JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

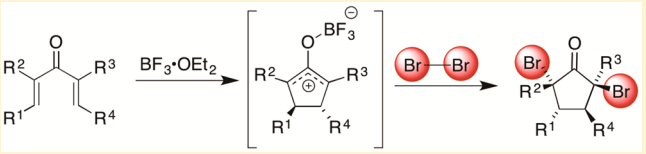
Interrupting the Nazarov Cyclization with Bromine

Devon J. Schatz, Yonghoon Kwon, Thomas W. Scully, and F. G. West*

Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB, Canada

Supporting Information

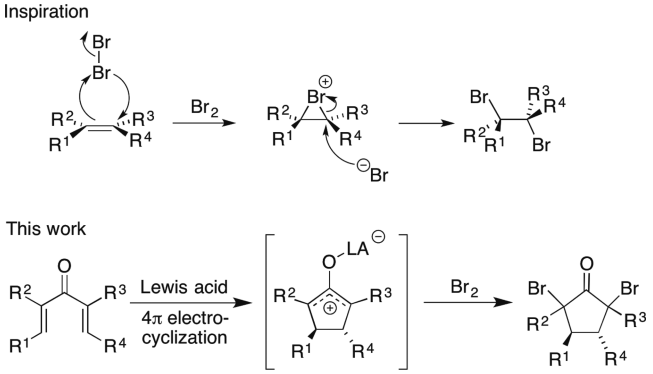
ABSTRACT: The generation of dibrominated cyclopentenones via an interrupted Nazarov cyclization is reported. The installation of two bromine atoms occurs at the α and α' positions of the cyclopentenyl scaffold via successive nucleophilic and electrophilic bromination of the 2-oxidocyclopentenyl cation and its resulting enolate. Notably, the reaction proceeds with good diastereoselectivity, favoring the symmetrical product.



The Nazarov cyclization has provided a convenient approach to cyclopentanoid scaffolds for years, affording cyclopentane or cyclopentene-containing products from readily available cross-conjugated 1,4-dien-3-ones.[1,2] Current activity concerning this transformation has focused on expansion to alternative substrates,[3] catalytic asymmetric reactions,[4] and domino/cascade processes.[5] With respect to the latter, various nucleophiles have been demonstrated to trap the oxyallyl cation produced from the electrocyclization of dienone precursors. This process delivers additional functionality adjacent to a cyclopentanone carbonyl group and, by circumventing the usual eliminative termination step, preserves the newly generated stereocenters at the former C-1 and C-5 atoms of the dienone. Proven nucleophiles include σ donors such as organoaluminum reagents[6] and azides[7] as well as π nucleophiles such as enol derivatives, alkynes, and electron-rich arenes and heterocycles.[8] When the oxyallyl cation is nucleophilically trapped, a reactive enolate moiety remains. While this intermediate is most often consumed via protonation, use of ambiphilic traps permits a second bond-forming step in which the enolate and an electrophilic site on the former nucleophile can combine in an overall cycloaddition process.[5,7,8] Reactions of this sort have afforded stereochemically enriched polycyclic frameworks, often ready for further functionalization. Recently, the concept of dual nucleophilic/electrophilic trapping has been established by employing an added external electrophile to give doubly substituted cyclopentanones.[6b]

As a rule, molecular halogen species are electrophilic, reacting with a variety of olefins through a well-established mechanism proceeding via opening of an intermediate bromonium ion by its bromide counterion (Scheme 1).[9] Given the potential for sequential electrophilic and nucleophilic reactivity by Nazarov intermediates, we were interested in seeing how it may behave in the presence of traps with analogous electronic characteristics such as bromine. An important consequence of this proposed reaction is the necessary inversion of polarity through the requirement of an initial nucleophilic attack by the bromine trap, followed by electrophilic bromination of the resulting enolate.

Scheme 1. Olefin Bromination versus Oxyallyl Cation Bromination



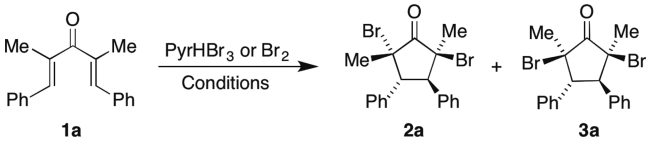
While trapping the Nazarov intermediate with halides has precedent, there have been no reports of installation of halogen atoms at both α positions. Our group,[10] as well as Burnell's group,[11] has described nucleophilic trapping with a single halide originating from Lewis acid reagents. Unfortunately, all of the published examples employ quite specialized substrates and are not generally applicable. On the other hand, electrophilic halogen sources have been employed for reaction with the dienolate species remaining after electrocyclization and the traditional elimination, though this approach entails the destruction of two stereocenters in the elimination step.[12]

We focused on the following questions. (1) Are bromination reagents compatible with Nazarov cyclization conditions to afford α,α'-dibromocyclopentanones? (2) If so, could the difunctionalized products be formed diastereoselectively? (3) Would competing bromination of the starting dienone interfere? Using dibenzylidenepentan-3-one **1a** as a test substrate, we attempted Nazarov cyclizations with various Lewis acids in the presence of the easily handled reagent pyridinium tribromide ($PyHBr_3$) as the bromine source (Table 1).

