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A Facile Three-Component One-Pot Synthesis of Structurally Constrained Tetrahydrofurans That Are t-RNA Synthetase Inhibitor Analogues

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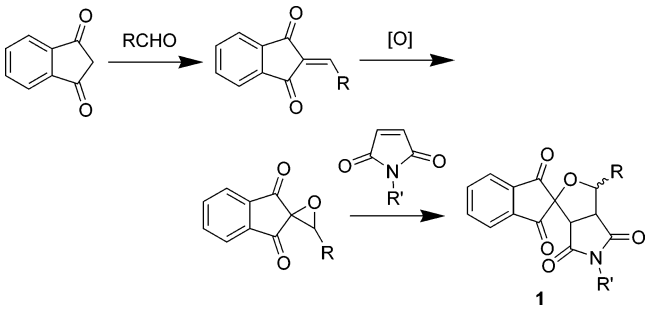
Abstract: A one-pot procedure for the efficient synthesis of tRNA inhibitor analogues was developed. Thus, three-component 1,3-dipolar cycloaddition reactions of carbonyl ylides derived from diazoindan-1,3-dione and aldehydes with other dipolarophiles in 1,1,2,2-tetrachloroethane in 80 °C gave ring-fused tetrahydrofurans having three stereocenters in good yield.

The synthesis of highly substituted tetrahydrofurans, which are found in many biologically interesting natural products, has attracted considerable attention in recent years.[1] Tandem carbonyl ylide/1,3-dipolar cycloaddition, especially via intramolecular reactions, is a powerful strategy for the construction of tetrahydrofurans,[2] and they have been applied broadly in the syntheses of natural products. In contrast, the utility of comparable intermolecular reactions has received limited attention. Pioneering studies initiated by Huisgen established a methodology for tetrahydrofuran synthesis through 1,3-dipolar cycloaddition of carbonyl ylides derived from diazo compounds and aromatic aldehydes with an electron-deficient alkene.[3] There are only a few diazo compounds that have been successfully employed in this three-component intermolecular process to give 1,3-dipolar addition products in good yield.[4] Since several reaction pathways may be involved to compete with the desired process (e.g., cycloaddition of carbonyl ylide give to a dioxolane[5]), we set out to explore and refine the reaction conditions to make the intermolecular carbonyl−ylide cycloaddition as a dominant pathway.

SCHEME 1



Ring-fused tetrahydrofurans **1** inhibit the enzymatic activity of transfer ribonucleic acid (tRNA) synthetase and are useful as antimicrobial agents.[6] Their amide hydrolysis products were also used for potential treatment of papilloma virus (PV) infection, particularly human papilloma virus (HPV).[7a] *cis-cis*-**1** (R = 4-ClPh, R′ = piperonyl) was the only lead out of 140 000 compounds screened for HPV inhibitors.[7b] The reported protocol for the synthesis of **1** involved multiple steps (condensation of indan-1, 3-dione with aldehyde, epoxidation, and then thermal 1,3-dipolar cycloaddition) (Scheme 1),[7b,8] and poor overall yields in some cases have limited this synthetic approach. For example, when cinnamaldehyde and *N*-4-acetophenylmaleimide were used, only 4% overall yield of product (**1**: R = *trans*-PhCH=CH, R′ = *p*-MeCOPh) was obtained (first step with 11% yield and 38% overall yield of second and third steps).[8]

Synthetically, metal-catalyzed three-component carbonyl ylide formation/cycloaddition reaction of 2-diazoindan-1,3-dione with aldehydes and maleimides could afford **1** in a one-pot process (Scheme 2). Unfortunately, previous studies toward this objective were frustrating. For example, dirhodium(II)-catalyzed diazo decomposition of **2** with piperonal (**3d**) and *N*-piperonylmaleimide (**4e**) in refluxing benzene gave the corresponding product **1** in only 8% yield,[7] and other examples from our laboratory gave a similar outcome. In this paper, we report our efforts to modify reaction conditions to optimize this convenient three-component 1,3-dipolar process.

(1) Reviews: (a) Greve, S.; Reck, S.; Friedrichsen, W. *Prog. Hetercycl. Chem.* **1998**, *10*, 129. (b) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303.

