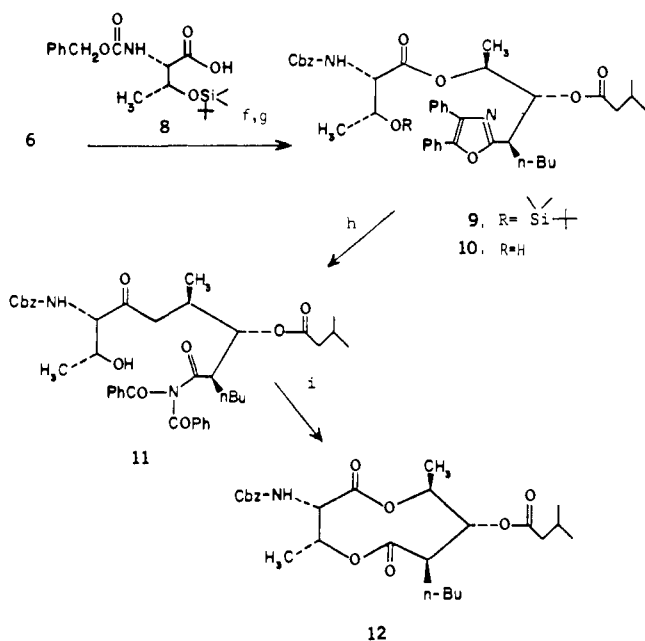


Scheme II^a

^a (f) DCC, DMAP, CH₂Cl₂; (g) *n*-Bu₄NF, THF, 0 °C; (h) ¹O₂, CH₂Cl₂, Sensitox, 25 °C, 3 h; (i) pyridinium *p*-toluenesulfonate, xylenes, Δ.

(58%). The mixture **4a-d** was then acylated with isovaleryl chloride in pyridine, forming the corresponding esters **5a-d**¹⁵ (74%). From the ester mixture, which was more easily separated on a larger scale by chromatography than **4a-d**, it was possible to obtain stereoisomer **5**, having the natural configuration, as the major diastereomeric component.⁹ Deprotection was achieved with boton trifluoride etherate and thiophenol¹⁰ affording the hydroxy oxazole **6**¹⁵ (57%).

At this stage of our work, we were able to establish the absolute stereochemistry of **6** by converting it to (+)-blastmycinone (**7**)^{2,11} (Scheme I), a product of mild saponification¹² of antimycin A₃ (**13**). This was accomplished by photooxygenation of **6** (Sensitox, CH₂Cl₂, 25 °C, 3 h), forming **7** (35%) as the sole isolable lactone species.

Continuing the synthesis, stereoisomer **6** was then condensed with the *N*-carbobenzoxy-L-threonine derivative **8**¹³ (DCC, DMAP, CH₂Cl₂)¹⁴ to give ester **9**¹⁵ (95%). In this esterification process, the latent carboxylate in the molecule remained well protected within the oxazole framework. The *tert*-butyldimethylsilyl ether was then removed (*n*-Bu₄NF, THF, 0 °C), yielding the ω-hydroxy oxazole **10**¹⁵ (64%). Dye-sensitized photooxygenation of **10** (Sensitox, CH₂Cl₂, 25 °C, 3 h) led cleanly to the activated triamide **11**, which was dissolved in xylenes and added slowly to a refluxing solution of pyridinium *p*-toluenesulfonate in xylenes. Under these conditions of buffered acid catalysis, the desired nine-membered dilactone **12** was isolated (20%) (Scheme II).

Compound **12** exhibited physical and spectroscopic properties (melting point, [α]_D²⁵, IR, high-resolution MS) in complete accord with those values reported by M. Kinoshita.³ In addition, the 100-MHz ¹H NMR spectrum of **12** was indistinguishable from the spectrum of authentic dilactone kindly provided by M. Kinoshita. The final steps in the conversion of compound **12** to (+)-antimycin A₃ (**13**)³ have previously been reported by Kinoshita,³ and our work thus constitutes a formal synthesis of the naturally occurring macrolide. The construction of the medium-ring dilactone system in **12** by this method further illustrates the applicability of the oxazole-triamide rearrangement to the formation of macrolides.

(15) Satisfactory IR, ¹H NMR, elemental analyses, and/or high-resolution mass spectra were obtained.

