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Iron(II)-promoted rearrangement of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes: a mechanism distinct from that postulated previously

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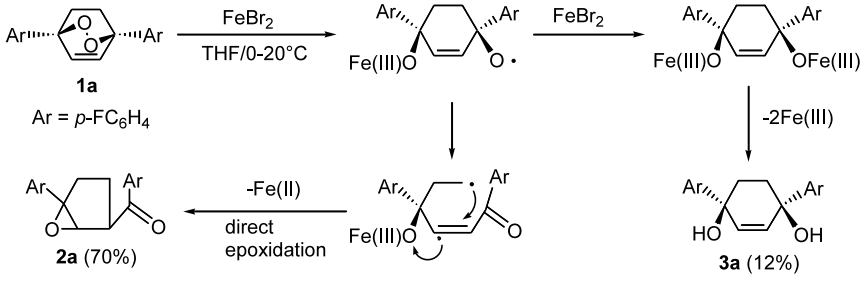
Abstract—Reactions of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes **1a–c** (**1a**: Ar = *p*-FC_6H_4, **1b**: Ar = C_6H_5, **1c**: Ar = *p*-MeC_6H_4) with $FeBr_2$ afforded *syn*-1,2;3,4-bis(epoxy)-1,4-diarylcyclohexanes **4a–c** and *cis*-3,6-diaryl-2,3-epoxycyclohexanones **5a–c** as major products instead of the previously reported 1-aroyl-3-aryl-2,3-epoxycyclopentanes **2a–c**.

Much attention has been paid to bicyclic peroxides from both the synthetic and mechanistic viewpoints because of their antimalarial activity.[1] Particularly, mechanistic studies on the degradation of aryl-substituted bicyclic peroxides promoted by Fe(II) compounds are important to disclose potent antimalarial intermediates and to prepare more effective antimalarial bicyclic peroxides.[1c–g] Posner and coworkers reported that structurally simple and easily prepared 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes **1a–b** (**1a**: Ar = *p*-FC_6H_4, **1b**: Ar = C_6H_5) are potent antimalarials.[1e] In the reaction of fluorinated cyclic peroxide **1a** with $FeBr_2$ in THF, 1-(*p*-fluorobenzoyl)-3-(*p*-fluorophenyl)-2,3-epoxycyclopentane **2a**, whose stereochemistry was not determined, and 1,4-di(*p*-fluorophenyl)cyclohex-2-ene-1,4-diol **3a** were reported to be produced through a mono-oxyl radical intermediate (Scheme 1).[1e] On the contrary, Suzuki and Noyori reported that the reaction of **1b** with $FeCl_2(PPh_3)_2$ in CH_2Cl_2 produced the corresponding diepoxide **4b** through a similar mono-oxyl radical intermediate (Scheme 2).[2†] These contrasting results stimulated us to reinvestigate the reaction of **1** with $FeBr_2$ in connection with our ongoing program studying the degradation mechanism of aryl-substituted bicyclic peroxides with $FeBr_2$.[4] Herein we wish to report that **1a–c** reacted with $FeBr_2$ to produce *syn*-1,2;3,4-bis(epoxy)-1,4-diarylcyclohexanes **4a–c** and *cis*-3,6-diaryl-2,3-epoxycyclohexanones **5a–c** as major



Scheme 1.

Keywords: 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-ene; antimalarial cyclic peroxide; malaria; bicyclic peroxide; $FeBr_2$; rearrangement; diepoxide; epoxyketone; mechanism.

