JOC The Journal of Organic Chemistry

Note

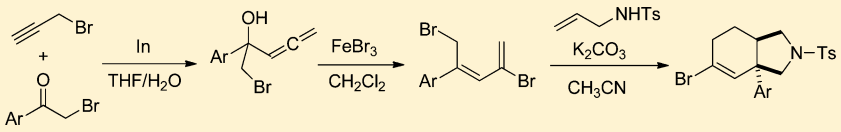
pubs.acs.org/joc

Synthesis of Hexahydro-1*H*-isoindole Derivatives from Arylacyl Bromides via Homoallenic Bromohydrins

Mei-Huey Lin,* Yi-Syuan Li, Chung-Kai Kuo, Chung-Hao Chen, Yen-Chih Huang, Kung-Yu Liang, Yu-Chun Chen, Chang-Hsien Tsai, and Tsung-Hsun Chuang

Department of Chemistry, National Changhua University of Education, Changhua, Taiwan 50007

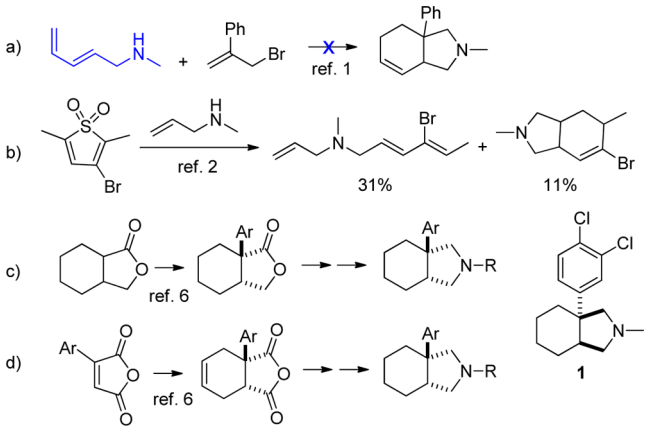
Supporting Information



ABSTRACT: A procedure has been developed for the concise synthesis of hexahydro-1*H*-isoindole derivatives starting from phenacyl bromides. The approach employs a sequence involving an initial indium-mediated allenylation reaction of an arylacyl bromide with propargyl bromide. This process is followed by $FeBr_3$-mediated S_N2'-type substitution reaction of the formed homoallenic bromohydrin to produce a 2,5-dibromo-4-aryl-1,3-pentadiene, which then is subjected to a sequential, one-pot *N*-alkylation reaction with *N*-allyl-*N*-(*p*-tosyl)amine and a highly diastereoselective intramolecular Diels–Alder reaction of the formed ene-diene to generate the target hexahydro-1*H*-isoindole.

Substances possessing the 3a-phenyl-isoindoline ring system display potent analgesic activities.[1] As a result, methods for the preparation of this unique structural scaffold are in high demand. One obvious approach to construct this fused heterocyclic framework, by using an intramolecular [4 + 2] cycloaddition and N-alkylation protocol starting with α-bromomethylstyrene and pentadienyl amine, failed, owing to the inherent instability of the amine (a, Scheme 1).[1] In another approach to the polyhydro-1*H*-isoindole scaffold, initial secondary amine induced ring opening of thiophene-1,1-dioxide to form the azatriene was found to take place in only a 31% yield, and the ensuing intramolecular Diels–Alder reaction was low yielding (11%, b, Scheme 1).[2] Other examples of strategies devised for synthesis of polyhydro-1*H*-isoindoles rely on key rhodium(I)-catalyzed,[3] thermo,[4] and BCl_3-promoted intramolecular Diels–Alder reactions.[5] Recently, the novel *cis*-octahydro-1*H*-isoindole **1** was shown to be a potent triple serotonin, norepinephrine, and dopamine transporter inhibitor for use as a potential drug to treat depression.[6] The construction of the skeleton of **1** was accomplished by employing either a palladium-catalyzed arylation reaction of a fused γ-lactone or a Diels–Alder reaction of an aryl-maleic anhydride (c and d, Scheme 1).

Scheme 1. Synthesis of Polyhydro-1*H*-isoindoles



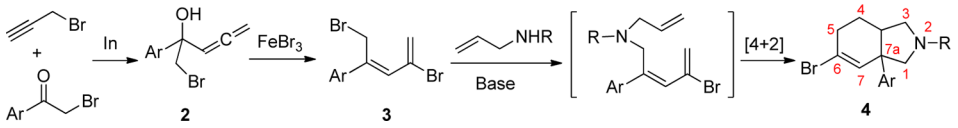
In the study described below, we explored a new method for the synthesis of *cis*-bicyclic-polyhydro-1*H*-isoindoles containing a stereogenic, quaternary, aryl-substituted bridgehead carbon. For this purpose, we designed an approach that relies on an intramolecular [4 + 2] cycloaddition reaction of an amine tethered ene-aryldiene. Recently, we described a method for the efficient synthesis of homoallenic halohydrins **2** (Scheme 2) that involves an indium-mediated allenylation reaction of arylacyl halides with propargyl bromide in aqueous media.[7] In a manner that is similar to the reported generation of 2-halo-1,3-dienes by using halide-ion-promoted S_N2'-type substitution reactions of allenols,[8] we observed that 2-aryl-1,4-dibromo-penta-2,4-dienes **3** can be prepared by reactions of homoallenic bromohydrins **2** with $FeBr_3$. We envisioned that bromo-dienes **3** would serve as effective substrates in reactions with allylamines that take place by a one-pot, sequential nucleophilic substitution and intramolecular [4 + 2] cycloaddition of the intermediate amine tethered ene-dienes. If valid, the proposed pathway would serve as a simple method for the synthesis of 7a-aryl-6-bromo-hexahydro-1*H*-isoindoles **4** (Scheme 2).

