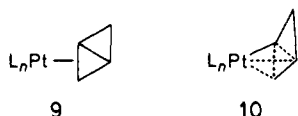


The question of mechanism of the interconversion between the center-opened type complex **3** and the side-opened type **7** remains to be answered. The lack of ligand exchange reactions is against the process in which the edge-on complexes **4** and **9** are important transient intermediates. Moreover, as described above, MO



considerations suggest that the formation of **9** is energetically unfavorable. Thus, we think that an intramolecular concerted process via a transition state like **10** is most probable.²² This type of rearrangement is formally related to the cyclobutyl-cyclopropylcarbinyl interconversions which have been well-documented in carbonium ion chemistry.²³

Acknowledgment. We are grateful to Professors J. Halpern (University of Chicago), R. Noyori (Nagoya University), and R. Pettit (University of Texas, Austin) for helpful discussions. We thank the Ministry of Education, Japan, for partial support of this research (Grant 574206).

(21) Jorgensen, W. L.; Salem, L. In "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973; pp 203-205.

(22) Such species could be stable complexes, and rapid interconversion among this kind of species also may explain our experimental findings.

(23) Staral, J. S.; Yavari, I.; Roberts, J. D.; Surya Prakash, G. K.; Donovan, D. J.; Olah, G. A. *J. Am. Chem. Soc.* **1978**, *100*, 8016-8018 and references therein.

Mechanism of the Reppe Cyclooctatetraene Synthesis from Ethyne: A Labeling Experiment

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The mechanism of the remarkable nickel-catalyzed cyclo-tetramerization of ethyne discovered by Reppe¹ is little understood, despite the synthetic significance of the reaction² and the mechanistic curiosity it has generated.³ Originally formulated as a concerted "zipper" process,⁴ recent work has suggested the possibility of the occurrence of a stepwise topological equivalent possibly involving dinuclear metallacycles.⁵ Particularly sig-

* Camille and Henry Dreyfuss Teacher-Scholar, 1978-1983.

(1) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Liebigs Ann. Chem.*, **560**, 1 (1948).

(2) A. C. Cope and H. C. Campbell, *J. Am. Chem. Soc.*, **74**, 179 (1952); A. C. Cope and D. S. Smith, *ibid.*, **74**, 5136 (1952); A. C. Cope and D. F. Rugen, *ibid.*, **75**, 3215 (1953); A. C. Cope and R. M. Pike, *ibid.*, **75**, 3220 (1953); J. R. Leto and M. F. Leto, *ibid.*, **83**, 2944 (1961); P. Chini, N. Palladino, and A. Santambrogio, *J. Chem. Soc. C* **836** (1967); G. A. Chukhadzhyan, E. L. Sarkisyan, and T. S. Elbakyan, *Zh. Obshch. Khim.*, **43**, 2302 (1973); V. K. Shitikov, T. N. Kolosova, V. A. Sergeev, V. V. Korshak, and P. O. Okulevich, *Zh. Org. Khim.*, **10**, 1007 (1974); L. H. Simons and J. J. Lagowski, *J. Org. Chem.*, **43**, 3247 (1978).

(3) For a review, see L. P. Yur'eva, *Russ. Chem. Rev.*, **43**, 48 (1974).

(4) G. N. Schrauzer and S. Eichler, *Chem. Ber.*, **95**, 550 (1962); G. N. Schrauzer, P. Glockner, and S. Eichler, *Angew. Chem.*, **76**, 28 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 185 (1964); G. N. Schrauzer, *Adv. Organomet. Chem.*, **2**, 1 (1964); E.-A. Reinsch, *Theoret. Chim. Acta*, **17**, 309 (1970).

(5) See (a) V. Hinrich-Dierks and H. Dietrich, *Acta Crystallogr., Sect. B*, **B24**, 58 (1968); (b) D. J. Brauer and C. Krüger, *J. Organomet. Chem.*, **122**, 265 (1976); (c) G. Wilke, *Pure Appl. Chem.*, **50**, 677 (1978); (d) S. P. Kolesnikov, J. E. Dobson, and P. S. Skell, *J. Am. Chem. Soc.*, **100**, 999 (1978); (e) W. Geibel, G. Wilke, R. Goddard, C. Krüger, and R. Mynott, *J. Organomet. Chem.*, **160**, 139 (1978); (f) S. A. R. Knox, R. F. D. Stansfield, F. G. A. Stone, M. J. Winter, and P. Woodward, *J. Chem. Soc., Chem. Commun.* **221** (1978); (g) M. Green, N. C. Norman, and A. G. Orpen, *J. Am. Chem. Soc.*, **103**, 1269 (1981); (h) E.-A. Reinsch, *Theoret. Chim. Acta*, **11**, 296 (1968).

