as a brown oil: NMR (60 MHz) δ 3.63–2.53 (complex m, 3 H, HC–N–CH_2), 2.37 (s, 3 H, NCH_3), 1.97–1.21 (m, 12 H, cyclohexyl), 0.9 (s, 3 H, CH_3). An analytical sample was obtained by the addition of HCl to an ether solution of the amine, followed by repeated crystallizations from ethanol–ether. The hydrochloride was obtained as a white solid, mp 201–203 °C. Anal. Calcd for $C_{10}H_{20}NCl·0.5H_2O$: C, 60.43; H, 10.65; N, 7.05. Found: C, 60.27; H, 10.68; N, 6.98.

Acknowledgment. We are grateful for the award of a Biomedical Research support grant to Duke University for partial support of this work. G.M. acknowledges an NIH predoctoral fellowship.

Registry No. **2**, 39778-70-6; **3**, 82732-39-6; **4**, 39778-77-3; **5**, 82732-43-2; **6**, 39778-69-3; **6** oxime, 39778-89-7; **7**, 5212-68-0; **7** oxime, 82732-42-1; **9**, 82732-41-0; **10**, 82769-24-2; **11**, 82769-23-1; **12**, 82732-40-9; **13**, 39778-79-5; **14**, 39778-78-4; **16**, 27655-70-5; **17**, 31996-70-0; **18**, 82732-32-9; **19**, 1196-52-7; **20**, 39778-84-2; **21**, 82732-44-3; **22**, 82732-45-4; **23**, 82732-46-5; **24**, 82732-47-6; *O*-(mesitylsulfonyl)hydroxylamine, 36016-40-7; *N*-methylhydroxylamine hydrochloride, 4229-44-1.

Synthesis of (±)-Mesembranol and (±)-*O*-Methyljoubertiamine. Aza-Ring Expansion of *cis*-Bicyclo[4.2.0]octanones[1]

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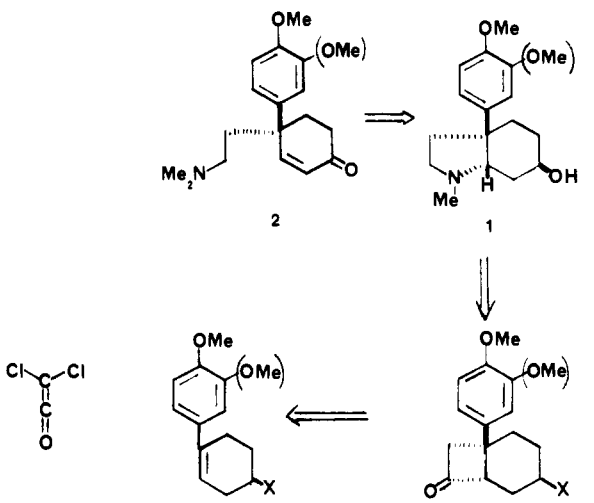
The syntheses of (±)-mesembranol (**1**) and (±)-*O*-methyljoubertiamine (**2**) are described. Each synthesis is developed from a regio- and stereospecific heteroannelation sequence of the respective 1-arylcyclohexenes **4** and **10** to provide the 3a-aryl-*cis*-octahydroindolone skeleton of the mesembrine alkaloid series represented by the intermediates **6** and **14**. The transformation of **6** to (±)-mesembranol is readily accomplished by reduction with diborane and subsequent cleavage of the *O*-benzyl protecting group by hydrogenolysis. Similarly, the octahydroindolone **14** is converted to (±)-*O*-methyljoubertiamine by hydrolysis of the acetate **14** to the alcohol **15**, reduction of **15** with diborane, and oxidation of the resulting 6-hydroxy compound **16** to the ketone **17** which is then converted to (±)-*O*-methyljoubertiamine on reaction with methyl iodide and base.

