acid (dithio-BNP) was prepared in the following manner.[10] A mixture of 2,2'-dihydroxy-1,1'-binaphthyl (28.6 g, 0.10 mol) and phosphorus pentasulfide (11.0 g, 0.05 mol) was refluxed in dry xylene (200 mL). After the P_2S_5 dissolved completely, the reaction mixture was refluxed for 0.5 h and then kept for 48 h at room temperature. The crude product was collected in nearly quantitative yield. When it was recrystallized from dry toluene, colorless prisms were obtained (32.3 g, 85% yield). Anal. Calcd for $C_{20}H_{13}O_2S_2P$: C, 63.14; H, 3.45. Found: C, 63.29; H, 3.31. mp 232-234 °C; MS ($M^+ + 1$) 381; ^{31}P NMR ($CDCl_3$) 97.03 ppm. The ^{31}P NMR spectrum ($CDCl_3$) of its cinchonine salt showed resonances at 129.56 and 129.89 ppm. The *R*-dithio-BNP and *S*-dithio-BNP were prepared in the same manner using (*R*)-(+)-binaphthol ($[\alpha]_D$ +35.2°) and (*S*)-(-)-binaphthol ($[\alpha]_D$ -35.2°, respectively, as starting materials. After removal of solvent under reduced pressure, the crude acid was neutralized with an equivalent amount of cinchonine. In each case, the ^{31}P NMR spectrum ($CDCl_3$) of te salt, without any purification, showed a single signal only, indicating the 100% enantiomeric purity of each binaphthol.

(9) Mikolajezk, M.; Omelaneznk, J.; Leitloff, M.; Drabowicz, J.; Fjchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003.
(10) Hu, B.-F.; Sheng, Q.-F.; Li, Z.-M. *Phosphorus Sulfur* **1988**, *35*, 371.

Attempted Synthesis of Furanocyclobutenes from γ-Ketocyclobutanones

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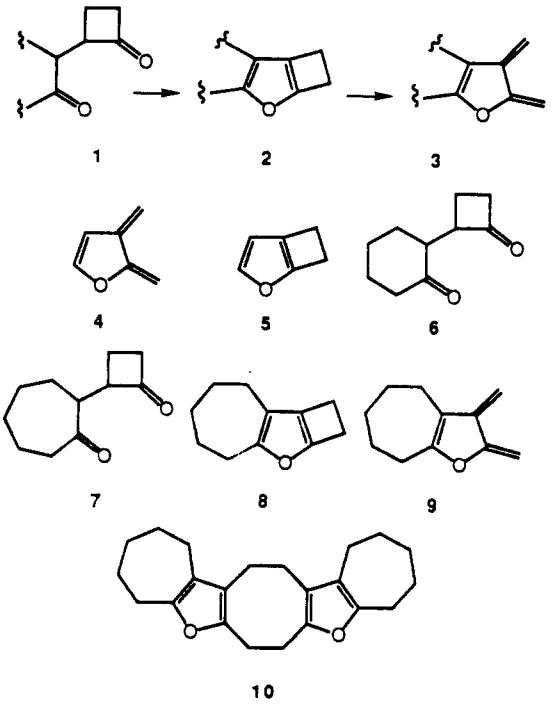
One of the classical methods for the synthesis of furans is Paal-Knorr dehydration of enolizable 1,4-dicarbonyl compounds.[1] If such a procedure could be successfully applied to γ-ketocyclobutanones[2,3] (**1**), the products would be furanocyclobutenes (**2**). At the time this investigation was undertaken, it seemed highly probable that no successful preparation of any furanocyclobutene had been achieved.[4] There were, however, several reports of syntheses of the ring-opened isomeric 2,3-dimethylene-2,3-dihydrofurans (**3**),[5-7] and it was anticipated on the basis of the exclusive formation of **3** in all cases that if **2** were indeed formed from **1** it would spontaneously isomerize to the more stable **3**.[8] Recently, the first unequivocal synthesis of a furanocyclobutene was reported by Münzel and Schweig,[9] who photolyzed 2,3-dimethylene-2,3-dihydrofuran (**4**) in an argon matrix to afford the parent **5**.