In order to evaluate the feasibility of the new strategy for aryl-hexahydro-1*H*-isoindole synthesis, homoallenic bromohy-

Received: January 11, 2015
Published: February 1, 2015

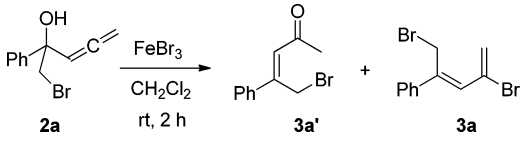
DOI: 10.1021/acs.joc.5b00072
J. Org. Chem. 2015, 80, 2462–2466

Scheme 2



drin **2a** was subjected to S_N2'-type substitution reaction conditions using various amounts of ferric bromide (Table 1). The results show that bromo-diene **3a** is produced as the

Table 1. $FeBr_3$-Mediated S_N2'-Type Substitution Reactions[a]



entry	$FeBr_3$ (mol %)	**3a′**, yield (%)	**3a**, yield (%)
1	30	4	60
2	35	5	63
3	40	5	86
4	60	5	86

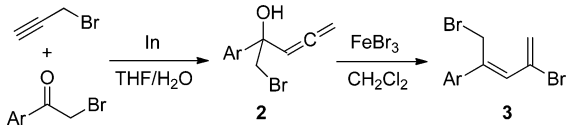
[a]Conditions: **2a** (0.5 mmol) and $FeBr_3$ as indicated in CH_2Cl_2 (4.0 mL) at 25−28 °C for 2 h.

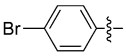
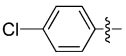
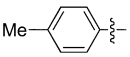
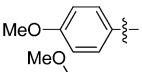
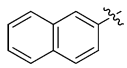
major product in these reactions along with small amounts of enone **3a′**, which can be easily removed by using chromatography. Because the yield of **3a** is not improved significantly by using larger amounts of ferric bromide (Table 1, entry 3 vs 4), ideal conditions for this process involve the use of 40 mol % of ferric bromide. An examination of the **3a** showed that it is stable when stored below 0 °C but that it slowly decomposes at room temperature.

The preparation and $FeBr_3$-promoted reactions of a variety of aryl-substituted homoallenic bromohydrins **2** were explored next (Table 2). The results show that indium-mediated allenylation reactions of arylacyl bromides with propargyl bromide in aqueous media take place to form the desired homoallenic bromohydrins in high yields along with small amounts of both the propargyl analogues and corresponding methylketones, generated by direct reduction of the arylacyl bromides. Pure homoallenic bromohydrins **2a**, **2e**, and **2g**, obtained by using the previously described chromatographic procedure,[7] were observed to undergo $FeBr_3$-mediated S_N2'-type substitution reactions to give the respective bromo-dienes **3a**, **3e**, and **3g** in high yields (Table 2, entries 1, 5, and 7). Alternatively, the crude mixtures generated in the indium-mediated allenylation reactions were subjected to the $FeBr_3$-mediated S_N2'-type substitution reaction conditions. The results of these two-step reactions, listed in Table 2 (entries 2−4, 6, and 8), show that bromo-dienes **3** are generated in modest yields even when purifications of the intermediate homoallenic bromohydrins **2** are not performed. It is worth noting that the $FeBr_3$-mediated S_N2'-type substitution reactions of homoallenic bromohydrins **2** not only occur with high levels of regioselectivity but also form the *Z*-stereoisomers selectively, as was demonstrated by using X-ray crystallographic analysis of **3e**.[9]

The key step in the proposed route for synthesis of 7a-aryl-6-bromo-hexahydro-1*H*-isoindoles **4**, involving one-pot formation of ene-diene, followed by intramolecular Diels−Alder cycloaddition, was examined next. For this purpose, reactions of **3c**

Table 2. Preparation of 2-Aryl-1,4-dibromopenta-2,4-dienes 3[a,b]

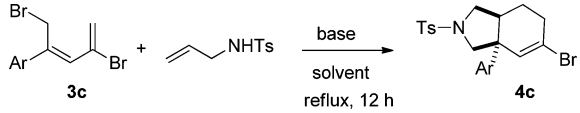


entry	Ar	**2**, yield (%)	**3**, yield (%)[a]
1		**2a**, 62	**3a**, 86
2		--	**3b**, 58[b]
3		--	**3c**, 49[b]
4		--	**3d**, 50[b]
5		**2e**, 60	**3e**, 70
6		--	**3f**, 45[b]
7		**2g**, 66	**3g**, 75
8		--	**3h**, 46[b]

[a]Conditions: **2** (0.5 mmol) and $FeBr_3$ (0.2 mmol) in CH_2Cl_2 (4.0 mL) at 25−28 °C for 2 h. [b]Two-step overall yield.

