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An Efficient Stereoselective Synthesis of 4,5-*trans*-1,5-*cis*-3-Oxabicyclo[3.1.0]hexan-2-ones via the Iodolactonization of Alkylidenecyclopropyl Esters

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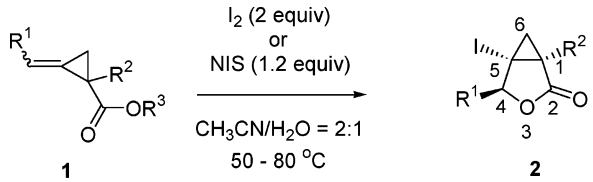

A highly stereoselective iodolactonization of alkylidenecyclopropyl esters with iodine or *N*-iodosuccinimide (NIS) in aqueous CH_3CN to afford 4,5-*trans*-1,5-*cis*-3-oxabicyclo-[3.1.0]hexane-2-ones is described. The reaction is very general, accommodating a wide range of substituents. A plausible mechanism that explains the essential role of water in this reaction is proposed.

Introduction

3-Oxabicyclo[3.1.0]hexan-2-ones is an important structural motif frequently found in numerous biologically active natural products or pharmacologically interesting structures.[1] Compounds of this class can also serve as useful starting materials for the preparation of *cis*- or *trans*-1,2-disubstituted chiral cyclopropane units,[2] furofuranone derivatives,[3] and cycloheptadienes.[4] There are many methods available for their preparation, for example, oxidation of *cis*-1,2-bis(hydroxymethyl)cyclopropanes,[5a] hydrolysis of *cis*-1,2-bis(methoxycarbonyl)-cyclopropanes,[5b,c] tandem radical cyclization of allyl ethyl dichloromalonates,[6] and intramolecular cyclopropanation of allylic diazoacetates.[7] Synthesis of 3-oxabicyclo[3.1.0]-hexan-2-ones from methylenecyclopropyl carboxylic acids (MCP acids) have been very briefly studied.[8] However, these acids were usually synthesized from the corresponding esters with low yields.[8b,c] Thus, straightforward methodology of 3-oxabicyclo[3.1.0]hexan-2-ones from MCP esters is highly desirable. We wish to report in this paper an efficient route to 3-oxabicyclo[3.1.0]hexan-2-ones via the highly stereoselective iodolactonization of alkylidenecyclopropyl esters with iodine or NIS under aqueous conditions, which was more efficient than the cyclization of MCP acids.

Methylenecyclopropanes (MCPs) or alkylidenecyclopropanes are widely investigated due to the presence of an *exo*-cyclic carbon−carbon double bond and a strained three-membered carbocycle.[9,10] Recently, our group reported reactions of alkylidenecyclopropyl ketones under the catalysis of Pd(II), Pd(0), or I^- to afford different

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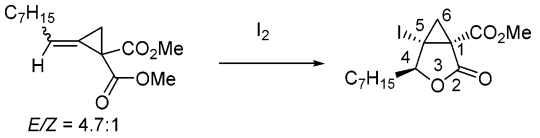
products (i.e., 4*H*-pyrans, 2,3,4-trisubstituted furans (or 4,5-disubstituted-3-alkylidene-2,3-dihydrofurans), and 2,3,4,5-tetrasubtituted furans (or 2,4,5-trisubstituted-3-alkylidene-2,3-dihydrofurans)) in good yields, respectively, depending on the nature of the catalyst and reaction conditions.[11] To explore the chemistry of alkylidenecyclopropane derivatives further, we investigated the lactonization of alkylidenecyclopropyl esters as an efficient entry into 3-oxabicyclo[3.1.0]hexan-2-ones.

Results and Discussion

Synthesis of Starting Materials. Alkylidenecyclopropyl esters **1a**−**o** used in this study were easily prepared via the $Rh_2(OAc)_4$-catalyzed cyclopropanation[12] of the corresponding 1,2-allenes[13] with the α-diazo carboxylic acid esters[14] according to our previous report.[11b] The configuration of the C=C bond in the starting material was tentatively assigned on the basis of the $^1H-^1H$ NOESY studies of *E*-**1c** and *E*-**1d**.