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† Turner and Herz also reported that the reaction of ascaridole with $FeSO_4$ in aqueous THF produced the corresponding diepoxide through a mono-oxyl radical intermediate.[3]

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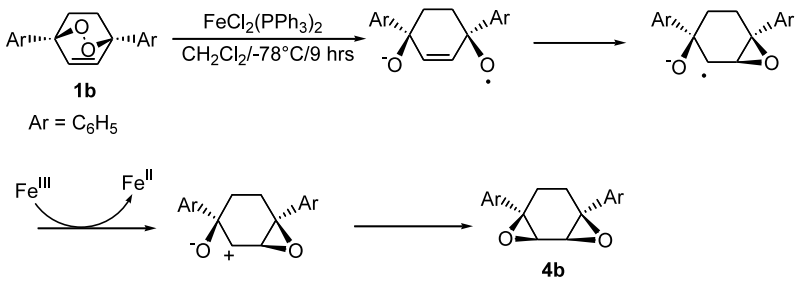
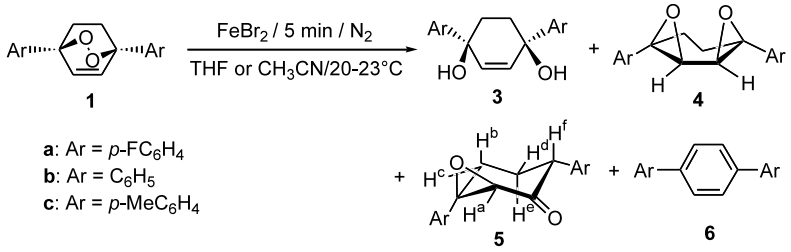


Scheme 2.

products instead of the previously reported epoxycyclopentanes **2a–c**.

When bicyclic peroxide **1a** (0.2 mmol) was treated with 1 equiv. of $FeBr_2$ (0.2 mmol) in dry THF (10 ml) under nitrogen (5 min) at 20–23°C,[‡] *cis*-3,6-di(*p*-fluorophenyl)-2,3-epoxycyclohexanone **5a** (58%)[§] was produced as a major product accompanied with trace amounts of *cis*-1,4-di(*p*-fluorophenyl)cyclohexan-1,4-diol **3a** (<1%) and 4,4″-difluoro-[1,1′,4′,1″]terphenyl **6a** (3%) (Scheme 3, run 1 in Table 1). Interestingly, *syn*-1,2;3,4-bis(epoxy)-1,4-diphenylcyclohexane **4a** (52%) was obtained along with **3a** (<1%), **5a** (26%), and **6a** (<1%) in the reaction of **1a** with a catalytic amount of $FeBr_2$ (0.2 equiv.) in THF (run 2). Likewise, *syn*-1,2;3,4-bis(epoxy)-1,4-di(*p*-fluorophenyl)cyclohexane **4b** (52%) was obtained from **1b** (run 3). On the other hand, a similar catalytic reaction of **1c** with $FeBr_2$ resulted in the formation of epoxyketone **5c** (65%) as a major product (run 4). In contrast to the reactions in THF, **4a–c** were produced as major products in the reactions of **1a–c** with $FeBr_2$ in CH_3CN (runs 6–8).



Scheme 3.

[‡] *General experimental procedure*: To a solution of **1** (0.2 mmol) in dry THF (10 ml) was added $FeBr_2$ (0.04–0.20 mmol, 98%, Aldrich). The mixture was stirred at 20–23°C under nitrogen atmosphere for 5 min. The mixture was passed through a silica gel short column using CH_2Cl_2 as a solvent to remove inorganic iron compounds. The eluent was concentrated and the residue was separated by TLC (*n*-hexane/CH_2Cl_2). All products were characterized by their spectral data and **4b** was confirmed by the reported spectral data.[2,5] Selected data for the representative products are described below.

Compound **4a**: colorless needles; mp 155–156°C; IR (KBr, cm^{-1}); 3020, 2980, 2940, 2890, 1607, 1518, 1509, 1446; ^1H NMR (200 MHz, $CDCl_3$) δ 2.17–2.37 (m, 2H), 2.41–2.60 (m, 2H), 3.30 (s, 2H), 6.96–7.17 (m, 4H), 7.28–7.45 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.30 (t, 2C), 56.76 (s, 2C), 57.80 (d, 2C), 115.39 (d, 4C, $J_{C-F}=21.5$ Hz), 126.76 (d, 4C, $J_{C-F}=8.2$ Hz), 130.03 (s, 2C, $J_{C-F}=3.1$ Hz), 162.22 (s, 2C, $J_{C-F}=245$ Hz). Anal. calcd for $C_{18}H_{14}F_2O_2$; C, 71.99; H, 4.70. Found: C, 71.78; H, 4.86%. MS (EI) 300 (M^+, 2.1%), 121 (100%).