with *N*-allyl-*N*-(*p*-tosyl)amine in the presence of various bases and solvents were explored (Table 3). The results show that the nature of the base plays a crucial role in this process, exemplified by the observation that the Diels−Alder product **4c**

Table 3. Reactions of Bromo-Diene 3c through One-Pot, Sequential Formation of Ene-Diene, Followed by Intramolecular Diels−Alder Reaction[a]



entry	substrate	base	solvent	**4c**, yield (%)
1	**3c**	Et_3N	CH_3CN	0
2	**3c**	DBU	CH_3CN	0
3	**3c**	guanidine carbonate	CH_3CN	0
4	**3c**	Cs_2CO_3	CH_3CN	58
5	**3c**	K_2CO_3	CH_3CN	70
6	**3c**	K_2CO_3	DCE	0
7	**3c**	K_2CO_3	EtOH	41
8	**3c**	K_2CO_3	dioxane	31
9	**3c**	K_2CO_3	toluene	0

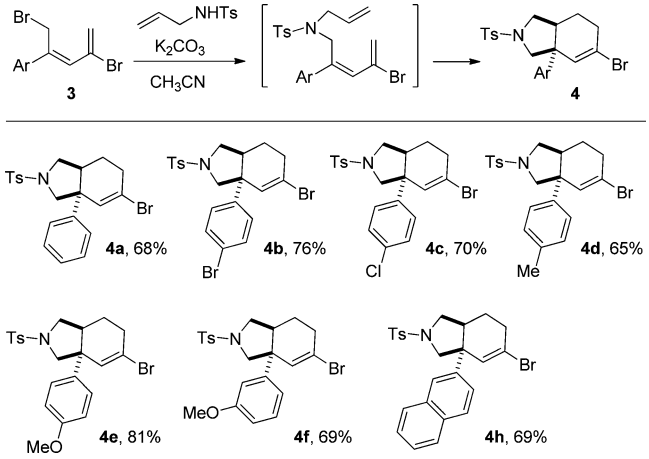
[a]Conditions: **3c** (0.6 mmol), *N*-allyl-*N*-(*p*-tosyl)amine (0.5 mmol), and indicated base (1.0 mmol) in solvent (3.0 mL) at reflux for 12 h.

DOI: 10.1021/acs.joc.5b00072
J. Org. Chem. 2015, 80, 2462−2466

is not formed when triethylamine, DBU, and guanidine carbonate are employed (Table 3, entries 1−3). In contrast, inorganic bases such as cesium carbonate and potassium carbonate promoted formation of the target **4c** in respective 58% and 70% yields (Table 3, entries 4 and 5). A screen of solvents showed that acetonitrile is an ideal solvent for the two-step process. Importantly, neither the precursor ene-diene nor the cyclization product **4c** is formed in reactions in dichloroethane or toluene (Table 3, entries 6 and 9) and that **4c** is generated in low yields when ethanol and dioxane are employed as solvents (Table 3, entries 7 and 8). A single diastereoisomer is produced in the reaction of **3c** with *N*-allyl-*N*-(*p*-tosyl)amine. The stereochemistry of the fused-bicyclic ring system in **4c** was shown to be *cis* by using X-ray crystallographic analysis.[10]

An exploration of the scope of the one-pot reaction of bromo-dienes **3** with *N*-allyl-*N*-(*p*-tosyl)amine showed that it serves as a general method for the synthesis of a variety of 7a-aryl-6-bromo-hexahydro-1*H*-isoindoles **4** (Scheme 3).[11] Finally,

Scheme 3. Scope of One-Pot Formation of Ene-Diene, Followed by an Intramolecular Diels−Alder Reaction[a]



[a]Conditions: **3** (0.6 mmol), *N*-allyl-*N*-(*p*-tosyl)amine (0.5 mmol), and K_2CO_3 (1.0 mmol) in CH_3CN (3.0 mL) at reflux for 12 h.

in contrast to these processes, reaction of bromo-diene **3c** with allylamine leads to formation of the *N*-allyl-pyrrole **5c** (Scheme 4). The formation of **5c** likely occurs by intramolecular *N*-vinylation of the secondary amine **4c′** formed by initial substitution reaction of bromo-diene **3c** with allylamine.

In conclusion, the studies described above have led to the development of a simple method for the preparation of (*Z*)-2-aryl-1,4-dibromopenta-2,4-dienes **3** from phenacyl bromides and an application of these dienes to the synthesis of hexahydro-1*H*-isoindole derivatives.

EXPERIMENTAL SECTION

General Information and Materials. All commercially available chemicals were used without further purification. TLC analyses were run on a TLC glass plate (Silica gel 60 F254) and were visualized using UV and a solution of phosphomolybdic acid in ethanol (5 wt %) or *p*-anisaldehyde stain. Flash chromatography was performed using silica gel (70−230 mesh). ^{1}H spectra were recorded on a 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a 75 MHz with complete proton decoupling spectrometer. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line) 77.0]. Mass spectra were recorded under electron impact ionization (EI) conditions, and high-resolution mass spectra were recorded by electron impact ionization with magnetic sector.