(16) Polymer-bound Rose Bengal, available commercially from Hydron Laboratories, New Brunswick, NJ.

Acknowledgment. This work was supported by NIH Grant GM-13854. The support of the NSF/NMR Northeast Regional Facility at Yale University (Grant CHE-7916210) is acknowledged. We thank Dr. M. Kinoshita, Keio University, Yokohama, for spectroscopic data on (±)-blastmycinone (**7**) and the dilactone **12** and Dr. William Murray, Ortho Pharmaceuticals, for assistance in determining the 100-MHz NMR spectra of **12**.

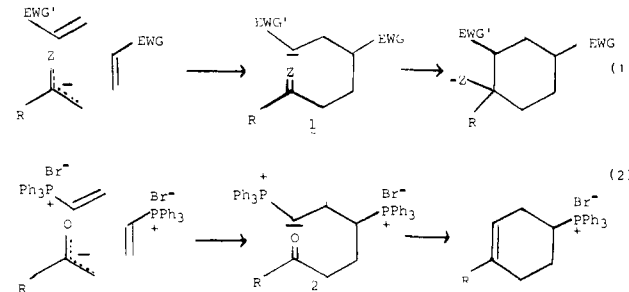
An Extremely Efficient Method for One-Pot, Three-Component, 2 + 2 + 2 Construction of Functionalized Cyclohexenes

Gary H. Posner* and Shu-Bin Lu

Department of Chemistry
The Johns Hopkins University
Baltimore, Maryland 21218

Received October 26, 1984

Formation of more than one carbon-carbon bond in a reaction vessel allows rapid and efficient conversion of simpler into structurally more complex organic molecules. Such very fundamental and popular operations as Diels-Alder cycloadditions¹ and Robinson annulations² attest to the great importance of multiple C-C bond-forming processes in rapid and efficient construction of cyclohexene structural units from two simpler components.³ We envisioned that formation in one pot of *three* carbon-carbon bonds producing a six-membered carbocycle should be possible via sequential Michael-Michael-ring closure (MIMIRC) reactions as illustrated in general by eq 1 (Z = O or NR); polymerization



of the Michael acceptor should be interrupted by the anticipated cyclization of reactive intermediate **1**.^{4,5} This communication describes the development⁶ of this idea in the form of a powerful method for connecting three separate two-carbon units in an efficient 2 + 2 + 2 construction of some phosphorus-substituted cyclohexenes (eq 2); the annulation sequence is consummated by an intramolecular Wittig reaction of intermediate keto ylide **2**.

(1) (a) Kloetzel, M. C. *Org. React.* **1948**, *4*, 1. (b) Holmes, H. L. *Ibid.* **1948**, *4*, 60. (c) Butz, L. W.; Rytina, A. W. *Ibid.* **1949**, *5*, 136. (d) Wasserman, A. "Diels-Alder Reactions"; Elsevier Publishing Co.: New York, 1965. (e) Wollweber, H. "Diels-Alder Reaktion"; Georg Thieme Verlag: Stuttgart, 1972. (f) Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.*, **1977**, *42*, 4095.

(2) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: New York, 1972; pp 606-611, 621-623.

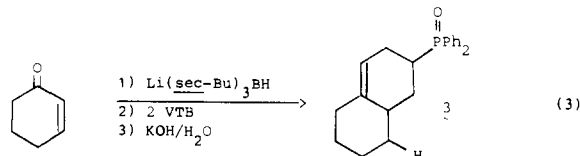
(3) Other important multiple C-C bond-forming reactions include the following: (a) Robinson-Schopf synthesis of tropane alkaloids by a series of Mannich condensations (four C-C bonds are formed in one pot) (Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762, 876. Schopf, C. *Angew. Chem.* **1937**, *50*, 779, 797). (b) Stevens alkaloid synthesis (three C-C bonds in one pot) (Stevens, R. V. *J. Chem. Soc., Chem. Commun.* **1983**, 1425). (c) Gadek, T. R.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 802.

(4) For our first example of the validity of this concept, see: Posner, G. H.; Mallamo, J. P.; Black, A. *Tetrahedron* **1981**, *37*, 3921.