Iodolactonization of Alkylidenecyclopropyl Esters with I_2 or NIS. With different alkylidenecyclopropyl esters in hand, our initial work began with the iodolactonization of 1,1-bis(methoxycarbonyl)-2-octylidenecyclopropane (**1a**) with I_2. Some typical results are summarized in Table 1. It should be noted that H_2O played an important role in this reaction. When H_2O was added to the reaction mixture, the yield of **2a** was improved (entries 1 and 2, Table 1). The best ratio of CH_3CN/H_2O is 2:1 (entries 2−5, Table 1), while THF/H_2O mixture worked equally well. Other mixed solvent systems were also tested, but gave inferior results (entries 7−9, Table 1). Further investigation showed that the reaction gave the product **2a** in 79% yield when we used 2 equiv of I_2 at 80 °C after 3 h in aqueous MeCN (CH_3CN/H_2O = 2:1) (entry 11, Table 1). ^1H NMR spectra of the crude product indicated the formation of only one stereoisomer. The 4,5-*trans*-1,5-*cis*-stereochemistry of **2** was established by the X-ray diffraction study of 4,5-*trans*-1,5-*cis*-**2c**[15] and 4,5-*trans*-1,5-*cis*-**2n**.[16]

TABLE 1. Iodolactonization of Bis(methoxycarbonyl)-2-octylidenecyclopropane (1a) with I_2 under Different Conditions[a]



1a **2a**

entry	I_2 (equiv)	solvent	*T* (°C)	time (h)	yield of **2a** (%)
1	1.2	CH_3CN	80	12	39
2	1.2	CH_3CN/H_2O = 2:1	80	8	56
3	1.2	CH_3CN/H_2O = 1:1	80	11	46
4	1.2	CH_3CN/H_2O = 4:1	80	11	54
5	1.2	CH_3CN/H_2O = 8:1	80	10.5	53
6	1.2	THF/H_2O = 2:1	50	66	53[b]
7	1.2	DMF/H_2O = 2:1	50	66	7
8	1.2	$AcOH/H_2O$ = 2:1	80	9	46
9	1.2	ethyl acetate/H_2O = 2:1	80	23	44
10	1.5	CH_3CN/H_2O = 2:1	80	24	59
11	2.0	CH_3CN/H_2O = 2:1	80	3	79

[a] The reactions were carried out using 0.25−0.5 mmol of **1a** and 2 equiv of I_2 in 1.5−3 mL of solvent under 80 °C. [b] 15% of **1a** was recovered.

Based on these results, it was obvious that the product should be formed by an electrophilic iodolactonization mechanism. Therefore, other I^+ sources were tested (Table 2). It is obvious that NIS offered better results than ICl (entries 1 and 2, Table 2). Further investigation on temperature showed that the yield of **2a** was excellent when the reaction was carried out at 50 °C under the effect of NIS (entry 4, Table 2).

The results for the iodolactonization reaction of differently substituted alkylidenecyclopropyl esters **1** with I_2 (conditions A) or NIS (conditions B) in CH_3CN/H_2O (2:1) are summarized in Table 3. The yields are moderate to good with excellent 4,5-*trans*-1,5-*cis*-selectivity for a wide range of substrates. From Table 3, it can be concluded that R^1 can be an alkyl or aryl group. It was also proven that R^2 does not necessarily have to be an electron-withdrawing group because the corresponding product was obtained in moderate to good yields when R^2 is phenyl or H (entries 8−11, Table 3).