Compound **5a**: colorless needles; mp 146–149°C; IR ($CHCl_3$, cm^{-1}) 3050, 3020, 2970, 2890, 1711(C=O), 1612, 1517; ^1H NMR (200 MHz, $CDCl_3$) δ 1.97–2.12 (m, 1H), 2.23–2.70 (m, 3H), 3.29 (dd, 1H, $J=12.2$ Hz, 6.5 Hz), 3.38 (s, 1H), 6.98–7.27 (m, 6H), 7.30–7.42 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.11 (t, 1C), 27.29 (t, 1C), 52.68 (d, 1C), 63.25 (s, 1C), 64.26 (d, 1C), 115.63 (d, 2C, $J_{C-F}=21.4$ Hz), 115.68 (d, 2C, $J_{C-F}=21.5$ Hz), 126.99 (d, 2C, $J_{C-F}=8.3$ Hz), 129.96 (d, 2C, $J_{C-F}=8.1$ Hz), 134.12 (s, 1C, $J_{C-F}=2.9$ Hz), 161.88 (s, 1C, $J_{C-F}=244$ Hz), 162.63 (s, 1C, $J_{C-F}=246$ Hz), 203.93 (s, 1C). Anal. calcd for $C_{18}H_{14}F_2O_2$: C, 71.99; H, 4.70. Found: C, 72.05; H, 4.90%. MS (EI) 300 (M^+, 9.9%), 122 (100%).

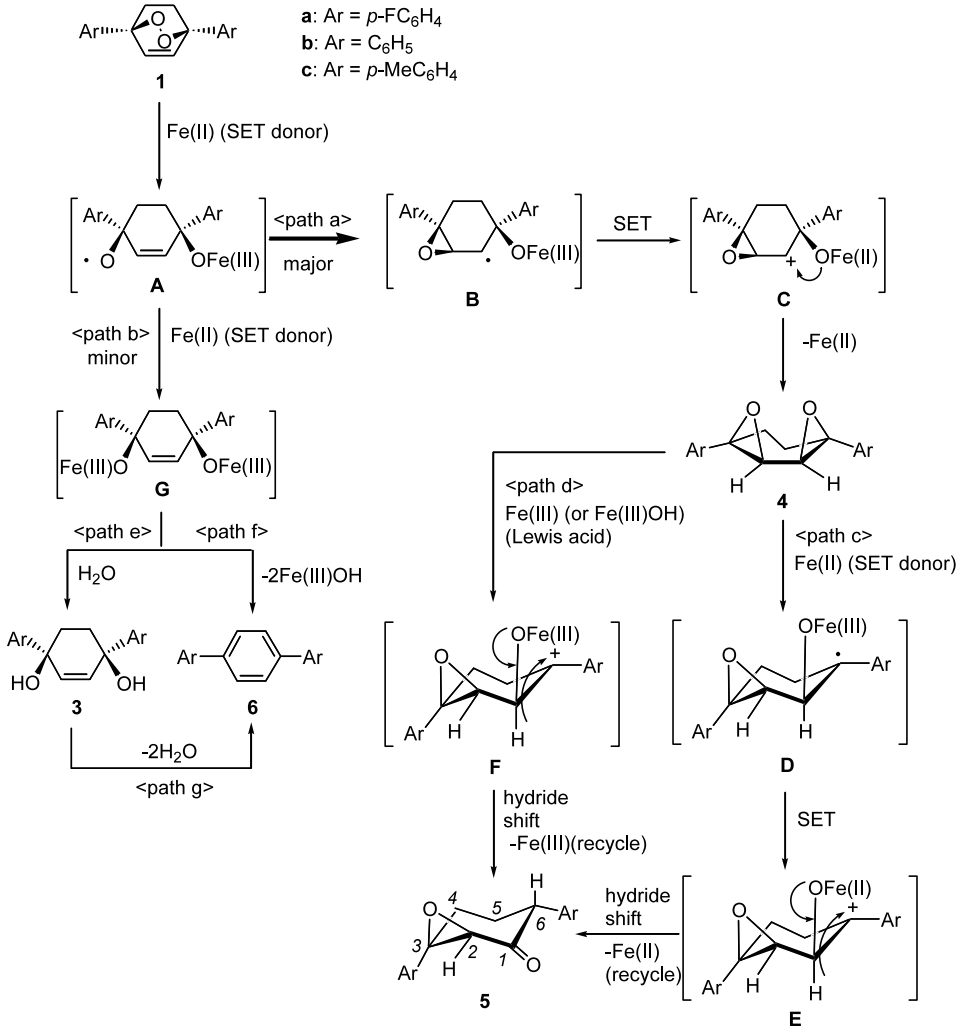
Compound **6a**: colorless prisms; mp 219–222°C; IR (KBr, cm^{-1}) 3070, 1605, 1517, 1491, 1396, ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.22 (m, 4H), 7.52–7.64 (m, 4H), 7.61 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 115.68 (d, 4C, $J_{C-F}=21.2$ Hz), 127.36 (d, 4C), 128.52 (d, 4C, $J_{C-F}=8.2$ Hz), 136.65 (s, 2C, $J_{C-F}=3.3$ Hz), 139.09 (s, 2C), 162.46 (s, 2C, $J_{C-F}=245$ Hz). Anal. calcd for $C_{18}H_{12}F_2$: C, 81.19; H, 4.54. Found: C, 80.80; H, 4.76%. MS (EI) 266 (M^+, 100%).