Efforts to apply the Paal-Knorr approach to the synthesis of furanocyclobutenes were undertaken with γ-ketocyclobutanones **6** and **7**.[3] As noted above, if **7**, for example, could be converted to furanocyclobutene **8**, ring opening to **9** and formation of polymer and dimers such as **10** might be expected by analogy to results obtained by Trahanovsky.[7] In the event, treatment of **7** with *p*-toluenesulfonic acid (*p*-TsOH) in benzene at reflux for 24 h afforded mostly unreacted **7** plus a less polar, rather unstable material which intriguingly did have spectroscopic properties suggesting that it might contain some furan. The complex ^{13}C NMR spectrum of this crude product had peaks at ca. 110 ppm and at ca. 140 ppm, consistent with the presence of β and α furan carbon atoms, respectively.[10] Furthermore, bands in the IR spectrum at 1450 and 1560 cm^{-1} were reminiscent of signals previously noted in the spectra of tetrasubstituted furans.[11]



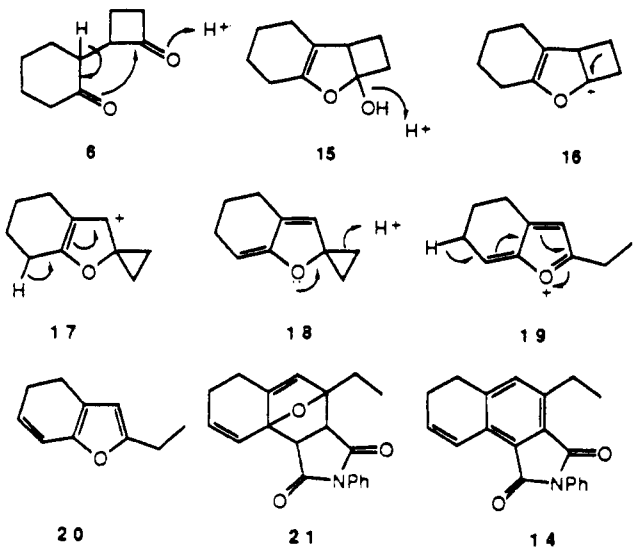
Instead of seeking initially to purify and identify this product, it was decided to run the dehydration reaction in the presence of a dienophile to trap diene **9** if indeed it were formed. A variety of dienophiles was examined, but most met with little success. The best results were obtained by using *N*-phenylmaleimide (**11**). When **7** was refluxed in toluene containing excess **11** and a small amount of *p*-TsOH, 33% of a product with mp 154.5-155.5 °C was isolated for which spectroscopic data (IR 1695, 1760 cm^{-1}; ^1H NMR 7.5 ppm, 5 H) indicated incorporation of **11**.

However, the spectral data also showed clearly that this product was not the desired adduct **12** which would be formed by reaction of **11** with **9**. In addition to the five phenyl protons there were three more ^1H NMR signals in the δ 6.0-7.9 range due to vinyl and/or aromatic protons. Surprisingly, there were also a quartet (δ 3.18, J = 8 Hz)