(2) Reviews: (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998. (f) Padwa, A.; Pearson, W. H. *The Chemistry of Heterocyclic Compounds*; Wiley & Sons: New York, 2002; Chapter 4. (g) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477. (h) Hodgson, D. M.; Pierad, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.

(3) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953.

(4) (a) Alt, M.; Maas, G. *Tetrahedron* **1994**, *50*, 7435. (b) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (c) Wenkert, E., Khatuya, H. *Tetrahedron lett.* **1999**, *40*, 5439. (d) Hamaguchi, M.; Matsubara, H.; Nagai, T. *J. Org. Chem.* **2001**, *66*, 5395. (e) Johnson, T.; Cheshire, D. R.; Stocks, M. J.; Thurston, V. T. *Synlett* **2001**, 646. (f) Skaggs, A. J.; Lin, E. Y.; Jamison, T. F. *Org. Lett.* **2002**, *4*, 2277. (g) Nair, V.; Mathai, S.; Varma, R. L.; *J. Org. Chem.* **2004**, *69*, 1413.

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(7) (a) Yoakim, C.; Hache, B.; Ogilvie, W.; O'Meara, J. A.; White, P. W.; Goudreau, N. PCT Int. Appl. WO 0250082, 2002; *Chem. Abstr.* **2002**, *137*, 63181. (b) Yoakim, C.; Ogilvie, W. W.; Goudreau, N.; Naud, J.; Haché, B.; O′Meara, J. A.; Cordingley, M. G.; Archambault, J.; White, P. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2539.

(8) Krysin, M. Yu.; Anokhina, I. K.; Zalukaev, L. P. *Khim. Geterotsikl. Soedin.* **1987**, *11*, 1463.

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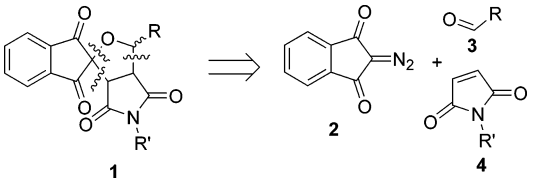
SCHEME 2



SCHEME 3

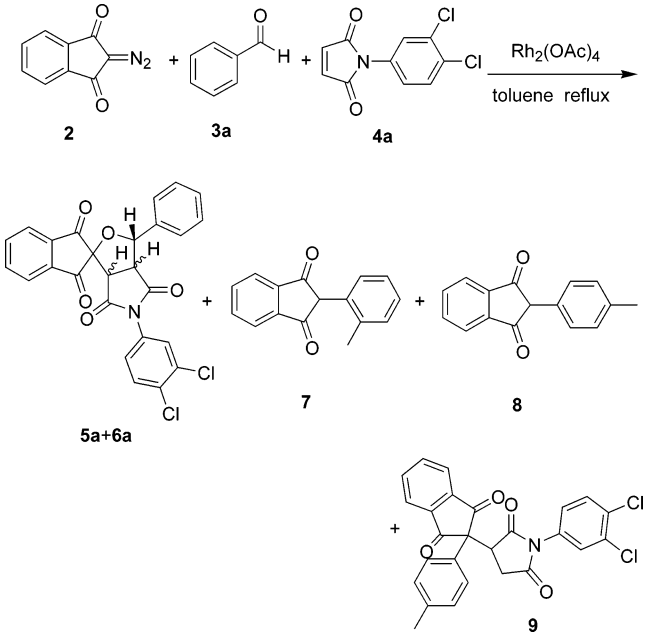
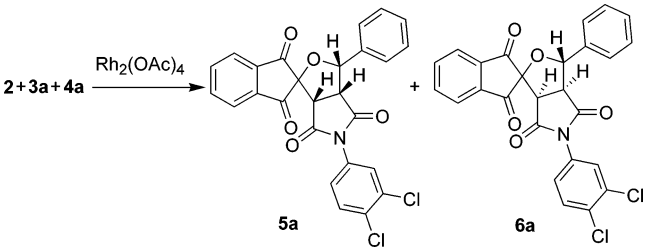


TABLE 1. Reaction of Diazoindan-1,3-dione (2) with Benzaldehyde (3a) and *N*-3,4-Dichlorophenylmaleimide (4a) in Different Reaction Conditions[a]