[§] The structure of **5a** was determined on the basis of the following data (see also Scheme 3). The ^{13}C NMR spectrum exhibited a one-carbon singlet at 203.93 ppm assigned to the aliphatic carbonyl carbon (C_1). The IR spectrum exhibited a carbonyl absorption at 1711 cm^{-1} assigned to the cyclohexanone skeleton. In the ^1H NMR spectrum was found the one-proton singlet at 3.38 ppm assigned to the hydrogen (H^a) attached to the epoxy ring. The one-proton doublet of doublets ($J=12.2$ Hz, 6.5 Hz) at 3.29 ppm was assigned to the hydrogen (H^f) under the aryl α to the carbonyl group. These data supported the structure of **5a** rather than that of **2a**. The stereochemistry of **5a** was then determined by ^1H–^1H COSY and NOE experiments. When the peak at 3.29 ppm (H^f) was irradiated, NOE effects were observed for H^b (3.0%) and H^d (3.9%), but not for H^a, H^c, and H^e. Furthermore, no NOE effect was observed for all cyclohexyl ring protons when the peak at 3.38 ppm (H^a) was irradiated. These data suggest that H^a and H^f are located in equatorial and axial positions, respectively. Thus, the relationship of the two aryl groups in **5a** was concluded to be cis. The structures and stereochemistries of **5b** and **5c** were similarly determined.