Received: September 26, 2016
Published: November 18, 2016

DOI: 10.1021/acs.joc.6b02350
J. Org. Chem. 2016, 81, 12494−12498

Table 1. Optimization of Reaction Conditions on Substrate 1a



entry	bromine source (equiv)	Lewis acid[a]	solvent[b]	temp (°C)	yield of **2a**[c] (**2a**:**3a** ratio)[d]
1	$PyHBr_3$ (2)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	51 (7.1:1)
2	$PyHBr_3$ (2)	TMSOTf	CH_2Cl_2	−78	41 (8.6:1)
3	$PyHBr_3$ (2)	$TiCl_4$	CH_2Cl_2	−78	66 (>20:1)[e]
4	$PyHBr_3$ (3)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	68 (8.6:1)
5	Br_2 (2)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	75 (5.4:1)
6	Br_2 (2)	$TiCl_4$	CH_2Cl_2	−78	79 (9.5:1)
7	$PyHBr_3$ (1)	$BF_3{\cdot}OEt_2$	MeCN/CH_2Cl_2 (4:1)	−41	68 (3.9:1)

[a]For all reactions, 1.2 equiv of Lewis acid was used. [b]Reactions were performed at 0.1 M. [c]Yields given for **2a** are for isolated product after purification by column chromatography. [d]Product ratios determined by integration of the methine proton signals in the ^{1}H NMR spectra. [e]Minor isomer could not be observed.

The dienone concentration and the number of equivalents of Lewis acid were held constant at 0.1 M and 1.2 equiv, respectively. Using $BF_3{\cdot}OEt_2$ as a Lewis acid, we immediately observed evidence of successful dibromination. Spectroscopic analysis indicated that the major product was symmetrical α,α'-dibrominated compound **2a**, formed in 51% yield (entry 1). Minor amounts of a diastereomeric product (**3a**) were isolated in most cases. Compound **3a** could be distinguished from **2a** by the lack of molecular symmetry observed in its NMR spectra, and the large chemical shift difference seen for the two methyl groups (δ 1.34 and 1.94) due to anisotropic shielding of the methyl that is *cis* to the neighboring phenyl substituent. Two other Lewis acids (TMSOTf and $TiCl_4$) were screened, and both furnished the desired dibrominated products. Despite slightly higher yields seen with $TiCl_4$, $BF_3{\cdot}OEt_2$ was selected for subsequent evaluations because of the greater ease of handling.

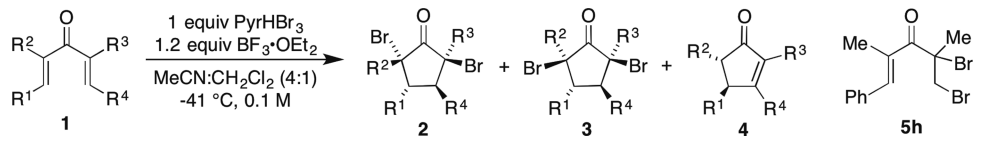
Given an acceptable yield of 68% using 3 equiv of $PyHBr_3$ (entry 4), we were curious to see how molecular bromine compared (entries 5 and 6). In this event, yields were slightly higher, with similar product ratios. Nonetheless, we judged $PyrHBr_3$ to be preferable because of its greater convenience and consequently used it initially in subsequent studies of reaction scope.

Our evaluation of substrate scope (Table 2) began with dienone **1b**. However, the bulky naphthyl groups along with the poor solubility of perbromide in dichloromethane seemed to disfavor bromide trapping (entry 3). Instead, the reaction was directed to elimination product **4b**. To circumvent the solubility issue, we switched to a $MeCN/CH_2Cl_2$ (4:1) two-solvent system and performed the reaction at −41 °C. The number of equivalents of perbromide was also decreased to 1 out of fear of overbrominating the electron-rich substrate.[13] This resulted in a cleaner reaction, and the desired product was obtained in 47% yield. The reaction conditions were also applied to **1a** and furnished products in a combined 80% yield, despite the reduced amount of $PyrHBr_3$. In light of this result, subsequent examples were conducted under these conditions, which proved to be successful with substrates containing at least one aromatic substituent (entries 1, 2, 4, 6, and 7). Notably, electron-rich difuryl substrate **1f** did not suffer any undesired overbromination (entry 7).