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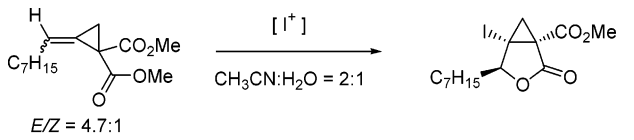
(15) X-ray data for compound **2c**: $C_{14}H_{13}O_4I$, Mw = 372.14, triclinic, space group *P*-1, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0679, wR2 = 0.1827, a = 11.1268 (11) Å, b = 11.8072 (12) Å, c = 13.0058 (13) Å, α = 112.480 (2)°, β = 108.985 (2)°, γ = 97.156 (2)°, V = 1431.0 (2) Å^3, T = 293(2) K, Z = 4, reflections collected/unique, 8473/6092 (R_{int} = 0.0983), parameters 346. CCDC 261536 contains the supplementary crystallographic data.

(16) X-ray data for compound **2n**: $C_{12}H_{19}O_4SiI$, Mw = 382.26, monoclinic, space group $P2(1)/n$, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0305, wR2 = 0.0673, a = 12.1972 (14) Å, b = 8.5235 (10) Å, c = 15.2518 (18) Å, α = 90°, β = 96.356 (2)°, γ = 90°, V = 1575.9 (3) Å^3, T = 293(2) K, Z = 4, reflections collected/unique, 8728/3410 (R_{int} = 0.0704), parameters 187. CCDC 261537 contains the supplementary crystallographic data.

TABLE 2. Effects of Different I^+ Sources and Reaction Temperature[a]



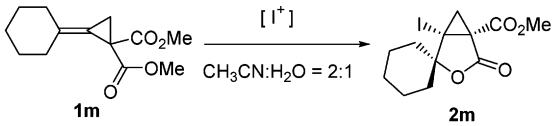
E/*Z* = 4.7:1

1a **2a**

entry	I^+ (equiv)	*T* (°C)	time (h)	yield of **2a** (%)
1	ICl (1.2)	80	1.5	66
2	NIS (1.2)	80	2	85
3	NIS (1.2)	rt	1.5	83
4	NIS (1.2)	50	1.5	91

[a] The reactions were carried out using 0.25−0.5 mmol of **1a** and 1.2 equiv of ICl or NIS in 1.5−3 mL of solvent.

When we applied the standard reaction conditions to 4,4-cyclohexyl methylidenecyclopropyl ester **1m**, a tricyclic product **2m** was obtained with good yields under both conditions A and B (eq 1).



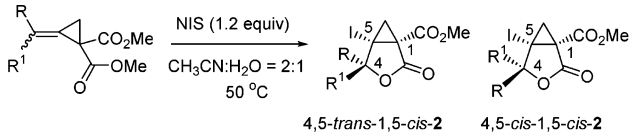
1m **2m** (1)

Conditions A: 1 h yield: 86%
Conditions B: 1 h yield: 82%

Mechanistic Considerations. To explore the origin of the 4,5-*trans*-1,5-*cis*-selectivity, we synthesized compounds **1n** and **1o**, in which R and R^1 groups are sterically different. As we expected, the ratio of 4,5-*trans*-1,5-*cis*-/4,5-*cis*-1,5-*cis*-isomers decreased. It is obvious that the reaction showed excellent 1,5-*cis*-stereochemistry, while the stereochemistry for 4- and 5-positions depends on the relative steric hindrance of R and R^1 with the bulkier group *trans* to the iodine atom (Scheme 1).

Based on these facts, a rationale for this iodolactonization reaction is depicted in Scheme 2. Electrophilic interaction of I^+ with the C=C bond would form the intermediate **3**, which would open up to generate a carbocation **3A**. Due to the steric hindrance of groups R^1 and R, **3A** would adopt conformation **3B** by the rotation of bond C4−C5, in which the bulkier group R^1 is *trans* to the iodine atom, which accounts for the fact that only one isomer was obtained regardless of the stereochemistry of the starting material (**1a**−**k**). The subsequent intramolecular nucleophilic attack of the carbonyl oxygen at the positively charged carbocation would lead to the stereoselective formation of the intermediate **4**. A possible mechanism for the formation of **2** with excellent stereoselectivity may proceed via the attack of **4** by water to form intermediate **6**, which then produced lactone **2** by the elimination of R^3OH.

