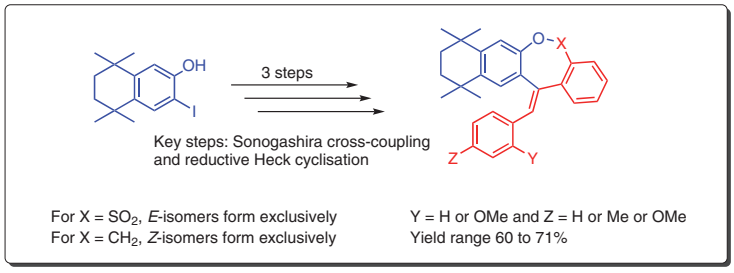
Palladium-Mediated Reductive Heck Cyclization for the Synthesis of Fused Retinoid Derivatives

Trisha Mitra[a]
Soumen Joardar[a]
Santanu Chakravorty*[b]
Manoj Majumdar[b]
Mrinalkanti Kundu*[c]
Brindaban Roy*[a]

[a] University of Kalyani, Kalyani, Nadia, West Bengal 741235, India
broybs@rediffmail.com
[b] Mathabhanga College, Mathabhanga, West Bengal 736146, India
santanuorg34@gmail.com
[c] TCG Lifescience Pvt. Ltd., BN-7, Sector V, Salt Lake City, Kolkata 700091, India
mrinal.kundu@tcgls.com



Received: 17.12.2022
Accepted after revision: 30.01.2023
Published online: 30.01.2023 (Accepted Manuscript), 15.02.2023 (Version of Record)
DOI: 10.1055/a-2022-3227; Art ID: SO-2022-12-0077-OP

Crowd-Reviewed

Abstract Linearly fused retinoid derivatives have been synthesized via a straightforward pathway using a palladium-catalyzed reductive Heck cyclization strategy. The synthesis involved a four-step linear approach utilizing iodination, sulfonylation or benzylation or esterification, palladium-catalyzed Sonogashira cross-coupling and palladium-mediated reductive Heck cyclization.

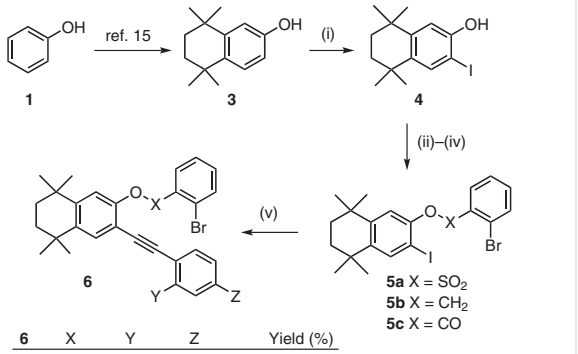
Key words retinoids, Heck, Sonogashira, cross-coupling

Retinoids regulate various biological functions such as cell differentiation, proliferation, and embryogenesis in vertebrates.[1–3] In the fields of dermatology and oncology, retinoids also have potential chemo-preventive and therapeutic applications.[4] Retinoic acid has significant therapeutic effects in acute promyelocytic leukemia. Furthermore, the inhibitory effects of retinoids on IL-6 production suggest the potential utility of retinoids in various IL-6-related diseases, including psoriasis and rheumatoid arthritis,[5] and some synthetic retinoids have also been successfully used to treat psoriasis.[6] However, retinoid therapy is still limited by a wide range of undesirable side-effects. Over the years, various approaches have been developed to design and synthesize new types of retinoids to minimize the side effects of potential drugs used in retinoids therapy.[7] However, most of the approaches concentrate on the synthesis of linear retinoids derivatives.[8] In 1997, Kagechika et al.[9] designed, synthesized, and measured retinoid-regulatory activities of various dibenzodiazepines and related compounds. Later, Li et al.[10] synthesized four novel classes of retinoid antagonists and evaluated their inhibitory effects on AP-1 activity and retinoic acid-induced apoptosis in human breast cancer cells. All the compounds they synthesized contain a retinoid ring fused linearly with benzo-fused or naphtho-fused medium-sized heterocycles. Recently, Huang et al.[11] synthesized a similar type of ring system by using a palladium-catalyzed [4+3] annulation procedure. Yet, there have been very limited efficient approaches to synthesize linearly fused retinoid derivatives that may be useful for retinoid therapy. Recently, direct cyclization methods using transition-metal catalysts have been introduced to produce seven-, eight-, and nine-membered rings using a variety of gold, indium, copper, and other catalysts.[12] Of these transition-metal-catalyzed reactions, the Pd-catalyzed transformation is widely used in the cyclic carbo-palladation of alkynes for the rapid construction of four- to nine-membered rings. Van der Eycken, Majumdar, Joardar, Mondal, Ghosh and Balalaie prepared a variety of seven-membered benzazepines, azepines, and benzoxepines, as well as eight-membered dibenzazocinones, dibenzoxocines, benzodiazepines, and azocininoindoles.[13,14]

Keeping in mind the wide utility of retinoids, and based upon our long experience in the use of metal-catalyzed cyclization to synthesize medium-ring heterocycles, herein, we report the synthesis of linearly fused retinoid derivatives.[14]

Starting with phenol, precursors for the synthesis of a seven-membered heterocyclic framework **6a–j**, were synthesized in four steps by using the method shown in Scheme 1. Compound **3** was prepared using Friedel–Crafts alkylation strategy, and was converted into its *ortho*-iodo derivative **4** by reacting with *N*-iodo succinimide in DMF. The phenolic-hydroxy group of compound **4** was subse-

quently converted into either the 2-bromo benzene sulfonyl derivative **5a**, 2-bromo-benzyl derivatives **5b**, or ester derivative **5c**, by treatment with either 2-bromobenzne sulphonyl chloride in DCM in the presence of NEt_3 as a base and DMAP as a catalyst, or by refluxing with 2-bromo benzyl chloride in acetonitrile in the presence of K_2CO_3 as a base, or by reacting with 2-bromobenzoyl chloride in the presence of NEt_3 as a base and DMAP as a catalyst by stirring at room temperature for 2 h. Compounds **5a–c** were then subjected to Sonogashira cross-coupling reaction with phenyl acetylenes using $Pd(PPh_3)_2Cl_2$ as catalyst and copper(I) iodide as a co-catalyst in THF-NEt_3 at room temperature for 12 h to obtain the required precursors **6a–j** of reductive Heck cyclization.