Isolation and structural studies on alkaloids from *Sceletium* species (family Aizoaceae) carried out in this laboratory during the past 15 years have led to the characterization of some 25 new bases.[2] This family of alkaloids, which belong to four different ring systems, has been the target of considerable effort on the part of several research groups in developing syntheses of representative members. Several of these approaches are elegant both in their concept and generality[3] while, in addition, the recently described synthesis of (±)-mesembrine by Martin provides the alkaloid in good overall yield.[4]

The initial impetus to develop an efficient synthetic procedure was provided by the need for synthetic analogues of mesembrine for conformational studies. In particular, design of the synthetic plan was constructed to permit a rather flexible approach to *cis*-octahydroindoles containing a variety of different substituents at the 3a-position.

The approach which forms the basis of the two syntheses discussed in this report is summarized in retrosynthetic terms in Scheme I. The transformation of this formalism to practice relies on the development of the synthesis of 1-aryl-*cis*-bicyclo[4.2.0]octan-7-ones from 1-arylcyclohexenes and the unidirectional aza-ring expansion of the bicyclooctanones to the 3a-aryl-*cis*-octahydroindoles to

Scheme I



effect what amounts to a regioselective and stereoselective heteroannelation of a carbocycle. The reactions employed which lead to the desired regio- and stereocontrol in the formation of these systems are explicitly defined by previous studies which are reported in the two preceding papers.[1,5] Extension of this particular approach to the synthesis of (±)-mesembranol (**1**)[6] and (±)-*O*-methyljoubertiamine (**2**)[7] constitutes the work described in this paper.

(1) This paper is part 13 in the series "Sceletium Alkaloids". For part 12 see: Jeffs, P. W.; Molina, G.; Cortese, N. A.; Hauck, P. R.; Wolfram, J. *J. Org. Chem.*, previous paper in this issue.

(2) Jeffs, P. W. In "The Alkaloids"; Rodrigo, R., Ed., Academic Press: New York, 1981; Vol. XIX, p 1.

(3) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. Keely, S. L.; Tahk, F. C. *Ibid.* **1968**, *90*, 5584. Wijnburg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. Stevens, R. V.; Lesko, P. M.; Lapalme, R. *J. Org. Chem.* **1975**, *40*, 3495.

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(5) Jeffs, P. W.; Molina, G.; Cortese, N. A., submitted for publication in *J. Org. Chem.*

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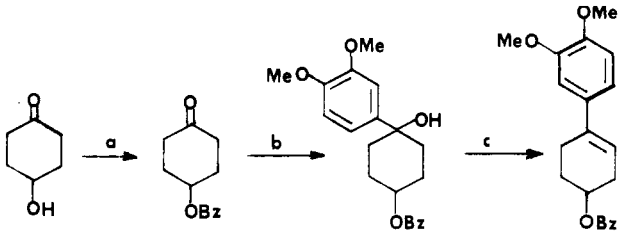
0022-3263/82/1947-3881$01.25/0

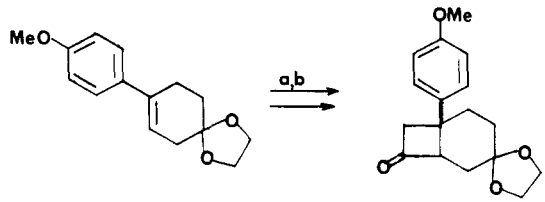
Scheme II[a]



4

[a] (a) KH/THF, $C_6H_5CH_2Br$. (b) (3,4-Dimethoxyphenyl)lithium/THF/−78 °C, H_2O. (c) *p*-Tosyl acid/Me_2CO.

Synthesis of the (±)-Mesembranol. Several different 1-arylcyclohexenes were selected for initial investigation as the alkene component for the [2 + 2] cycloaddition reaction with the dichloroketene–zinc system. In preliminary studies with the ketal **3** prepared from cyclo-



3

(a) Cl_3CCOBr/Zn-Cu/ether. (b) Zn-Cu/NH_4Cl/MeOH, Δ.

