Synthesis of Carbon-Bridged Dibenzazocines and Dibenzodiazocines. Regiochemical Control Elements in the Beckmann Rearrangement†

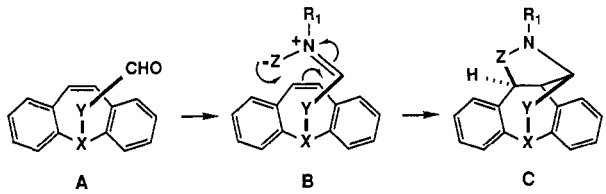
Pat N. Confalone* and Edward M. Huie

Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received July 1, 1986

A synthetic route for the conversion of carbon-bridged dibenzocycloheptanes and dibenzazepines, readily available by intramolecular [3 + 2] cycloaddition methodology, to carbon-bridged dibenzazocines and dibenzodiazocines is presented. The key transformations involve the Beckmann rearrangement of intermediates **5**, **12**, **14**, and **15** to the various possible lactam products. Factors controlling the observed regiochemistry of the rearrangement process, leading to regiochemical control of the Beckmann products, are discussed from a mechanistic viewpoint. A rationale for the observed selectivity in the hydride reduction of the urethane lactams **16**, **21**, **22**, and **24** is also presented. The overall approach affords a facile and generally useful transformation of olefin aldehydes of general structure D to the bicyclics F and/or G via the cycloadducts E.

Reports of significant biological activity for selected carbon-bridged polycyclics have generated a renewed interest in their synthesis.[1] We recently described an efficient entry into carbon-bridged dibenzocycloheptanes and dibenzazepines utilizing a series of intramolecular [3 + 2] cycloaddition reactions (A → B → C).[2] Observations

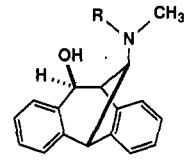


A B C

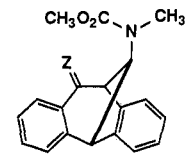
X = CH, N Y = $(CH_2)_n$ n = 0-2 Z = O, $NCOR_2$, $CHCO_2R_3$

attributing antihypertensive activity to carbon-bridged dibenzazocines prompted us to study various conversions of our novel cycloadducts, readily prepared by this methodology, into an analogous series of dibenzazocines and dibenzodiazocines, relying upon the Beckmann rearrangement for the key transformation. In the course of this approach, we observed several regiospecific Beckmann rearrangements of oximes and oxime tosylates under neutral and acidic conditions, including several cases that apparently violate the Beckmann rule. We report herein the results of our studies that clarify some factors controlling regiochemistry in the Beckmann rearrangement and provide a rationale for the experimental facts.

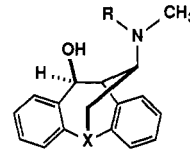
The required starting materials, the 1,3-amino alcohols **1**, **6**, and **8**, were synthesized by zinc reduction of the N–O bond of the pentacyclic isoxazolidine cycloadducts of general structure C (Z = O), available by intramolecular nitrone–olefin [3 + 2] cycloaddition methodology.[2] The amino functionality was selectively protected under Schotten–Baumann conditions to yield the carbamates **2**, **7**, and **9**, respectively. Oxidation with buffered pyridinium chlorochromate[3] occurred smoothly, yielding the desired ketones **3**, **10**, and **13** in overall yields of 76%, 84%, and 98% after purification. Although quite hindered, these ketones could be forced to undergo oximation with hydroxylamine in refluxing pyridine to produce the corresponding oximes **4**, **11**, and **14**, respectively. The preparation of the substrates for the Beckmann rearrangement was completed by conversion to the oxime tosylates by treatment with *p*-toluenesulfonyl chloride, again in refluxing pyridine, affording the desired products **5**, **12**, and **15** in overall yields of 52%, 86% and 65%.



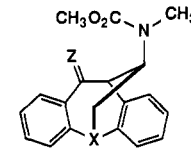
1 R = H
2 R = CO_2CH_3



3 Z = O
4 Z = NOH
5 Z = NOTs



6 X = CH, R = H
7 X = CH, R = CO_2CH_3
8 X = N, R = H
9 X = N, R = CO_2CH_3



10 X = CH, Z = O
11 X = CH, Z = NOH
12 X = CH, Z = NOTs
13 X = N, Z = O
14 X = N, Z = NOH
15 X = N, Z = NOTs

Although the oximes and oxime tosylates were obtained as single stereoisomers in each case, their stereochemistry could not be assigned unambiguously by the usual spectroscopic methods. Therefore, the structure of the oxime tosylate **5** was determined by single-crystal X-ray diffraction to be that presented in Figure 1. As shown, the bulky sulfonate group is positioned anti to the peri hydrogen (starred), thus avoiding a destabilizing steric interaction. The degree of crowding in the alternate syn orientation is very severe and accounts for the production of single stereoisomers in this series. The related, albeit less serious, interaction present in the oxime precursors **4**, **11**, and **14** presumably controls the stereochemical outcome of the oximation reaction as well. This stereochemical result presumably remains unaltered during the tosylation step.

The oximes and oxime tosylates are very reactive under the conditions of the Beckmann rearrangement[4] since these molecules are not only strained but also have available a ready fragmentation pathway leading initially to a stabilized benzylic carbonium ion. The oxime tosylate **5**, for example, yielded a lactam product only under a precise set of experimental conditions. Thus, treatment of **5** with

† Contribution no. 4141.

(1) Escale, R.; Elkhaydt, A.; Vidal, J. P.; Girard, J. R.; Rossi, J. C. *J. Heterocycl. Chem.* **1984**, *21*, 1033. Pinard, G. *Curr. Ther. Res.* **1977**, *21*, 368. U.S. Pat. 3 969 467, 3 976 774, 4 242 810; *Chem. Abstr.* **1981**, *94*, 47304*h*. Japanese Patents 80 124 783 (*Chem. Abstr.* **1981**, *94*, 156774*g*), 56 063 984, and 6 803 185; Swiss Patent 452 511, E.P. Patent 24 258.