6	X	Y	Z	Yield (%)
a	SO_2	H	H	75
b	SO_2	H	Me	80
c	SO_2	OMe	H	79
d	SO_2	H	OMe	83
e	CH_2	H	H	81
f	CH_2	H	Me	79
g	CH_2	OMe	H	80
h	CH_2	H	OMe	82
i	CO	H	H	80
j	CO	OMe	H	74

Scheme 1 Synthesis of precursors. *Reagents and conditions*: (i) NIS, DMF, r.t., 2 h; (ii) 2-bromobenzene-1-sulfonyl chloride, Et_3N, DMAP (cat.), DCM, 0 °C to r.t., 2 h; (iii) 2-bromobenzyl bromide, K_2CO_3, MeCN, reflux, 16 h; (iv) 2-bromobenzoyl chloride, DCM, r.t., 2 h; (v) phenyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, r.t., 12 h.

A systematic study was performed, varying the catalysts, solvents, temperature, and time period on our model precursor **6d**, to optimize the yield of the reductive Heck reaction product (Scheme 2, product **7**). Catalysts $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $PdCl_2dppf$, $Pd(OAC)_2$, PPh_3, $Pd(dba)_3$, PPh_3 with reducing agents (sodium formate) in DMF and water or 1,4-dioxane and water mixture gave poor to moderate yield of the product (30–45%, Table 1, entries 1, 3, 4, and 17). Increasing the reaction time or temperature did not improve the yield of the product, respectively (entries 2 and 5). Changing the solvent pairs either to THF/water, acetontrile/water, or toluene/water using catalyst $Pd(PPh_3)_4$ and sodium formate as reducing agent did not improve the yield, as of our expectation (entries 9–11). It was noted that when the reaction was carried out in DMF/H_2O (7:3) mixture in the presence of $Pd(PPh_3)_4$ using sodium formate as reducing agent under conventional heating conditions (100 °C) for 1 h, the best result (71%) was obtained (entry 16). The same reaction, when carried out above or below the optimal temperature or running for a longer period, reduced yields of the product were obtained (entries 13–15). The reaction failed to produce any product in the absence of water (entry 12). The results are summarized in Table 1.

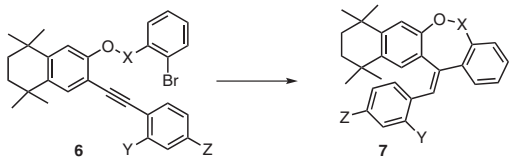
Table 1 Optimization of the Reaction Conditions for the Synthesis of Seven-Membered Heterocycles[a]

Entry	Solvent	Catalyst	Time (h)	Temp. (°C)	Yield (%)
1	DMF/H_2O	$Pd_2(dba)_3$	1	100	45
2	DMF/H_2O	$Pd_2(dba)_3$	1.5	100	40
3	DMF/H_2O	$Pd_2(dba)_3$, PPh_3	1	100	45
4	1,4-dioxane/H_2O	$Pd_2(dba)_3$	1	100	35
5	DMF/H_2O	$Pd_2(dba)_3$	1	120	30
6	DMF/H_2O	$Pd(PPh_3)_2Cl_2$	1	100	35
7	DMF/H_2O	$Pd(OAc)_2$	1	100	30
8	DMF/H_2O	$Pd(OAc)_2$, PPh_3	1	100	35
9	THF/H_2O	$Pd(PPh_3)_4$	1	70	35
10	MeCN/H_2O	$Pd(PPh_3)_4$	1	80	30
11	toluene/H_2O	$Pd(PPh_3)_4$	1	100	25
12	DMF	$Pd(PPh_3)_4$	1	100	0
13	DMF/H_2O	$Pd(PPh_3)_4$	1	120	50[b]
14	DMF/H_2O	$Pd(PPh_3)_4$	1	80	20
15	DMF/H_2O	$Pd(PPh_3)_4$	1.5	100	60[b]
16	DMF/H_2O	$Pd(PPh_3)_4$	1	100	71[c]
17	DMF/H_2O	$PdCl_2dppf$	1	100	42

[a] All the reactions were carried out using 3 mol% of catalyst. Sodium formate was used as a reducing agent in all cases.
[b] Decomposition may occur at higher temperature and by running the reaction for a longer time at optimum temperature.
[c] Mixed solvent was used in 7:3 ratio.

To explore the generality of the protocol, we applied the same methodology to other substrates, and, in all cases (except **6i** and **6j**), the desired *exo*-products were obtained in moderate to good yields (Scheme 2). Attempted cyclization using the optimized protocol of **6i–j** did not afford the expected cyclized products **7i** and **7j**. Lowering the temperature and varying the catalysts and solvents did not have a fruitful outcome. Probably, hydrolysis of the starting materials took place under the reaction conditions.