(5) For other examples of one-pot MIMIRC reactions, see: (a) Cory, R. M.; Chan, D. M. T. *Tetrahedron Lett.* **1975**, 4441. (b) Spitzner, D.; Engler, A.; Liese, T.; Spletstosser, G.; Meizere, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 791. (c) Fouchet, B.; Joucha, M.; Messenger, J. C.; Toupet, L. *J. Chem. Soc., Chem. Commun.* **1982**, 858. (d) Danishefsky, S.; Chackalamannil, S.; Silvestri, M. *J. Org. Chem.* **1983**, *48*, 3615. (e) Danishefsky, S.; Harrison, P.; Silvestri, M.; Segmuller, B. *Ibid.* **1984**, *49*, 1319.

(6) The first example of this process is due to: Cory, R. M.; Chan, D. M. T.; Nagrub, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem.* **1980**, *45*, 1852.

Conjugate reduction of 2-cyclohexenone (1.76 mmol) with 1.0 equiv of L-Selectride⁷ (Aldrich) in 2 mL of THF for 2 h at -72 °C was followed by diluting the enolate intermediate with 20 mL of THF and then adding 2.0 equiv of vinyltriphenylphosphonium bromide (VTB, Aldrich)⁸ in 9 mL of DMF via motor-driven syringe over 3.5 h at -55 °C. After the mixture was stirred an additional 12 h at -55 °C, aqueous potassium hydroxide was added to hydrolyze the cyclohexenyltriphenylphosphonium intermediate^{6,9} into the more easily handled cyclohexenyl diphenylphosphine oxide 3, which was formed in a stunning 70% overall yield (eq 3). The



average yield for each of the four bond-forming steps (one carbon-hydrogen and three carbon-carbon bonds) in eq 3, therefore, was greater than 91%!

Ketone enolate ions generated by base abstraction of a *methine* hydrogen (Table I, entry 1) or of a *methylene* hydrogen (entries 2-6) underwent very effective MIMIRC annulation reactions to form spiro and fused bicyclic products from monocyclic precursors (Table I). A ketone enolate ion generated by base abstraction of a *methyl* hydrogen (entry 7) also led smoothly to a phosphorus-substituted cyclohexene product. In entries 2, 5, and 6, adding 1 equiv of triethylboron to the enolate ion before adding VTB, gave about a 10% improvement in overall yield; no such effect was observed in the other cases involving α,β -unsaturated ketones. Converting cyclohexanone lithium enolate into the corresponding titanium¹⁰ [(*i*-PrO)₃TiCl] or tin¹¹ (Ph₃SnCl) enolates offered no advantage. Ketone enolization using lithium hexamethyldisilazide was sometimes better (~10% higher overall yield, for example, with cyclohexanone) than using lithium diisopropylamide (LDA); comparable results were obtained by making the lithium enolate via methyl lithium cleavage of the corresponding enol trimethylsilyl ether (e.g., entry 2). Methyl-substituted cyclohexene **8** appeared to be only one stereoisomer having a clean doublet at δ 1.05 (J = 7.0 Hz) in its ¹H NMR spectrum. In entry 4, no bridged polycyclic products were observed.^{5a,b} Aldehyde enolate ions were not very useful (<20% overall yield) in this cyclohexene annulation process.

The structurally diverse and previously hard-to-prepare¹³ cyclohexenyl phosphine oxides **3-9** are very versatile synthetic in-

(7) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

(8) For pioneering use of vinyltriphenylphosphonium salts, see: (a) Schweizer, E. E.; Smucker, L. D.; Votral, R. J. *J. Org. Chem.* **1966**, *31*, 467. (b) Zbiral, E. In "Organic Phosphorus Reagents in Organic Synthesis"; Academic Press: New York, 1979; 223-265. Cf.: Meyers, A. I.; Lawson, J. P.; Carver, D. R. *J. Org. Chem.* **1981**, *46*, 3119. Cf.: Bestmann, H. J.; Schmid, G. *Tetrahedron Lett.* **1984**, *25*, 1441.

(9) Alkyltriphenylphosphonium salts are known to be hydrolyzed into alkylidiphenylphosphine oxides: (a) Fenton, G. W.; Ingold, C. K. *J. Chem. Soc.* **1929**, 2342. (b) Salch, G.; Minami, T.; Ohshvio, Y.; Agawa, T. *Chem. Ber.* **1979**, *112*, 355.