(2) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994.

(3) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(4) For Beckmann rearrangements of the parent bicyclic compound, see: Krow, G.; Szczepanski, S. *J. Org. Chem.* **1982**, *47*, 1153.

0022-3263/87/1952-0079$01.50/0

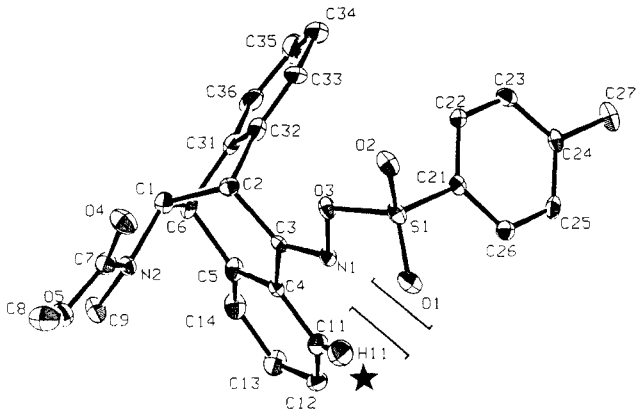
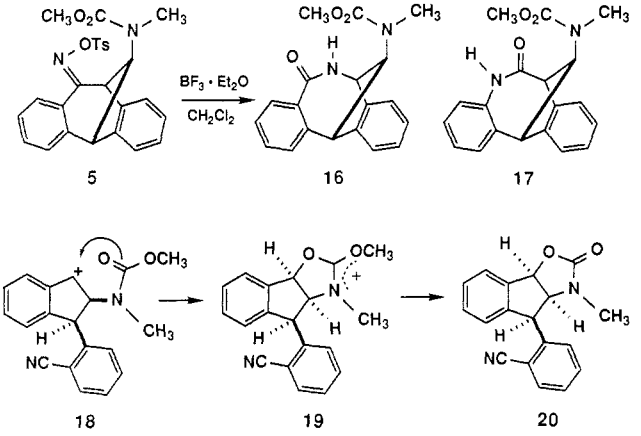


Figure 1. X-ray crystal structure of the oxime tosylate **5**.

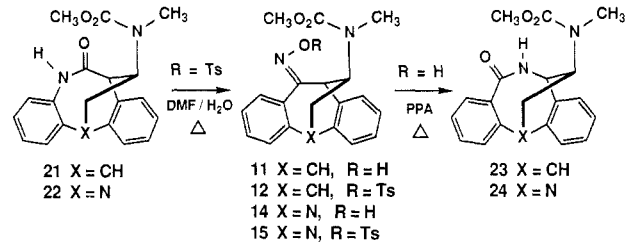
boron trifluoride etherate[5] in methylene chloride at room temperature afforded the desired lactam **16** in 45% yield. A byproduct arising from the fragmentation pathway was isolated in this reaction and found to be the tricyclic **20** rather than the expected cyanoolefin. Presumably, the initial benzylic carbonium ion **18** is trapped by the urethane carbonyl to give the cyclic stabilized species **19**, which is then demethylated to give the observed byproduct **20** in 22% yield.



The orientation of the lactam **16**, which was obtained as the sole rearrangement product, was assigned unambiguously by IR, UV, and NMR as well as subsequent chemistry. The alternate lactam isomer **17** was not detected in the reaction mixture. Of course, the lactam orientation present in **16** is *opposite* to that predicted by the Beckmann rule given the anti oxime tosylate configuration present in the substrate **5** as determined unequivocably by the X-ray study. This result is also counter to the established migratory abilities of an aryl group vs a secondary aliphatic carbon atom. A possible rationalization for this apparent violation of the Beckmann rule lies in the assumption that the Lewis acid present in this reaction catalyzes the isomerization[6] of the oxime tosylate from the thermodynamically more stable anti configuration to the higher energy syn orientation with its destabilizing peri interaction.[7] The strain in this syn species is expeditiously relieved by undergoing a Beckmann rearrangement, a pathway not available to the corresponding anti isomer under these mild conditions. A bimolecular recombination mechanism has also been suggested to account for abnormal Beckmann rearrangements.[8] In our case, this would require reclosure of the cation **18** by attack of the nitrile nitrogen to form a strained seven-membered ring in the polyclic system, an unlikely occurrence. These observation draw attention to the potential inaccuracies of assigning oxime stereochemistry on the basis of lactam orientation found in a subsequent Beckmann rearrangement.

Similar considerations apply to the rearrangements of the oxime **14**, which incorporates a two-carbon bridge spanning the dibenzazepine nucleus. Thus, heating **14** in polyphosphoric acid produces exclusively the abnormal lactam **24**. Again, an acid-catalyzed isomerization, interconverting syn and anti oximes prior to rearrangement, can be invoked. When identical conditions are applied to the bridged dibenzocycloheptane **11**, the analogous lactam **23** is not isolated. Rather, only byproducts arising from the alternate Beckmann fragmentation pathway are detectable in the reaction mixture. The absence of any such products in the rearrangement of **14** is presumably a result of the protonation of the tertiary nitrogen, thereby destabilizing the incipient benzylic carbonium ion that would be generated in the competing fragmentation process.

A test of the rationale offered above to account for the apparent violations of the Beckmann rule is to run the reaction under neutral conditions in which the oxime or oxime tosylate isomerization does not occur. Accordingly, simple heating of the oxime tosylates **12** and **15** in dimethylformamide/water (2:1) yields the isomeric lactams **21** and **22**, respectively, without a trace of the alternate lactams **23** and **24**. Compound **5** gave no detectable



amounts of either lactam under these conditions. Presumably, therefore, no isomerization of the oxime stereochemistry takes place under these essentially neutral conditions and the normal Beckmann lactams are obtained.