Product stereochemistry was confirmed by NMR and NOE studies. The stereochemistry of **7f** was thoroughly investigated by NOE NMR spectroscopic analysis (Figure 1). The resulting exocyclic double bond configurations were assigned based on NOE effects between the vinyl proton of



6, 7	X	Y	Z	Yield (%) of 7
a	SO_2	H	H	65%
b	SO_2	H	Me	68%
c	SO_2	OMe	H	70%
d	SO_2	H	OMe	71%
e	CH_2	H	H	67%
f	CH_2	H	Me	60%
g	CH_2	OMe	H	60%
h	CH_2	H	OMe	62%
i	CO	H	H	not obtained
j	CO	OMe	H	not obtained

Scheme 2 Cyclization protocols. *Reagents and conditions*: sodium formate, $Pd(PPh_3)_4$, DMF, H_2O (7:3), 100 °C, 1 h.

the double bond and the adjacent proton of the aryl ring. The presence of strong NOE cross-peaks between H8-H1 and H8-H10 indicates that H8 is oriented in such a way that it can only interact with H10 and H-1, thus the structure is established.

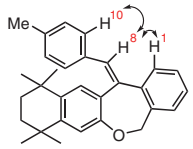
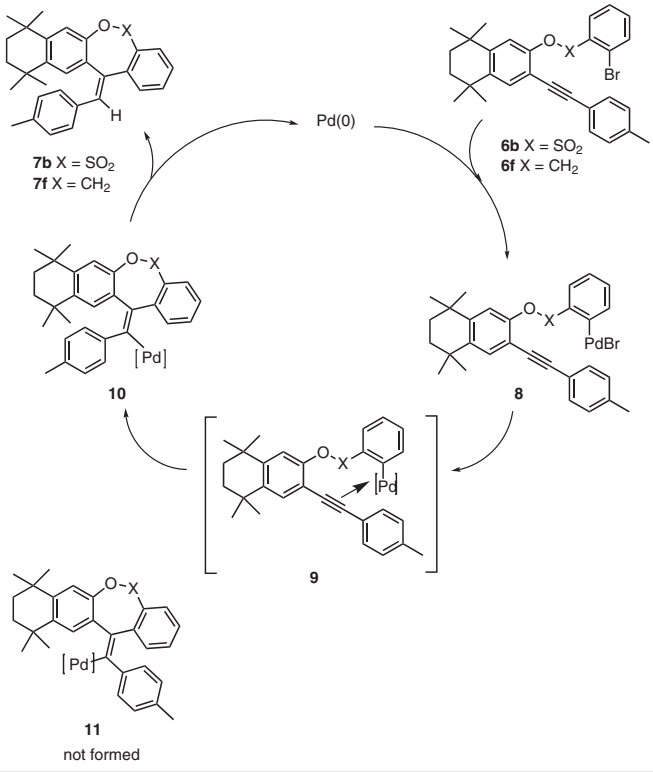


Figure 1 Characteristic NOE correlations for structure **7f**

The formation of regioselective *exo*-cyclization products during Heck reductive cyclization can be streamlined via mechanisms as shown in Scheme 3. The regioselective formation of the product can be explained by considering that intermediate **11** is less stable than intermediate **10** due to steric interactions between the bulky ligands on palladium and the two methyl groups of the dihydro-naphthalene moiety.

In conclusion, we have developed an efficient method using Sonogashira cross-coupling followed by Pd(0)-catalyzed reductive Heck cyclization methodology to synthesize linearly fused retinoid derivatives. The reaction afforded moderate to good yields of retinoids having oxepane and seven-membered sulfone fused systems; however, the reaction to produce seven-membered lactone fused retinoid derivatives was unsuccessful. These Heck types of cyclizations are regioselective.



Scheme 3 Probable mechanism of cyclization

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros, and Rankem, and, unless otherwise noted, were used without further purification. Melting points were determined in open capillary tubes with a Reichert (285980) (Austria) melting-point apparatus and are uncorrected. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, LCMS, HRMS, and IR spectroscopy. ^{1}H NMR, ^{13}C NMR spectra were recorded with Bruker AV 300, Bruker AV 400, and Bruker AV 500 spectrometers. The ^{1}H NMR, ^{13}C NMR chemical shifts are reported relative to the center of solvent resonance ($CDCl_3$: 7.25 (^{1}H), 77.0 (^{13}C)). Chemical shifts are reported in δ units (ppm); *J* values given in Hz; splitting patterns δ are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Analytical thin-layer chromatography (TLC) was performed on precoated 0.2 mm silica gel 60F-254 (E. Merck), and the spots were visualized with UV irradiation and using an iodine chamber. Column chromatography was performed on silica gel (100–200 mesh, and 230–400 mesh). Elemental analyses (C, H, and N) were carried out with a Perkin–Elmer 240C analyzer. A complete assignment of the ^{1}H NMR, ^{13}C NMR is given. EI mass spectra were recorded with an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded with at 6700 (Thermo ELECTRO CORPORATION) as KBr plates or liquid films. LCMS were performed with an Alliance 2695 Separations Module (Waters, Milford, MA, USA) coupled to a Micro mass Quattro triple quadruple mass spectrometer (Micro mass, Manchester, UK) with Mass Lynx 4.0 software using Symmetry® -C18, 5 µm, 2.1 × 100 mm column. All yields reported referring to the isolated yield.

Preparation of Compounds 3 and 4

Compound **3** was prepared from phenol according to a reported procedure.[15]

To a stirred solution of compound **3** (2.0 g, 9.7 mmol), in DMF (20 mL) was added *N*-iodosuccinimide (2.40 g, 10.67 mmol) and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was then poured into water (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layer was further washed with water (3 × 50 mL). The organic layer was dried using Na_2SO_4. The product was purified by column chromatography (20% EtOAc/hexane) to give compound **4**.