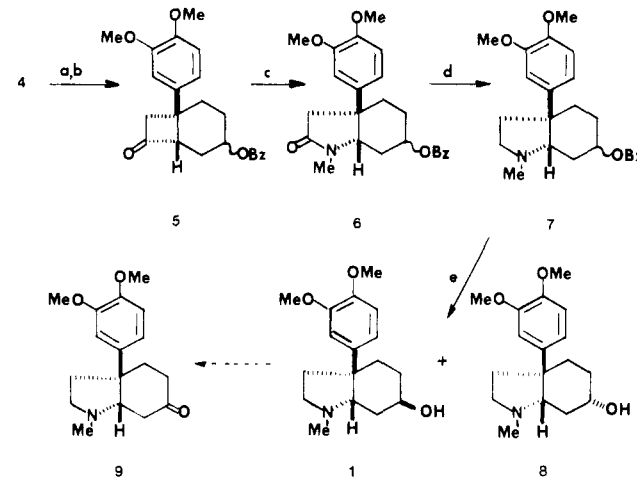
hexane-1,4-dione ethylene ketal, the [2 + 2] cycloaddition proceeded successfully, but the reaction product was difficult to purify because of contamination by side products resulting from the partial loss of the ketal group.

After several other 1-arylcyclohexenes were examined, the 4-benzyloxy compound **4** was chosen as the most appropriate for further study. Its synthesis from 4-hydroxycyclohexanone was readily accomplished by the reaction sequence shown in Scheme II.

Conversion of the cyclohexene **4** to the *cis*-bicyclo[4.2.0]octan-7-one **5** (Scheme III) as a mixture of C-4 diastereoisomers, proceeded in 80% yield in the two-step sequence involving [2 + 2] cycloaddition with dichloroketene and reductive dechlorination of the intermediate α,α-dichlorocyclobutanone with zinc–ammonium chloride in refluxing methanol. The aza-ring expansion of the latter product via the rearrangement of its *N*-methylnitrone with *p*-toluenesulfonyl chloride provided the lactam **6** in 46% yield with the material balance from this reaction recovered as unchanged starting ketone. Reduction of the lactam **6** to the pyrrolidine **7** proceeded poorly with $LiAlH_4$, but it was reduced in excellent yield by diborane in tetrahydrofuran. The benzyl protecting group was somewhat more resistant to removal than expected. However, catalytic hydrogenolysis over palladium at 60 psi in ethanol containing HCl proceeded to give a mixture of (±)-mesembranol (**1**) and (±)-6-epimesembranol (**8**) in 75% yield. These alcohols were separated by preparative layer chromatography to afford crystalline (±)-mesembranol and (±)-**8** in a 1.4:1 ratio. The synthesis of epimeric alcohols **1** and **8** is, in a formal sense, a synthesis of (±)-mesembrine (**9**) since the oxidation of each of these alcohols to the alkaloid has been described previously.[6]

The ratio of the two alcohols **1** and **8** of 1.4:1 shows that little discrimination is exhibited by dichloroketene toward the two diastereotopic faces of the 1,2 double bond in 4-(benzyloxy)cyclohexene **4**.

Scheme III[a]



[a] (a) Cl_3CCOBr/Zn-Cu. (b) Zn-Cu/NH_4Cl/MeOH. (c) NHMeOH·HCld/Py, 72 h; *p*-tosyl chloride, 24 h; H_2O. (d) BH_3-THF/N_2, 0–60 °C. (e) H_2/Pd, 60 lb/in.^{2}.

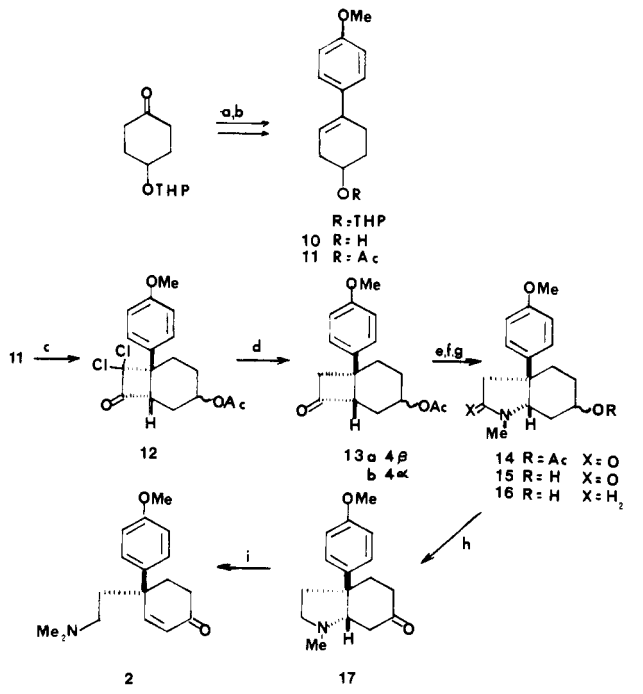
The eight-step synthesis of the (±)-mesembranols proceeds in a quite acceptable 7% overall yield from 4-hydroxycyclohexanone, especially since no significant attempt was made to optimize yields for the majority of the reactions employed.