The final phase of this study required the reduction of the lactam functionality generated during the successful Beckmann rearrangements. This served not only to generate the final targeted compounds but also provided chemical support for the structures assigned to the various lactam regioisomers cited above. Thus, reduction of the "normal" Beckmann lactams **21** and **22** to the desired carbon-bridged dibenzazocine and dibenzodiazocine systems **25** and **26** occurred readily at room temperature with lithium aluminum hydride. The *N*-methylurethane group was concomitantly reduced to an *N,N*-dimethyl substituent as expected. In constrast to these results, reduction of "abnormal" Beckmann lactams such as **16** and **24** under identical conditions had no effect on the lactam group, reducing only the urethane moiety to afford the *N,N*-dimethylamino lactams **27** and **28**, respectively. These re-

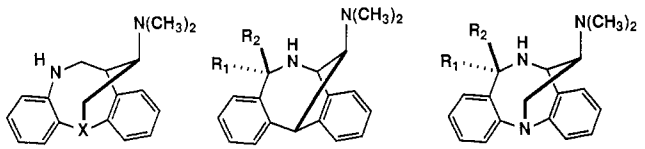
(5) For other exmples of Lewis acid assisted Beckmann rearrangements, see: (a) Ishida, Y.; Susatani, S.; Marnoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 3255. (b) Marnoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(6) For an example of acid-catalyzed syn/anti oxime sulfonate isomerization, see: Brown, R. F.; Van Gulick, N. M.; Schmid, G. H. *J. Am. Chem. Soc.* **1955**, *77*, 1094.

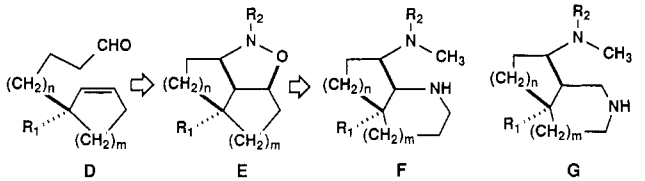
(7) For a discussion of related examples, see: March, J. In *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 2nd. ed.; McGraw-Hill: New York, 1977; pp 1008–1010.

(8) Hill, R. K.; Conley, R. T.; Chorty, O. T. *J. Am. Chem. Soc.* **1965**, *87*, 5646.

sults support our previous regiochemical structural assignments since the "abnormal" Beckmann lactams possess an aromatic lactam carbonyl and are expected to be more reluctant to undergo reduction, whereas the "normal" series has a simple aliphatic lactam and therefore reduces completely under the same mild conditions. Reduction of the lactam group in this series is achieved by carrying out the reaction under reflux conditions, thereby affording the desired target compounds **29** and **30** from either **27** and **28** or directly from **16** and **24**, respectively.



In conclusion, this study of the conversion of pentacyclic carbon-bridged isoxazolidine systems to tetracyclic carbon-bridged azocines extends the utility of the nitrone–olefin cycloaddition reaction by appending the following sequence of reactions to the [3 + 2] cycloaddition step: (1) N–O bound reduction, (2) amino protection, (3) alcohol oxidation, (4) Beckmann rearrangement, and (5) reduction of the lactam. This serves to transform an olefin aldehyde of general structure D to that of the final products F and/or G via the cycloadduct E, a conversion predicted to be of some value in a number of applications in synthetic organic chemistry.