(1) Paal, C. *Chem. Ber.* **1884**, *17*, 2756. Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.
(2) Byers, J. H.; Spencer, T. A. *Tetrahedron Lett.* **1985**, *26*, 717.
(3) Kaydos, J. A.; Byers, J. H.; Spencer, T. A. *J. Org. Chem.* **1989**, *54*, 4698.
(4) Ruhlmann, K.; Kokkali; A.; Berker, H.; Seefluth, J.; Frieden, U. *J. Prakt. Chem.* **1969**, *311*, 844 claim the synthesis of 2-amino-3-cyanofuranocyclobutene. However, since the only data reported for this substance are melting point and elemental analysis, and since there is good reason to regard furanocyclobutenes as highly unstable (refs 5-9), it seems reasonable to question the structural assignment.
(5) Winberg, H. E.; Fawcett, F. S.; Mochel, W. E.; Theobald, C. W. *J. Am. Chem. Soc.* **1960**, *82*, 1428.
(6) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron Lett.* **1979**, 3079.
(7) Trahanovsky, W. S.; Cassady, T.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691.
(8) MNDO calculations (ref 8), as well as the failure to detect any **2** experimentally (refs 4-6), indicate that **3** is significantly more stable than **2**.
(9) Münzel, N.; Schweig, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 471.
(10) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; John Wiley & Sons: New York, 1981; p 297, report ^{13}C NMR δ values of 142.8 and 109.7 ppm for the α and β carbons of furan.
(11) Unpublished data concerning compounds described in: Spencer, T. A.; Britton, R. W.; Watt, D. S. *J. Am. Chem. Soc.* **1967**, *89*, 5727.

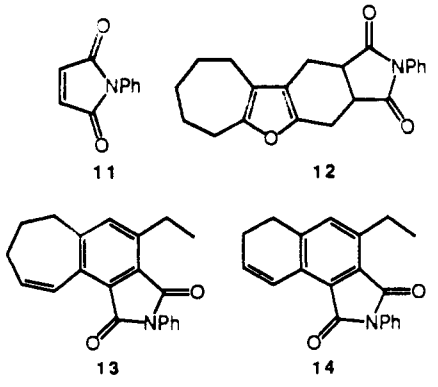
0022-3263/91/1956-0425$02.50/0

Scheme I



and a triplet (δ 1.30, J = 8 Hz), strongly suggesting the presence of an ethyl group. The ^{13}C NMR spectrum showed only five signals in the aliphatic region, and the highest molecular weight peak in the mass spectrum was at m/e 317, whereas M^+ for **12** = 337.

Eventually, these data and the mechanistic rationale presented in Scheme I led us to propose **13**, rather than **12**, as the structure of the crystalline product derived from "dehydration" of **7** in the presence of **11**. The NMR data were completely compatible with **13** with the exception of the fact that there was one less peak in the aromatic–olefinic region of the ^{13}C NMR spectrum than would be predicted for **13**. That this observation was caused by peak overlap or an unusually weak signal was demonstrated by analogous treatment of γ-ketocyclobutanone **6** with *p*-TsOH acid and **11**, which afforded 33% of a compound having properties entirely consistent with structure **14**, including a ^{13}C NMR spectrum comprising signals for 2 carbonyl carbons, 12 nonequivalent olefinic–aromatic carbons, and 4 aliphatic carbons.



A proposed mechanism for the formation of **14** is shown in Scheme I. Enolization and ring closure could lead to **15** and then to carbocation **16**, which, instead of losing a proton to form the desired furanocyclobutene, could rearrange to **17**. Loss of proton to form **18**, followed by acid-catalyzed opening of the spirocyclopropane ring to produce **19** and another proton loss, would afford furan **20**. Formation of **14** could then occur via Diels–Alder addition of **11** to **20** to yield **21**, which could undergo acid-catalyzed dehydration to form **14**. Clearly, there are plausible alternative sequences of steps which could be proposed, but carbocation rearrangement as in **16** → **17** is an essential feature of any reasonable mechanism. Consistent with such a scheme is the fact that γ-ketocyclobutanone **22**,[3] which lacks an α proton analogous to the one lost in the formation of putative intermediate **18**, failed to yield any adduct with **11** under the same reaction conditions.