Synthesis of (±)-*O*-Methyljoubertiamine. With the completion of the synthesis of (±)-mesembrine by the aza-ring expansion route, extension of the approach to the synthesis of (±)-*O*-methyljoubertiamine (**2**) was explored. The overall strategy followed closely that used for the synthesis of the (±)-mesembranols. One modification planned was to examine the replacement of the benzyl protecting group for what ultimately becomes the C-6 oxygen function of the alkaloid; the second objective was to explore the possibility of improving the overall yield.

The protection of the hydroxy function in compounds subjected to cycloaddition with dichloroketene, in principle at least, did not appear to be essential. In the event, when the 4-hydroxycyclohexenol **10**, which was obtained in a 72% yield from 4-hydroxycyclohexanone by the reactions shown in Scheme IV, was subjected to a slow addition of trichloroacetyl bromide in the presence of activated zinc, a very vigorous reaction ensued. Analysis of the product by GC/MS revealed a complex reaction mixture containing the required dichlorocyclobutanone system in which the hydroxy function was esterified with both trichloroacetyl (**12**, OAc = $OCOCCl_3$) and dichloroacetyl (**12**, OAc = $COCHCl_2$) groups. Reduction of the crude reaction mixture with a zinc–NH_4Cl–MeOH system did provide the required 4-acetoxy-*cis*-bicyclo[4.2.0]octanone **13** in an acceptable 56% yield; however, the overall yield of **13** was much improved (85%) when the cyclohexenol **10** was converted to the *O*-acetate **14** prior to carrying out the cycloaddition–reduction sequence.

The product from the latter reaction consisted of the C-4 epimeric acetates **13a** and **13b** in a 73:27 ratio as indicated by GC/MS analysis. This indicates that the C-4 acetoxy function provides for somewhat more descrimination than the C-4 tetrahydropyranyl group in influencing the [2 + 2] cycloaddition to occur predominantly from the cyclohexene face which is anti to the C-4 substituent. A further enrichment (>95%) in the major isomer occurred on chromatographic purification. For the purpose of the synthesis of (±)-*O*-methyljoubertiamine reported herein, the production of both stereoisomers at the C-4 position is of no consequence since the stereochemical integrity of

Scheme IV[a]



[a] (a) 4-Methoxyphenyl)magnesium bromide/THF. (b) *p*-Toluenesulfonic acid/Me_2CO. (c) Cl_3CCOBr/Zn-Cu. (d) Zn-Cu/NH_4Cl/MeOH, Δ. (e) NHMeOH·HCld/Py, 72 h; *p*-tosyl chloride, 24 h; H_2O. (f) K_2CO_3/MeOH, N_2. (g) BH_3-THF, Δ, 2 h. (h) Cr^{VI}/Me_2CO. (i) MeI/Me_2CO then K_2CO_3/H_2O.

this group in the alkene is eventually lost by its subsequent conversion to the C-6 carbonyl group in the alkaloid.