SCHEME 1



R = Et, R^1 = TMS (**1n**) *E*/*Z* = 13:1 — yield of **2n**: 46%, 4,5-*trans*:*cis* = 19:1

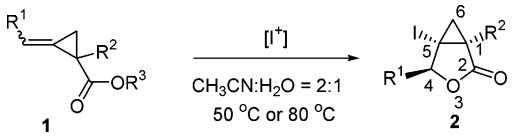
R = Me, R^1 = Et (**1o**) *E*/*Z* = 2:1 — yield of **2o**: 86%, 4,5-*trans*:*cis* = 2:1

To probe the real nature of the mechanism, the iodolactonization of **1j** was performed. Either conditions A or conditions B afforded **2h** and 3-phenyl propanol[17] in ∼1:1 ratio, indicating that the reaction proceeded via the pathway we postulated (Scheme 3).

Conclusion

We have developed a highly stereoselective iodolactonization reaction of alkylidenecyclopropyl esters with iodine or NIS under aqueous conditions leading to the formation of 4,5-*trans*-1,5-*cis*-3-oxabicyclo[3.1.0]hexan-2-ones in moderate to good yields. The stereoselectivity may be controlled by the steric effects of the substituent group of the C=C bond. Further investigation in this area is being carried out in our laboratory.

TABLE 3. Iodolactonization of Alkylidenecyclopropyl Esters 1 with I_2 (Conditions A)[a] or NIS (Conditions B)[b]

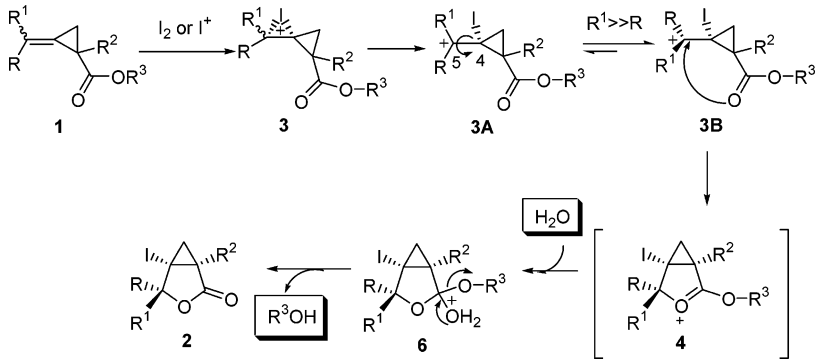


1 **2**

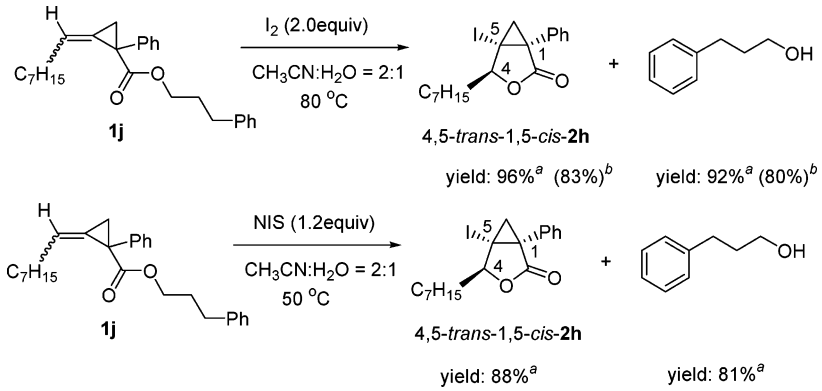
	1				conditions A		conditions B	
entry	R^1	R^2	R^3	*E*/*Z*	time (h)	yield of **2** (%)	time (h)	yield of **2** (%)
1	C_7H_{15}	CO_2Me	Me (**1a**)	4.7:1	3	79 (**2a**)	1.5	91 (**2a**)
2	C_4H_9	CO_2Me	Me (**1b**)	6.3:1	12	56 (**2b**)	2	76 (**2b**)
3	Bn	CO_2Me	Me (**1c**)	100:0	3	74 (**2c**)	2	77 (**2c**)
4	Ph	CO_2Me	Me (**1d**)	100:0	1.5	63 (**2d**)	0.75	73 (**2d**)
5	CH_2CO_2Et	CO_2Et	Et (**1e**)	100:0	1	40 (**2e**)	1.5	71 (**2e**)
6	C_7H_{15}	SO_2Ph	Me (**1f**)[c]	100:0	4.5 days	58 (**2f**)	24	74 (**2f**)
7	C_7H_{15}	CO_2Et	Et (**1g**)	3.5:1	24	71 (**2g**)	2	84 (**2g**)
8	C_7H_{15}	Ph	Me (**1h**)	100:0	1.5	85 (**2h**)	1	87 (**2h**)
9	C_7H_{15}	Ph	Bn (**1i**)	100:0	2	96 (**2h**)	2	42 (**2h**)
10	C_7H_{15}	Ph	C_3H_6Ph (**1j**)	100:0	5	83 (**2h**)	4.5	58 (**2h**)
11	C_7H_{15}	H	Et (**1k**)	1.5:1	1	40 (**2k**)	2	43 (**2k**)