Although this mechanistic rationalization led us to favor structures **13** and **14** for the adducts from **7** and **6** plus **11**, there were two possible structural ambiguities which could not be resolved with certainty on the basis of the available spectroscopic data. The first was the location of the ethyl group. The data did not rule out the possibility that it was at the alternate position on the pentasubstituted aromatic ring. This uncertainty was resolved by once again running the Paal–Knorr reaction of γ-ketocyclobutanone **7** in the absence of dienophile and isolating the rather unstable product which had initially led us to believe that a furan had been formed. After considerable chromatography a small amount (8%) of a pure furan could indeed be isolated from such a reaction. The lone aromatic proton in this product had a ^1H NMR chemical shift of 5.89 ppm, a value consistent with its being a β furan hydrogen (6.37 ppm in furan itself),[12] but far too upfield to be an α furan hydrogen (7.42 ppm in furan).[12] Thus, structure **23** could be assigned to this furan, and the presumed formation of **13** from **23** was confirmed by treatment of **23** with **11** and *p*-TsOH to afford 93% of **13**.

The second structural ambiguity concerned the location of the double bond in **13**, and hence, in **23** as well. Since one of the vinyl protons appeared simply as a doublet, it was believed that that proton was at a benzylic position rather than at a position further removed from the aromatic ring, so we were confident that the structure was either **13** or **24**. The markedly downfield chemical shift of 7.76 ppm for that doublet strongly suggested that **13** was indeed the correct structure, because in **13** the benzylic vinyl proton would lie in the deshielding cone of the proximate imide carbonyl group. The adduct from **6** plus **11** likewise showed a strongly deshielded doublet at 7.52 ppm. Although these facts suggested that **13** and **14** were indeed the correct structures, unequivocal proof of the location of the double bond was sought.[13]

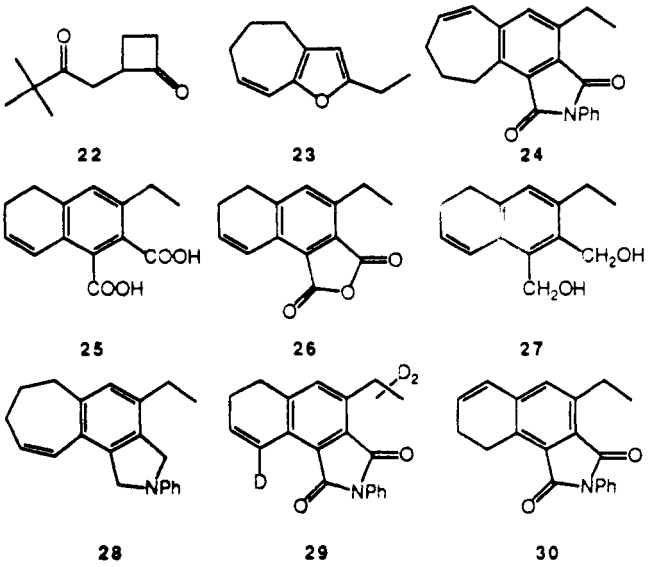
The first approach involved attempted conversion of the presumed **14** to diacid **25**, with the hope that **25** could be induced to undergo iodolactonization.[14] Unfortunately, all efforts to hydrolyze the imide functionality to a diacid, under either acidic or basic conditions, failed, and only an anhydride, putatively **26**, could be obtained as a pure product. Steric congestion in the pentasubstituted aromatic ring apparently makes anhydride formation unusually favorable. Reduction of **26** with $LiAlH_4$ led uneventfully to a ring-opened diol, presumably **27**, in which the chemical shift of the vinyl benzylic proton had changed from 7.27 ppm in the anhydride to 6.82 ppm in the diol, consistent with removal of the proximate carbonyl group's deshielding cone. A similar, but larger, shift from 7.76 to 6.47 ppm for the ^1H NMR signal of that benzylic proton was observed when imide **13** was reduced with aluminum hydride to amine **28**.

The final piece of evidence for the location of the double bond in the imides thought to be **13** and **14** was obtained by a deuterium labeling experiment. Exchange of protons α to carbonyl groups of γ-ketocyclobutanone **6** was effected

(12) *Varian High Resolution NMR Spectra Catalog*; Varian Associates, 1962; Vol. 1.

(13) Details of the several investigations conducted in search of such proof may be found in Kaydos, J. A. Ph.D. Dissertation, Dartmouth College, 1988.