The occurrence of a broad multiplet at δ 4.80 in the ^1H NMR of the major isomer was indicative of a C-4 α-axial hydrogen is in accord with **13a** on the basis of the assumption that it exists in a conformation which places the phenyl group axial. The accompanying minor isomer observed in the mixture prior to chromatography exhibited a multiplet at δ 5.08. A firm basis for assigning the stereochemistry of **13a** rested ultimately on its conversion to the indolone **14** via the previously described *N*-methylnitrone rearrangement. The ^1H NMR spectra properties of this compound as a member of the well-studied *cis*-octahydroindole system could be clearly assigned from ^1H coupling and chemical shift data. The axial nature of H-6 and the equatorial disposition of H-7a provided by these results established the cis relationship of the phenyl group and the acetoxy group and further indicated that the cyclohexane ring adopts the axial-aryl conformation in conformity with the conformational situation which as been found to be characteristic of *cis*-octahydroindoles[6] and related systems.[1]

The nitrone-rearrangement step in the synthesis of the mesembranols had not proceeded in high yield and had led to recovery of considerable amounts of the starting ketone. In the case of the cyclobutanone **13a** the presence of the acetate carbonyl permitted the use of IR spectroscopy to monitor the extent to which nitrone formation takes place by using the change in relative intensities of the carbonyl peaks at 1785 and 1730 cm^{-1}. Despite the variation of solvent and temperature, examination of differing reagent/ketone ratios, and addition of 3A molecular sieves, the optimum conditions determined (see the Experimental Section) led only to a 50% conversion to the nitrone as estimated from the reduction in the 1785-cm^{-1} band. On a preparative scale a reaction carried out under these optimized conditions gave the lactam **14** in 45% yield together with recovered cyclobutanone (40%). Two methods were explored in the conversion of the lactam acetate **14** to the 6β-hydroxy-*cis*-octahydroindole **16**. Reduction of the lactam carbonyl and simultaneous cleavage of the acetate is readily accomplished to give **16** in 80% yield by the action of diborane–THF complex in refluxing THF when followed by the addition of 1 equiv of LiAlH to complete reduction of the acetate. Alternatively, the same transformation of **14** → **16** is similarly achieved in 83% yield by a two-step procedure in which the acetate is first hydrolyzed to the lactam–alcohol **18** in methanolic base and then conversion of the latter to **16** with diborane–THF. Oxidation of the alcohol **16** to 3′-demethoxymesembrine **17** with Jones reagent proceeded quantitatively. The latter compound, which has been previously converted to (±)-joubertiamine by Stevens and Lai,[8] gave (±)-*O*-methyljoubertiamine when reacted with methyl iodide followed by a workup in aqueous base. The spectral characteristics (^1H NMR, ^{13}C NMR, and mass spectra) of the synthetic material were identical with those reported.[8] The overall yield of (±)-*O*-methyljoubertiamine from 4-hydroxycyclohexanone in the ten-step sequence was over 40% and as such represents a considerable improvement over previous syntheses of this compound.[9]

The synthesis of (±)-mesembranol (**1**) and (±)-*O*-methyljoubertiamine described in this report represents a new approach for the synthesis of these octahydroindole and secooctahydroindole alkaloids. It also represents a new synthetic strategy for the cis heteroannelation of a five-membered nitrogen-containing ring onto a 1-substituted carbocyclic alkene with regiochemical control.

Experimental Section

1-(4-Methoxyphenyl)-1-hydroxycyclohexan-4-one Ethylene Ketal. Cyclohexane-1,4-dione monoethylene ketal (3.4 g) in THF (25 mL) was added dropwise to the Grignard reagent prepared from 4-bromoanisole (5.80 g) and magnesium (0.75 g) in THF (25 mL). After the mixture was refluxed for 17 h, the reaction was quenched with NH_4Cl, and an extractive workup gave a solid (90%). Crystallization from $CHCl_3$–Et_2O gave an analytical sample, mp 124–125 °C. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.57. Found: C, 68.17; H, 7.61.

1-(4-Methoxyphenyl)cyclohex-1-en-4-one Ethylene Ketal (3). The Grignard product (528 mg) from the previous reaction was converted to its ethylene ketal **3** [mp 46–47 °C[6]; 400 mg (85%)] by standard procedures: ^1H NMR, (100 MHz) δ 7.36 (2, d, J = 8 Hz), 6.84 (2, d, J = 8 Hz), 5.92 (2, br s), 4.04 (4, s) 3.80 (3, s), 2.72–2.52 (2, m), 2.44 (2, br s), 1.92 (2, t, J = 6 Hz). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.09; H, 7.25.