(10) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.

(11) (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 162. (b) Baxter, A. D.; Roberts, S. M.; Wakefield, B. J.; Wooley, G. T.; Newton, R. F. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1809.

(12) A typical experimental procedure involves adding 578 mg (3.25 mmol) of phenyl cyclopentyl ketone dropwise via syringe during 1 min to 3.40 mmol of lithium hexamethyldisilazide [*n*-BuLi + HN(SiMe₃)₂] in 5 mL of stirring THF at -78 °C in a 100-mL round-bottomed flask under argon. After an additional 0.5 h of stirring at -78 °C, 3.25 mL of a 1.0 M THF solution of triethylboron (3.25 mmol) was added dropwise during 4 min. After 1.5 h at -50 to -55 °C, 45 mL of THF was added followed by 2.49 g (6.5 mmol) of VTB (aldrich) in 10 mL of DMF, which was added via motor-driven syringe over 7.7 h while maintaining the reaction mixture at -50 to -55 °C. After the mixture was stirred overnight at this temperature, 50 mL of 33% aqueous potassium hydroxide was added; stirring was continued for 4 h at 25 °C. Standard workup followed by HPLC analysis with a calibrated standard indicated a 79% yield of spiro bicyclic product **4**. One crystallization of the crude product from acetonitrile gave analytically pure **4**, 424 mg (69% yield).

(13) Cf.: Yamashita, M.; Soeda, Y.; Suzuki, N.; Yamada, M.; Tsunekawa, K.; Oshikawa, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1871 and references therein.

Table I

entry		isolated yield (HPLC yield ^a)
1		69% ^b (79%) ¹²
2		61% ^c (78%)
3		58% ^b
4		54% ^b
5		48% ^d
6		(54%)
7		53% ^b

^a Yield determined by calibrated analytical HPLC. ^b Yield of pure material isolated by crystallization of the crude product from acetonitrile. ^c Yield of pure material isolated by preparative HPLC. ^d Yield of pure material isolated by short-path column chromatography.

intermediates. Deprotonation adjacent to phosphorus produces anions that are known to react with molecular oxygen to form ketones having inverted polarity¹⁴ and to add across aldehyde and ketone carbonyl groups to form very useful (β -hydroxyalkyl)-phosphine oxides.¹⁵ Thermolysis of phosphine oxides **3-9** should produce the corresponding 1,3-cyclohexadienes,^{6,16} oxidation of which should lead to formation of aromatic systems. These operations represent efficient overall transformations of ketones into very different annulation products of broad synthetic utility.

Extending our previous interest in developing methods for efficient formation of *multiple* carbon-carbon bonds,¹⁷ this annulation process represents an extraordinarily powerful synthetic method for sequential construction of two single bonds and one double bond in the form of cyclohexene rings carrying versatile

(14) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046.

(15) (a) Buss, A. D.; Mason, R.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 5293. (b) Buss, A. D.; Warren, S.; Leake, J. S.; Whitham, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2215. (c) Bell, A.; Davidson, A. H.; Earnshaw, C.; Norrish, H. K.; Torr, R. S.; Trowbridge, D. B.; Warren, S. *Ibid.* **1983**, 2879. (d) Yamashita, M.; Tsunekawa, K.; Sugiura, M.; Oshikawa, T.; Inokawa, S. *Chem. Lett.* **1983**, 1673.

(16) (a) Bailey, W. J.; Muir, W. M.; Markscheffel, F. *J. Org. Chem.* **1962**, *27*, 4404. (b) Hays, H. R. *Ibid.* **1969**, *33*, 3690.

(17) (a) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180. (b) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661. (c) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H. *Tetrahedron Lett.* **1978**, 4209. (d) Posner, G. H.; Whitten, C. E.; Sterling, J. J.; Brunelle, D. J.; Lentz, C. M.; Runquist, A. U.; Alexakis, A. *Ann. N. Y. Acad. Sci.* **1978**, *295*, 249. (e) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

phosphorus substituents. We expect that this one-pot, three-component, 2 + 2 + 2 reaction sequence will find many different applications for preparation of useful synthetic intermediates and valuable natural products containing various cyclohexenyl or cyclohexenyl-derived structural and functional units.