Experimental Section

General Methods. Melting points were determined with a Fisher-Johns hotplate instrument or a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 7199 FT-IR spectrophotometer. Frequencies are reported in reciprocal centimeters (cm^{-1}) and were calibrated with use of polystyrene's 1601.8-cm^{-1} reference peak. ^1H NMR spectra were obtained with Varian EM360 and EM390 instruments in the solvent indicated. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (δ = 0.00). Coupling constants (J) are given in cycles per second (Hz). Mass spectra were recorded at 70 eV on a VG Micromass 70-70H double-focusing high-resolution spectrometer. Column chromatography was carried out with 230–400-mesh silica gel and with a Waters Prep-500 instrument by using the solvent system indicated.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-*syn*-hydroxy-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (2).** To a solution of 20.0 g (79.7 mmol) of amine **1** in 900 mL of methanol was added 300 mL of saturated $NaHCO_3$ followed by 7.4 mL (96 mmol) of methyl chloroformate. The slurry was mechanically stirred for 1.5 h. After acidification with 4 N HCl, the product was extracted with CH_2Cl_2 and dried (Na_2SO_4). Evaporation gave 22.34 g (91%) of a white solid. Recrystallization from benzene gave pure **2**: mp 181–183 °C; IR (KBr) 3420, 3020, 2950, 2940, 2850, 1675, 1480, 1460, 1370, 1160 cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 7.1–7.5 (m, 9 H), 4.65 (m, 1 H), 4.41 (m, 2 H), 4.18 (d, 1 H, J = 5.5 Hz), 3.77 (s, 3 H), 2.79 (s, 3 H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 74.15; H, 6.20; N, 4.56.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-oxo-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (3).** To a solution of 10.0 g (37.3 mmol) of **2** in 300 mL of CH_2Cl_2 was added 8.1 g (97 mmol) of sodium acetate followed by 13.9 g (64.6 mmol) of PCC. The slurry was mechanically stirred at 25 °C for 1 h. To the black mixture was added 1.5 L of ether with stirring. After decanting, the colored solution was passed through a small column of Florisil, rinsing the column with ethyl acetate. Evaporation of the clear liquid gave 9.30 g of a solid. Recrystallization from ethyl acetate gave 7.52 g (76%) of **3**: mp 180–182 °C; IR (KBr) 3020, 3010, 2950, 1690, 1600, 1460, 1205, 1165, 1155 cm^{-1}; NMR ($CDCl_3$, 80 MHz) 7.91 (m, 1 H), 7.05–7.5 (m, 7 H), 4.76 (m, 2 H), 4.44 (d, 1 H, J = 5.0 Hz), 3.70 (s, 3 H), 2.84 (s, 3 H). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.42; H, 5.60; N, 4.54.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(hydroxyimino)-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (4).** A mixture of 13.6 g (44.3 mmole of **3** and 7.7 g (110 mmol) of hydroxylamine hydrochloride in 150 mL of pyridine was refluxed under nitrogen for 2.5 h. The bulk of the pyridine was evaporated, and the dark mixture was added to 200 mL of 4 N HCl and extracted with 10% methanol/CH_2Cl_2 (3 × 300 mL). The organic layer was dried (Na_2SO_4) and evaporated to give 14.5 g (100%) of a white solid. Recrystallization from CH_2Cl_2/methanol gave **4** as white crystals: mp 229–230 °C; IR (KBr) 3280, 3070, 3020, 2960, 1695, 1680, 1480, 1470, 1460, 1170 cm^{-1}; NMR (acetone-d_6, 80 MHz) 8.11 (m, 1 H), 7.1–7.5 (m, 7 H), 5.58 (d, 1 H, J = 3.5 Hz), 4.80 (m, 1 H), 4.27 (m, 1 H), 3.68 (s, 3 H), 2.72 (s, 3 H); mass spectrum, m/e 322, 305, 290, 273, 245. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.49; H, 5.67; N, 8.64.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(*p*-toluenesulfonylimino)-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (5).** A solution of 16.4 g (51.0 mmol) of **4** and 29.0 g (153 mmol) of *p*-toluenesulfonyl chloride (recrystallized from petroleum ether) in 300 mL of anhydrous pyridine was refluxed for 4.5 h. The pyridine was evaporated, and the residue was partitioned between 1 N HCl/CH_2Cl_2 (3 × 300 mL). The organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated. The brown oil was chromatographed on silica gel by using 25% ethyl acetate/hexanes as eluent. The solid obtained was recrystallized from ethyl acetate/hexanes, giving a total of 15.6 g (64%) of **5** as white flakes: mp 174–176 °C; IR (KBr) 3030, 2960, 1700, 1595, 1470, 1460, 1375, 1190, 1180, 1095 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 7.0–8.0 (m, 12 H), 5.32 (d, 1 H, J = 3.5 Hz), 4.50 (m, 2 H), 3.63 (s, 3 H), 2.67 (s, 3 H), 2.41 (br, 3 H); mass spectrum, m/e 322, 304, 290. Anal. Calcd for $C_{26}H_{24}N_2O_5S$: C, 64.89; H, 4.97; N, 5.76; S, 6.59. Found: C, 65.12; H, 4.78; N, 5.87; S, 6.34.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-*syn*-hydroxy-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (7).** Using 10.76 g (40.6 mmol) of amine **6**, 420 mL of methanol, 140 mL of saturated $NaHCO_3$, and 3.8 mL of methyl chloroformate, and the same procedure as above, 13.41 g (100%) of a white solid were obtained. Recrystallization from ethyl acetate/hexanes gave pure **7**: mp 140–142 °C; IR (KBr) 3430, 1675, 1485, 1455 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 7.05–7.55 (m, 8 H), 5.03 (dd, 1 H, J = 7.0, 3.5 Hz), 4.3–4.6 (m, 1 H), 3.6–3.9 (m, 2 H), 3.68 (s, 3 H), 3.25 (d, 1 H, J = 7.0 Hz), 2.77 (s, 3 H), 2.3–2.7 (m, 2 H).

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-*syn*-hydroxy-5,10-ethano-5*H*-dibenz[*b*,*f*]azepin-12-yl)methylamine (9).** A mixture of 15.16 g (56.9 mmol) of amine **8**, 500 mL of methanol, 200 mL of saturated $NaHCO_3$, and 5.3 mL (68 mmol) of methyl chloroformate were stirred at 25 °C for 18 h. The mixture was partitioned between saturated $NaHCO_3$/CH_2Cl_2, dried (Na_2SO_4), and concentrated to give 18.3 g (99%) of a tan solid. Recrystallization of ethyl acetate/hexanes gave white crystals of **9**: mp 163–165 °C; IR (KBr) 3410, 2950, 1680, 1480, 1455, 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 7.05–7.55 (m, 8 H), 4.96 (dd, 1 H, J = 6.0, 2.0 Hz), 4.67 (m, 1 H), 3.6–3.9 (m, 3 H), 3.69 (s, 3 H), 3.47 (d, 1 H, J = 6.0 Hz), 2.75 (s, 3 H); mass spectrum, m/e 324, 306, 292, 234, 218. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.38; H, 6.28; N, 8.59.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-oxo-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (10).** In the same manner as alcohol **2**, alcohol **7** (11.27 g, 34.9 mmol) was oxidized with PCC (15.0 g, 69.7 mmole in 32.5 mL of CH_2Cl_2 containing sodium acetate (8.58 g, 105 mmol). After adding 2 L of ether and passing through Florisil, evaporation gave 9.38 g