Yield: 2.5 g (7.6 mmol, 78%); off-white solid; R_f 0.55; mp 110–112 °C.

IR (KBr): 3350, 1621 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 6.91 (s, 1 H), 5.01 (s, 1 H), 1.63 (bs, 4 H), 1.22 (d, 12 H, *J* = 4.5 Hz).

Preparation of Compound 5a

To a stirred solution of 3-iodo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**4**) (500 mg,1.51 mmol), in DCM (10 mL) was added Et_3N (0.6 mL,4.53 mmol) and 2-bromobenzene-1-sulfonyl chloride (386 mg,1.51 mmol) at 0 °C and DMAP (18 mg, 0.151 mmol). The reaction mixture was stirred for 2 h. The product was purified by column chromatography (20% EtOAc/hexane) to yield compound **5a**.

Yield: 720 mg (86%); off-white solid; mp 129–131 °C; R_f 0.50.

IR: (KBr): 2958, 1566, 1475 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 6.6 Hz, 1 H), 7.86 (d, *J* = 7.72 Hz, 1 H), 7.65 (s, 1 H), 7.44–7.51 (m, 2 H), 6.69 (s, 1 H), 1.53 (s, 4 H), 1.23 (s, 6 H), 1.01 (s, 6 H).

GCMS: *m*/*z* calcd for $C_{20}H_{22}BrIO_3S$: 547.9; found: 548.0.

Preparation of Compound 5b

A stirred solution of 3-iodo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**4**) (500 mg, 1.51 mmol), 2-bromobenzyl bromide (377 mg, 1.51 mmol) and K_2CO_3 (417 mg, 3.02 mmol) in MeCN (5 mL) was heated to reflux for 16 h. The reaction mixture was cooled to r.t., filtered, and concentrated. The resultant residue was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford **5b**.

Yield: 680 mg (90%); white solid; mp 113–115 °C; R_f 0.50.

IR (KBr): 2953, 1585, 1483 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.64 Hz, 1 H), 7.65 (s, 1 H), 7.55 (d, *J* = 7.84 Hz, 1 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 6.71 (s, 1 H), 5.15 (s, 2 H), 1.62 (s, 4 H), 1.23 (s, 12 H).

Preparation of Compound 5c

To a stirred solution of 3-iodo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**4**) (500 mg,1.51 mmol), in DCM (10 mL) was added Et_3N (0.6 mL,4.53 mmol) and 2-bromobenzoyl chloride (365 mg,1.66 mmol) at 0 °C and DMAP (18 mg, 0.151 mmol). The reaction mixture was stirred for 2 h. The product was purified by column chromatography (20% EtOAc/hexane) to yield compound **6c**.

Yield: 680 mg (87%); off-white solid; mp 119–121 °C; R_f 0.45.

IR (KBr): 2957, 1748, 1585 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 1.8, 7.56 Hz, 1 H), 7.73 (d, *J* = 7.88 Hz, 1 H), 7.71 (s, 1 H), 7.38–7.47 (m, 2 H), 7.13 (s, 1 H), 1.55 (s, 4 H), 1.26 (s, 12 H).

Preparation of Precursors 6a–j; Typical Procedure

To a stirred solution of compound **5a** (297 mg, 0.54 mmol, 1 equiv) in anhydrous THF (5 mL) was added Et_3N (2 mL) and the reaction mixture was degassed with argon for 5 min. Catalyst $Pd(PPh_3)_2Cl_2$ (19 mg, 5 mol%) and co-catalyst CuI (12 mg, 12 mol%) were then added to the reaction mixture and stirred for another 5 min. Phenyl acetylene derivative (0.06 mL, 0.59 mmol, 1.1 equiv) was then added dropwise and the reaction mixture was stirred for 12 h at r.t. under argon atmosphere. Most of the solvent and Et_3N were removed under reduced pressure and the residue was subjected to silica gel chromatography (6–10% EtOAc/hexane) to afford compound **6a** (75%) as a pale-yellow semi-solid. Compounds **6b**–**h** were prepared similarly.

Compound 6a

Yield: 213 mg (75%); pale-yellow semi-solid; R_f 0.55.

IR (KBr): 2961, 2221, 1498, 1451, 1383 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.00 (d, *J* = 6.8 Hz, 1 H), 7.70 (d, *J* = 7.04 Hz, 1 H), 7.43–7.51 (m, 3 H), 7.31–7.38 (m, 5 H), 6.81 (s, 1 H), 1.53 (s, 4 H), 1.21 (s, 6 H), 1.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 144.1, 136.6, 135.7, 134.6, 132.5, 131.9, 131.7, 128.3, 128.1, 127.4, 123.0, 121.4, 120.3, 115.2, 93.3, 84.3, 34.7, 34.5, 34.1, 31.7, 31.4, 29.7.

Compound 6b

Yield: 234 mg (80%); pale-yellow semi-solid; R_f 0.50.

IR (KBr): 2958, 2221, 1498, 1451, 1383 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 2.4, 7.16 Hz, 1 H), 7.71–7.73 (m, 1 H), 7.41 (s, 1 H), 7.33–7.39 (m, 4 H), 7.10 (d, *J* = 7.8 Hz, 2 H), 6.81 (s, 1 H), 2.35 (s, 3 H), 1.61 (s, 4 H), 1.24 (s, 6 H), 1.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 147.0, 144.1, 138.5, 136.6, 135.7, 134.6, 132.5, 131.9, 131.7, 128.9, 127.5, 121.4, 120.3, 119.9, 115.5, 93.6, 83.7, 34.7, 34.5, 34.1, 31.7, 31.4, 21.6.