Scheme I

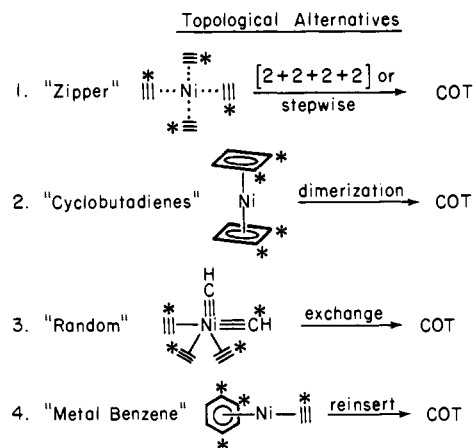


Table I. Theoretical Isomer Distribution of Labeled Cyclooctatetraenes According to Various Mechanisms of Formation

zipper	0%	0%	0%	0%	50%	25%	12.5%	12.5%		
cyclobutadiene	3.1	12.5	6.25	6.25	37.5	15.6	6.25	12.5		
random	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5		
metal benzene	0	6.25	6.25	6.25	43.75	18.75	6.25	12.5		

Table II. Calculated Relative Abundance of Labeled C₄ Fragments Derived From COT.*C₄

	zipper	cyclo-butadiene	random	metal-benzene
*C ₄	0.00	0.39	1.56	0.00
C* ₃	12.50	17.19	18.75	15.62
C ₂ *C ₂	75.00	64.84	59.37	68.75
C ₃ *C	12.50	17.19	18.75	15.62
C ₄	0.00	0.39	1.56	0.00

nificant has been the discovery of metal-mediated alkyne-linking processes resulting in flyover bridges between two metal centers composed of four alkyne units^{5f,g} and the detection of a remarkably facile reversible cyclooctatetraene (COT) ring-opening reaction.^{5c,e}

Other work has implicated the intermediacy of nickel-cyclobutadiene complexes.⁵ Such intermediates were originally discounted as unlikely due to the stability of isolated representatives of this class of compounds.⁷ Through the use of isotopic labeling they were also shown to be absent in a number of transition-metal-catalyzed alkyne cyclizations leading to aromatic compounds.⁸ On the other hand, recently several cyclobutadiene-nickel complexes have been isolated which appear to be good models for potential intermediates in COT synthesis,⁶ particularly some which may be decomposed to COT under mild conditions.^{6b}

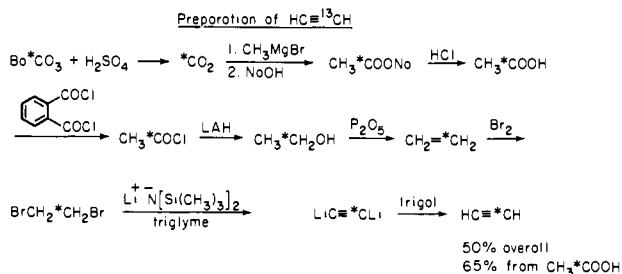
In addition to the "zipper-stepwise" (hereafter called "zipper") and the "cyclobutadiene" mechanisms, there are other major topological alternatives⁹ (Scheme I): a "random" process in which

(6) (a) C. Fröhlich and H. Hoberg, *J. Organomet. Chem.*, **204**, 131 (1981); H. Hoberg and C. Fröhlich, *ibid.*, **197**, 105 (1980); P. Mauret, G. Guerch, and S. Martin, *C. R. Hebd. Seances Acad. Sci. Ser. C*, **284**, 747 (1977); (b) H. Hoberg and C. Fröhlich, *Angew. Chem.*, **92**, 131 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 145 (1980); H. Hoberg and W. Richter, *J. Organomet. Chem.*, **195**, 355 (1980); see also H. Hoberg and W. Richter, *ibid.*, **195**, 347 (1980).

