BENZOCYCLOBUTYLDIHYDROOXEPINS VIA INTRAMOLECULAR CYCLOADDITIONS OF ENYNE [3]CUMULENALS

Tawfeq Kaimari, Lawrence M. Pratt and Augusto Rodríguez*
Department of Chemistry
Clark Atlanta University
Atlanta, GA 30314

Abstract: The synthesis of 2-(3-phenyl-1-trimethylsilanyl-9H-8-oxa-benzo[a]cyclobuta[d]cyclohepten-2-ylidene)propionaldehyde is described. The strategy applied for the synthesis of this compound involves the [2+2] intramolecular cycloaddition across the internal double bond of a [3]cumulenal.

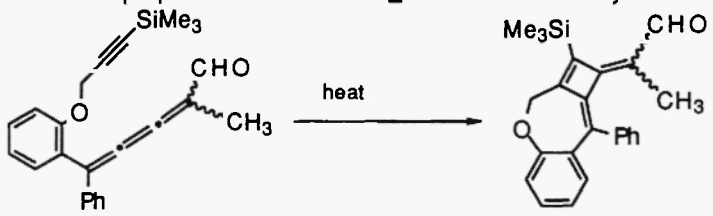
Introduction

In spite of the numerous examples of natural products that contain the oxepin ring (1-3), there are only a handful of synthetic procedures to construct this ring (4-6).

Given the limited number of synthetic methods for the construction of the dihydrooxepin nucleus, an intramolecular [2+2] cycloaddition strategy involving [3]cumulenes was formulated.

Results and Discussion

Efforts were focused on the preparation of cumulenal 1 to be used for the synthesis of dihydrooxepin 2.

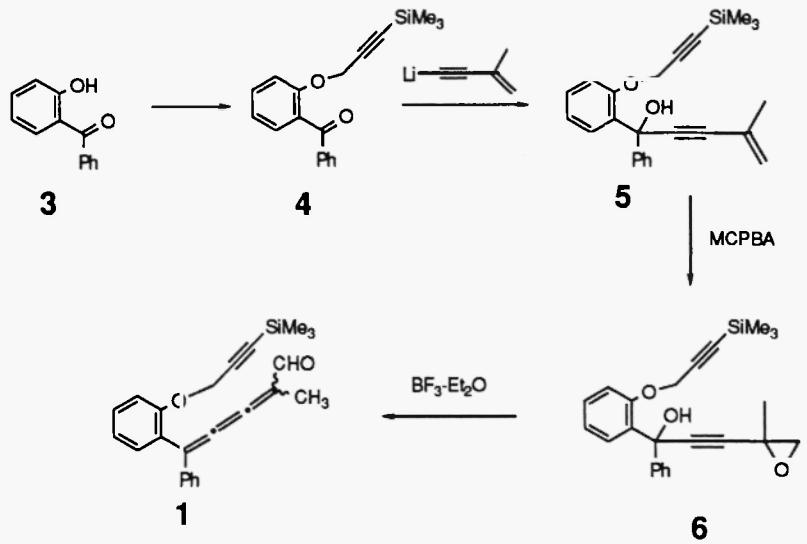


1 **2**

The synthesis of cumulenal 1 was accomplished in four steps from o-hydroxybenzophenone. Alkylation of the o-hydroxybenzophenone with trimethylsilyl propargyl bromide gave ketone 4 in 83% yield. Addition of the lithio anion of 2-methyl-3-butyne gave alcohol 5 which was epoxidized (MCPBA) to render 6. Rearrangement of 6 with boron trifluoride (at -78°C) gave a 1:1 mixture of E/Z cumulenal 1 in 80% yield. Attempts to separate the mixture of E and Z isomers of 1 via silica gel chromatography were not successful.

Having completed the synthesis of cumulenal 1, we next focused on its conversion to benzodihydrooxepin 2. Heating a sample of a 1:1 mixture of 1E:1Z in o-dichlorobenzene at 180°C produced a mixture of E and Z dihydrooxepines 2 in 59% yield and 27% yield respectively. Upon standing, 2Z was slowly converted to 2E. The structural assignments of these isomers was unequivocally established with the aid of a NOE difference experiment. Irradiation of the trimethylsilyl peak of 2E shows an enhancement of the methyl signal at δ 1.86 ppm, thus establishing the E configuration about the double bond. The structural assignment is also consistent with the results of a DEPT experiment which reveal the presence of 8 methine signals and 9 quarternary carbon signals.