Reaction yields for symmetrically substituted starting materials containing aromatics proceeded in generally good yields (entries 1, 2, and 4). Among the unsymmetrical substrates, **1e**, bearing a larger alkyl substituent at one α position, furnished product in a somewhat diminished yield. Likewise, monoaryl dienone **1g** also provided lower yields, and only **2g** could be isolated (entry 8). We cannot rule out the formation of **3g**, as other components could not be isolated from an intractable mixture of side products. Attempts to isolate **3g** from large-scale reactions were unsuccessful; however, it is notable that very little diminution in yield was observed (38% vs 40%) at this scale (5.6 mmol of **1g** used).

The one dienone lacking any aromatic substitution (**1d**) failed to yield any identifiable Nazarov-derived products, indicating a limitation of this methodology for the time

Table 2. Examination of Substrate Scope



entry	substrate	R^1	R^2	R^3	R^4	product [yield (%)]
1	**1a**	Ph	Me	Me	Ph	**2a** (66) and **3a** (14)
2	**1b**	1-naphth	Me	Me	1-naphth	**2b** (47) and **4b** (15)
3[a]	**1b**	1-naphth	Me	Me	1-naphth	**4b** (20) and intractable mixture
4	**1c**	4-ClC_6H_4	Me	Me	4-ClC_6H_4	**2c** (64) and **3c** (12)
5	**1d**	*i*-Pr	Me	Me	*i*-Pr	NA[b]
6	**1e**	Ph	Me	*n*-Pr	Ph	**2e** (48) and **3e** (7)
7	**1f**	2-furyl	Me	Me	2-furyl	**2f** (59) and **3f** (23)
8	**1g**	Ph	Me	Me	*i*-Pr	**2g** (40)[c]
9	**1g**	Ph	Me	Me	*i*-Pr	**2g** (38)[d]
10	**1h**	Ph	Me	Me	H	**5h** (70)

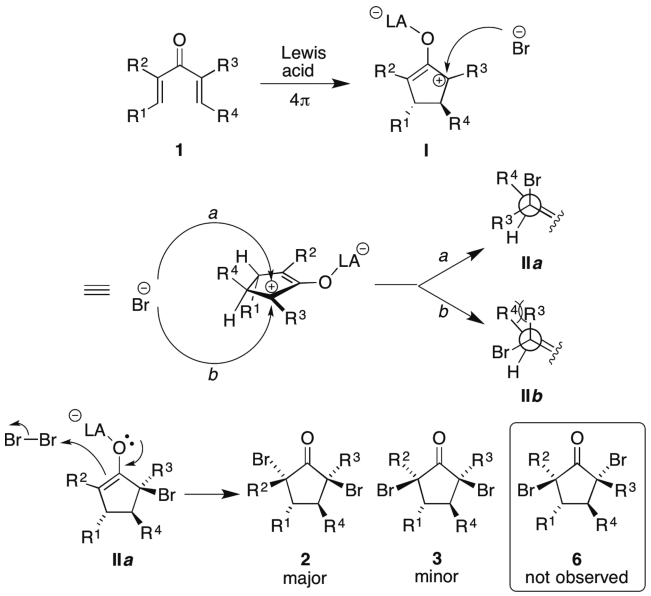
[a]This result was obtained when initial optimized conditions (entry 4, Table 1; condition 1 in the Supporting Information) were used. [b]An intractable mixture was formed upon the addition of any of the Lewis acids from Table 1. [c]Product **3g** was undetected by TLC and subsequently not isolated. [d]This reaction was run using 1.0 g (5.6 mmol) of **1g**.

DOI: 10.1021/acs.joc.6b02350
J. Org. Chem. 2016, 81, 12494−12498

being. Moreover, substrate **1h**, which lacks a β substituent on one of the dienone alkenes, did not afford any products derived from electrocyclization and/or trapping (entry 10). Although this compound is a proven reactive Nazarov substrate,[8b] under these conditions the less substituted olefin readily undergoes bromination to provide **5h**, presumably as a result of diminished steric demand at this site.[14]

A general preference for C_2-symmetric products **2**, with an all-*anti* disposition of R groups, was confirmed by single-crystal X-ray diffraction analysis of **2a**[15] and spectral analogy.[16] This may be attributed to the steric demand of the large β substituents. Initial nucleophilic attack of the 2-oxidocyclopentenyl cation by bromide prefers to follow path a (Scheme 2).