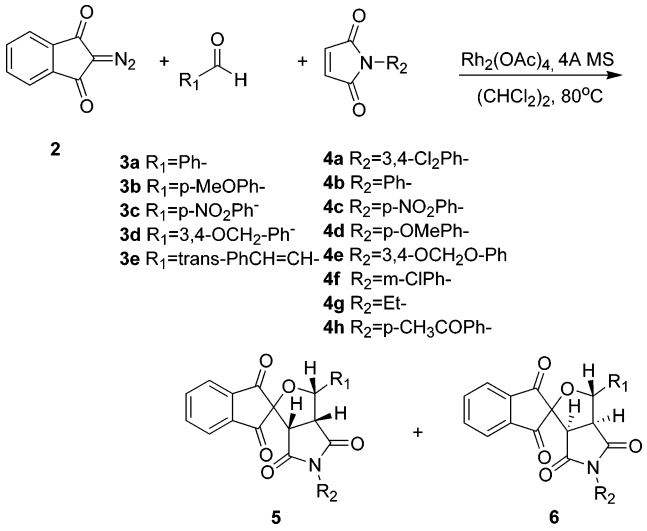


entry	solvent	$Rh_2(OAc)_4$ (mol %)	time (h)	4 Å MS	yield[b] (%)	endo/exo[c] (**5a**/**6a**)
1	$(CH_2Cl)_2$	2	1.0	no	35	79:21
2	$(CHCl_2)_2$	2	1.0	no	60	71:29
3	$(CHCl_2)_2$	1	2.0	no	61	72:28
4	$(CH_2Cl)_2$	1	2.0	yes	43	79:21
5	$(CHCl_2)_2$	1	2.0	yes	78	72:28

[a] **2**/**3a**/**4a**=1:4:4 mmol at 80 °C. [b] Isolated yield of **5a** and **6a** diastereomers. [c] The ratios of two diastereomers were determined by crude ^{1}H NMR.

Initially, we thought a higher temperature might improve product yields. Reexamination of this reaction in refluxing toluene instead of benzene, however, did not enhance earlier results. The reaction of **2**, benzaldehyde (**3a**), and *N*-3,4-dichlorophenylmaleimide (**4a**) catalyzed by 2 mol % $Rh_2(OAc)_4$ in refluxing toluene afforded desired product (**5a** + **6a)** in less than 5% yield. Examination of the side reaction from the reaction performed

SCHEME 4



in toluene revealed that aromatic substitution[9] occurred to give **7** and **8** together with a three-component side product **9** (Scheme 3). However, solvent was found to have a pronounced effect on the reaction. With 1,2-dichloroethane product yield was increased from less than 5% to 35% to give diastereomers **5a** and **6a** favoring endo selectivity (**5a**/**6a** = 79:21). We were pleased to find that an even higher yield (60%, **5a**/**6a** = 79:21) could be obtained by using 1,1,2,2-tetrachloroethane, also at 80 °C. Addition of molecular sieves 4 Å powder[10] in 1,1,2,2-tetrachloroethane gave the best result 78% yield (**5a**/**6a** = 79:21). Detailed results are summarized in Table 1. Compounds **5a** and **6a** were reported as potent tRNA synthetase inhibitors with IC_{50} in 0.6 and 0.004 μM, respectively.[6]

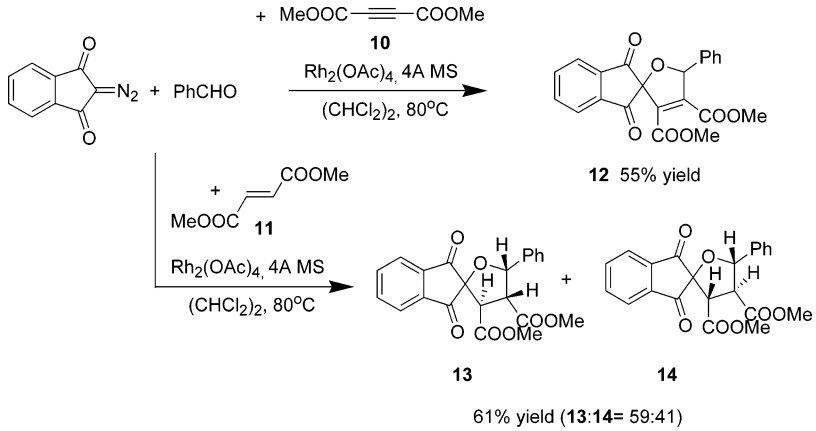
In addition to dirhodium acetate, copper catalysts were also employed in this reaction, but they were less efficient than the rhodium catalyst. For example, the reaction proceeded slowly with CuOTf or $Cu(OTf)_2$ even at elevated reaction temperature (120 °C), and a complex mixture of products was observed. This system was not examined further.