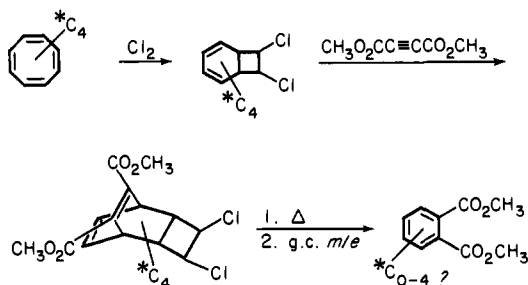
(7) P. M. Maitlis, *Adv. Organomet. Chem.*, **4**, 95 (1966); R. S. Dickson and P. J. Fraser, *ibid.*, **12**, 323 (1974); A. Efraty, *Chem. Rev.*, **77**, 691 (1977); see also J. R. Fritch and K. P. C. Vollhardt, *Angew. Chem.*, **91**, 439 (1979); *Angew. Chem., Int. Ed. Engl.*, **18**, 409 (1979).

(8) G. M. Whitesides and W. J. Ehmman, *J. Am. Chem. Soc.*, **91**, 3800 (1969); **92**, 5625 (1970).

Scheme II



Scheme III



individual carbyne units are recombined arbitrarily¹⁰ and a "metal-benzene" intermediate (formed by the stepwise process⁸) which inserts another molecule of ethyne en route to COT.¹¹ As indicated in Scheme I one might be able to distinguish between these possibilities by using singly labeled ethyne. A simple statistical analysis (neglecting ¹³C isotope effects) gives the expected distribution of the eight possible isomeric tetralabeled products (Table I). One will note that in the zipper mechanism it is impossible to generate three or four adjacent labels.

If one were to employ ethyne-*l*-¹³C as starting material,¹² a possible way of interpreting the data arising from such a labeling experiment would be by inspection of the C₄H₄-fragment ion peak envelope. Unfortunately, we found that significant randomization of the COT carbon skeleton takes place prior to fragmentation.¹³ A chemical degradation to a C₄ unit would lead to the label distribution depicted in Table II (assuming 100% label purity).

(9) Scheme I is not meant to imply specific mechanisms, but simply (as stated) topological variations of assembling four two-carbon fragments to give an eight-membered ring. However, there are numerous transition-metal complexes, the structure of which may or may not be relevant in this context: M. A. Bennett, *Adv. Organomet. Chem.*, **4**, 375 (1966); L. A. Paquette, *Tetrahedron*, **31**, 2855 (1975); F. L. Bowden and A. B. P. Lever, *Organomet. Chem. Rev.*, **3**, 227 (1968); A. Konietzky, P. M. Bailey, and P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, **78** (1975); P. M. Bailey, B. E. Mann, I. D. Brown, and P. M. Maitlis, *ibid.*, **238** (1976); P. F. Heveldt, B. F. G. Johnson, J. Lewis, P. R. Raithby, and G. M. Sheldrick, *ibid.*, **340** (1978); M. E. E. Veldman, H. R. van der Wal, S. J. Veenstra, and H. J. de Liefde Meijer, *J. Organomet. Chem.*, **197**, 59 (1980).

(10) Transition metals may convert alkynes to carbyne complexes: J. R. Fritch, K. P. C. Vollhardt, M. R. Thompson, and V. W. Day, *J. Am. Chem. Soc.*, **101**, 2768 (1979); J. R. Fritch and K. P. C. Vollhardt, *Angew. Chem.*, **92**, 570 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 559 (1980), and references therein.

(11) We have cyclotetramerized ethyne in the presence of C₆D₆ and found no COT-*d*₄ (GC/MS) in product, only a small amount of COT-*d*_{1,2}. This result suggests that, should the metal-benzene mechanism (Scheme I) be operating, the metal may not reversibly dissociate benzene. Variations of the alternatives in Scheme I may be conceived of: (a) metal cyclobutadienes which react further via metallacyclopentadienes in a stepwise manner; this is equivalent to the metal benzene process; (b) metal cyclobutadienes which convert to Dewar benzenes and subsequently tricyclo[4.2.0.0^{2,5}]octa-1,7-dienes en route to COT; (c) metal cyclobutadienes which add one ethyne to give a metal-benzene complex which inserts the fourth ethyne to give COT. The last two possibilities produce numbers very close to the cyclobutadiene mechanism.

(12) Initial experiments were directed at using monodeuterioethyne. However, the results in ref 11 and literature data discouraged this approach: L. S. Meriwether, M. F. Leto, E. C. Colthup, and G. W. Kennerly, *J. Org. Chem.*, **27**, 3930 (1962).

(13) See also: J. F. Franklin and S. R. Carroll, *J. Am. Chem. Soc.*, **91**, 5940 (1969).