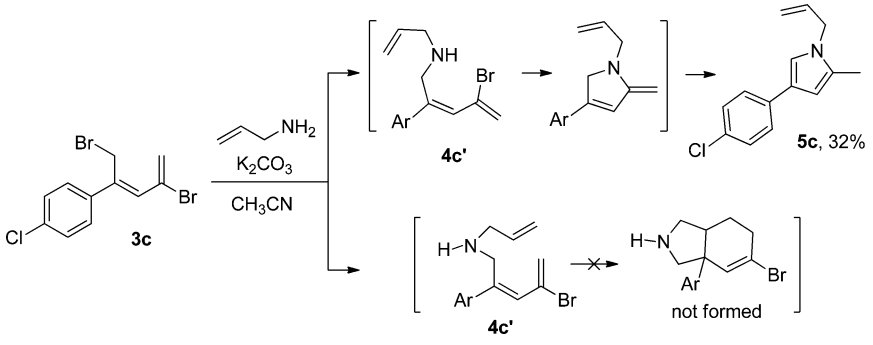
General Procedure for the Synthesis of Bromo-Dienes 3 from Homoallenic Bromohydrins 2. A mixture of homoallenic bromohydrin **2** (0.5 mmol)[7] and $FeBr_3$ (59 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) was stirred at ambient temperature (25−28 °C), After 2 h, CH_2Cl_2 (2 mL) and 2 N HCl aqueous solution (2 mL) were added to the reaction, and the mixture was transferred to a separatory funnel. The aqueous layer was back extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in a rotary evaporator. The residue was purified by silica gel chromatography using hexanes as eluent to give the product **3**.

*(Z)-(1,4-Dibromopenta-2,4-dien-2-yl)benzene (**3a**).* Following the general procedure, the title compound was obtained (130 mg, 86%). A yellow oil; TLC (Et_2O/hexanes (1:5)) R_f = 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (s, 2 H), 5.89 (d, J = 1.8 Hz, 1 H), 6.17 (t, J = 1.8 Hz, 1 H), 6.43 (d, J = 1.8 Hz, 1 H), 7.34−7.40 (m, 3 H), 7.48 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (CH_2), 121.0 (CH_2), 125.1 (C), 126.4 (CH × 2), 128.6 (CH × 2), 128.7 (CH), 130.7 (CH), 137.9 (C), 139.1 (C); IR (neat) 3068, 1688, 1595 cm^{-1}; EI-MS m/z (rel intensity) 300 ([M]$^+$, 0.1), 223 (11), 141 (100), 115 (20); HRMS [M]$^+$ calcd for $C_{11}H_{10}Br_2$: 299.9149, found 299.9142.

*(Z)-1-(1,4-Dibromopenta-2,4-dien-2-yl)-4-methoxybenzene (**3e**).* Following the general procedure, the title compound was obtained (116 mg, 70%). A yellow solid, mp 58−59 °C; TLC (Et_2O/hexanes (1:4)) R_f = 0.60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3 H), 4.50 (s, 2 H), 5.85 (d, J = 1.8 Hz, 1 H), 6.13 (t, J = 1.8 Hz, 1 H), 6.37 (d, J = 1.8 Hz, 1 H), 6.90 (d, J = 7.8 Hz, 2 H), 7.43 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9 (CH_2), 52.2 (CH_3), 113.9 (CH × 2), 120.6 (CH_2), 125.4 (C), 127.5 (CH × 2), 129.0 (CH), 129.8 (C), 138.4 (C), 159.9 (C); IR (KBr) 3030, 1607, 1506 cm^{-1}; EI-MS m/z (rel intensity) 332 ([M + 2]$^+$, 7), 330 ([M]$^+$, 4), 251 (100), 172 (88); HRMS [M]$^+$ calcd for $C_{12}H_{12}Br_2O$: 329.9255, found 329.9265.

*(Z)-1-(1,4-Dibromopenta-2,4-dien-2-yl)-2-methoxybenzene (**3g**).* Following the general procedure, the title compound was obtained

Scheme 4. Formation of *N*-Allyl-Pyrrole 5c



DOI: 10.1021/acs.joc.5b00072
J. Org. Chem. 2015, 80, 2462−2466

(125 mg, 75%). An off-white solid, mp 47−49 °C; TLC (Et_2O/hexanes (1:5)) R_f = 0.70; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 4.67 (s, 2 H), 5.89 (d, J = 1.8 Hz, 1 H), 6.17 (t, J = 1.8 Hz, 2 H), 6.90 (d, J = 7.8 Hz, 1 H), 6.99 (t, J = 7.8 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2 (CH_2), 55.2 (CH_3), 110.5 (CH), 120.5 (CH), 120.8 (CH_2), 124.7 (C), 127.8 (C), 129.7 (CH), 131.0 (CH), 132.4 (CH), 139.7 (C), 156.3 (C); IR (KBr) 3003, 1590, 1488 cm^{-1}; EI-MS m/z (rel intensity) 330 ($[M]^+$, 0.2), 298 (39), 251 (100), 172 (55); HRMS $[M]^+$ calcd for $C_{12}H_{12}Br_2O$: 329.9255, found 329.9245.