With optimum reaction conditions in hand, various aldehydes and maleimides were explored to demonstrate the generality of the reaction (Scheme 4). Product yields were good in this three-component reaction, and the results are summarized in Table 2. The electronic effects of substituents of Scheme 4**,** both *N*-arylmaleimides and aromatic aldehydes, on the diastereoseletivity and the product yields were insignificant in this reaction (entries 3, 4 and 7, 8). Satisfactory yields were obtained in most entries. Extension of applicability from aromatic aldehydes to cinnamaldehyde also resulted in ylide-derived tetrahydrofuran products in moderate yields (entries 11 and 12). For example, treatment of diazoindan-1,3-dione with cinnamaldehyde and *N*-4-acetophenylmaleimide resulted in the desired product, formed in 53% yield. This is encouraging in contrast to the reported three-step approach (condensation, epoxidation, and thermal 1,3-

(9) Rosenfeld, M. J.; Ravi Shankar, B. K.; Shecheter, H. *J. Org. Chem.* **1988**, *53*, 2699.

(10) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Org. Lett.* **2000**, *2*, 3145.

SCHEME 5



dipolar cycloaddition). The ratios of endo/exo were consistent in favoring endo selectivity. Finally, the structures and configurations of the two diastereomers were ascertained by single-crystal X-ray analyses of **5a** and **6b**.

To further explore the generality of this reaction, other dipolarophiles such as DMAD (**10**) and dimethyl fumarate (**11**) were employed. These reactions underwent cycloaddition smoothly to give **12** and **13/14** in moderate yields; the relative stereochemistry of **13/14** was determined by ref 3 (Scheme 5).

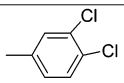
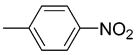
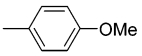
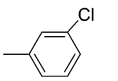
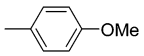
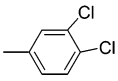
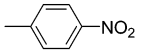
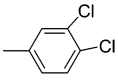
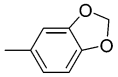
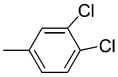
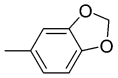
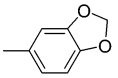
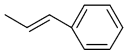
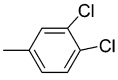
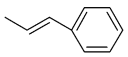
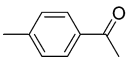
The overall process can be considered to proceed via an initial formation of 1,3-dipolar intermediates from the diazo compound and aldehydes. These intermediates are further trapped by dipolarophiles such as *N*-arylmaleimide to give the corresponding tetrahydrofuran derivatives favoring the endo diastereoisomer. The reason for the formation of the predominant endo isomer is unclear at present, but may result from secondary orbital overlap in the transition state for cycloaddition between aromatic substituent of aldehyde and dipolarophile[11] (Scheme 6).

The solvent has a profound effect on this intermolecular three-component 1,3-dipolar reaction. To obtain a better understanding of the predominant formation of the three-component side product **9** in toluene, aromatic substitution products **7** and **8** were isolated as a mixture, and the mixture was treated with maleimide **4a** in refluxing toluene (Scheme 7). Compound **9** was formed from the reaction of **4a** and **8**, and a similar product derived from the reaction of **4a** and **7** was not observed. The structure of **9** was further confirmed by its single-crystal X-ray structure. Compound **9** was formed by initial aromatic substitution yielding **8** followed by Michael addition to maleimide **4a**.