(14) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.



by treatment with K_2CO_3 in D_2O. The deuterated **6** thus obtained was treated with **11** and a catalytic amount of *p*-TsOH in the usual manner to afford 39% of the familiar imide product in which the doublet for the benzylic vinyl proton at 7.52 ppm had almost completely disappeared (along with the signals for two protons in the ethyl group). This result showed unequivocally that deuterium had been incorporated at the methylene group α to the cyclohexanone carbonyl group of **6** and that the product obtained was **29**. Therefore, the imide derived from **6** is indeed **14**, and not **30**. By analogy, the imide formed from **7** is **13**, not **24**. With the benefit of hindsight, the transformations leading to furans **23** and **20**, and thence to **13** and **14**, seemed sufficiently inevitable that no further efforts were made to modify reaction conditions in an attempt to induce the formation of furanocyclobutenes from γ-ketocyclobutanones.

Experimental Section

Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualization was accomplished with 254-nm UV light or ceric sulfate–ammonium molybdate–sulfuric acid spray. Preparative TLC was performed on precoated silica gel 60 F_{254} plates from EM Reagents. Flash chromatography was performed in the manner of Still[15] with EM Reagents silica gel 60 (230–440 mesh).

Reactions requiring anhydrous conditions were performed in glassware that had been flame-dried or heated in an oven overnight at 155 °C and then allowed to cool in a desiccator containing anhydrous $CaSO_4$ prior to assembly. The term "under N_2" refers to maintenance of a positive pressure of Airco nitrogen gas over the reaction mixture. Brine refers to a saturated aqueous solution of NaCl. Solvents were purified as follows: tetrahydrofuran (THF) was distilled from sodium or potassium with benzophenone indicator; benzene and toluene were dried by distillation from calcium hydride; methylene chloride (CH_2Cl_2) was dried by distillation from phosphorus pentoxide; diethyl ether was obtained by distillation from $LiAlH_4$. All other solvents were used as received, with the exception of reagent grade hexane which was distilled prior to use.

2-Ethyl-4*H*-5,6-dihydrocyclohepta[*b*]furan (23). A solution of 0.20 g (1.1 mmol) of 2-(1-cyclobutanon-2-yl)cycloheptanone (**7**)[3] and 0.030 g of *p*-TsOH·H_2O in 20 mL of benzene was heated at reflux for 18 h under a Dean–Stark trap. The reaction mixture was cooled to room temperature and combined with 50 mL of CH_2Cl_2. The mixture was washed with 1% Na_2CO_3 (2 × 50 mL) and 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to afford a brown oil which upon flash chromatography (gradient, hexane to 1:4 ether–hexane) gave several minor uncharacterized products, unreacted **7**, and 0.014 g (8%) of clear oily **23**: IR (film) 3025, 2970, 2845, 1560, 1445, 1270, 815, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, t, J = 8 Hz), 1.64–2.17 (2 H, m), 2.17–3.10 (4 H, m), 2.61 (2 H, q, J = 8 Hz), 5.42–6.02 (1 H, m), 5.89 (1 H, s), 6.32 (1 H, d, J = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 12.2, 21.3, 23.8, 26.9, 30.7, 108.1, 119.5, 123.5, 126.7, 147.8, 155.7; HRMS m/e calcd for $C_{11}H_{14}O$ 162.1035, found 162.1045.