Table 1. Fe(II)-promoted degradation of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes **1** and *syn*-1,2;3,4-bis(epoxy)-1,4-diarylcyclohexanes **4**[a]

Run	Substrate	Solvent	Additive	Conv. (%)	Yield (%)[b]			
					3	**4**	**5**	**6**
1[c]	**1a**	THF	None	100	<1	0	58	3
2	**1a**	THF	None	100	<1	52	26	<1
3	**1b**	THF	None	100	<1	52	20	3
4	**1c**	THF	None	100	2	0	65	3
5[c]	**1a**	THF	HMDB[d]	100	<1	64	22	3
6	**1a**	CH_3CN	None	95	<1	69	<1	2
7	**1b**	CH_3CN	None	100	<1	73	<1	2
8	**1c**	CH_3CN	None	91	0	50	22	2
9	**4a**	THF	None	63	0	0	34	0
10	**4b**	THF	None	73	0	0	34	0
11	**4c**	THF	None	100	0	0	76	0
12[c]	**4a**	CH_3CN	None	24	0	0	11	0
13[c]	**4b**	CH_3CN	None	22	0	0	10	0
14[c]	**4c**	CH_3CN	None	65	0	0	48	0

[a] **1** (or **4**) = 0.20 mmol; $FeBr_2$ = 0.04 mmol; solvent = 10 ml; at 20–23°C; reaction time: runs 1–8 = 5 min, runs 9–14 = 30 min.
[b] Isolated yield by silica gel TLC.
[c] $FeBr_2$ = 0.20 mmol.
[d] Hexamethyl Dewar benzene (0.20 mmol).



Scheme 4.

Detailed mechanistic studies further provided the following results: (i) addition of hexamethyl Dewar benzene (HMDB) to capture a high-valent Fe(IV)=O species, which is proposed as a potent antimalarial intermediate,[1e,7–10] did not produce the expected hexamethylbenzene (HMB), but changed the product distribution (compare run 1 with run 5); (ii) when the diepoxides **4a**–**c**¶ were treated with $FeBr_2$ (0.2–1.0 equiv.) for 30 min, the epoxyketones **5a**–**c** were produced in both THF and CH_3CN (runs 9–14); and (iii) the reaction of 1,4-diol **3a** with $FeBr_2$ (2.0 equiv.) produced the terphenyl **6a** (31%) at 50% conversion of **3a**.

On the basis of the above results, we propose a mechanism for the Fe(II)-promoted rearrangement of **1** as shown in Scheme 4. Both in THF and CH_3CN, the mono-oxyl radical intermediate **A** is generated by single electron transfer (SET) from Fe(II) to **1**.[1e,4,11] As for the transformation of the intermediate **A**, two different pathways are possible. One is the generation of the carbon radical intermediate **B** through an intramolecular oxyl radical addition to the olefin in **A** (path a). The other is the generation of the intermediate **G** by successive SET from Fe(II) to **A** which is a minor pathway (path b). The intermediate **B** undergoes intramolecular SET to form the carbocation intermediate **C** followed by the formation of the diepoxide **4** with concomitant elimination of Fe(II). As for the formation of the epoxyketone **5** from **4**, two different pathways are possible. One is the reductive SET pathway by Fe(II) (path c) and the other is the Lewis acid-catalyzed pathway by Fe(III) species (path d). Thus, SET from Fe(II) to **4** regioselectively generates the carbon radical intermediate **D** since the aryl group at C_6 stabilizes the carbon radical (path c). The intermediate **D** undergoes intramolecular SET to form the intermediate **E** followed by a 1,2-hydride shift. The 1,2-hydride shift stereoselectively occurs in **E** since the aryl group at C_6, which stabilizes the carbocation, should favor the equatorial position. As described above, the rearrangement from **4** to **5** required a catalytic amount of Fe(II) as a SET donor (path c; runs 9–11)** and was also accelerated by electron-donating aromatic groups (p-MeC_6H_4>C_6H_5, p-FC_6H_4: runs 4, 8, 11 and 14), while the rearrangement was significantly inhibited by HMDB and CH_3CN (solvent) which may form complexes with Fe(II) to interfere with the action of Fe(II) (runs 5–8, 12–14). The possibility that the Fe(III) species, as a Lewis acid, formed in the reaction should catalyze the rearrangement through the carbocation intermediate **F** is considered as an alternative pathway (path d).†† As for the product formation from **G**, two different pathways are possible. One is the formation of the 1,4-diol **3** presumably derived from the reaction of **G** with moisture (path e). The other is the formation of the terphenyl **6** by elimination of the Fe(III)OH (path f). Dehydration of **3** by Fe(II) may be an alternative route to give **6** (path g). Finally, it should be stressed that the high-valent Fe(IV)=O species was not generated in the reaction because of the absence of rearrangement from HMDB to HMB (run 5).[1e,7–10]

We are conducting further studies on the Fe(II)-promoted degradation of various aryl-substituted cyclic peroxides to clarify the generality of the reaction and the relationship between the reaction intermediates and the antimalarial activity.