GCMS: *m*/*z* calcd for $C_{29}H_{29}BrO_3S$: 536.1; found: 536.0.

Compound 6c

Yield: 238 mg (79%); pale-yellow semi-solid; R_f 0.50.

IR (KBr): 2961, 2220, 1602, 1571, 1514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (dd, *J* = 2.4, 7.52 Hz, 1 H), 7.70–7.72 (m, 1 H), 7.46 (s, 1 H), 7.41 (dd, *J* = 1.44, 7.52 Hz, 1 H), 7.26–7.37 (m, 3 H), 6.85–6.91 (m, 2 H), 6.75 (s, 1 H), 3.89 (s, 3 H), 1.58 (s, 4 H), 1.28 (s, 6 H), 1.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 147.2, 146.8, 143.9, 136.7, 135.6, 134.4, 133.8, 132.5, 131.9, 129.8, 127.3, 121.3, 120.3, 120.0, 115.6, 112.3, 110.5, 89.9, 88.2, 55.7, 34.7, 34.4, 34.0, 31.6, 31.3.

LCMS: *m*/*z* calcd for $C_{29}H_{29}BrO_4S$: 552.9; found: 570.1 [M$^+$+18]

Compound 6d

Yield: 250 mg (83%); pale-yellow semi-solid; R_f 0.55.

IR (KBr): 2961, 2219, 1571, 1513 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.68 Hz, 1 H), 7.71 (d, *J* = 7.4 Hz, 1 H), 7.35–7.40 (m, 5 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.78 (s, 1 H), 3.82 (s, 3 H), 1.61 (s, 4 H), 1.23 (s, 6 H), 1.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.1, 146.8, 144.0, 136.6, 135.7, 134.5, 133.2, 132.4, 131.7, 127.4, 121.4, 120.3, 115.6, 115.2, 113.8, 93.4, 83.0, 55.3, 34.7, 34.4, 34.1, 31.7, 31.4.

LCMS: *m*/*z* [M + 1] calcd for $C_{29}H_{29}BrO_4S$: 553.09; found: 553.0.

Compound 6e

Yield: 20 mg (81%); pale-yellow semi-solid; R_f 0.45.

IR (KBr): 2959, 2212, 1595, 1504 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.68 (t, *J* = 8.52 Hz, 2 H), 7.36–7.48 (m, 7 H), 7.30–7.33 (m, 1 H), 6.96 (s, 1 H), 5.24 (s, 2 H), 1.62 (s, 4 H), 1.23 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 149.0, 147.5, 143.0, 134.7, 133.2, 132.3, 131.5, 131.1, 128.2, 127.2, 123.1, 122.6, 119.9, 114.3, 93.2, 84.9, 34.9, 34.7, 34.1, 31.9, 31.7.

Compound 6f

Yield: 231 mg (79%); pale-yellow semi-solid; R_f 0.55.

IR (KBr): 2959, 1607, 1571, 1508 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.67 (t, *J* = 8.64 Hz, 2 H), 7.28–7.44 (m, 5 H), 7.20 (d, *J* = 7.92 Hz, 2 H), 6.97 (s, 1 H), 5.23 (s, 2 H), 2.32 (s, 3 H), 1.61 (s, 4 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 146.9, 137.9, 137.8, 136.8, 132.2, 131.4, 129.0, 128.8, 128.7, 128.6, 127.5, 121.6, 120.8, 111.1, 111.0, 92.7, 85.6, 69.8, 35.0, 34.9, 34.7, 33.7, 31.8, 31.6, 21.5

GCMS: *m*/*z* calcd for $C_{30}H_{31}BrO$: 486.1; found: 486.1.

Compound 6g

Yield: 241 mg (80%); pale-yellow semi-solid; R_f 0.45.

IR (KBr): 2959, 1607, 1571, 1508 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.73 (d, *J* = 6.68 Hz, 1 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.29–7.42 (m, 4 H), 7.05 (d, *J* = 8.32 Hz, 1 H), 6.97 (s, 1 H), 6.93 (d, *J* = 7.32 Hz, 1 H), 5.23 (s, 2 H), 3.78 (s, 3 H), 1.62 (s, 4 H), 1.23 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 156.4, 147.0, 137.9, 136.9, 133.5, 132.1, 131.6, 129.3, 128.9, 128.8, 127.5, 121.6, 120.4, 111.2, 111.1, 110.7, 90.3, 88.9, 69.8, 55.8, 35.0, 34.9, 34.7, 33.7, 31.8, 31.7.

GCMS: *m*/*z* calcd for $C_{30}H_{31}BrO_2$: 502.1; found: 502.1.

Compound 6h

Yield: 247 mg (82%); pale-yellow semi-solid; R_f 0.55.

IR: (KBr): 2960, 2219, 607, 1571, 1508 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (t, *J* = 8.52 Hz, 2 H), 7.38–7.45 (m, 4 H), 7.28 (t, *J* = 7.72 Hz, 1 H), 6.98 (s, 1 H), 6.96 (s, 2 H), 5.23 (s, 2 H), 3.78 (s, 3 H), 1.61 (s, 4 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 156.3, 146.8, 137.9, 136.8, 132.9, 132.2, 131.3, 128.9, 128.7, 127.5, 121.6, 116.0, 113.9, 111.2, 111.0, 92.5, 84.9, 69.9, 55.3, 34.99, 34.97, 34.7, 33.7, 31.8, 31.6.