General Procedure for the 2-Step Sequence To Form Bromo-dienes 3 from Arylacyl Bromides. A mixture of propargyl bromide (1.0 mL, 14.4 mmol), indium powder (325 mesh, 1.4 g, 12.0 mmol), and arylacyl bromide (8.0 mmol) in THF/H_2O (12.0 mL/4.0 mL) was stirred at ambient temperature (25−28 °C). Reaction was monitored by TLC until no starting material was observed, and normally the reaction was stirred at rt overnight. Et_2O (20 mL) and water (20 mL) was then added to the reaction, and the mixture was transferred to a separatory funnel. The aqueous layer was back extracted with Et_2O (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue was purified by a short silica gel plug with using hexanes (100 mL) and then Et_2O/hexanes (1:20, 100 mL) as eluent to give the crude product **2**. The crude mixture was dissolved in CH_2Cl_2 (42 mL), and then $FeBr_3$ (612 mg, 2.1 mmol)) was added. The resulting mixture was stirred at ambient temperature (25−28 °C) for 2 h. Then, CH_2Cl_2 (20 mL) and 2 N HCl aqueous solution (20 mL) were added to the reaction, and the mixture was transferred to a separatory funnel. The aqueous layer was back extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in a rotary evaporator. The residue was purified by silica gel chromatography using hexanes as eluent to give the product **3**.

*(Z)-1-Bromo-4-(1,4-dibromopenta-2,4-dien-2-yl)benzene (**3b**).* Following the general procedure, the title compound was obtained (1.8 g, 58%). A yellow oil; TLC (Et_2O/hexanes (1:5)) R_f = 0.75; ^1H NMR (300 MHz, $CDCl_3$) δ 4.46 (s, 2 H), 5.89 (d, J = 1.8 Hz, 1 H), 6.15 (t, J = 1.8 Hz, 1 H), 6.40 (d, J = 1.8 Hz, 1 H), 7.34 (d, J = 8.7 Hz, 2 H), 7.48 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (CH_2), 121.3 (CH_2), 122.9 (C), 124.7 (C), 128.0 (CH × 2), 131.0 (CH), 131.8 (CH × 2), 136.8 (C), 138.0 (C); IR (neat) 3030, 1587, 1496 cm^{-1}; EI-MS m/z (rel intensity) 378 ($[M]^+$, 0.3), 303 (22), 221 (33), 141 (100); HRMS $[M]^+$ calcd for $C_{11}H_9Br_3$: 377.8254, found 377.8253.

*(Z)-1-Chloro-4-(1,4-dibromopenta-2,4-dien-2-yl)benzene (**3c**).* Following the general procedure, the title compound was obtained (1.3 g, 49%). A yellow solid, mp 42−44 °C; TLC (Et_2O/hexanes (1:5)) R_f = 0.75; ^1H NMR (300 MHz, $CDCl_3$) δ 4.47 (s, 2 H), 5.89 (d, J = 1.8 Hz, 1 H), 6.15 (t, J = 1.8 Hz, 1 H), 6.40 (d, J = 1.8 Hz, 1 H), 7.35 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 (CH_2), 121.3 (CH_2), 124.7 (C), 127.7 (CH × 2), 128.8 (CH × 2), 131.0 (CH), 134.7 (C), 136.3 (C), 138.0 (C); IR (KBr) 3030, 1597, 1440 cm^{-1}; EI-MS m/z (rel intensity) 334 ($[M]^+$, 4), 257 (68), 176 (99), 141 (100); HRMS $[M]^+$ calcd for $C_{11}H_9Br_2Cl$: 333.8760, found 333.8761.

*(Z)-1-(1,4-Dibromopenta-2,4-dien-2-yl)-4-methylbenzene (**3d**).* Following the general procedure, the title compound was obtained (1.3 g, 50%). A yellow oil; TLC (Et_2O/hexanes (1:5)) R_f = 0.75; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 4.54 (s, 2 H), 5.91 (d, J = 1.8 Hz, 1 H), 6.19 (t, J = 1.8 Hz, 1 H), 6.46 (d, J = 1.8 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2 H), 7.42 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_3), 28.8 (CH_2), 120.7 (CH_2), 125.2 (C), 126.1 (CH × 2), 129.3 (CH × 2), 129.8 (CH), 134.7 (C), 138.6 (C), 138.8 (C); IR (neat) 3038, 1605, 1441 cm^{-1}; EI-MS m/z (rel intensity) 314 ($[M]^+$, 5), 251 (36), 237 (82), 156 (100); HRMS $[M]^+$ calcd for $C_{12}H_{12}Br_2$: 313.9306, found 313.9303.

*(Z)-1-(1,4-Dibromopenta-2,4-dien-2-yl)-3-methoxybenzene (**3f**).* Following the general procedure, the title compound was obtained (1.2 g, 45%). A yellow oil; TLC (Et_2O/hexanes (1:5)) R_f = 0.63; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 4.49 (s, 2 H), 5.87 (d, J = 1.8 Hz, 1 H), 6.16 (t, J = 1.8 Hz, 1 H), 6.42 (d, J = 1.8 Hz, 1 H), 6.87−6.90 (m, 1 H), 7.00−7.07 (m, 2 H), 7.29 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (CH_2), 55.1 (CH_3), 112.2 (CH), 113.8 (CH), 118.6 (CH), 121.0 (CH_2), 124.9 (C), 129.5 (CH), 130.7 (CH), 138.9 (C), 139.2 (C), 159.5 (C); IR (KBr) 2938, 1616, 1487 cm^{-1}; EI-MS m/z (rel intensity) 332 ($[M + 2]^+$, 4), 330 ($[M]^+$, 2), 251 (100), 172 (73); HRMS $[M]^+$ calcd for $C_{12}H_{12}Br_2O$: 329.9255, found 329.9260.