¶ Compounds **4a**–**c** were independently prepared by the direct irradiation (λ >290 nm) of **1a**–**c** in CH_2Cl_2 with a 2 kW Xe lamp.[5,6] The structures of **4a** and **4c** were also confirmed by comparison of their spectral data with that of known **4b**.[2,5]

** A referee pointed out the possibility that the Fe(III) species, as a Lewis acid, which may be contained in the purchased $FeBr_2$, promoted the rearrangement from **4** to **5** rather than $FeBr_2$, as a SET donor, did. At the present stage, it is difficult to rule out such a possibility. Further experiments will be needed for clarification of this point.

†† Iranpoor and Salehi reported that $FeCl_3$, as a SET oxidant, underwent a catalytic ring opening of epoxides in various alcohols.[12]

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References

1. (a) Meshnick, S. R.; Jefford, C. W.; Posner, G. H.; Avery, M. A.; Peters, W. *Parasitol. Today* **1996**, *12*, 79 and references cited therein; (b) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601; (c) Posner, G. H.; Wang, D.; Gonzares, L.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 815; (d) Posner, G. H.; Gonzares, L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron* **1997**, *53*, 37; (e) Posner, G. H.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 7225; (f) Bloodworth, A. J.; Hagen, T.; Johnson, K. A.; Lenoir, I.; Moussy, C. *Tetrahedron Lett.* **1997**, *38*, 635; (g) O'Neil, P. M.; Bishop, L. P.; Searle, N. L.; Maggs, J. L.; Ward, S. A.; Bray, P. G.; Storr, R. C.; Park, B. K. *Tetrahedron Lett.* **1997**, *38*, 4263; (h) Takaya, Y.; Kurumada, K.; Takeuji, Y.; Kim, H.-S.; Shibata, Y.; Ikemoto, N.; Wataya, Y.; Ohshima, Y. *Tetrahedron Lett.* **1997**, *39*, 1361; (i) Kim, H.-S.; Shibata, Y.; Wataya, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M. *J. Med. Chem.* **1999**, *42*, 2604; (j) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357; (k) Hindley, S. H.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052; (l) Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Ono, K.; Ogura, N.; Wataya, Y. *J. Med. Chem.* **2002**, *45*, 1374 and references cited therein.
2. Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292.
3. Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1895.

4. (a) Kamata, M.; Kudoh, T.; Kaneko, J.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett*. **2002**, *43*, 617; (b) Kamata, M.; Ohta, M.; Komatsu, K.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett*. **2002**, *44*, 2063.
5. Takahashi, Y.; Wakamatsu, K.; Morishima, S.; Miyashi, T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 243.
6. Rigaudy, J. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M.; Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1995; pp. 325–334.
7. Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc*. **1995**, *117*, 5885.
8. Posner, G. H.; Park, S. B.; Gonzalez, L.; Wang, D.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A.; Bachi, M. D. *J. Am. Chem. Soc*. **1996**, *118*, 3537.
9. Cumming, J. N.; Wang, D.; Park, S. B.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem*. **1998**, *41*, 952.
10. Traylor, T. G.; Miksztsal, A. R. *J. Am. Chem. Soc*. **1987**, *109*, 2770.
11. Abe, M.; Inakazu, T.; Munakata, J.; Nojima, M. *J. Am. Chem. Soc*. **1999**, *121*, 6556 and references cited therein.
12. Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152.