(84%) of pure **8**. Recrystallization from ethyl acetate gave **10** as white cubes: mp 166–167 °C; IR (KBr) 2950, 1690, 1670, 1595, 1480, 1450, 1345, 1145 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 8.11 (m, 1 H), 7.05–7.5 (m, 7 H), 4.8–5.1 (m, 1 H), 4.38 (d, 1 H, J = 5.0 Hz), 4.24 (m, 1 H), 3.69 (s, 3 H), 2.57 (s, 3 H), 2.1–2.7 (m, 2 H); mass spectrum, m/e 321, 303, 232, 206. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.50; H, 5.93; N, 4.31.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(hydroxyimino)-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (11).** By refluxing 7.53 g (23.4 mmol) of **10** with 4.88 g (70.3 mmol) of hydroxylamine hydrochloride in 100 mL of pyridine for 5 h followed by workup as above, 8.11 g (100%) of a white solid was obtained. Recrystallization from CH_2Cl_2/methanol gave **10** as white crystals: mp 231–233 °C; IR (KBr) 3260, 1670, 1480, 1460 cm^{-1}; NMR (Me_2SO-d_6, 90 MHz) 11.50 (s, 1 H), 8.00 (m, 1 H), 7.05–7.5 (m, 7 H), 5.41 (d, 1 H, J = 4.5 Hz), 4.45–4.8 (m, 1 H), 4.23 (d, 1 H, J = 5.0 Hz), 3.63 (s, 3 H), 2.62 (s, 3 H), 2.0–2.7 (m, 2 H); mass spectrum, m/e 336, 319, 230. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.23; H, 5.97; N, 8.25.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(*p*-toluenesulfonylimino)-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptan-12-yl)methylamine (12).** In the same manner as above oxime **11** (3.00 g, 8.93 mmol) was converted to oxime tosylate **12** using *p*-toluenesulfonyl chloride (2.55 g, 13.4 mmol) and 45 mL of anhydrous pyridine. Recrystallization from ethyl acetate gave 3.83 g (86%) of **12** as white crystals: mp 173–174 °C dec; IR (KBr) 2950, 1695, 1480, 1455, 1375, 1190, 1180 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 1.9–8.1 (m, 3 H), 7.1–7.5 (m, 9 H), 5.39 (d, 1 H, J = 5.0 Hz), 4.6–5.0 (m, 1 H), 4.10 (m, 1 H), 3.79 (s, 3 H), 2.48 (s, 3 H), 2.0–2.7 (m, 2 H); mass spectrum (M^+ – TsO) measured 320.1498 (calcd for $C_{20}H_{20}N_2O_2$ 320.1525). Anal. Calcd for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71; S, 6.54. Found: C, 65.89; H, 5.35; N, 5.80; S, 6.28.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-oxo-5,10-ethano-5*H*-dibenz[*b*,*f*]azepin-12-yl)methylamine (13).** In the same manner as above, alcohol **9** (3.70 g, 1.4 mmol) was oxidized with PCC (4.92 g, 22.8 mmol) in 100 mL of CH_2Cl_2 containing 2.84 g (34.2 mmol) of sodium acetate. Obtained was 3.55 g (98%) of a light tan solid. Recrystallization from ethyl acetate gave pure **13** as white crystals: mp 147.5–148.5 °C; IR (KBr) 2950, 1690, 1675, 1590, 1480, 1465, 1450, 1345, 1150 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 8.05 (m, 1 H), 7.1–7.6 (m, 7 H), 5.14 (m, 1 H), 4.36 (d, 1 H, J = 5.0 Hz), 3.86 (dd, 1 H, J = 14, 10 Hz), 3.67 (s, 3 H), 3.44 (dd, 1 H, J = 14, 7.0 Hz), 2.57 (s, 3 H). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 71.21; H, 5.79; N, 8.59.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(hydroxyimino)-5,10-ethano-5*H*-dibenz[*b*,*f*]azepin-12-yl)methylamine (14).** After refluxing 31.4 g (97 mmol) of **13** in 750 mL of pyridine containing 20 g (290 mmol) for 5 h, the solvent was evaporated. To the oil was added 500 mL of saturated $NaHCO_3$, and the product was extracted with 10% methanol/CH_2Cl_2. Drying (Na_2SO_4) and concentration gave a yellow solid. Recrystallization from CH_2Cl_2/methanol gave a total of 26.1 g (80%) of **14** as white crystals: mp 226.5–227.5 °C; IR (KBr) 3420, 2960, 1680, 1480, 1460, 1450, 1355 cm^{-1}; NMR (Me_2SO-d_6, 80 MHz) 11.7 (s, 1 H), 7.98 (m, 1 H), 7.1–7.5 (m, 7 H), 5.39 (d, 1 H, J = 4.5 Hz), 4.87 (m, 1 H), 3.65 (s, 3 H), 3.5–3.7 (m, 2 H), 2.66 (s, 3 H); mass spectrum, m/e 337, 319, 305, 248, 231.

***N*-Carbomethoxy-*N*-(10,11-dihydro-11-(*p*-toluenesulfonylimino)-5,10-ethano-5*H*-dibenz[*b*,*f*]azepin-12-yl)methylamine (15).** After refluxing 1.97 g (5.86 mmol) of **14** and 3.35 g (17.5 mmol) of *p*-toluenesulfonyl chloride in 40 mL of anhydrous pyridine for 4 h, the solvent was removed in vacuo. After adding saturated $NaHCO_3$, the product was extracted with CH_2Cl_2 (3 × 100 mL). Evaporation of the organic layer followed by column chromatography on silica gel using 33% ethyl acetate/hexanes as eluent afforded 2.23 g of a brown solid. Recrystallization from ethyl acetate/hexanes gave 1.85 g (65%) of **15** as white crystals: mp 171–173 °C; IR (KBr) 2950, 1700, 1480, 1450, 1380, 1195, 1180, 825 cm^{-1}; NMR ($CDCl_3$, 90 MHz), 8.0 (m, 3 H), 7.1–7.5 (m, 9 H), 5.34 (d, 1 H, J = 4.5 Hz), 5.03 (m, 1 H), 3.76 (s, 3 H), 3.2–3.9 (m, 2 H), 2.48 (s, 3 H), 2.42 (s, 3 H); mass spectrum (M^+ – TsO), m/e 321.1454 (calcd for $C_{19}H_{19}N_3O_2$, 321.1477). Anal. Calcd for $C_{26}H_{25}N_3O_5S$: C, 63.52; H, 5.13; N, 8.55; S, 6.52. Found: C, 63.57; H, 5.27; N, 8.25; S, 6.29.