Compound 6i

Yield: 241 mg (80%); pale-yellow semi solid; R_f 0.50.

IR (KBr): 2952, 2211, 1750, 1591 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18–8.19 (m, 1 H), 7.85–7.86 (m, 1 H), 7.60–7.63 (m, 3 H), 7.33–7.38 (m, 6 H), 1.63 (s, 4 H), 1.30 (s, 6 H), 1.27 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 148.9, 147.5, 142.9, 134.6, 133.1, 132.3, 131.5, 131.4, 131.0, 128.2, 127.2, 123.1, 122.6, 119.8, 114.2, 93.1, 84.9, 114.3, 34.8, 34.7, 34.6, 34.07, 31.8, 31.6.

GCMS: *m*/*z* calcd for $C_{29}H_{27}BrO_2$: 486.1; found: 487.1 [M$^+$+1], 504.1 [M$^+$+18].

Compound 6j

Yield: 223 mg (74%); pale-yellow semi-solid; R_f 0.55.

IR (KBr): 2950, 2212, 1753, 1592 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17–8.19 (m,1 H), 7.85–7.87 (m, 1 H), 7.58–7.60 (m, 3 H), 7.37 (s, 1 H), 7.20 (d, *J* = 8.04 Hz, 2 H), 7.13 (d, *J* = 7.92 Hz, 2 H), 2.32 (s, 3 H), 1.67 (s, 4 H), 1.27 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 148.9, 147.2, 142.9, 138.3, 134.6, 133.1, 132.3, 131.4, 131.3, 131.1, 128.9, 127.2, 122.6, 120.0, 119.8, 114.4, 93.3, 84.2, 34.8, 34.7, 34.6, 34.0, 31.8, 31.6, 21.4.

LCMS: *m*/*z* calcd for $C_{30}H_{29}BrO_2$: 500.1; found: 501.0 [M$^+$+1], 518.1 [M$^+$+18].

Preparation of Compound 7a–h; General Typical

To a mixture of compound **6a** (220 mg, 0.42 mmol, 1 equiv.) and sodium formate (43 mg, 0.63 mmol) in DMF/H_2O (7:3, 10 mL), $Pd(PPh_3)_4$ (14.5 mg, 3 mol%) was added and the mixture was heated at 100 °C for 1 h. The mixture was cooled, H_2O (10 mL) was added, and it was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with H_2O (4 × 10 mL) and brine (10 mL), and dried over Na_2SO_4. The solvent was distilled off to furnish a viscous mass that was purified by column chromatography (silica gel, 3–5%EtOAc/hexane) to afford **7a** (65%) as an off-white solid. Compound **7b–h** was prepared similarly.

Compound 7a

Yield: 121 mg (65%); off-white solid; mp 175–177 °C; R_f 0.45.

IR (KBr): 2955, 1610, 1487, 1378 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.56 HZ, 1 H), 7.65 (br s, 2 H), 7.48 (br s, 1 H), 7.15–7.20 (m, 6 H), 6.99 (s, 1 H), 6.93 (s, 1 H), 1.55–1.59 (m, 4 H), 1.25 (s, 6 H), 1.026 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.7, 143.3, 139.9, 136.7, 136.1, 135.8, 135.0, 133.9, 130.4, 129.4, 129.1, 128.4, 128.3, 127.6, 127.5, 125.4, 119.4, 34.7, 34.6, 34.5, 33.7, 31.7, 31.3.

HRMS: *m*/*z* [M +1] calcd for $C_{28}H_{28}O_3S$: 445.1759; found: 445.1878.

Compound 7b

Yield: 127 mg (68%); white solid; mp 172–174 °C; R_f 0.45.

IR (KBr): 2959, 1600, 1484, 1357.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.72 (d, *J* = 7.72 HZ, 1 H), 7.81–7.84 (m, 2 H), 7.62–7.66 (m, 1 H), 7.40 (s, 1 H), 7.00–7.11 (m, 6 H), 2.22 (s, 3 H), 1.55–1.58 (m, 4 H), 1.23 (s, 6 H), 0.89 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 145.6, 143.3, 140.1, 137.6, 135.8, 135.6, 135.1, 133.8, 133.2, 130.3, 129.3, 129.1, 128.9, 128.3, 127.5, 125.9, 119.5, 34.7, 34.6, 33.8, 31.7, 31.2, 21.2.

HRMS: *m*/*z* [M + 1] calcd for $C_{29}H_{30}O_3S$: 459.1916; found: 459.2050.

Compound 7c

Yield: 132 mg (70%); white solid; mp 179–181 °C; R_f 0.45.

IR (KBr): 2960, 1603, 1510, 1375 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.94 (d, *J* = 7.96 Hz, 1 H), 7.77–7.84 (m, 2 H), 7.64 (t, *J* = 7.96 Hz, 1 H), 7.34 (s, 1 H), 7.19 (t, *J* = 7.68 Hz, 1 H), 7.12 (s, 1 H), 6.99 (d, *J* = 8.2 Hz, 1 H), 6.89 (s, 1 H), 6.81 (d, *J* = 6.24 Hz, 1 H), 6.70 (t, *J* = 7.12 Hz, 1 H), 3.77 (s, 3 H), 1.49–1.54 (m, 4 H), 1.17 (s, 6 H), 0.80 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 147.4, 145.8, 142.9, 139.9, 136.6, 135.7, 133.9, 131.4, 130.5, 129.5, 128.9, 128.2, 127.4, 125.5, 125.3, 120.4, 119.0, 110.3, 55.5, 34.7, 34.6, 33.6, 31.6, 31.2, 29.7.