Table III. Calculated and Experimental Relative Peak Intensities for the M⁺ - OCH₃ Ion Peak of Dimethyl Phthalate Containing Varying Amounts of Label According to Several Mechanisms

<i>m/e</i>	zipper	cyclo-butadiene	random	metal-benzene	exptl ^a
163	0.6	1.5	3.6	0.8	2.9 ± 0.1
164	22.4	31.7	36.5	28.2	21.1 ± 0.6
165	100.0	100.0	100.0	100.0	100.0
166	23.6	32.6	37.3	29.2	22.8 ± 0.4
167	1.9	3.1	5.2	2.3	1.3 ± 0.5

^a Average of five runs including standard deviations. The mass spectral line intensities ranged from 900 to 2200 counts for the smallest *m/e* 167. This eliminates any significant ion statistical error in measuring the ratio of the ion peaks *m/e* 164-166 (B. J. Millard, "Quantitative Mass Spectrometry", Heyden, Philadelphia, PA, Chapter 3). The deviation in *m/e* 167 could be ascribed to such errors while the disparity of the *m/e* 163 peak appears to be due to the presence of a small amount of impurity.

In order to analyze results correctly, two further corrections have to be applied, one which takes into account the isotopic purity of both carbon atoms (¹²C, 98.89%; ¹³C, 97%¹⁴).¹⁵ The other incorporates these numbers into the fragmentation pattern of the ions containing the C₄ unit originally derived from the labeled COT. We chose dimethyl phthalate as the target of degradation (vide infra) because the base peak in its mass spectrum at *m/e* 163 (M⁺ - OCH₃) is essentially isolated, i.e., it has no near neighbors except those due to natural ²H, ¹³C, ¹⁷O, and ¹⁸O. The resulting theoretically expected label distributions for the various mechanisms are shown in Table III normalized to the most abundant fragment, *m/e* 165.¹⁶

The required singly labeled ethyne¹⁷ was prepared starting from commercially available Ba¹³CO₃ or CH₃¹³COOH¹⁴ by literature methods¹⁸ (Scheme II) up to the 1,2-dibromoethane stage. Elimination and protonation was achieved as shown.¹⁹ Cyclization²⁰ was followed by degradation²¹ according to Scheme III. The mass spectrum of the labeled COT revealed the absence of any COT-¹³C₃ isomer in excess of the amount expected based on the natural abundance of ¹³C in the ¹²C label. This rules out random carbon exchange processes of any kind in the cyclization. After degradation, the peaks for the dimethyl phthalate fragment *m/e* C₉H₇O₃ give the relative intensities shown in Table III. The observed figures are clearly incompatible with the significant occurrence of cyclobutadiene, random, and metal-benzene mechanisms or any other conceivable topologically equivalent sequence leading to COT. A separate experiment using a different catalytic system with less enriched ethyne-*l*-¹³C is in remarkable agreement with these conclusions.²² It follows that the predom-

(14) We thank Dr. N. A. Matwiyoff (Stable Isotope Resource, Los Alamos Scientific Laboratory) for a generous sample of 99% ¹³C labeled acetic acid.

(15) Label purity was ascertained at the stage of rigorously purified 1,2-dibromoethane.

(16) These numbers do not incorporate negligible deviations due to natural abundance ²H or ¹³C isotope effects. See E. Buncl and C. C. Lee, Eds., "Carbon-13 in Organic Chemistry", Vol. 3, Elsevier, New York, 1977. Calculations were carried out by using binomial statistics, both by hand and employing a simple BASIC program: R. E. Colborn, Ph.D. thesis, University of California, Berkeley, CA, 1981.

(17) A more cumbersome and less efficient approach has been reported: R. F. C. Brown, F. W. Eastwood, and G. P. Jackman, *Aust. J. Chem.*, **31**, 579 (1978).

(18) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P. F. Yankwich, "Isotopic Carbon", Wiley, New York, 1949; J. D. Cox and H. S. Turner, *J. Chem. Soc.*, 3176 (1950); B. Bak, J. Christiansen, and J. T. Nielsen, *Acta Chem. Scand.*, **14**, 1865 (1960); B. Bak, J. T. Nielsen, and M. Schöttlander, *ibid.*, **16**, 123 (1962).

(19) Details will be published separately.