***N*-Carbomethoxy-*N*-(5,6,7,12-tetrahydro-5-oxo-7,12-methanodibenz[*c*,*f*]azocin-13-yl)methylamine (16).** To a solution of 15.57 g (32.7 mmol) of **5** in 325 mL of anhydrous CH_2Cl_2 was added 12 mL (98 mmol) of boron trifluoride etherate (distilled from CaH_2) under argon. After stirring for 5 h at 25 °C, 240 mL of 1 N NaOH was added. The mixture was stirred vigorously overnight. Water (250 mL) was added, and the products were extracted with ether (3 × 500 mL). Drying ($MgSO_4$) and evaporation gave 13.31 g of a solid. Column chromatography on silica gel using 25–50% ethyl acetate/hexanes gave two major products: A (R_f 0.5 in 50% ethyl acetate/hexanes) yielded 2.89 g of **20** as a white solid [IR (KBr) 2210, 1750 cm^{-1}; NMR (80 MHz, $CDCl_3$) 6.9–7.8 (n, 8 H), 5.92 (d, 1 H, J = 7 Hz), 5.22 (d, 1 H, J = 7 Hz), 4.80 (t, 1 H, J = 7 Hz), 2.50 (s, 3 H); mass spectrum, m/e 290 (M^+), 233, 204]; B (R_f 0.2 in 50% ethyl acetate/hexanes) yielded 4.79 g (45%) of pure **16**. B was recrystallized from ethyl acetate, giving **16** as a white crystal: mp 199–200 °C; IR (KBr) 3400, 3010, 2970, 1695, 1630, 1590, 1565, 1450, 1365, 1330 cm^{-1}; UV (EtOH) λ_{max} 265 mm (ϵ 3390), 271 (2840); NMR ($CDCl_3$, 90 MHz) 8.38 (m, 1 H), 7.1–7.5 (m, 7 H), 6.80 (d, 1 H, J = 6.5 Hz), 5.23 (dd, 1 H, J = 6.5, 5.5 Hz), 4.68 (d, 1 H, J = 5.5 Hz), 4.49 (t, 1 H, J = 5.5 Hz), 3.67 (s, 3 H), 2.76 (s, 3 H); mass spectrum, m/e 322.1318 (calcd for $C_{19}H_{18}N_2O_3$, 322.1317). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.82; H, 5.60; N, 8.57.

***N*-Carbomethoxy-*N*-(5,6,7,12-tetrahydro-6-oxo-7,12-ethanodibenz[*b*,*e*]azocin-14-yl)methylamine (21).** After dissolving 6.00 g (12.2 mmol) of **14** in 200 mL of dimethylformamide, 100 mL of water was added and the solution was refluxed for 72 h. The solvent was evaporated and the residue was chromatographed on silica gel using 33% ethyl acetate/hexanes as eluent to afford a tan solid (R_f 0.4 in 20% ethyl acetate/CH_2Cl_2). Recrystallization from ethyl acetate/hexanes provided 2.64 g (64%) of pure **21** as white cubes: mp 215–216.5 °C; IR (KBr) 3550, 3500, 2950, 1690, 1670, 1650, 1580, 1485, 1455, 1370, 1355, 750 cm^{-1}; UV (EtOH) λ_{max} 258 nm (ϵ 11 300); NMR ($CDCl_3$, 90 MHz) 8.35 (br, 1 H), 6.7–7.35 (m, 8 H), 4.62 (dt, 1 H, J = 10, 3.5 Hz), 4.30 (m, 2 H, 3.70 (s, 3 H), 2.98 (s, 3 H), 2.4–2.7 (m, 2 H).

***N*-Carbomethoxy-*N*-(5,6,7,12-tetrahydro-6-oxo-7,12-ethanodibenzo[*b*,*g*][1,4]diazocin-14-yl)methylamine (22).** After dissolving 8.00 g (16.3 mmol) of **15** completely in 100 mL of DMF, 50 mL of water was added and the solution was heated in an oil bath at 120 °C for 72 h. The solvent was evaporated and the residue was chromatographed on silica gel using 40% ethyl acetate/hexanes as eluent to afford 1.24 g (23%) of a tan foam (R_f 0.4 in 50% EtOAc/hexanes). Recrystallization from ethyl acetate/hexanes provided **22** as light tan cubes: mp 215–216 °C; IR (KBr) 3440, 3220, 3070, 2950, 1700, 1650, 1485, 1460, 1370, 1325 cm^{-1}; UV (methanol) λ_{max} 253 (ϵ 16 600); mass spectrum, m/e 337, 308, 294. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.31; H, 5.54; N, 12.16.

***N*-Carbomethoxy-*N*-(5,6,7,12-tetrahydro-5-oxo-7,12-ethanodibenzo[*b*,*g*][1,5]diazocin-14-yl)methylamine (24).** A mixture of 1.00 g (2.96 mmol) of **14** and 36 g of PPA was mechanically stirred under nitrogen in an oil bath at 80 °C for 3 h. Ice (100 g) was added, and the slurry was stirred until a free-flowing liquid was obtained. To the yellow liquid was added 3 N NaOH until the solution was basic. The product was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and evaporated. Column chromatography on silica gel using 75% ethyl acetate/hexanes afforded 0.76 g (76%) of an amorphous solid. Recrystallization from ethyl acetate/hexanes gave pure **24**: mp 205–207 °C; IR (KBr) 3440, 2950, 1675, 1495, 1475, 1455 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 23 700), 280 (8720), 346 (4750); NMR ($CDCl_3$, 90 MHz) 8.05 (m, 1 H), 6.8–7.5 (m, 8 H), 5.04 (dd, 1 H, J = 8.5, 1.0 Hz), 4.5 (m, 1 H), 3.75 (s, 3 H), 2.94 (s, 3 H), 2.85 (m, 2 H); mass spectrum, m/e 337, 304, 278, 248, 220.