4-(Benzyloxy)cyclohexanone. Into a suspension of 4.8 g (125 mmol) of KH in 10 mL of dry THF was dripped the ethylene ketal of 4-hydroxycyclohexanone (14.8 g, 93.7 mmol) in 20 mL of dry THF with stirring until hydrogen evolution ceased. Benzyl bromide (11.1 mL, 93.7 mmol) was added to the reaction mixture over a period of 15 min with stirring at 0 °C, and after a further 30 min the solution was quenched with water and 10% HCl. An extractive workup with CH_2Cl_2 and flash evaporation yielded 22.0 g (94.7%) of a light yellow oil which was used without further purification: ^1H NMR (100 MHz) δ 7.28 (5, s), 4.46 (2, s), 3.82 (4, s), 1.98–126 (8, m). The yellow oil from above (22 g, 88.9 mmol) was then dissolved in 125 mL of acetone to which 15 mL of H_2O and 644.4 mg (3.39 mmol) of *p*-toluenesulfonic acid had been added, and the solution was stirred under nitrogen for 3 days. The reaction was then halted and the acetone flash evaporated. The residue was dissolved in CH_2Cl_2 and extracted with small quantities of saturated $NaHCO_3$. The organic layer was then dried

(8) Stevens, R. V.; Lai, J. T. *J. Org. Chem.* **1972**, *37*, 2138.
(9) Strauss, M. F.; Wiechers, A. *Tetrahedron* **1978**, *34*, 127. Sanchez, I. H.; Tallabs, F. R. *Chem. Lett.* **1981**, 891. See also ref 4 and 8.

over Na_2SO_4, filtered, and flash evaporated, leaving 4-(benzyloxy)cyclohexanone (16.8 g, 92.8%) as a pale yellow oil: IR (neat) 1720 cm^{-1}; ^1H NMR (100 MHz) δ 7.28 (5, s), 4.48 (2, s), 3.64 (1, m), 2.6–1.6 (8, m).

1-(3,4-Dimethoxyphenyl)-4-(benzyloxy)cyclohexene (4). To a three-necked round-bottomed flask equipped with an overhead stirrer, dropping funnel, low-temperature thermometer, and nitrogen inlet were added 40 mmol (8.86 g) of 4-bromoveratrole and 150 mL of freshly distilled THF. The solution was stirred at −78 °C. under N_2. To the solution was then added 40.8 mmol (16.4 mL) of *n*-butyllithium at such a rate so that the temperature in the reaction vessel did not exceed −75 °C. During the addition of white precipitate formed. The suspension of the lithium reagent was used without further purification as follows: to the lithioveratrole solution was added 8.16 g (40 mmol) of (benzyloxy)cyclohexanone over a period of 40 min, with the temperature not rising more than 6 °C during the course of the ketone addition. After the addition was complete, all the precipitate was gone and the solution was clear yellow. Stirring was continued for 2 h at −78 °C under N_2. The bath was then removed, and the reaction mixture was warmed to room temperature. It was then quenched with 100 mL of saturated salt solution, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. Filtration followed by flash evaporation of the solvent yielded a solid which was used without further purification. The crude product was treated with 1.70 g of *p*-toluenesulfonic acid in 300 mL of dry acetone and stirred at room temperature for 48 h. The acetone was then flash evaporated, leaving a solid which on recrystallization from petroleum ether gave the alkene 4: 7.8 g (60%); mp 79–80 °C; ^1H NMR (100 MHz) δ 7.24 (5, s), 6.76–6.64 (3, m), 5.80 (1, s), 4.52 (2, s), 3.76 (3 s), 3.60 (1, m), 2.6–1.84 (6, m). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.58; H, 7.19.