Scheme 2. Proposed Mechanism of the Reaction



Although this entails approach *syn* to the neighboring β substituent (R^4 in this case), it allows R^3 to avoid the developing eclipsing interaction with R^4 that would result from attack of the opposite face (path b). Placing the bromine atom in this orientation is favored, given its relatively small *A* value. The resulting enolate is then quenched by reaction with Br_2, regenerating a bromide nucleophile. In analogy to the first bromination, the relative stereochemistry is guided by avoidance of an R^1/R^2 eclipsing interaction to furnish **2**. In the case of symmetrical substrates ($R^1 = R^4$ and $R^2 = R^3$), minor isomer **3** could result from the disfavored approach in either bromination step. The absence of the other symmetrical dibromide **6** from any of these examples is unsurprising, as it would require two successive disfavored trapping processes to occur.

In summary, we have developed a convenient and simple route to α,α'-dibrominated cyclopentanones, via an unprecedented diatomic halogenation of the Nazarov intermediate. Assuming sequential addition of bromine atoms, both reactions occur with high selectivity, leading to symmetrical products. These stereochemically enriched scaffolds could prove to be useful synthetic building blocks. Further development employing other halogen traps is underway and will be reported elsewhere.

EXPERIMENTAL SECTION

General Information. Reactions were conducted in oven-dried glassware under a positive nitrogen atmosphere. Solvents were distilled before use: dichloromethane and acetonitrile from calcium hydride. Thin layer chromatography was performed on glass plates precoated with silica gel (0.25 mm, 60 Å porosity, F-254 indicator). Flash chromatography columns were packed with standard silica gel (60 Å porosity, 230−400 mesh). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz, and coupling constants (*J*) are reported in hertz. Standard notation is used to describe the multiplicity of signals observed in ^{1}H NMR spectra: broad (br), apparent (app.), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz and are reported (parts per million) relative to the center line of the triplet from chloroform-*d* (77.06 ppm). Infrared (IR) spectra were recorded using the ATIR method. Spectra with selected resonances are reported as the frequency of absorption in inverse centimeters. High-resolution mass spectrometry (HRMS) data (APPI/APCI/ESI technique) were recorded using an orthogonal time-of-flight analyzer. HRMS data (EI technique) were recorded using a double-focusing sector mass spectrometer. Divinyl ketones **1a**,[17] **1c**,[18] **1d**,[7b] **1e**,[7b] **1f**,[6a] **1g**,[19] and **1h**[20] were prepared via literature procedures.

Preparation of Divinyl Ketone 1b. Divinyl ketone **1b** was synthesized using a modification of a known procedure.[17] NaOH (4.00 g, 100.0 mmol, 6.3 equiv) was dissolved in H_2O (30 mL) followed by the addition of EtOH (20 mL). 3-Pentanone (1.69 mL, 16.0 mmol) and 1-naphthaldehyde (2.61 mL, 19.2 mmol, 1.2 equiv) were added to the basic solution simultaneously. The reaction mixture was warmed to 80 °C and stirred overnight. The aqueous solution was extracted with diethyl ether (3 × 50 mL) and the organic layer washed with 10% HCl (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL) and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation, and purified by column chromatography (silica gel, hexanes/EtOAc, column volume ratios of 20:1 to 17:1) to yield the enone that was carried onto the next step.

To a solution of enone (1.50 g, 6.7 mmol) in CH_2Cl_2 (50 mL, 0.13 M) at −78 °C was added $TiCl_4$ (0.73 mL, 6.7 mmol, 1.0 equiv) followed by *i*-Pr_2NEt (1.40 mL, 8.0 mmol, 1.2 equiv), and the mixture was stirred for 1.5 h. 1-Naphthaldehyde (1.36 mL, 10.0 mmol, 1.5 equiv) was diluted in 5 mL of CH_2Cl_2 and added dropwise via an addition funnel. The reaction mixture was stirred for 2.5 h, the reaction quenched with H_2O (50 mL), and the mixture extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was then washed with H_2O (2 × 50 mL) and brine (1 × 50 mL) and dried ($MgSO_4$). After rotary evaporation, ^{1}H NMR showed full conversion to a mixture of diastereotopic β-hydroxyketones, which were carried directly onto the next step.

To a solution of β-hydroxyketones (1.80 g, 4.7 mmol) in CH_2Cl_2 (30 mL, 0.16 M) in an argon-flushed flask at 0 °C was added TEA (1.64 mL, 11.8 mmol, 2.5 equiv). MsCl (0.40 mL, 5.2 mmol, 1.1 equiv) was then added dropwise. The reaction mixture was stirred for 15 min before the addition of DBU (3.16 mL, 21.1 mmol, 4.5 equiv) and then continued to stir overnight. The solution was concentrated by rotary evaporation and purified by column chromatography (silica gel, hexanes/EtOAc, column volumes of 20:1 to 16:1).