*(Z)-2-(1,4-Dibromopenta-2,4-dien-2-yl)naphthalene (**3h**).* Following the general procedure, the title compound was obtained (1.3 g, 46%). A yellow solid, mp 57−58 °C; TLC (Et_2O/hexanes (1:5)) R_f = 0.70; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2 H), 5.91 (d, J = 1.8 Hz, 1 H), 6.21 (t, J = 1.8 Hz, 1 H), 6.57 (d, J = 1.8 Hz, 1 H), 7.47−7.60 (m, 3 H), 7.80−7.87 (m, 3 H), 7.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (CH_2), 121.1 (CH_2), 123.7 (CH), 125.1 (C), 125.9 (CH), 126.4 (CH), 126.5 (CH), 127.5 (CH), 128.3 (CH × 2), 131.0 (CH), 133.1 (C), 133.2(C), 134.9 (C), 138.9 (C); IR (KBr) 3067, 1601, 1217 cm^{-1}; EI-MS m/z (rel intensity) 352 ($[M + 2]^+$, 3), 350 ($[M]^+$, 1), 271 (33), 192 (100); HRMS $[M]^+$ calcd for $C_{15}H_{12}Br_2$: 349.9306, found 349.9315.

General Procedure for the Synthesis Hexahydro-1*H*-isoindoles 4. A mixture of bromo-diene **3** (0.6 mmol), *N*-allyl-*N*-(*p*-tosyl)amine (110 mg, 0.5 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (3.0 mL) was stirred at 87 °C overnight. The mixture was cooled to ambient temperature (25−28 °C) and filtered through a filter paper. The filtrate was transferred to a separatory funnel, followed by addition of CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was back extracted with CH_2Cl_2 (5 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in a rotary evaporator. The crude product was triturated with Et_2O (5 mL), followed by filtration to give the product **4**.

*6-Bromo-7a-phenyl-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4a**).* Following the general procedure, the title compound was obtained (176 mg, 68%). A yellow solid, mp 86−87 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.50; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36−1.60 (m, 2 H), 2.32−2.43 (m, 3 H), 2.45 (s, 3 H), 3.14 (dd, J = 9.9, 7.5 Hz, 1 H), 3.42 (d, J = 10.5 Hz, 1 H), 3.50 (dd, J = 9.9, 7.5 Hz, 1 H), 3.72 (d, J = 10.5 Hz, 1 H), 5.76 (s, 1 H), 7.15−7.35 (m, 7 H), 7.71 (d J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_3), 22.2 (CH_2), 31.0 (CH_2), 42.5 (CH), 49.8 (CH_2), 52.4 (C), 58.3 (CH_2), 123.5 (C), 126.3 (CH × 2), 127.0 (CH × 2), 127.2 (CH), 128.5 (CH × 2), 129.7 (CH × 2), 131.3 (CH), 133.4 (C), 142.2 (C), 143.6 (C); IR (neat) 2931, 1596, 1339 cm^{-1}; EI-MS m/z (rel intensity) 431 ($[M]^+$, 3), 352 (34), 239 (33), 198 (100); HRMS $[M]^+$ calcd for $C_{21}H_{22}BrNO_2S$: 431.0555, found 431.0559.

*6-Bromo-7a-(4-bromophenyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4b**).* Following the general procedure, the title compound was obtained (233 mg, 76%). A yellow solid, mp 188−190 °C; TLC (Et_2O/hexanes (1:5)) R_f = 0.75; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41−1.61 (m, 2 H), 2.32−2.38 (m, 3 H), 2.43 (s, 3 H), 3.12 (dd, J = 9.9, 7.2 Hz, 1 H), 3.38 (d, J = 10.8 Hz, 1 H), 3.49 (dd, J = 9.9, 7.5 Hz, 1 H), 3.69 (d, J = 10.8 Hz, 1 H), 5.72 (s, 1 H), 7.04 (d, J = 8.4 Hz, 2 H), 7.32−7.39 (m, 4 H), 7.69 (d J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 22.5 (CH_2), 31.2 (CH_2), 42.8 (CH), 50.0 (CH_2), 52.2 (C), 58.1 (CH_2), 121.1 (C), 124.0 (C), 127.2 (CH × 2), 128.2 (CH × 2), 129.8 (CH), 130.7 (CH × 2), 131.6 (CH × 2), 133.4 (C), 141.5 (C), 143.8 (C); IR (neat) 2931, 1474, 1340 cm^{-1}; EI-MS m/z (rel intensity) 509 ($[M]^+$, 2), 411 (25), 343 (38), 198 (100); HRMS $[M]^+$ calcd for $C_{21}H_{21}Br_2NO_2S$: 508.9660, found 508.9654.