Acknowledgment. We thank Dr. Ernest Silversmith (PRF Summer Research Fellow, 1984), Ellen Shulman, and Erik Roskes for their collaboration on this project. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. Purchase of a 400-MHz NMR spectrometer was made possible by the NSF (PCM83-03176) and by the NIH (1 S10 RR01934).

Supplementary Material Available: ^1H NMR, IR, mp, and elemental analysis data for products 3-9 (1 page). Ordering information is given on any current masthead page.

Barrier to Coupled Internal Rotation in Di-9-triptycyl Ether. Kinetics of Intramolecular Exciplex Formation in Racemic 2,3-Benzo-9-triptycyl 2-[(Dimethylamino)methyl]-9-triptycyl Ether

Noboru Koga and Hiizu Iwamura*

Department of Applied Molecular Science
Institute for Molecular Science, Okazaki 444, Japan

Received October 2, 1984

Di-9-triptycylmethanes and di-9-triptycyl ethers (Tp_2X , X = CH_2 and O, respectively) are unique in that two torsional degrees of freedom are very mobile and yet perfectly coupled in the double-rotor molecules. As a stereochemical consequence, new stereoisomerism due to a different phase relationship of the appropriately labeled benzene rings was generated.^{1,2} Since the two wheels of the "bevel gear" were tightly meshed, the gear-slipping process was found to require an activation energy of 32-33 and 42-43 kcal/mol for Tp_2CH_2 and Tp_2O , respectively. One last remaining question as regards the stereochemistry and dynamics of these molecules is how fast the geared rotation is taking place and/or how high the barrier to that torsional motion is. Our preliminary NMR study on these di-9-triptycyl derivatives has shown the presence of only one kind of the averaged benzene ring at temperature as low as -94 °C, placing the highest limit of the activation energy value for the coupled rotation at ca. 7-8 kcal/mol.^{1,3} We therefore thought the system would be appropriate for inspection of exciplex fluorescence dynamics⁴ and

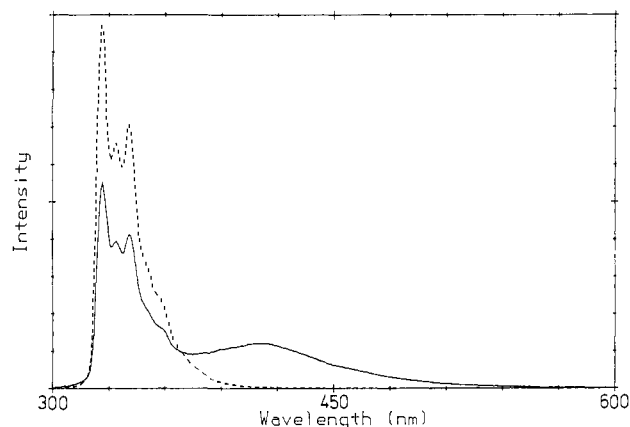
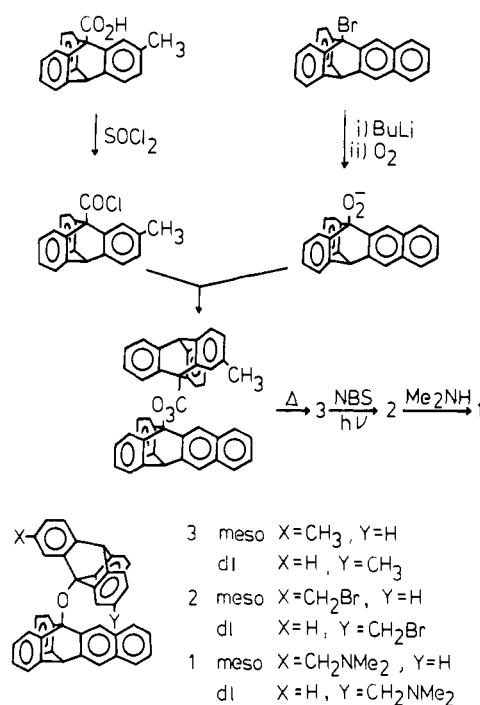


Figure 1. Emission spectra of 1 obtained by excitation at 290 nm in *n*-Bu₂O at 23 °C: (—) racemic isomer; (---) meso isomer.