***N*-(5,6,7,12-Tetrahydro-7,12-ethanodibenz[*b*,*e*]azocin-14-yl)dimethylamine (25).** A mixture of 100 mg (0.30 mmol) of **21** and 114 mg (3.0 mmol) of lithium aluminum hydride in 3 mL of THF was stirred at ambient temperature for 18 h. Following workup as before and filtration through a short column of activity III alumina (25% ethyl acetate/hexanes), 59 mg (71%) of **25** as a clear oil was obtained: IR ($CHCl_3$) 3350, 1485, 1450 cm^{-1}; NMR ($CDCl_3$, 300 MHz) 7.1–7.3 (m, 4 H), 7.06 (m, 1 H), 6.96 (t, 1 H,

J = 8 Hz), 6.82 (t, 1 H, J = 8 Hz), 6.60 (d, 1 H, J = 8 Hz), 4.26 (dd, 1 H, J = 12, 2 Hz), 3.84 (dd, 1 H, J = 14, 6 Hz), 3.44 (m, 1 H),m 3.22 (dd, 1 H, J = 14, 4 Hz), 2.3–2.6 (m, 4 H), 2.42 (s, 6 H); mass spectrum, measd 278.1785 (calcd for $C_{19}H_{22}N_2$, 278.1778).

***N*-(5,6,7,12-Tetrahydro-7,12-ethanodibenzo[*b*,*g*][1,4]diazocin-14-yl)dimethylamine (26).** To a solution of **22** (89 mg, 0.26 mmol) in 5 mL of dry THF was added lithium aluminum hydride (100 mg, 2.6 mmol). The mixture was stirred at 25 °C for 20 h. After adding 0.5 mL of concentrated NH_4OH and stirring 15 min, the slurry was filtered thrugh Celite and evaporated. Column chromatography on activity III neutral alumina (33% ethyl acetate/hexanes) gave 57 mg (77%) of **26** as a white solid: mp 135–137 °C; IR (KBr) 3330, 3050, 3020, 2980, 2960, 2930, 2900, 2870, 2770, 1590, 1490, 760, 750 cm^{-1}; NMR ($CDCl_3$, 360 MHz) 7.35 (d, 1 H, J = 8 Hz), 7.17 (t, 1 H, J = 8 Hz), 7.03–7.12 (m, 3 H), 6.91 (t, 1 H, J = 8 Hz), 6.81 (t, 1 H, J = 8 Hz), 6.57 (d, 1 H, J = 8 Hz), 3.84 (dd, 1 H, J = 14, 4 Hz), 3.77 (dd, 1 H, J = 13, 8.5 Hz), 3.46 (dd, 1 H, J = 13, 8 Hz), 3.37 (m, 1 H), 3.23 (dd, 1 H, J = 14, 4 Hz), 2.52 (m, 1 H), 2.28 (s, 6 H); mass spectrum, m/e 279.1726 (calcd for $C_{18}H_{21}N_3$, 279.1735).

***N*-(5,6,7,12-Tetrahydro-5-oxo-7,12-methanodibenz[*c*,*f*]azocin-13-yl)dimethylamine (27).** To a solution of 400 mg (1.24 mmol) of **16** in 10 mL of anhydrous THF was added 190 mg (5.0 mmol) of lithium aluminum hydride. The slurry was stirred under argon for 1 h. After adding 0.2 mL of concentrated NH_4OH and stirring for 0.5 h, the slurry was filtered through Celite. Evaporation of the filtrate gave 0.32 g (93%) of a white solid. Recrystallization from ethyl acetate/hexanes gave pure **27**: mp 232–235 °C; IR (KBr) 3270, 1640, 1460, 1445, cm^{-1}; NMR ($CDCl_3$, 90 MHz) 8.38 (m, 1 H), 7.05–7.4 (m, 7 H), 6.96 (br, 1 H), 4.51 (dd, 1 H, J = 6.0, 6.5 Hz), 4.35 (d, 1 H, J = 6.0 Hz), 2.90 (t, 1 H, J = 6.0 Hz), 2.22 (s, 6 H); mass spectrum, m/e 278.1393 (calcd for $C_{18}H_{18}N_2O$, 278.1419).

***N*-(5,6,7,12-Tetrahydro-5-oxo-7,12-ethanodibenzo[*b*,*g*][1,5]diazocin-14-yl)dimethylamine (25) and *N*-(5,6,7,12-Tetrahydro-7,12-ethanodibenzo[*b*,*g*][1,5]diazocin-14-yl)dimethylamine (30).** Compound **24** (1.50 g, 4.45 mmol) was reduced in the same manner as lactam **16** by using lithium aluminum hydride (1.35 g, 35.6 mmol) in 45 mL of THF. After stirring 18 h and adding 5 mL of concentrated NH_4OH, the slurry was filtered through Celite. Evaporation of the solvent left an amorphous solid. Column chromatography on activity III alumina using 25% ethyl acetate/hexanes gave two compounds. The first compound off was diazocine **30** (0.43 g, 35%): clear oil; NMR ($CDCl_3$, 360 MHz) 6.8–7.3 (m, 8 H), 4.37 (d, 1 H, J = 17 Hz), 4.25 (d, 1 H, J = 8.2 Hz), 4.10 (d, 1 H, J = 17 Hz), 2.77 (dd, 1 H, J = 12, 4.3 Hz), 2.63 (t, J = 12 Hz), 2.5–3 (m, 1 H), 2.43 (s, 6 H), 2.01 (br, 1 H); mass spectrum, m/e 279.1722 (calcd for $C_{18}H_{21}N_3$, 279.1735). The next compound off was lactam **28** (0.36 g, 28%). Recrystallization from ethyl acetate/hexanes gave pure **25**: mp 191–192 °C; IR (KBr) 3430, 3380, 1670, 1595 cm^{-1}; NMR ($CDCl_3$, 90 MHz) 8.08 (m, 1 H), 6.7–7.5 (m, 8 H), 4.93 (d, 1 H, J = 10 Hz), 2.5–3.0 (m, 3 H), 2.37 (s, 6 H); mass spectrum, m/e 293.1531 (calcd for $C_{18}H_{19}N_3O$, 293.1528).