[a] The reactions were carried out using 0.25−0.5 mmol of **1a** and 2 equiv of I_2 in 1.5−3 mL of solvent at 80 °C. [b] The reactions were carried out using 0.25−0.5 mmol of **1a** and 1.2 equiv of NIS in 1.5−3 mL of solvent at 50 °C. [c] 3 equiv of I_2 were used.

SCHEME 2



SCHEME 3



[a] The yield was based on ^{1}H NMR analysis. [b] Isolted yield.

Experimental Section

Synthesis of Starting Materials. General Procedure for the Synthesis of Alkylidenecyclopropyl Esters: 1-(Methoxycarbonyl)-2-(octylidene)-cyclopropanecarboxylic Acid Methyl Ester (1a). A solution of 2-diazomalonic acid dimethyl ester (3.159 g, 20 mmol) in 15 mL of CH_2Cl_2 was added with a syringe to a solution of deca-1,2-diene (9.530 g, 70 mmol) and $Rh_2(OAc)_4$ (22 mg, 0.05 mmol) in 5 mL of CH_2Cl_2 under reflux. After the addition was over, the mixture was stirred overnight under reflux. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether = 10:1) to afford 3.878 g (72%) of **1a**: liquid, a mixture of stereoisomers, *E*/*Z* ratio = 4.7:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ [5.97−6.04 (m, 0.82H), 5.82−5.95 (m, 0.18H)], [3.72 (s, 1.05H), 3.71 (s, 4.95H)], 2.13−2.27 (m, 4H), 1.40−1.53 (m, 2H), 1.18−1.40 (m, 8H), [0.86 (t, J = 6.6 Hz, 2.46H), 0.857 (t, J = 6.6 Hz, 0.54H)]; MS *m*/*z* 268 (M^+, 1.90), 183 (100); IR (neat) 1737, 1274, 1107 cm^{-1}. HRMS calcd for $C_{15}H_{24}O_4$: 268.1674. Found: 268.1670.

General Procedure for Iodolactonization of Alkylidenecyclopropyl Esters (1) with Iodine (Conditions A): Synthesis of 4,5-*trans*-1,5-*cis*-1-Methoxycarbonyl-4-heptyl-5-iodo-3-oxabicyclo[3.1.0]-hexan-2-one (2a). In a flask, a solution of **1a** (134 mg, 0.5 mmol) and I_2 (255 mg, 1.0 mmol) in 2 mL of CH_3CN and 1 mL of H_2O was stirred for 3 h at 80 °C. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution, extracted with ether, and dried over anhydrous $MgSO_4$. Evaporation and column chromatography (eluent: petroleum ether/Et_2O = 10/1) on silica gel afforded **2a** (151 mg, 79%).