*(1E,4E)-2,4-Dimethyl-1,5-di(naphthalen-1-yl)penta-1,4-dien-3-one (**1b**).* Off-white solid (1.35 g, 79%): R_f = 0.44 (9:1 hexanes/EtOAc); mp 113−115 °C; IR (cast film) 3058, 2954, 2920, 1639, 1507, 1441 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.92−7.85 (m, 6H), 7.56−7.47 (m, 8H), 2.14 (d, *J* = 1.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 201.5, 139.4, 137.2, 133.6, 133.2, 131.5, 128.7, 128.7, 126.8, 126.6, 126.2, 125.3, 124.6, 15.1; HRMS (EI) calcd for $C_{27}H_{22}O$ *m*/*z* 362.1671, found *m*/*z* 362.1678.

Standard Procedure for Bromination (condition 1). To a stirred solution of divinyl ketone (0.2 mmol, 0.1 M) in CH_2Cl_2 at −78 °C was added pyridinium bromide perbromide (0.19 g, 0.6 mmol). The solution was stirred for 5 min before $BF_3{\cdot}OEt_2$ (0.030 mL, 0.24 mmol) was added. The mixture was stirred for 30 min and then the

DOI: 10.1021/acs.joc.6b02350
J. Org. Chem. 2016, 81, 12494−12498

reaction quenched with $HCl_{(aq)}$ (2 mL, 2 M) and the mixture extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (1 × 20 mL) and brine (1 × 20 mL) and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation, and purified by column chromatography (silica gel, hexanes/EtOAc, column volumes of 19:1 to 9:1).

Standard Procedure for Bromination (condition 2). Pyridinium bromide perbromide (0.064 g, 0.2 mmol) was stirred in a MeCN/CH_2Cl_2 solvent (4:1, 2 mL) and cooled to −41 °C before BF_3·OEt_2 (0.030 mL, 0.24 mmol) was added. The solution was stirred for 5 min before the addition of divinyl ketone (0.2 mmol, 0.1 M) in a single addition. The mixture was stirred for 30 min, the reaction quenched with $HCl_{(aq)}$ (2 mL, 1 M), and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (1 × 20 mL) and brine (1 × 20 mL) and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation, and purified by column chromatography (silica gel, hexanes/EtOAc, column volumes of 19:1 to 9:1).

Divinyl ketone **1a** (52 mg, 0.2 mmol) was subjected to condition 2, yielding **2a** (56 mg, 66%) and **3a** (12 mg, 14%) as white solids.

(2S,3R*,4R*,5S*)-2,5-Dibromo-2,5-dimethyl-3,4-diphenylcyclopentan-1-one (**2a**).* R_f = 0.48 (9:1 hexanes/EtOAc); mp 150−152 °C; IR (cast film) 3031, 2912, 1754, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.21 (m, 10H), 3.76 (s, 2H), 2.10 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.0, 134.5, 129.8, 128.1, 127.8, 68.4, 54.1, 26.0; HRMS (EI) calcd for $C_{19}H_{18}{}^{79}Br^{81}BrO$ m/z 421.9704, found m/z 421.9708.

(2R,3R*,4R*,5S*)-2,5-Dibromo-2,5-dimethyl-3,4-diphenylcyclopentan-1-one (**3a**).* R_f = 0.19 (9:1 hexanes/EtOAc); mp 140−141 °C; IR (cast film) 3063, 3032, 2971, 2922, 1754, 1602, 1499, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.22 (m, 10H), 4.80 (d, J = 13.1 Hz, 1H), 3.25 (d, J = 13.0 Hz, 1H), 1.94 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 206.1, 133.9, 133.8, 129.5, 129.1, 128.5, 128.3, 128.1, 127.8, 65.5, 59.9, 55.4, 53.9, 24.6, 24.6; HRMS (EI) calcd for $C_{19}H_{18}{}^{79}Br^{81}BrO$ m/z 421.9704, found m/z 421.9698.

Divinyl ketone **1b** (72 mg, 0.2 mmol) was subjected to condition 2, yielding **2b** (49 mg, 47%) and **4b** (11 mg, 15%) as white solids.

(2S,3R*,4R*,5S*)-2,5-Dibromo-2,5-dimethyl-3,4-di(naphthalen-1-yl)cyclopentan-1-one (**2b**).* R_f = 0.39 (9:1 hexanes/EtOAc); mp 178−180 °C; IR (cast film) 3050, 2971, 1754, 1599, 1511, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 16.7 Hz, 2H), 7.65 (m, 4H), 7.52 (app. t, J = 7.5 Hz, 2H), 7.38 (d, J = 7.5 Hz, 2H), 7.17 (t, J = 7.8 Hz, 2H), 4.29 (s, 2H), 2.11 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.2, 133.9, 133.1, 130.5, 129.4, 128.4, 127.4, 126.5, 125.5, 124.9, 122.8, 70.8, 49.1, 27.6; HRMS (EI) calcd for $C_{27}H_{22}{}^{79}Br^{81}BrO$ m/z 520.0037, found m/z 520.0033.