Direct conversion of **24** to **30** was accomplished as follows: To a solution of **24** (1.00 g, 2.97 mmol) in 30 mL of dry THF was added lithium aluminum hydride (1.14 g, 30 mmol). The mixture was refluxed for 18 h. Concentrated NH_4OH (3 mL) was added and the solution stirred until white, filtered through Celite, and dried over Na_2SO_4. Evaporation gave 0.81 g of a yellow foam. Column chromatography on activity III neutral alumina using 25% ethyl acetate/hexanes provided 0.66 g (80%) of pure **30**.

***N*-(5,6,7,12-Tetrahydro-7,12-methanodibenz[*c*,*f*]azocin-13-yl)dimethylamine (29).** A mixture of 200 mg (0.72 mmol) of **27** and 0.27 g (7.2 mmol) lithium aluminum hydride in 7 mL of THF was refluxed for 7 h. To the slurry was added 10 drops of concentrated NH_4OH, and the mixture was stirred for 0.25 h. Filtration through Celite and evaporation gave a solid. This material was passed through a small column of activity III alumina using 33% ethyl acetate/hexanes as eluent. A total of 85 mg (45%) of pure **29** was obtained as an amorphous solid: NMR ($CDCl_3$, 90 MHz) 6.85–7.55 (m, 8 H), 4.50 (d, 1 H, J = 4.5 Hz), 4.22 (d, 1 H, J = 6.0 Hz), 3.55 (d, 1 H, J = 16 Hz), 3.13 (d, 1 H, J = 16 Hz), 2.77 (br, 1 H), 2.53 (dd, 1 H, J = 6.0, 4.5 Hz), 2.21 (s, 6 H); mass spectrum, m/e 264.1617 (calcd for $C_{18}H_{20}N_2$, 264.1626).

Acknowledgment. We thank Dr. Joseph C. Calabrese for the determination of the X-ray structure, Mr. Dennis Chidester for technical assistance, and Ms. Theresa A. Bonnes for help in the prepartion of this manuscript.

Supplementary Material Available: Detailed X-ray crystal data (atomic coordinates, bond lengths, bond angles, etc.) (7 pages). Ordering information is given on any current masthead page.

Synthesis of Cyclobutanated Butyrolactones via Copper(I)-Catalyzed Intermolecular Photocycloadditions of Homoallyl Vinyl or Diallyl Ethers[1]

Subrata Ghosh, Swadesh R. Raychaudhuri, and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-2699

Received July 28, 1986

Intramolecular copper(I)-catalyzed $2\pi + 2\pi$ photocycloaddition provides an effective route for the synthesis of 2-oxa- and 3-oxabicyclo[3.2.0]heptanes from homoallyl vinyl or diallyl ethers, respectively. Ruthenium-catalyzed oxidation of these multicyclic tetrahydrofuran products provides a novel annulation of cyclobutanated butyrolactones. For intermediates incorporating both methine and methylene groups next to the tetrahydrofuran oxygen, a remarkable selectivity was found for oxidation at the methylene position. Highly stereoselective generation of *exo*-2-alkylsubstituted 3-oxabicyclo[3.2.0]heptanes occurred upon photobicyclization of diallyl ethers bearing an α-alkyl substituent.

The synthetic utility of copper(I)-catalyzed olefin photoreactions[2] depends on their stereoselectivity and their compatibility with functional groups that may be required in the synthetic target molecule or that may facilitate subsequent transformations of synthetic intermediates. We now report that intramolecular copper(I)-catalyzed $2\pi + 2\pi$ photocycloaddition provides an effective route for the synthesis of a variety of multicyclic tetrahydrofurans from either diallyl ethers[3] or homoallyl vinyl ethers. These photoreactions tolerate hydroxyl, acetoxy, allyl, and vinyl

(1) Copper(I) Catalysis of Olefin Photoreactions. 15. For paper 14 in this series, see: Avasthi, K.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 2556.

(2) For a review of homogeneous metal catalysis in organic photochemistry, see: Salomon, R. G. *Tetrahedron* **1983**, *39*, 485.

(3) The seminal discovery that copper(I) trifluoromethanesulfonate catalyzes photobicyclization of diallyl ether to produce *cis*-3-oxabicyclo-[3.2.0]heptane was reported by Evers and Mackor (Evers, J. Th. M.; Mackor, A. *Tetrahedron Lett.* **1978**, 821). An analogous reaction, photobicyclization of 1,6-heptadiene to produce *cis*-bicyclo[3.2.0]heptane, is sensitized by mercury: (a) Srinivasan, R.; Hill, K. A. *J. Am. Chem. Soc.* **1965**, *87*, 4988. (b) Srinivasan, R.; Carlough, K. H. *Ibid.* **1967**, *89*, 4932.

0022-3263/87/1952-0083$01.50/0