4-Ethyl-7,8-dihydro-2-phenylcyclohept[*e*]isoindole-1,3-(2*H*,6*H*)-dione (13). Method A. To a solution of 0.129 g (0.716 mmol) of 2-(1-cyclobutanon-2-yl)cycloheptanone (**7**)[3] in 25 mL of toluene were added 2.3 g (13 mmol) of *N*-phenylmaleimide (**11**) and 0.025 g of *p*-TsOH·H_2O. The resulting mixture was heated at reflux under a Dean–Stark trap for 4 days. The reaction mixture was cooled to room temperature, combined with 50 mL of CH_2Cl_2, washed with 10% Na_2CO_3, (2 × 50 mL) and 50 mL of brine, dried over $MgSO_4$, filtered, and evaporated to afford a yellow solid which was subjected to flash chromatography (gradient, hexane to 4:1 ether–hexane) to give 0.17 g (75%) of **13**, which TLC analysis indicated was still slightly impure. Further purification by flash chromatography (gradient, hexane to 1:4 ether–hexane) gave 0.075 g (33%) of **13** as a white solid, which was homogeneous by TLC. Repeated recrystallization from ether afforded an analytical sample of **13**: mp 154.5–155.5 °C; IR (KBr) 3055, 2980, 2915, 2845, 1760, 1695, 1595, 1495, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 8 Hz), 2.10 (2 H, m), 2.50 (2 H, m), 2.95 (2 H, m), 3.18 (2 H, q, J = 8 Hz), 6.27 (1 H, m), 7.33 (1 H, s), 7.54 (5 H, m), 7.76 (1 H, d, J = 13 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9, 24.4, 27.9, 31.9, 35.6, 123.4, 126.7, 127.6, 127.7, 128.8, 131.9, 134.2, 135.2, 136.7, 142.8, 149.7, 167.5, 167.9; MS m/e 317 (M^+, 100), 302, 288, 77. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.48; H, 6.06; N, 4.39.

Method B. To a solution of 0.053 g (0.324 mmol) of **23** in 20 mL of benzene was added 0.030 g of *p*-TsOH·H_2O and 0.56 g (32 mmol) of **11**. The resulting mixture was heated at reflux under a Dean–Stark trap for 18 h. The reaction mixture was cooled to room temperature, combined with 50 mL of CH_2Cl_2, washed with 2% Na_2CO_3 (2 × 50 mL) and 50 mL of brine, dried over Na_2SO_4, filtered, and evaporated to afford a yellow solid which was subjected to flash chromatography (gradient, hexane to 1:1 ether–hexane) to give 0.095 g (93%) of **13**, which after two recrystallizations from ether had mp 153–154 °C and which was identical spectroscopically (IR) with that prepared according to method A.

1*H*-4-Ethyl-6,7-dihydro-2-phenylbenz[*e*]isoindole-1,3-dione (14). To a solution of 0.30 g (1.8 mmol) of 2-(1-cyclobutanon-2-yl)cyclohexanone (**6**)[3] in 25 mL of toluene were added 0.075 g of *p*-TsOH·H_2O and 5.92 g (34.2 mmol) of **11**. The resulting mixture was heated at reflux under a Dean–Stark trap for 2 days after which time TLC analysis indicated the presence of unreacted **6**. An additional 0.070 g of *p*-TsOH·H_2O was added, and reflux was maintained for 24 h. The reaction mixture was then cooled to room temperature and combined with 50 mL of toluene and 100 mL of CH_2Cl_2. The solution was washed with 10% Na_2CO_3 (2 × 50 mL) and 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give an orange solid which was subjected to flash chromatography (gradient, hexane to ether) to afford 0.18 g (33%) of **14** as a white solid. Repeated recrystallization from ether gave an analytical sample of **14**: mp 131–131.5 °C; IR (KBr) 3040, 2960, 2880, 2830, 1760, 1705, 1600, 1495, 1465, 1375, 1360, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 8 Hz), 2.35 (2 H, M), 2.85 (2 H, m), 3.05 (2 H, q, J = 8 Hz), 6.27 (1 H, m), 7.18 (1 H, s), 7.25–7.47 (5 H, m), 7.52 (1 H, d, J = 12 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9, 22.7, 24.5, 27.7, 122.5, 124.2, 125.8, 126.7, 127.6, 128.8, 130.8, 131.8, 133.5, 133.7, 143.1, 143.2, 167.6, 167.9; MS m/e 303 (M^+, 100), 274, 258, 183, 77, 44. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.02; H, 5.70; N, 4.57.