(20) HC≡¹³CH (5 mmol), Ni(acac)₂ (2%), Et₂AlOEt (1-1.8%), THF, N₂ (85 psig), 1 day, 85 °C. Yield of COT, 50-60%.

(21) R. Pettit and J. Hennery, *Org. Synth.*, **50**, 36 (1970). GC mass spectral data were obtained on a Finnigan 4000 instrument equipped with an IncoS data system. Glass and fused silica capillary columns coated with SP-2250 or SE-54 served to separate products. All spectra were obtained at 70 eV.

inant way in which four ethynes are linked by nickel catalysts en route to COT leaves the initial connectivity of the starting carbon pairs intact. This is currently best accommodated by the postulate of a zipper-stepwise-type mechanism.

Acknowledgment. This work was supported by NSF-CHE-79-03954 and the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U. S. Department of Energy, under Contract W-7405-ENG-48. We are grateful for useful discussions with Dr. A. Falick on mass spectral analyses and the tireless efforts of L. Fanning expended on the recording of GC mass spectral data.

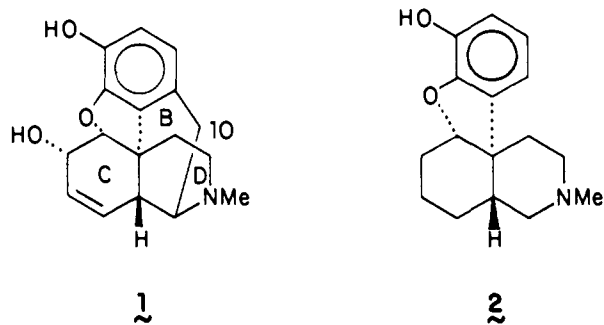
(22) $\text{HC}\equiv^{13}\text{C}$ (90% labeled), $\text{Ni}(\text{acac})_2$, CaC_2 , THF, N_2 (50–60 psig), 2–3 days, 85–90 °C. For this label purity the following values are calculated (standardized to m/e 165 = 100%, ^{13}C in $^{12}\text{C}\sim 1\%$) (m/e , 163, 164, 166, 167): zipper, 3.0, 38.2, 21.6, 1.7; cyclobutadiene, 4.6, 46.9, 29.3, 2.7; random, 7.3, 51.3, 33.5, 4.4; metal-benzene, 3.6, 43.6, 26.3, 2.0. Found: 7.0, 36.5, 20.4, 1.2.

2,3,4,4a,5,6,7,7a-Octahydro-1H-benzofuro[3,2-e]-isoquinoline: A New Morphine Fragment

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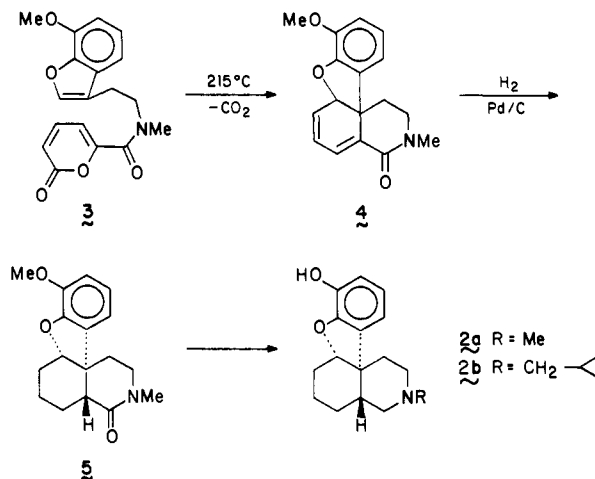
Generations of medicinal chemists have used the morphine molecule (1) as a model in their search for a strong, nonaddictive analgesic.¹ We now report the synthesis of a new morphine fragment, 2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]-isoquinoline (2), which lacks ring B but contains the complete skeleton of morphine with the exception of C-10.^{2,3}



The key reaction in the synthesis of 2 is the intramolecular Diels–Alder reaction⁴ (0.5% in 1,2,4-trichlorobenzene, reflux, 10 h) of *N*-(7-methoxy-3-benzofuranylethyl)-*N*-methyl-6 α -pyrone-carboxamide (3)⁵ to give 9-methoxy-3-methyl-2,3-dihydro-1H-

benzofuro[3,2-e]isoquinolin-4(7aH)-one (4)^{6,7}, mp 175–176 °C, in 53% yield.⁸ The *N*-benzyl and *N*-cyclopropylmethyl analogues of 4 were obtained in the same manner in 50 and 67% yields, respectively. Diels–Alder additions involving benzofuran as the dienophile do not appear to have been reported previously;⁹ the reverse reaction has been observed in the case of the Diels–Alder adducts of thebaine with esters of acetylenedicarboxylic acid.¹⁰