*6-Bromo-7a-(4-chlorophenyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4c**).* Following the general procedure, the title compound was obtained (196 mg, 70%). A white solid, mp 169−171 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.38; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−1.59 (m, 2 H), 2.31−2.39 (m, 3 H), 2.42 (s, 3 H), 3.11 (dd, J = 9.9, 7.2 Hz, 1 H), 3.38 (d, J = 10.5 Hz, 1 H), 3.47 (dd, J = 9.9, 7.2 Hz, 1 H), 3.68 (d, J = 10.5 Hz, 1 H), 5.72 (s, 1 H), 7.09 (d, J = 8.1 Hz, 2 H), 7.21 (d, J = 8.1 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.68 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_3), 22.4

DOI: 10.1021/acs.joc.5b00072
J. Org. Chem. 2015, 80, 2462−2466

(CH_2), 31.1 (CH_2), 42.7 (CH), 49.9 (CH_2), 52.1 (C), 58.2 (CH_2), 124.0 (C), 127.2 (CH × 2), 127.8 (CH × 2), 128.6 (CH × 2), 129.7 (CH × 2), 130.7 (CH), 132.9 (C), 133.4 (C), 140.9 (C), 143.7 (C); IR (KBr) 2967, 1569, 1474 cm^{-1}; EI-MS *m*/*z* (rel intensity) 465 ($[M]^+$, 1), 386 (11), 284 (15), 198 (100); HRMS $[M]^+$ calcd for $C_{21}H_{21}BrClNO_2S$: 465.0165, found 465.0154.

*6-Bromo-7a-(p-tolyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4d**).* Following the general procedure, the title compound was obtained (174 mg, 65%). A white solid, mp 164−165 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.38; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43−1.62 (m, 2 H), 2.31 (s, 3 H), 2.32−2.43 (m, 3 H), 2.46 (s, 3 H), 3.13 (dd, *J* = 9.9, 7.2 Hz, 1 H), 3.39 (d, *J* = 10.5 Hz, 1 H), 3.50 (dd, *J* = 9.9, 7.2 Hz, 1 H), 3.70 (d, *J* = 10.5 Hz, 1 H), 5.75 (s, 1 H), 7.06 (m, 4 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.4 (CH_3), 22.1 (CH_2), 31.9 (CH_2), 42.4 (CH), 49.8 (CH_2), 52.1 (C), 58.4 (CH_2), 123.3 (C), 126.1 (CH × 2), 127.1 (CH × 2), 129.1 (CH × 2), 129.7 (CH × 2), 131.4 (CH), 133.4 (C), 136.6 (C), 139.0 (C), 143.5 (C); IR (KBr) 2933, 1329, 1172 cm^{-1}; EI-MS *m*/*z* (rel intensity) 445 ($[M]^+$, 2), 366 (31), 290 (42), 198 (100); HRMS $[M]^+$ calcd for $C_{22}H_{24}BrNO_2S$: 445.0711, found 445.0701.

*6-Bromo-7a-(4-methoxyphenyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4e**).* Following the general procedure, the title compound was obtained (225 mg, 81%). A yellow solid, mp 164−166 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.38; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−1.59 (m, 2 H), 2.33−2.38 (m, 3 H), 2.41 (s, 3 H), 3.11 (dd, *J* = 9.9, 7.2 Hz, 1 H), 3.38 (d, *J* = 10.5 Hz, 1 H), 3.46 (dd, *J* = 9.9, 7.2 Hz, 1 H), 3.66 (d, *J* = 10.5 Hz, 1 H), 3.73 (s, 3 H), 5.72 (s, 1 H), 6.77 (d, *J* = 8.7 Hz, 2 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_3), 22.1 (CH_2), 30.9 (CH_2), 42.6 (CH), 49.8 (C), 51.8 (CH_2), 55.1 (CH_3), 58.4 (CH_2), 113.7 (CH × 2), 123.3 (C), 127.1 (CH × 2), 127.4 (CH × 2), 129.7 (CH × 2), 131.4 (CH), 133.4 (C), 133.9 (C), 143.5 (C), 158.3 (C); IR (KBr) 2925, 1329, 1172 cm^{-1}; EI-MS *m*/*z* (rel intensity) 461 ($[M]^+$, 8), 306 (58), 242 (33), 198 (100); HRMS $[M]^+$ calcd for $C_{22}H_{24}BrNO_3S$: 461.0660, found 461.0657.

*6-Bromo-7a-(3-methoxyphenyl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4f**).* Following the general procedure, the title compound was obtained (191 mg, 69%). A yellow solid, mp 164−166 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.38; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41−1.62 (m, 2 H), 2.31−2.49 (m, 6 H), 3.14 (dd, *J* = 9.6, 7.8 Hz, 1 H), 3.41 (d, *J* = 10.8 Hz, 1 H), 3.50 (dd, *J* = 9.6, 7.8 Hz, 1 H), 3.68 (d, *J* = 10.8 Hz, 1 H), 3.75 (s, 3 H), 5.74 (s, 1 H), 6.72−6.76 (m, 3 H), 7.15−7.21 (m, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 22.2 (CH_2), 31.0 (CH_2), 42.4 (CH), 49.9 (CH_2), 52.5 (C), 55.2 (CH_3), 58.7 (CH_2), 111.7 (CH), 113.2 (CH), 118.7 (CH), 123.7 (C), 127.3 (CH × 2), 129.7 (CH), 129.9 (CH × 2), 131.3 (CH), 133.5 (C), 143.8 (C), 143.9 (C), 159.7 (C); IR (KBr) 2946, 1143, 1573 cm^{-1}; EI-MS *m*/*z* (rel intensity) 461 ($[M]^+$, 7), 382 (34), 306 (56), 198 (100); HRMS $[M]^+$ calcd for $C_{22}H_{24}BrNO_3S$: 461.0660, found 461.0657.