(4S,5R*)-2,5-Dimethyl-3,4-di(naphthalen-1-yl)cyclopent-2-en-1-one (**4b**).* R_f = 0.20 (9:1 hexanes/EtOAc); mp 122−124 °C; IR (cast film) 3056, 2974, 2932, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.91 (app. d, J = 8.4 Hz, 1H), 7.81 (app. d, J = 8.3 Hz, 1H), 7.79 (app. d, J = 8.1 Hz, 1H), 7.73 (m, 1H), 7.64−7.56 (m, 2H), 7.54−7.48 (m, 2H), 7.48−7.40 (m, 1H), 7.35−7.27 (m, 2H), 7.25−7.14 (m, 2H), 5.68 (d, J = 6.2 Hz, 1H), 3.29 (app. pent, J = 7.3 Hz, 1H), 1.79 (d, J = 1.7 Hz, 3H), 0.73 (d, J = 8.5, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 211.5, 167.7, 140.6, 134.7, 134.1, 133.9, 133.7, 132.8, 130.1, 129.0, 128.9, 127.4, 126.6, 126.3, 126.1, 126.0, 125.6, 125.3, 125.1, 125.0, 122.9, 48.9, 45.6, 12.5, 10.5; HRMS (EI) calcd for $C_{27}H_{22}O$ m/z 362.1671, found m/z 362.1673.

Divinyl ketone **1c** (66 mg, 0.2 mmol) was subjected to condition 2, yielding **2c** (62 mg, 64%) and **3c** (12 mg, 12%) as white solids.

*(2*S,3R*,4R*,5S*)-2,5-Dibromo-3,4-bis(4-chlorophenyl)-2,5-dimethylcyclopentan-1-one (**2c**).* R_f = 0.46 (9:1 hexanes/EtOAc); mp 182−185 °C; IR (cast film) 2971, 2918, 1755, 1495, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.25 (m, 4H), 7.17−7.13 (m 4H), 3.68 (s, 2H), 2.07 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 202.2, 134.0, 132.7, 131.0, 128.5, 67.6, 53.7, 25.9; HRMS (EI) calcd for $C_{19}H_{16}{}^{79}Br_2{}^{35}Cl_2O$ m/z 487.8945, found m/z 487.8939.

(2R,3R*,4R*,5S*)-2,5-Dibromo-3,4-bis(4-chlorophenyl)-2,5-dimethylcyclopentan-1-one (**3c**).* R_f = 0.17 (9:1 hexanes/EtOAc); mp 187−189 °C; IR (cast film) 2971, 2919, 1756, 1494, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 6H), 7.21−7.17 (m, 2H), 4.70, (d, J = 13.1 Hz, 1H), 3.17 (d, J = 13.1 Hz, 1H), 1.92 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.2, 134.3, 134.0, 132.1, 132.0, 130.7, 130.3, 128.9, 128.7, 64.8, 59.1, 55.1, 53.5, 24.5, 24.4; HRMS (EI) calcd for $C_{19}H_{16}O^{79}Br^{81}Br^{35}Cl_2$ m/z 489.8925, found m/z 489.8924.

Divinyl ketone **1e** (116 mg, 0.4 mmol) was subjected to condition 2, with the exception of the eluent system for column chromatography (hexanes/ether, column volumes of 99:1 to 20:1), yielding **2e** (112 mg, 62%) and **3e** (12 mg, 7%) as white solids.

(2S,3R*,4R*,5S*)-2,5-Dibromo-2-methyl-3,4-diphenyl-5-propylcyclopentan-1-one (**2e**).* R_f = 0.59 (9:1 hexanes/EtOAc); mp 139−142 °C; IR (cast film) 3031, 2964, 2932, 1751, 1499, 1452, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27−7.18 (m, 10H), 3.92 (d, J = 12.2 Hz, 1H), 3.80 (d, J = 12.3 Hz, 1H), 2.43 (ddd, J = 14.2, 12.5, 4.0 Hz, 1H), 2.11 (ddd, J = 14.0, 12.5, 4.4 Hz, 1H), 2.08, (s, 3H), 1.92−1.81 (m, 1H), 1.60−1.49 (m, 1H), 1.08 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 202.5, 134.8, 134.7, 129.9, 129.9, 128.1, 128.1, 127.7, 127.7, 73.4, 68.5, 54.1, 49.4, 39.0, 26.2, 19.9, 14.2; HRMS (EI) calcd for $C_{21}H_{22}{}^{79}Br^{81}BrO$ m/z 450.0017, found m/z 450.0009.