Previous reports on related intramolecular [2+2] cycloaddition reactions with [3]cumulenes indicate that cycloaddition can occur at the terminal or at the internal double bond of the cumulene system (7 &8).



Calculations on the thermodynamics of intramolecular cycloadditions (9) are consistent with our experimental results. These calculations indicate that in the absence of kinetic effects, [2+2] intramolcular cycloadditions of 1 will be made across the internal double bond exclusively since this is thermodynamically favored over the others by 15-20 kcal/mole.

Curent efforts are underway to apply this new synthetic method for oxepin rings in the preparation of analogs of the powerfull antidepressant, Doxepin (10).

Experimental

Elemental Analyses were obtained from Atlantic Micro Lab Inc. (Norcross, GA) and are within ± 0.5 of the theoretical values. IR spectra were recorded on a Nicolet Impact 400. Mass spectral data were obtained on a Hewlett Packard GC/MS Model HP 5890 at 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded employing a Bruker 250 MHz or Bruker 400 MHZ spectrometer and chemical shifts (δ) are in ppm relative to TMS. High resolution mass spectra were obtained from Emory University Mass Spectrometry Center.

Pheny-[2-3-trimethylsilanyl-prop-2ynyloxy)phenyl]-methanone 4

A reaction mixture containing 2-hydroxybenzophenone (3.96 g, 20 mmol), potassium carbonate (4.1 g, 30 mmol), potassium iodide (4.98 g, 30 mmol) and 2-butanone (25 mL) was stirred at room temperature for 20 min. To this solution, 3-bromo-1-(trimethylsilyl)-1-propyne (4.2 g, 22 mmol) was added and the resulting mixture was heated to reflux for 8 h. The reaction mixture was then poured into 100 mL of water and extracted with ether (3 x 25 mL). The combined organic layers were washed with brine (15 mL), dilute sodium hydroxide (10%) (3 x 20 mL) and dried over magnesium sulfate. The organic solvents were removed on a rotatory evaporator affording a pale yellow oil which was purified via silica gel chromatography using 15:1 hexane/ethyl acetae as eluents. The product was obtained in 88% yield as a pale yellow oil. 4: IR (neat, cm^{-1}) 3067, 2968, 2190, 1677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J= 1.25 Hz, J=7.82 Hz, 2H); 7.41 (t, J=7.39 Hz, 1H); 7.33 (dt, J=7.73 Hz, 1H); 7.28 (t, J=7.68 Hz, 3H); 7.01 (d, J=8.37 Hz, 1H); 6.96 (t, J=7.51, 1H); 4.44 (s,2H); 0.04 (s,9H); Anal. calcd. for $C_{19}H_{20}O_2Si$: C, 73.99; H, 6.54, found: C, 73.74, H, 6.63;

4-Methyl-1-phenyl-1-[2-(3-trimethylsilanyl-prop-2-ynyloxy)-phenyl]-pent-4-en-2-yn-1-ol 5

A solution containing 50 mL of dry THF and 2-methyl-1-buten-3-yne (0.7 g. 11 mmol) was cooled to -78 °C by means of an external Dry Ice/acetone bath. This solution was then treated with 6.0 mL of a 2 M nBuLi solution. The reaction was kept at -78°C for 10 min after which a solution of ketone 4 (5.4 g, 11 mmol) in 50 mL of THF was added dropwise via syringe. Stirring was continued at -78°C for 20 min. and the reaction mixture was slowly allowed to warm to 25°C where it was kept for 1 h. The resulting solution was concentrated on a rotatory evaporator, the residue was diluted with 60 mL of ether, washed with brine, and the organic layers dried over magnesium sulfate. The solvent was removed on a rotatory evaporator recovering 3.8 g of crude product. This material was purified by flash chromatography (10:1 hexane/ethyl acetate), giving pure 5 in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J=7.38 Hz, 2H); 7.26 (d,J=7.65 Hz, 1H); 7.17-7.08 (m,4H); 6.83 (t, J=7.49 Hz, 2H); 5.19 (s,1H); 5.07 (s,1H);4.36 (s,J=8.75 Hz,2H); 1.76 (s,3H); 0.04 (s,9H); IR (neat, cm^{-1}) 3539, 3065, 2368, 2184, 1677, 1604; ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.80, 155.68, 144.753, 134.02, 132.06, 129.66, 128.63, 128.58, 127.97, 127.83, 122.02, 114.67, 100.05, 99.89, 93.51, 90.40, 88.48, 57.98, 57.47, 23.79, 23.62, 0.34; HRMS : Calcd. mass 374.1702, found 374.1702.

