArH), 6.98–7.04 (m, 3 H, ArH), 6.78 (d, 1 H, *J* = 7.9 Hz, ArH), 6.05–6.08 (m, 2 H, ArH), 5.05 (tt, 1 H, *J* = 1.1, 5.7 Hz, CH), 4.96 (d, 1 H, *J* = 15.4 Hz, one H of CH_2), 4.87 (d, 1 H, *J* = 15.4 Hz, one H of CH_2), 4.40 (br, 1 H, NH), 2.62–2.73 (m, 2 H, CH_2), 1.67 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 144.3, 141.9, 138.1, 135.6, 131.7 (2 C), 129.5, 129.0, 128.7 (2 C), 127.7, 127.6 (2 C), 123.8, 122.9, 117.0 (2 C), 115.4, 111.1, 109.6, 64.4, 44.1, 39.0, 26.0, 18.1. IR (neat): 3328, 2917, 1700, 1592, 1486, 1369, 1320, 812, 754, 731 cm^{-1}. ESI-MS: *m/z* calcd for $[C_{26}H_{25}ON_2BrNa]^+$ [M + Na]$^+$: 483.1042; found: 483.1036.

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