1-(3,4-Dimethoxyphenyl)-4α- and -4β-(benzyloxy)-*cis*-bicyclo[4.2.0]octan-7-ones (5). A three-necked flash equipped with two reflux condensers with drying tubes, a dropping funnel, and a stirring bar was charged with 400 mL of dry ether, 8.02 g of activated zinc, and 5.2 g (16.05 mmol) of 1-(3,4-dimethoxyphenyl)-4-(benzyloxy)cyclohexene. To this was added freshly distilled Cl_3CCOBr (7.3 mL in 25 mL of dry ether). Reaction did not begin until after the addition was complete, and then a vigorous exothermic reaction occurred. Stirring was continued for 3 h after the exothermic reaction subsided. The reaction mixture was then quenched by pouring it into water and extracting the water layer with additional portions of ether. The combined organic layers were then dried over Na_2SO_4, filtered, and flash evaporated, leaving a dark oil [IR 1811 cm^{-1} (C=O)]. This oil was then treated with 16.0 g of zinc dust, 6.2 g of NH_4Cl, and 100 mL of CH_3OH, and the reaction mixture was refluxed for 16 h. The reaction was then worked up in the usual manner, leaving 5.7 g of a crude product which was subjected to Al_2O_3 (grade I) chromatography. Elution with benzene gave 3.0 g of starting olefin while the $CHCl_3$ eluate gave 1.50 g (60.5% conversion) of the cyclobutanone 5 which as a mixture of the 4α and 4β isomers on gas chromatography on a 4% OV-17 column at 200 °c gave a single peak: IR (neat) 1776 cm^{-1}; ^1H NMR (100 MHz) δ 7.24 (5, s), 6.72 (3, s), 4.52 (2, brs), 3.80 (6, s), (1 m), 3.2–2.76 (2, AB q, J = 16 Hz), 2.6–1.4 (6, m); Calcd for $C_{23}H_{26}O_4$ m/e 366.1831 (M^+), found m/e 366.1836 (M^+).

1-Methyl-3a-(3,4-dimethoxyphenyl)-6α- and -6β-(benzyloxy)-*cis*-octahydroindol-2-ones (6). A mixture of the cyclobutanone 5 (790 mg; 2.30 mmol) and *N*-methylhydroxylamine hydrochloride (786 mg; 9.4 mmol) in pyridine (110 mL) containing 10–20 pellets of 3A molecular sieves was stirred at 25 °C for 24 h. The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride added. Stirring was continued for 15 min at 0 °C and then for 6 h at room temperature, at which time 1.0 mL of H_2O was added and stirring continued a further 46 h. The reaction mixture was then worked up by first diluting with $CHCl_3$ and distilling off as much solvent as possible. The residue was then redissolved in $CHCl_3$ and made acidic with concentrated HCl. The organic layer was separated and the HCl layer diluted with H_2O. The aqueous layer was then extracted with $CHCl_3$. The combined organic layers were then dried over Na_2SO_4, filtered, and flash evaporated, leaving a brown oil (700 mg). Chromatography of the oil on grade III Al_2O_3 in 1:1 benzene/chloroform yielded the starting ketone (250 mg) and the desired lactam 6 (423 mg, 46%). The lactam 6 gave a single peak on gas chromatography with a 4% OV-17 column at 200 °C: IR (neat) 1683 cm^{-1} (CO); mass spectrum calcd for $C_{24}H_{29}NO_4$, m/e 395.2096 (M^+), found m/e 395.2091 (M^+).

1-Methyl-3a-(3,4-dimethoxyphenyl)-6α- and -6β-(benzyloxy)-*cis*-octahydroindoles (7). A solution of the lactam 6 (213 mg, 0.54 mmol) in 2.0 mL of dry THF was added to 1.5 mmol (1.5 mL) of BH_3–THF under nitrogen over a 10-min period at 0 °C. When the addition was complete, the solution was refluxed for 1 h, and when it cooled to room temperature, 6 N HCl (5 mL) was added to destroy any excess BH_3–THF complex. The THF was then evaporated, and the aqueous phase was saturated with NaOH pellets. An extractive workup with ether gave the amine 7: 198.6 mg (74.5%); ^1H NMR (100 MHz) δ 7.27 (5, s), 6.80 (3, s), 4.51 (2, s), 3.81 (6, s), 3.60 (1, m), 3.0–1.8 (11 complex signal pattern), 2.33 (3, s). This sample as a mixture of 6α- and 6β-benzyloxy isomers was then used without further purification.