3-(2-methyl-oxiran-2-yl)-1-phenyl-1-[2-(3-trimethylsilanyl-prop-2-ynyloxy)-phenyl]-prop-2-yn-1-ol 6

To a dichloromethane solution of 5 (1.12g, 3.13mmol) was added dropwise a solution of meta-chloroperbenzoic acid (MCPBA) (1.08g, 6.26 mmol) over 20 min. The reaction was complete after 2 h. To this mixture was added 10 mL of cold water. The organic layer was separated and washed with a 5% NaOH solution (50mL), 10% $NaHCO_3$, and water. The organic layer was dried over magnesium sulfate and the solvent removed on a rotatory evaporator. The crude product was purified via silica gel chromatography using (8:1 hexane/ethyl acetate) as eluent affording pure 6 (1.12g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=7.48 Hz,4H); 7.53 (dt, J=7.74 Hz, J = 1.7Hz, 2H); 7.05 (dt, J = 6.90 Hz, J = 1.05 Hz, 4H), 6.96 (dt, J=7.32 Hz, J = 0.85 Hz, 2H), 6.87 (t, J = 7.74 Hz, 2H), 6.67 (t,J=7.48 Hz,2H), 6.56 (d,J=8.11 Hz, 2H); 4.57 (s, J=8.75 Hz, 2H); 2.65 (d,J = 5.70 Hz, 1H); 2.58 (d, J = 5.68 Hz, 1H); 2.11 (d,J = 5.73 Hz, 1H); 2.09 (d, J = 5.80 Hz, 1H); IR (neat, cm^{-1}) 3532, 3064, 2971, 2257, 2189, 1605; ^{13}C NMR (250 MHz, $CDCl_3$) δ 155.13, 143.71, 133.13, 129.20, 127.95, 127.79, 127.72, 127.11, 126.19, 121.51, 113.82, 99.37, 93.25, 85.87, 83.86,73.76, 57.16, 55.21, 47.14, 22.79, 22.72, 0.02; HRMS : Calcd. mass 390.1651, observed 390.1661.

2-Methyl-5-phenyl-[2-(3-trimethyl-5-[2-(3-trimethyl-5-[2-(3-trimethyl-5-[2-(3-trimethylsilanyl-prop-2-ynloxy)-phenyl]-penta-2,3,4-trienal 1

A solution containing epoxide 6 (.57 g, 1.46 mmol) and 15 mL of dry THF was cooled to -78°C. To this solution was added boron trifluoride etherate (0.17 mL, 1.3 mmol) by means of a syringe. The mixture was stirred for 1 h at this temperature and then the cooling bath was removed and the reaction kept at room temperature for 5 h. The resulting mixture was diluted with 50 mL of ether, washed with water, brine and the organic layers dried over magnesium sulfate. The residue was purified via flash chromatography (6:1 hexane/ethyl acetate) giving 425 mg of 1 as a 1:1 mixture of E and Z isomers, (80% yield of a orange yellow oil). 1: IR (neat, cm^{-1}) 3065, 3026, 2960, 2927, 2855, 2177, 2052, 1670, 1611, 1512, 1223. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 9.39 (s, 1H), 7.41-7.37 (m, 4H), 7.28-7.24 (m, 2H), 7.24-7.21 (m, 8H), 6.99 (t, 2H, J = 7.3Hz), 6.93 (q, 2H, J = 14.5 Hz), 4.47 (s, 2H), 4.46 (s, 2H), 1.98 (s, 3H), 1.91 (s, 3H), 0.00 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 189.61, 189.33, 170.96, 155.66, 155.60,

153.12, 152.83, 137.94, 137.63, 131.49, 130.46, 130.43, 129.41, 129.32, 129.01, 128.69, 128.50, 128.36, 128.34, 126.92, 126.91, 121.51, 121.43, 117.12, 117.02, 113.52, 99.64, 99.55, 92.94, 92.83, 56.97, 56.89, 14.35, 14.08, 0.41, 0.40.; MS 372(M+), 57(100%). HRMS: calcd. mass 372.1545, observed mass 372.1522.