(2R,3R*,4R*,5S*)-2,5-Dibromo-2-methyl-3,4-diphenyl-5-propylcyclopentan-1-one (**3e**).* R_f = 0.39 (9:1 hexanes/EtOAc); mp 106−109 °C; IR (cast film) 3032, 2965, 2931, 1753, 1499, 1453, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 10H), 4.75 (d, J = 13.0 Hz, 1H), 3.56 (d, J = 13.0 Hz, 1H), 2.36 (ddd, J = 14.1, 12.4, 4.0 Hz, 1H), 2.06 (ddd, J = 14.1, 12.4, 4.7 Hz, 1H), 1.82−1.72 (m, 1H), 1.34 (s, 3H), 1.33−1.25 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.8, 134.3, 133.9, 129.5, 129.2, 128.5, 128.3, 127.9, 127.8, 70.1, 60.8, 55.2, 49.0, 38.6, 23.8, 19.9, 14.2; HRMS (EI) calcd for $C_{21}H_{22}{}^{79}Br^{81}BrO$ m/z 450.0017, found m/z 450.0017.

Divinyl ketone **1f** (48 mg, 0.2 mmol) was subjected to condition 2, yielding **2f** (49 mg, 59%) and **3f** (19 mg, 23%) as white solids.

(2S,3R*,4R*,5S*)-2,5-Dibromo-3,4-di(furan-2-yl)-2,5-dimethylcyclopentan-1-one (**2f**).* R_f = 0.48 (9:1 hexanes/EtOAc); mp 136−138 °C; IR (cast film) 1751, 1503, 1261, 1012, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 1.3 Hz, 2H), 6.32 (dd, J = 3.1, 1.8 Hz, 2H), 6.11 (d, J = 3.4 Hz, 2H), 3.76 (s, 2H), 2.14 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 202.0, 150.4, 142.2, 110.3, 108.7, 66.3, 48.6, 26.4; HRMS (EI) calcd for $C_{15}H_{14}{}^{79}Br^{81}BrO_3$ m/z 401.9289, found m/z 401.9291.

(2R,3R*,4R*,5S*)-2,5-Dibromo-3,4-di(furan-2-yl)-2,5-dimethylcyclopentan-1-one (**3f**).* R_f = 0.34 (9:1 hexanes/EtOAc); mp 118−122 °C; IR (cast film) 1756, 1504, 1252, 1013, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.0 Hz, 2H), 6.37−6.31 (m, 3H), 6.13 (d, J = 3.2 Hz, 1H), 4.55 (d, J = 12.7 Hz, 1H), 3.48 (d, J = 12.6 Hz, 1H), 2.03 (s, 3H), 1.46 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.2, 149.8, 148.7, 142.7, 142.3, 110.6, 110.3, 109.8, 108.6, 63.6, 58.1, 50.7, 48.3, 25.0, 24.7; HRMS (EI) calcd for $C_{15}H_{14}{}^{79}Br^{81}BrO_3$ m/z 401.9289, found m/z 401.9287.

Divinyl ketone **1g** (46 mg, 0.2 mmol) was subjected to condition 2, yielding **2g** (31 mg, 40%) as a white solid.

To determine the scalability of this reaction, condition 2 was slightly modified to the procedure described below, which allowed **1g** to be reacted on a 5.6 mmol scale with only a slight loss of yield (2%).

Pyridinium bromide perbromide (1.84 g, 5.8 mmol) was stirred in a MeCN/CH_2Cl_2 solvent (4:1, 110 mL) and cooled to −41 °C before BF_3·OEt_2 (0.87 mL, 6.91 mmol) was added dropwise over 10 min. The solution was stirred for 15 min before the slow addition of divinyl ketone **1g** (5.8 mmol, 0.1 M in a 4:1 MeCN/CH_2Cl_2 solvent), in a single addition via syringe. The mixture was stirred for 30 min and then the reaction quenched with HCl (aq) (30 mL, 1 M). The aqueous layer was rinsed with CH_2Cl_2 (2 × 25 mL), and combined organic layers were washed with water (1 × 25 mL) and brine (1 × 25 mL) and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation, and purified by column chromatography (silica gel, hexanes/EtOAc, column volumes of 19:1 to 9:1). Product **2g** was isolated as a white solid (0.848 g, 2.2 mmol) in a 38% yield compared to a 40% yield of **2g** when prepared on a small scale.

(2S,3S*,4R*,5S*)-2,5-Dibromo-3-isopropyl-2,5-dimethyl-4-phenylcyclopentan-1-one (**2g**).* R_f = 0.64 (9:1 hexanes/EtOAc); mp 98−

DOI: 10.1021/acs.joc.6b02350
J. Org. Chem. 2016, 81, 12494−12498

100 °C; IR (cast film) 2969, 1751, 1375, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 3.07 (d, J = 12.3 Hz, 1H), 2.34 (dd, J = 12.3, 3.6 Hz, 1H), 2.13 (doublet of septets, J = 7.3, 3.6 Hz, 1H), 2.06 (s, 3H), 1.87 (s, 3H), 1.10 (d, J = 7.3 Hz, 3H), 0.80 (d, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.7, 136.4, 130.5, 127.9, 127.8, 70.2, 69.5, 55.4, 52.9, 29.4, 27.4, 25.5, 24.8, 20.4; HRMS (EI) calcd for $C_{16}H_{20}{}^{79}Br^{81}BrO$ m/z 387.9861, found m/z 387.9861.