A similar outcome was found in the reaction between **2** and **4e** using benzene as solvent. Repeating the reaction in refluxing benzene, it was found that electrophilic substitution to benzene occurred similarly to give major side products **15** and three-component side product **16** (Scheme 8). Due to the competitive reaction with solvent (benzene and toluene), the desired tetrahydrofuran product derived from the three-component 1,3-dipolar reaction was obtained only in very low yield.[7] Padwa has also reported a number of examples of competitive electrophilic substitution with other diazo compounds.[12]

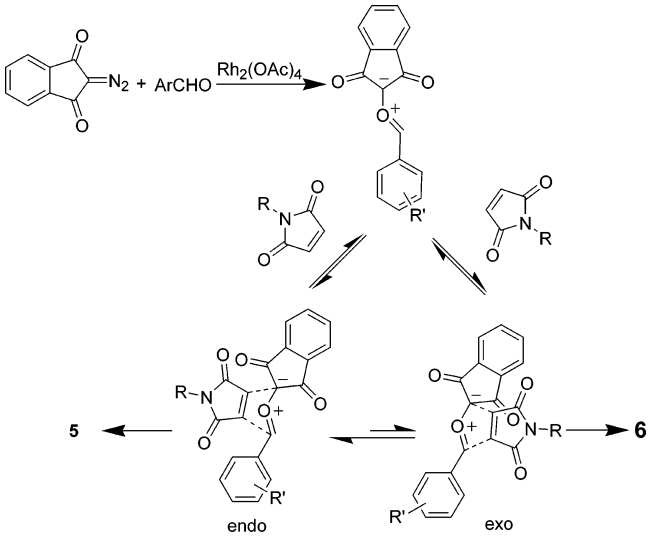
(11) For diastereoselectivity controlled by secondary π-orbital interactions, see: Tomohiko Ohwada, T. *Chem. Rev.* **1999,** *99,* 1337.

TABLE 2. Catalytic 1,3-Dipolar Cycloaddition of Diazoindan-1,3-dione(2) with Various Aromatic Aldehydes and Maleimides[a]

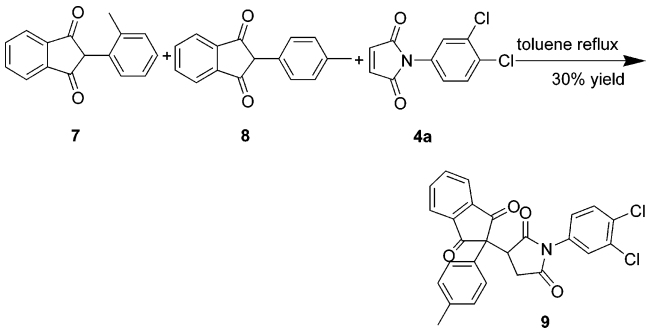
entry	R_1	R_2	Yield (%)[b]	endo:exo (**5**:**6**)[c]
1			78	69:31 (**5a**:**6a**)
2			65	67:33 (**5b**:**6b**)
3			40	70:30 (**5c**:**6c**)
4			51	66:34 (**5d**:**6d**)
5			58	69:31 (**5e**:**6e**)
6		—Et	47	75:25 (**5f**:**6f**)
7			61	80:20 (**5g**:**6g**)
8			60	65:35 (**5h**:**6h**)
9			63	74:26 (**5i**:**6i**)
10			60	67:33 (**5j**:**6j**)
11			43	72:28 (**5k**:**6k**)
12			53	74:26 (**5l**:**6l**)

[a] Reactions were carried out in 15 mL of $(CHCl_2)_2$ at 80 °C in the presence of 1 mol % $Rh_2(OAc)_4$ and1.0 g of 4 Å MS for 2 h with **2**/**3**/**4** = 1:4:4. [b] Same as Table 1. [c] Same as Table 1.