*6-Bromo-7a-(naphthalen-2-yl)-2-tosyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole (**4h**).* Following the general procedure, the title compound was obtained (200 mg, 69%). A yellow solid, mp 71−72 °C; TLC (Et_2O/hexanes (1:2)) R_f = 0.33; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45−1.63 (m, 2 H), 2.36−2.40 (m, 2 H), 2.41 (s, 3 H), 2.50−2.59 (m, 1 H), 3.20 (dd, *J* = 9.9, 7.5 Hz, 1 H), 3.49 (d, *J* = 10.8 Hz, 1 H), 3.55 (dd, *J* = 9.9, 7.5 Hz, 1 H), 3.86 (d, *J* = 10.8 Hz, 1 H), 5.87 (s, 1 H), 7.27−7.49 (m, 5 H), 7.56 (s, 1 H), 7.70−7.79 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 21.9 (CH_2), 30.8 (CH_2), 41.8 (CH), 49.6 (CH_2), 52.3 (C), 58.0 (CH_2), 123.4 (C), 123.8 (CH), 125.1 (CH), 125.8 (CH), 125.9 (CH), 126.8 (CH × 2), 127.0 (CH), 127.5 (CH), 128.1 (CH), 129.4 (CH × 2), 130.9 (CH), 131.7 (C), 132.5 (C), 133.1 (C), 139.1 (C), 143.2 (C); IR (KBr) 2933, 1643, 1341 cm^{-1}; EI-MS *m*/*z* (rel intensity) 481 ($[M]^+$, 9), 402 (21), 326 (56), 198 (100); HRMS $[M]^+$ calcd for $C_{25}H_{24}BrNO_2S$: 481.0711, found 481.0706.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data (**3e**, **4c**) and complete characterization data (^1H and $^{13}C\{^1H\}$ NMR data) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mhlin@cc.ncue.edu.tw (M.-H.L.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Ministry of Science and Technology of the Republic of China, Taiwan, is gratefully acknowledged. We are also thankful for the assistance from Chang-Chih Hsieh and Hung-Chang Hsiao for the X-ray structure determination.

■ REFERENCES

(1) Gschwend, H. W.; Hillman, M. J.; Kisis, B. *J. Org. Chem.* **1976**, *41*, 104.

(2) Tsirk, A.; Gronowitz, S.; Hörnfeldt, A. B. *Tetrahedron* **1995**, *51*, 7035.

(3) O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Org. Biomol. Chem.* **2003**, *1*, 2038.

(4) (a) Tsirk, A.; Gronowitz, S.; Hörnfeldt, A. B. *Tetrahedron* **1998**, *54*, 9529. (b) Clary, K. N.; Parvez, M.; Back, T. G. *Org. Biomol. Chem.* **2009**, *7*, 1226. (c) Thomas, E. J. *Acc. Chem. Res.* **1991**, *24*, 229. (d) Flores, B.; Molinski, T. *Org. Lett.* **2011**, *13*, 3932.

(5) Hyodo, K.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10337.

(6) Shao, L.; Hewitt, M. C.; Malcolm, S. C.; Wang, F.; Ma, J.; Campbell, U. C.; Spicer, N. A.; Engel, S. R.; Hardy, L. W.; Jiang, Z. D.; Schreiber, R.; Spear, K. L.; Varney, M. A. *J. Med. Chem.* **2011**, *54*, 5283.

(7) Lin, M.-H.; Huang, Y.-C.; Kuo, C.-K.; Tsai, C.-H.; Li, Y.-S.; Hu, T.-C.; Chuang, T.-H. *J. Org. Chem.* **2014**, *79*, 2751.

(8) (a) Ma, S.; Wang, G. *Tetrahedron Lett.* **2002**, *43*, 5723. (b) Cho, Y. S.; Jun, B. K.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H.; Han, S. Y. *Synthesis* **2004**, *16*, 2620. (c) Deng, Y.; Jin, X.; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901. (d) A, J. M.; Lee, P. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 471. (e) Eom, D.; Kim, H.; Lee, P. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 645. (f) Alcaide, B.; Almendros, P.; Luna, A.; Prieto, N. *J. Org. Chem.* **2012**, *77*, 11388.

(9) The structure has been deposited with the Cambridge Crystallographic Data Centre (**3e**: CCDC 1042388). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) The structure has been deposited with the Cambridge Crystallographic Data Centre (**4c**: CCDC 1042387). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Reaction of bromo-dienes **3** with *N*-propargyl-*N*-(*p*-tosyl)amine under the same condition gave the cyclization precursor yne-dienes, but no cyclization product was observed.

DOI: 10.1021/acs.joc.5b00072
J. Org. Chem. 2015, 80, 2462−2466