Divinyl ketone **1h** (37 mg, 0.2 mmol) was subjected to condition 2, yielding **5h** (48 mg, 70%) as a yellow oil.

*(E)-4,5-Dibromo-2,4-dimethyl-1-phenylpent-1-en-3-one (**5h**).* R_f = 0.74 (9:1 hexanes/EtOAc); IR (cast film) 3056, 3024, 2979, 2931, 1674, 1624, 1448, 769, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (q, J = 1.4 Hz, 1H), 7.45−7.32 (m, 5H), 4.40 (dd, J = 10.0, 0.8 Hz, 1H), 3.88 (d, J = 10.0 Hz, 1H), 2.18 (d, J = 1.6 Hz, 3H), 2.14 (d, J = 0.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.2, 136.8, 135.5, 134.5, 129.6, 128.5, 128.4, 59.0, 39.5, 28.0, 16.3; HRMS (EI) calcd for $C_{13}H_{14}{}^{79}Br^{81}BrO$ m/z 345.9391, found m/z 345.9390.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02350.

ORTEP structure and crystallographic experimental details for **2a** and ^1H NMR and ^{13}C NMR spectra of compounds **1b**, **2a−c**, **2e−g**, **3a**, **3c**, **3e**, **3f**, **4b**, and **5h** (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: frederick.west@ualberta.ca. Fax: +1 780 492 8231. Telephone: +1 780 492 8187.

ORCID

F. G. West: 0000-0001-7419-2314

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC (RGPIN 249822) for support of this work.

■ REFERENCES

(1) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, U.K., 2014; Vol. *5*, pp 827−866.

(2) For reviews on the Nazarov cyclization, see: (a) Wenz, D. R.; Read de Alaniz, J. *Eur. J. Org. Chem.* **2015**, *2015*, 23−37. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *2005*, 2193−2206. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479−6517.

(3) (a) Di Grandi, M. J. *Org. Biomol. Chem.* **2014**, *12*, 5331−5345. (b) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621−3633. (c) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979−3002.

(4) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851−5870.

(5) Review: Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676−5870.

(6) (a) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8616−8619; *Angew. Chem.* **2013**, *125*, 8778−8781. (b) Kwon, Y.; Scadeng, O.; McDonald, R.; West, F. G. *Chem. Commun.* **2014**, *50*, 5558−5560.

(7) (a) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703−706. (b) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114−117.

(8) (a) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876−877. (b) Wu, Y.-K.; Dunbar, C. R.; McDonald, R.; Ferguson, M. J.; West, F. G. *J. Am. Chem. Soc.* **2014**, *136*, 14903−14911. (c) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685−1689. (d) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2011**, *353*, 64−68. (e) Wu, Y.-K.; West, F. G. *Org. Lett.* **2014**, *16*, 2534−2537.

(9) Lenoir, D.; Chiappe, C. *Chem. - Eur. J.* **2003**, *9*, 1036−1044.

(10) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629−5632.

(11) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213−7216.

(12) For electrophilic trapping examples, see: (a) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284−2286. (b) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053−3056. (c) Kawatsura, M.; Kajita, K.; Hayase, S.; Itoh, T. *Synlett* **2010**, *2010*, 1243−1246. (d) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450−11452.

(13) Adimurthy, S.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. *Green Chem.* **2008**, *10*, 232−237.

(14) Grosjean, D.; Mouvier, G.; Dubois, J.-E. *J. Org. Chem.* **1976**, *41*, 3869−3872.

(15) CCDC 1481175 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) Symmetrical products **2a−c** and **2f** all showed fewer peaks, and the methine protons appeared as singlets as expected. There is also a reliable trend in the chemical shift of protons on the α groups. Those *syn* to an aryl at the β position experience an upfield shift relative to their *anti* counterparts, allowing us to assign the all-*anti* configuration to **2e** on the basis of the chemical shifts of the alkyl chain protons.

(17) Arnold, A.; Markert, M.; Mahrwald, R. *Synthesis* **2006**, *7*, 1099−1102.

(18) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50−56.

(19) Kwon, Y.; Schatz, D. J.; West, F. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 9940−9943.

(20) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750.

DOI: 10.1021/acs.joc.6b02350
J. Org. Chem. 2016, 81, 12494−12498