6,7-Dihydro-4-ethylnaptho[1,2-*c*]furan-1,3-dione (26). A solution of 0.103 g (0.340 mmol) of **14** in 7 mL of glacial acetic acid and 7 mL of concentrated HCl was heated at reflux for 2 days. The reaction mixture was cooled to room temperature and combined with 10 mL of water, at which point a white precipitate formed. The reaction mixture was extracted with ether (6 × 25 mL). The extracts were combined, washed with saturated Na_2CO_3

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

until bubbling ceased, dried over Na_2SO_4, filtered, and evaporated to give 0.13 g of solid. Recrystallization from hexane gave 0.050 g (64%) of **26** as pale orange crystals in two crops, both of which were homogeneous by TLC. An analytical sample of **26** was prepared by repeated recrystallization from hexane: mp 131–132.5 °C; IR (KBr) 2920, 1835, 1760, 1265, 1210, 1173, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 8 Hz), 2.31–2.50 (2 H, m), 2.91 (2 H, t, J = 6.5 Hz), 3.00 (2 H, q, J = 8 Hz), 6.43 (1 H, dt, J = 10.2, 5 Hz), 7.25–7.31 (1 H, m), 7.28 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 14.6, 22.5, 24.4, 27.5, 121.7, 123.8, 125.6, 132.2, 135.0, 135.2, 144.7, 145.0, 163.0, 163.3; MS m/e 228 (M^+), 200 185, 155 (100), 141, 128, 115; HRMS m/e calcd for $C_{14}H_{12}O_3$ 228.0786, found 228.0809.

3-Ethyl-1,2-bis(hydroxymethyl)-5,6-dihydronaphthalene (27). To a slurry of 0.127 g (3.18 mmol) of $LiAlH_4$ in 2.0 mL of dry THF under N_2 was added a solution of 0.102 g (0.446 mmol) of **26** in 8.0 mL of dry THF. The resulting mixture was heated at reflux for 3 days. The reaction mixture was cooled to room temperature and quenched with 1 mL of water while still under N_2. The mixture was extracted with ether (5 × 20 mL) and ethyl acetate (4 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 0.080 g of orange semisolid. Flash chromatography (gradient, hexane to ether, ethyl acetate) afforded 0.038 g (39%) of **27** as a white solid. Recrystallization from ether afforded an analytical sample of **27**: mp 81–82 °C; IR (film) 3340, 3060, 2980, 2945, 2895, 1445, 1435, 1275, 1050, 1000, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (3 H, t, J = 7.5 Hz), 2.18–2.27 (2 H, m), 2.64–2.77 (4 H, m), 3.24 (2 H, br s), 4.71 (2 H, s), 4.74 (2 H, s), 6.07–6.16 (1 H, dt, J = 10.1, 4.4 Hz), 6.82 (1 H, d, J = 10.1 Hz), 6.95 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 16.4, 22.6, 26.6, 28.4, 58.2, 58.6, 123.9, 128.6, 129.7, 131.2, 134.7, 135.6, 136.5, 141.9. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.01; H, 8.36.

4-Ethyl-1,2,3,6,7,8-hexahydro-2-phenylcyclohept[*e*]isoindole (28). The following procedure was adapted from that of Oppolzer et al.[16] A slurry of 0.031 g (0.814 mmol) of $LiAlH_4$ in 0.8 mL of dry ether and a mixture of 0.046 g (0.341 mmol) of aluminum trichloride in 0.3 mL of dry ether were combined at 0 °C under N_2 and stirred for several minutes. To this mixture was added dropwise a solution of 0.050 g (0.16 mmol) of **13** in 5 mL of dry ether. The reaction mixture was stirred for 30 min while warming to room temperature and was then heated at reflux for 3 h. The mixture was cooled to room temperature and quenched with saturated Na_2SO_4 while under N_2. The aqueous layer was separated and filtered. The filtrate was extracted with ether (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated to afford 0.048 g of a white solid which discolored when dissolved in CH_2Cl_2. The crude material was subjected to flash chromatography (hexane, 5:1 hexane–ether) which afforded 0.017 g (39%) of **28** as a pale yellow semisolid that was still nonhomogeneous by TLC. Preparative TLC (4:1 hexane–ether) followed by recrystallization from ether afforded **28**: mp 105.5–107 °C; IR (film) 3020, 2920, 1605, 1505, 1465, 1375, 1260, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 8 Hz), 1.92–2.07 (2 H, m), 2.36–2.49 (2 H, m), 2.62 (2 H, q, J = 8 Hz), 2.77–2.90 (2 H, m), 4.60 (2 H, s), 4.65 (2 H, s), 5.94–6.06 (1 H, dt, J = 12, 3.6 Hz), 6.47 (1 H, d, J = 12 Hz), 6.60–6.84 (3 H, m), 6.91 (1 H, s), 7.24–7.39 (2 H, m); HRMS m/e calcd for $C_{21}H_{23}N$ 289.1830, found 289.1788.