HRMS: *m*/*z* [M + 1] calcd for $C_{29}H_{30}O_4S$: 475.1865; found: 475.2008.

Compound 7d

Yield: 133 mg (71%); white solid; mp 180–182 °C; R_f 0.45.

IR (KBr): 2955, 1607, 1511, 1488 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.91 (d, *J* = 7.64 Hz, 1 H), 7.78–7.85 (m, 2 H), 7.61–7.65 (m, 1 H), 7.41 (s, 1 H), 7.04–7.10 (m, 4 H), 6.79 (d, *J* = 8.76 Hz, 2 H), 3.07 (s, 3 H), 1.58–1.59 (m, 4 H), 1.23 (s, 6 H), 0.85 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.19, 147.6, 145.5, 143.5, 140.2, 135.9, 134.6, 134.4, 133.7, 133.3, 130.8, 130.1, 129.0, 128.5, 128.2, 127.6, 126.2, 119.6, 113.7, 55.3, 34.7, 34.6, 34.4, 33.8, 31.7, 31.4.

HRMS: *m*/*z* [M + 1] calcd for $C_{29}H_{30}O_4S$: 475.1865; found: 475.1957.

Compound 7e

Yield: 122 mg (67%); white solid; mp 105–107 °C; R_f 0.50.

IR (KBr): 2923, 1651, 1616, 1456 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.50 (m, 6 H), 7.25 (t, *J* = 7 Hz, 2 H), 7.17 (d, *J* = 7.16 Hz, 1 H), 6.89 (s, 1 H), 6.71 (s, 1 H), 6.66 (s, 1 H), 5.24 (s, 2 H), 1.46–1.50 (m, 4 H), 1.15 (s. 6 H), 0.77 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 146.9, 146.0, 140.6, 137.2, 137.1, 134.1, 131.0, 130.3, 129.5, 129.2, 128.2, 127.8, 127.7, 126.8, 125.8, 120.6, 116.4, 70.2, 35.0, 34.9, 34.1, 33.2, 31.7, 31.5.

HRMS: *m*/*z* [M + 1] calcd for $C_{29}H_{30}O$: 395.2297; found: 395.4796.

Compound 7f

Yield: 116 mg (60%); white solid; mp 100–102 °C; R_f 0.50.

IR (KBr): 2950, 1608, 1596, 1456 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.46 (d, *J* = 7.36 Hz, 1 H), 7.39–7.42 (m, 2 H), 7.32–7.35 (m, 1 H), 7.25–7.27 (d, *J* = 7.88 Hz, 2 H), 7.06 (d, *J* = 7.84 Hz, 2 H), 6.91 (s, 1 H), 6.70 (s, 1 H), 6.61 (s, 1 H), 2.22 (s, 3 H), 1.50 (t, *J* = 7.96 Hz, 2 H), 1.45 (t, *J* = 7.2 Hz, 2 H), 1.15 (s, 6 H), 0.79 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 146.8, 146.2, 139.7, 137.0, 136.6, 134.2, 134.1, 130.9, 130.3, 129.4, 129.2, 128.9, 127.8, 127.5, 125.8, 120.8, 116.4, 70.2, 35.1, 34.9, 34.0, 33.2, 31.7, 31.4, 21.2.

HRMS: *m*/*z* [M + 1] calcd for $C_{30}H_{32}O$: 409.5745; found: 409.2195.

Compound 7g

Yield: 111 mg (60%); white solid; mp 108–110 °C; R_f 0.50.

IR (KBr): 2958, 1603, 1572, 1454 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.41–7.43 (m, 3 H), 7.34–7.36 (m, 1 H), 7.17–7.23 (m, 2 H), 7.01 (d, *J* = 8.12 Hz, 1 H), 6.77–6.80 (m, 2 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 5.24 (s, 2 H), 3.77 (s, 3 H), 1.48 (t, *J* = 8.0 Hz, 2 H), 1.42 (t, *J* =7 Hz, 2 H), 1.12 (s, 6 H), 0.72 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 153.0, 146.5, 146.2, 140.8, 136.9, 134.2, 130.7, 129.2. 128.2, 127.7, 127.5, 126.4, 126.1, 126.0, 121.3, 120.4, 116.2, 110.8, 70.3, 55.5, 35.1, 35.0, 34.0, 33.1, 31.7, 31.4.

HRMS: *m*/*z* [M + 1] calcd for $C_{30}H_{32}O_2$: 425.2402; found: 425.2606.

Compound 7h

Yield: 115 mg (62%); white solid; mp 107–109 °C; R_f 0.50.

IR (KBr): 2956, 1604, 1572, 1454 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.46 (d, *J* = 7.8 Hz, 1 H), 7.30–7.39 (m, 4 H), 6.96 (s, 1 H), 6.82 (d, *J* = 8.68 Hz, 2 H), 6.70 (s, 1 H), 6.58 (s, 1 H), 5.23 (s, 2 H), 3.71 (s, 3 H), 1.48–1.52 (m, 4 H), 1.15 (s, 6 H), 0.83 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 153.1, 146.8, 146.3, 138.7, 137.1, 134.2, 130.8, 129.8, 129.6, 129.2, 127.8, 127.5, 125.7, 120.9, 116.5, 113.7, 70.2, 55.3, 35.1, 34.9, 34.1, 33.3, 31.7, 31.6.

HRMS: *m*/*z* [M + 1] calcd for $C_{30}H_{32}O_2$: 425.2402; found: 425.2440.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

We are grateful to Kalyani University, Kalyani for spectral analysis. T.M. thanks Prasenjit Mistry for his assistance.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2022-3227.