2-(3-phenyl-1-trimethylsilanyl-9H-8-oxa-benzo[a]cyclobuta[d]cyclohepten-2-ylidene)propionaldehyde 2

A solution containing cumulenal 1 (80 mg, 0.21 mmole) and 20 mL of freshly distilled o-dichlorobenzene was added to a thick wall thermolysis tube. The tube was purged and evacuated with nitrogen and sealed under vacuum. The tube was immersed in a sand bath at a temperature of 180^{o}C for 40 h. After this time, the tube was opened and the contents poured into a 50 mL round bottom flask. The solvent was distilled under vaccum and the residue purified via preparative TLC (8:1 hexane/ethyl acetate) recovering 47 mg of 2E (59%) and 22 mg of 2Z (27% yield). 2E IR (neat, cm^{-1}) 3068, 2964, 2361, 2251, 2183, 1667, 1605; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.46 (dd, 2H, J1 = 2.08 Hz, J2 = 7.3 Hz), 7.35-7.28 (m, 3H), 7.25-7.21 (m, 2H), 7.02 (dt, 1H, J = 1.83 Hz, J2 = 8.06 Hz), 6.89 (dd, 1H, J = 1.46 Hz, J2 = 7.83 Hz), 5.1 (s, 2H), 1.86 (s, 3H), 0.33 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 192.69, 173.02, 158.97, 157.86, 150.52, 142.57, 139.12, 133.13, 131.94, 130.63, 128.84, 128.71, 128.63, 128.44, 124.48, 124.33, 122.91, 120.02, 76.86, 71.06, 12.45, 0.193. MS 372 (M+), 73 (100%).

Acknowledgements

Support from NSF (CHE #9014435), NIH (MBRS #GM08247), NIH (RCMI #RR03062) and the U. S. Army (contract #DAAA15-K-94-0004) is greatly appreciated. L. P. wishes to acknowledge the NSF Center for Theoretical Studies of Physical Systems, Army Center for Excellence in Information Sciences and the High Performance Polymers and Ceramics center (HiPPAC) at Clark Atlanta University.

References

(1) Faulker, D. J. J. Nat. Prod. Rep. 1, 551 (1986)

(2) Chou, W.-N; White, J. B.; Smith, W. B. J. Am. Chem. Soc. 114, 4658 (1992)

(3) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. Heterocycles 30, 507 (1990)

(4) (a) Clark, D. L.; Chou, W.-N.; White, J. B. J. Org. Chem. 55, 3975 (1990). (b) Chou, W.-N.; White, J. B. Tetrahedron Lett. 32, 157 (1991)

(5) Kitamura, T.; Takachi, T.; Kawasato, H.; Taniguchi, J. Chem. Soc. Perkin Trans. 1, 1969 (1992)

(6) Boyd, D. R.; Sharma, N.; Agarwal, S. K.; Gadaginamath, G. S.; O'Kane, G. A.; Jennings, W. B.; Yagi, H.; Jerina, D. M. J. Chem. Soc. Perkin Trans. 1, 423 (1993)

(7) (a) Garcia, J. G.; Ramos, B.; Pratt, L. M.; Rodriguez, A. Tetrahedron Lett. 36, 7391 (1995). (b) Wang, X.; Ramos, B.; Rodriguez, A. Tetrahedron Lett. 35, 6977 (1994)

(8) (a) Wang, K. K.; Liu, B.; Lu, Y. J. Org. Chem. 60, 1885 (1995). (b) Iyoda, M.; Nishioka, K.; Nose, M.; Tanaka, S.; Oda, M. Chem. Lett. 131 (1984) (c) Fujiwara, K.; Sakai, H.; Hirama, M. J. Org. Chem. 56, 1688 (1991). (d) Sakurai, H.; Kudo, M.; Sakamoto, K.; Nakadaira, Y.; Kira, M.; Sekiguchi, A. Chem. Lett. 1441 (1988)

(9) (a) Stewart, J. J. P. J. Comp. Chem. 10, 209 (1989). (b) Stewart, J. J. P MOPAC, A Semiempirical Molecular Orbital Program, QCPE 455 (1983)

(10) Adamczyk, M.; Fishpaugh, J. R.; Johnson, D.; J. of Labelled Compounds and Radiopharmaceuticals 33, 153 (1992)

Received December 15, 1995