1*H*-4-(Dideuterioethyl)-9-deuterio-6,7-dihydro-2-phenylbenz[*e*]isoindole-1,3-dione (29). To a solution of 1.66 g (12.0 mmol) of potassium carbonate in 16 mL of D_2O was added 1.0 g (6.0 mmol) of **6**. The resulting mixture was heated at reflux under N_2 for 5 days and then cooled to room temperature and extracted with ether (4 × 50 mL). The separated aqueous layer was acidified with 2 mL of 37% DCl and was then reextracted with ether (5 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 1.09 g of a mixture of orange oil and white solid. Flash chromatography (gradient, hexane to 4:1 ether–hexane) afforded 0.186 g (18%) of deuterated **6** as a clear oil: IR (film) 2940, 2870, 1780, 1712, 1455, 1295, 1250, 1110, 1055 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.4–2.5 (m), lacking the resonances at lower field than δ 2.5 characteristic of **6**.[3] To a solution of 0.18 g (1.1 mmol) of the deuterated **6** in 20 mL of dry toluene were added 0.052 g (0.27 mmol) of p-TsOH·H_2O and 1.77 g (10.2 mmol) of **11**. The resulting solution was heated at reflux under N_2 and a Dean–Stark trap for 6 days. After this time an additional 0.026 g (0.13 mmol) of p-TsOH·H_2O was added, and reflux was maintained for 18 h. The reaction mixture was cooled to room temperature, combined with 75 mL of CH_2Cl_2, washed with 20 mL of saturated Na_2CO_3 and 20 mL of brine, dried over Na_2SO_4, filtered, and evaporated to give 0.12 g (39%) of **29** as a white solid which was recrystallized from ether: mp 130–131 °C, IR (film) 2900, 1760, 1700, 1505, 1400, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) 1.13–1.28 (2 H, m), 2.35 (2 H, m), 2.84 (2 H, m), 2.97–3.08 (1 H, m), 6.27 (1 H, m), 7.19 (1 H, s), 7.26–7.47 (5 H, m).

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Synthesis, Photochemical Decomposition, and Tubulin Binding of 10-Azido-10-demethoxycolchicine and 9-Azido-9-demethoxyisocolchicine[1]

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Introduction

A variety of natural products inhibit cellular division by interfering with the normal assembly of microtubules. Many of these compounds (podophyllotoxin, stegnacin, combretastatin, and colchicine) exert their biological effects by binding to tubulin, a 100 000 Da protein that composes the central core of the microtubule and consists of two similar but nonidentical subunits designated as α and β.[2] The identity of the major drug binding site, known as the colchicine binding site, on the linear sequence of tubulin has been sought using affinity[3] and photoaffinity labeling colchicine derivatives.[4] In both of the photoaffinity labeling colchicine derivatives so far examined, the photolabile group is an aromatic azide attached to the C-7 position of the B ring.[4]

It has been shown that the entire B ring of colchicine participates only minimally in the thermodynamic stability of the colchicinoid–tubulin complex,[5] thus, photolabile

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