References

(1) Gudas, L. J.; Sporn, M. B.; Roberts, A. B. *In, The Retinoids*; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Ed.; Raven Press: New York, **1996**, 443–520.

(2) Lotan, R. *Biochim. Biophys. Acta* **1981**, *605*, 33.
(3) Roberts, A. B.; Sporn, M. B. *In, The Retinoids*; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Ed.; Academic Press: Orlando, **1984**, 209–286.
(4) (a) *Retinoid Therapy*; Cunliffe, W. J.; Miller, A. J., Ed.; MTP Press Limited: Lancaster, **1984**. (b) Bollag, W.; Holdener, E. E. *Ann. Oncol.* **1992**, *3*, 513. (c) Hill, D. L.; Grubbs, C. J. *Annu. Rev. Nutr.* **1992**, *12*, 161.
(5) (a) Zitnik, R. J.; Kotloff, R. M.; Latifpour, J.; Zheng, T.; Whiting, N. L.; Schwalb, J.; Elias, J. A. *J. Immunol.* **1994**, *152*, 1419. (b) Chen, J.-Y.; Penco, S.; Ostrowski, J.; Balaguer, P.; Pons, M.; Starrett, J. E.; Reczek, P.; Chambon, P.; Gronemeyer, H. *EMBO J.* **1995**, *14*, 1187. (c) Kagechika, H.; Kawachi, E.; Fukasawa, H.; Saito, G.; Iwanami, N.; Umemiya, H.; Hashimoto, Y.; Shudo, K. *Res. Commun.* **1997**, *231*, 243.
(6) (a) Ellis, C. N.; Voorhees, J. J. *J. Am. Acad. Dermatol.* **1987**, *16*, 267. (b) Ishibashi, Y. *Rinsho Iyaku* **1995**, *11*, 733.
(7) (a) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772. (b) Ostrowski, J.; Roalsvig, T.; Hammer, L.; Marinier, A.; Starrett, J. E. Jr.; Yu, K.-L.; Reczek, P. R. *J. Biol. Chem.* **1998**, *273*, 3490. (c) Géhin, M.; Vivat, V.; Wurtz, J. M.; Losson, R.; Chambon, P.; Moras, D.; Gronemeyer, H. *Chem. Biol.* **1999**, *6*, 519. (d) Haffez, H.; Chisholm, D. R.; Tatum, N. J.; Valentine, R.; Redfern, C.; Pohl, E.; Whiting, A.; Przyborski, S. *Bioorg. Med. Chem.* **2018**, *26*, 1560.
(8) (a) Dawson, M. I.; Jong, L.; Hobbs, P. D.; Xiao, D.; Feng, K.-C.; Chao, W.-r.; Pan, C.; Fontana, J. A.; Zhang, X.-k. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1311. (b) Zolfaghari, R.; Mattie, F. J.; Wei, C.-H.; Chisholm, D. R.; Whiting, A.; Ross, A. C. *Anal. Biochem.* **2019**, *577*, 98.
(9) Umemiya, H.; Fukasawa, H.; Ebisawa, M.; Eyrolles, L.; Kawachi, E.; Eisenmann, G.; Gronemeyer, H.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *J. Med. Chem.* **1997**, *40*, 4222.
(10) Li, Y.; Hashimoto, Y.; Agadir, A.; Kagechika, H.; Zhang, X.-k. *J. Biol. Chem.* **1999**, *274*, 15360.
(11) Yu, Y.; Ma, L.; Xia, J.; Xin, L.; Zhu, L.; Huang, X. *Angew. Chem. Int. Ed.* **2020**, *41*, 18261.
(12) (a) Blouin, S.; Blond, G.; Donnard, M.; Gulea, M.; Suffert, J. *Synthesis* **2017**, *49*, 1767. (b) Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187. (c) Moni, L.; Denißen, M.; Valentini, G.; Müller, T. J. J.; Riva, R. *Chem. Eur. J.* **2015**, *21*, 753. (d) Majumdar, K. C.; Ghosh, T.; Ponra, S. *Tetrahedron Lett.* **2013**, *54*, 4661. (e) Ghosh, T. *New J. Chem.* **2017**, *41*, 2927.
(13) (a) Peshkov, A. A.; Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Tetrahedron* **2015**, *71*, 3863. (b) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017. (c) Tietze, L. F.; Schimpf, R. *Chem. Ber.* **1994**, *127*, 2235. (d) Wang, G.; Liu, C.; Li, B.; Wang, Y.; Van Hecke, K.; Van der Eycken, E. V.; Pereshivko, O. P.; Peshkov, V. A. *Tetrahedron* **2017**, *73*, 6372. (e) Majumdar, K. C.; Ghosh, T.; Chakravorty, S. *Tetrahedron Lett.* **2010**, *51*, 3372. (f) Peshkov, V. A.; Van Hove, S.; Donets, P. A.; Pereshivko, O. P.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2011**, 1837. (g) Mondal, S.; Debnath, S.; Das, B. *Tetrahedron* **2015**, *71*, 476. (h) Ghazvini, H. J.; Müller, T. J. J.; Rominger, F.; Balalaie, S. *J. Org. Chem.* **2019**, *84*, 10740.
(14) (a) Joardar, S.; Chakravorty, S.; Das, S. *Synlett* **2015**, *26*, 359. (b) Jaoardar, S.; Chakravorty, S.; Das, S. P. *Lett. Org. Chem.* **2016**, *13*, 127.
(15) Wu, S.; Geng, F.; Dong, J.; Liu, L.; Zhou, Y. *J. Org. Chem.* **2022**, *87*, 9112.