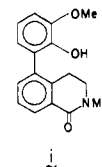
Catalytic hydrogenation of 4 (Pd/C, THF) stereospecifically introduced the trans C/D ring junction to give the lactam 5^{6,11} which on reduction (borane–methyl sulfide) and demethylation (*n*-PrSK, DMF) furnished 3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]isoquinolin-9-ol (2a), mp 218–220 °C,⁶ in 86% yield (based on 4). The assigned structure was confirmed by a single-crystal x-ray structure determination¹² carried out on the cyclopropylmethyl analogue 2b.¹³



Heating the *N*-(7-methoxy-3-benzofuranylethyl)-*N*-(cyclopropylmethyl)amide of 2,4-pentadienoic acid (6)¹⁴ in toluene (0.5% solution) to 240 °C for 10 h and isolating the product by HPLC gave the cis-fused intramolecular Diels–Alder adduct 7¹⁵ in 10%

(6) Correct elemental analyses have been obtained for all new compounds.
(7) NMR (220 MHz in CDCl_3): τ 3.1 (d, 1 H, $J = 6$ Hz), 3.3–3.5 (m, 2 H), 3.6 (d/d, 1 H, $J = 6/2$ Hz), 4.1 (d/d/d, 1 H, $J = 10/6/2$ Hz), 4.3 (d/d, 1 H, $J = 10/2$ Hz), 4.7 (narrow m, 1 H), 6.3 (s, 3 H), 6.6 (t/d, 1 H, $J = 12/4$ Hz), 6.9 (d/d/d, 1 H, $J = 12/6/2$ Hz), 7.7 (s, 3 H), 8.0 (t/d, 1 H, $J = 12/6$ Hz), 8.3 (d/d/d, 1 H, $J = 12/4/2$ Hz).

(8) Two other products were isolated in low yields: a Diels–Alder dimer of 4 of unknown regio- and stereochemistry and compound i, which was presumably formed by cleavage of the carbon–oxygen bond of the dihydrobenzofuran in 4 followed by phenyl migration and aromatization.



(9) For an intramolecular Diels–Alder reaction of a hexahydronaphthalene (diene) to a furan (dienophile), see: Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G. *Tetrahedron* 1974, 30, 3099.

(10) Rapoport, H.; Sheldrick, P. *J. Am. Chem. Soc.* 1963, 85, 1636.

(11) NMR (220 MHz in CDCl_3): τ 2.9–3.1 (m, 2 H), 3.2–3.4 (m, 1 H), 5.3 (d/d, $J = 8/6$ Hz, 1 H); 5.9 (s, 3 H), and 6.4–8.7 (m + s, 14 H).

(12) We are indebted to Dr. R. L. Harlow for this determination; details are available in the supplementary material.

(13) Mp 175 °C. NMR (220 MHz in CDCl_3): τ 2.5 (br s, 1 H), 3.1 (d, $J = 6$ Hz, split further, 1 H), 3.3 (m, 2 H), 5.6 (t, presumably d/d, $J \approx 5$ –6 Hz, 1 H), 6.9 (m, 2 H), 7.2–7.6 (m, 4 H), 7.9–9.2 (m, 10 H), 9.5 (m, 2 H), and 9.9 (m, 2 H).

(14) The amide 6 was prepared from 2,4-pentadienoic acid by treatment with methyl chloroformate (CH_2Cl_2 , *i*-PrNEt₃, 0 °C) followed by *N*-(cyclopropylmethyl)-7-methoxy-3-benzofuranylethylamine. NMR (60 MHz in CDCl_3): τ 2.5 (s, 1 H), 2.6–4.8 (m, 8 H), 6.0 (s, 3 H), 6.3 (m, 2 H), 6.4–7.2 (m, 4 H), and 8.8–9.9 (m, 5 H).

(15) NMR (220 MHz in CDCl_3): τ 3.1–3.2 (m, 3 H), 3.9 (d/d/d, $J = 9/4/2$ Hz, 1 H), 4.0 (m, 1 H); 5.3 (d/d, $J = 5.5/7$ Hz, 1 H), 6.1 (s, 3 H), and 6.2–9.8 (m, 14 H).