Scheme I



designed Tp_2O derivative 1, carrying an aliphatic tertiary amino group on one of the Tp unit and a naphtho chromophore on the other. We wish to report here the preparation and photostationary analysis of the internal exciplex formation of such an "exciplex gear molecule".

Preparation of the geared ether was performed as shown in Scheme I in a manner similar to those previously developed for other Tp_2O compounds.¹ The ether was separated into the racemic and meso isomers by means of HPLC on microsilica with CH_2Cl_2 -MeOH elution. The structural assignment was made straightforward by the comparison of their ¹³C NMR spectra; the racemic and meso isomers exhibited 15 and 11 lines for the quaternary benzene ring carbons, respectively. The absorption spectra of the two isomers of 1 and an isomeric mixture of 3 were superimposable to one another in various solvents. One can conclude that there is no meaningful interaction between tertiary amino donor (D) and naphthalene acceptor (A) in the ground state.

The fluorescence spectra of the isomers obtained by excitation at the naphthalene chromophore are presented in Figure 1. The racemic isomer of 1 has a broad and structureless emission at longer wavelength (max at 412 nm in *n*-Bu₂O at 23 °C) due to exciplex (D-A*) formation in addition to the emission from locally excited naphthalene (A*). On the other hand, the meso isomer

- (1) (a) Kawada, Y.; Iwamura, H. *J. Org. Chem.* 1980, 45, 2547. (b) Kawada, Y.; Iwamura, H. *J. Am. Chem. Soc.* 1981, 103, 958. (c) Kawada, Y.; Iwamura, H. *Tetrahedron Lett.* 1981, 22, 1533. (d) Kawada, Y.; Iwamura, H. *J. Am. Chem. Soc.* 1983, 105, 1449. (e) Kawada, Y.; Iwamura, H.; Okamoto, Y.; Yuki, H. *Tetrahedron Lett.* 1983, 24, 191. (f) Koga, N.; Kawada, Y.; Iwamura, H. *J. Am. Chem. Soc.* 1983, 105, 5498. (g) Kawada, Y.; Iwamura, H.; Okamoto, Y. *Tetrahedron Lett.* 1983, 24, 5359. (h) Iwamura, H.; Ito, T.; Ito, H.; Toriumi, K.; Kawada, Y.; Osawa, E.; Fugiyoshi, T.; Jaime, C. *J. Am. Chem. Soc.* 1984, 106, 4712.
(2) (a) Hounshell, W. D.; Johnson, C. A.; Guenzi, A.; Cozzi, F.; Mislow, K. *Proc. Natl. Acad. Sci. U.S.A.* 1980, 77, 6961. (b) Cozzi, F.; Guenzi, A.; Johnson, C. A.; Mislow, K.; Hounshell, W. D.; Blount, J. F. *J. Am. Chem. Soc.* 1981, 103, 957. (c) Johnson, C. A.; Guenzi, A.; Mislow, K. *Ibid.* 1981, 103, 6240. (d) Johnson, C. A.; Guenzi, A.; Nachbar, R. B., Jr.; Blount, J. F.; Wennerström, O.; Mislow, K. *Ibid.* 1982, 104, 5163. (e) Bürgi, H.-B.; Hounshell, W. D.; Nachbar, R. B., Jr.; Mislow, K. *Ibid.* 1983, 105, 1427. (f) Guenzi, A.; Johnson, C. A.; Cozzi, F.; Mislow, K. *Ibid.* 1983, 105, 1438.
(3) The barrier heights of 0.19 and 0.93 kcal/mol are predicted by empirical force field calculations for the interconversion of the preferred C_2 conformations of Tp_2CH_2 and the C_2 conformations of Tp_2O , respectively.^{1b,2}
(4) (a) Stevens, B. *Adv. Photochem.* 1971, 8, 161. (b) Klöpffer, W. In "Organic Molecular Photochemistry"; Birks, J. B., Ed.; Wiley: New York, 1973. (c) Van der Auweraer, M.; Gilbert, A.; De Schryver, F. C. *J. Am. Chem. Soc.* 1980, 102, 4007. (d) Mees, F.; Van der Auweraer, M.; De Schryver, F. C. *Ibid.* 1980, 102, 4017. (e) Geladé, E.; Boens, N.; De Schryver, F. C. *Ibid.* 1982, 104, 6288.