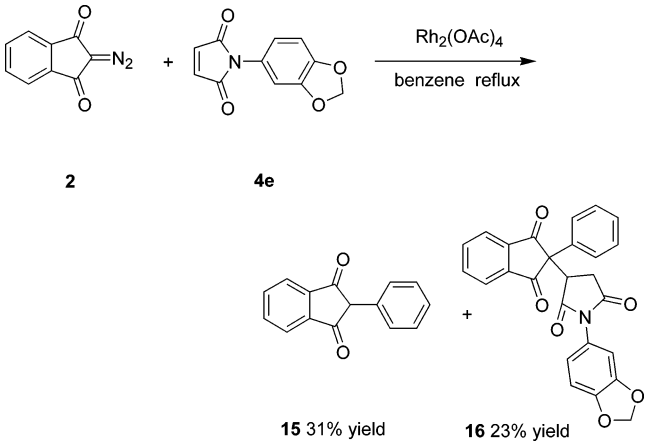
SCHEME 6



SCHEME 7



SCHEME 8



In summary, we have optimized a one-pot reaction for the synthesis of ring-fused tetrahydrofurans through intermolecular 1,3-dipolar cycloaddition derived from diazoindan-1,3-dione. Reported tRNA synthetase inhibitors such as **5a** and **6a** were prepared according to this method. By varying the substituents on aromatic aldehydes and dipolarphiles, structurally constrained tetrahydrofuran analogues were synthesized.

Experimental Section

Representative Procedure: Compounds 5a and 6a. A mixture of 2-diazo-1,3-indandione **2** (0.172 g, 1.0 mmol), benzaldehyde (4.0 mmol), *N*-3,4-dichlorophenylmaleimide (4.0 mmol), $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol), and 1.0 g molecular sieves 4 Å in 15 mL of $(CHCl_2)_2$ was stirred at 80 °C for ~2−3 h under argon atmosphere. The reaction mixture was filtered through Celite, the filtrate was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1−2:1) to give product **5a** and **6a**. The product ratio was determined by NMR spectral analysis of the crude reaction mixture.

(3*R*,3a*R*,6a*S*)-Spiro[1*H*-furo[3,4-*c*]pyrrole-1,2′-[2*H*]indene]-1′,3′4,6(3*H*,5*H*)-tetrone, 5-(3,4-dichlorophenyl)-3a,6a-dihydro-3-phenyl (5a): mp 194−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16−8.09 (m, 2 H), 8.03−7.99 (m, 2 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 2.4 Hz, 1 H), 7.45−7.35 (m, 5 H), 7.24 (dd, J = 8.4, 2.4 Hz, 1 H), 6.15 (d, J = 7.5 Hz, 1 H), 4.08 (dd, J = 8.1, 7.5 Hz, 1 H), 3.84 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 193.9, 172.5, 171.4, 141.5 (overlap, 2C), 139.4, 137.3, 137.2, 134.6, 132.9, 130.7, 130.4, 128.8, 128.4, 128.2, 126.1, 125.6, 124.4, 124.3, 84.4, 83.4, 51.5, 51.2; HRMS calcd for $C_{26}H_{15}Cl_2NO_5$ 491.0327, found 491.0314 $[M + H]^+$; the X-ray structure of **5a** confirms the product structure.

(3*R*,3a*S*,6a*R*)-Spiro[1*H*-furo[3,4-*c*]pyrrole-1,2′-[2*H*]indene]-1′,3′4,6(3*H*,5*H*)-tetrone,5-(3,4-dichlorophenyl)-3a,6a-dihydro-3-phenyl (6a): mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15−8.04 (m, 2 H), 8.01−7.97 (m, 2 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.58−7.56 (m, 2 H), 7.46−7.37 (m, 3 H), 7.24 (dd, J = 8.4, 2.4 Hz, 1 H), 5.85 (d, J = 6.9 Hz, 1 H), 4.21 (d, J = 10.2 Hz, 1 H), 3.89 (dd, J = 10.2, 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 194.0, 173.5, 172.6, 141.4, 141.0, 138.2, 137.24, 137.22, 133.4, 133.3, 130.9, 130.6, 128.9, 128.8, 128.7, 125.98, 125.95, 124.6, 124.3, 85.0, 83.1, 55.2, 51.0; HRMS calcd for $C_{26}H_{15}Cl_2NO_5$ 491.0327, found 491.0333 $[M + NH_4]^+$.

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Supporting Information Available: General experimental procedure; ^{1}H NMR and ^{13}C NMR spectra for **4a**,**c**−**f**,**h**, **5a**−**l**, **6a**−**l**, **9**, **12**, **13**, **14**, and **16**; crude ^{1}H NMR spectra of **5a** + **6a**; and X-ray crystal data for compound **5a**, **6b**, and **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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