General Procedure for Iodolactonization of Alkylidenecyclopropyl Esters (1) with NIS (Conditions B). In a flask, a solution of **1a** (68 mg, 0.25 mmol) and NIS (68 mg, 0.3 mmol) in 1 mL of CH_3CN and 0.5 mL of H_2O was stirred for 1.5 h at 50 °C. The reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution, extracted with ether, and dried over anhydrous $MgSO_4$. Evaporation and column chromatography (eluent: petroleum ether/Et_2O = 10/1) on silica gel afforded **2a** (86 mg, 91%) as a liquid. **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (dd, J = 8.7, 3.6 Hz, 1H), 3.87 (s, 3H), 2.18 (d, J = 6.4 Hz, 1H), 1.80−1.95 (m, 1H), 1.83 (d, J = 6.4 Hz, 1H), 1.40−1.62 (m, 3H), 1.20−1.40 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.2, 164.5, 86.3, 53.4, 36.6, 31.6, 30.1, 29.1, 28.9, 25.84, 25.76, 22.5, 14.0, 7.8; MS *m*/*z* 380 (M^+, 0.86), 41 (100); IR (neat) 1794, 1739 cm^{-1}. Anal. Calcd for $C_{14}H_{21}O_4I$: C, 44.22; H, 5.57. Found: C, 44.57; H, 5.66.

4,5-*trans*-1,5-*cis*-1-Phenyl-4-heptyl-5-iodo-3-oxabicyclo-[3.1.0]hexan-2-one (2h). The reaction of **1h** (143 mg, 0.5 mmol) and I_2 (255 mg, 1.0 mmol) in 2 mL of CH_3CN and 1 mL of H_2O under conditions A afforded **2h** (170 mg, 85%) as a solid, mp 72−74 °C (ether). The reaction of **1h** (145 mg, 0.5 mmol) and NIS (138 mg, 0.6 mmol) in 2 mL of CH_3CN and 1 mL of H_2O under conditions B afforded **2h** (176 mg, 87%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.50 (m, 3H), 7.25−7.35 (m, 2H), 4.85 (dd, J = 9.0, 3.4 Hz, 1H), 1.88−2.02 (m, 3H), 1.45−1.75 (m, 3H), 1.20−1.47 (m, 8H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.2, 132.5, 129.8, 128.64, 128.59, 86.3, 38.4, 31.7, 30.6, 29.3, 29.0, 26.0, 23.9, 22.6, 14.1, 12.3; MS *m*/*z* 398 (M^+, 2.94), 115 (100); IR (neat) 1766 cm^{-1}. Anal. Calcd for $C_{18}H_{23}O_2I$: C, 54.28; H, 5.82. Found: C, 54.37; H, 5.60.

The reaction of **1i** (181 mg, 0.5 mmol) and I_2 (252 mg, 1.0 mmol) in 2 mL of CH_3CN and 1 mL of H_2O under conditions A afforded **2h** (191 mg, 96%). The reaction of **1i** (176 mg, 0.49 mmol) and NIS (132 mg, 0.59 mmol) in 2 mL of CH_3CN and 1 mL of H_2O under conditions B afforded **2h** (82 mg, 42%).

The reaction of **1j** (95 mg, 0.24 mmol) and I_2 (131 mg, 0.5 mmol) in 1 mL of CH_3CN and 0.5 mL of H_2O under conditions

(17) Kajiro, H.; Mitamura, S.; Miro, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, 1553.

A afforded **2h** (79 mg, 83%) and 3-phenylpropanol (26 mg, 80%). The reaction of **1j** (195 mg, 0.5 mmol) and NIS (135 mg, 0.6 mmol) in 2 mL of CH_3CN and 1 mL of H_2O under conditions B afforded **2h** (116 mg, 58%) and 3-phenypropanol (27 mg, 40%).

3-Phenylpropanol.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.36 (m, 5H), 3.68 (t, J = 6.6 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 1.80−1.98 (m, 2H), 1.86 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.8, 128.4, 128.3, 125.8, 62.1, 34.1, 32.0; MS *m/z* 136 (M^+, 16.00), 117 (99.69), 91 (100); IR (neat) 3340, 744, 699 cm^{-1}.

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Supporting Information Available: Analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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