Mesembranol (1) and 6-Epimesembranol (8). The epimeric mixture of benzyl ethers (153 mg) was hydrogenolyzed in EtOH (1 mL) containing 2 μL of concentrated HCl over 40 mg of 5% Pd/C in a Paar apparatus at 60 lb of pressure for 3 h. After the catalyst was filtered, an acid–base extraction was done. The basic layer yielded the crude product (88.5 mg, 75.7%) consisting of mesembranol and its 6-epimer as evidenced by TLC. The alkaloids were then placed on a 5% K_2CO_3 impregnated silica gel preparative TLC plate and eluted twice with 19:1 $CHCl_3/CH_3OH$. The plate yielded two distinct bands which on extraction afforded mesembranol (50 mg) and 6-epimesanbranol (35 mg). The lower R_f material showed spectral, TLC, and GC behavior identical with that for an authentic sample of mesembranol: ^1H NMR (100 MHz) δ 6.88 (3, s), 3.88 (6, s), 3.20 (2, m), 2.76 (2, d), 2.38 (3, s), 2.28–1.6 (6, m); mp 154–156 °C (after crystallization from ethyl acetate). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.83; H, 8.71; N, 4.71.

The material at higher R_f on recovery showed TLC, GC, and mass spectra behavior identical with that of authentic 6-epimesembranol: mass spectrum calcd for $C_{17}H_{25}NO_3$, m/e 291.1834 (M^+), found m/e 291.1831 (M^+).

(±)-*O*-Methyljoubertiamine (2). 4-Oxocyclohexanyl 2-Tetrahydropyranyl Ether. 4-Hydroxycyclohexanone (10 g, 87 mmol) and 25 mL of dihydropyran containing a catalytic quantity of *p*-toluenesulfonic acid were stirred at room temperature for 40 min. The solution was then diluted with 100 mL of ether and extracted with a 50-mL portion of saturated $NaHCO_3$. Drying the ether solution over anhydrous $MgSO_4$ and removing the solvent in vacuo yielded a light yellow oil (14.5 g, 83%) that was purified by vacuum distillation [bp 100–107 °C (0.3 mmHg)] to give the pure THF ether: IR (neat) 1700 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 4.88 (1, m), 3.94 (2, m), 3.56 (1, m), 2.15–136 (14, m); ^{13}C NMR δ 211.46 (C=O), 97.27 (OCHO), 70.05 (OCHO—CH_2), 62.89 ($(RCH_2)_2CH$—O—THP), 37.69 and 37.30 ($CH_2C(O)CH_2$), 32.36, 31.25, 30.21, 25.52, 19.79 (RCH_2R).

1-(4-Methoxyphenyl)cyclohexen-4-yl 2-Tetrahydropyranyl Ether. A Grignard reagent was formed in the following manner. Mg turnings (1.25 g, 51.4 mmol) in 25 mL of dry THF and 4-bromoanisole (10.0 g, 50.7 mmol) in 75 mL of dry THF were added at a rate so as to maintain a steady reflux. After the reaction subsided, 4-oxocyclohexanyl 2-tetrahydropyranyl ether (10.0 g, 50.5 mmol) from the above-mentioned experiment in 75 mL of THF was added dropwise to the reaction mixture and the solution refluxed for an additional 4 h. After the reaction was quenched with 100 mL of saturated NH_4Cl solution, the workup provided an oil, 13.74 g (89%).

The oil was dissolved in 100 mL of benzene containing *p*-toluenesulfonic acid (50 mg) and refluxed in a Dean-Stark trap for 30 min. The workup of the reaction mixture gave the alkene (11.9 g, 92%) as an oil which crystallized from methanol to give the THP ether of 1-(4-methoxyphenyl)cyclohexen-4-ol: mp 48 °C; ^1H NMR (100 MHz) δ 7.25 (2, d) 6.78 (2, d) 6.78 (2, d) 5.89 (1, m) 4.76 (1, m) 3.91 (2, br m) 3.71 (3, s), 3.49 (1, br m), 2.71–2.09 (6, m), 2.09–1.44 (8, br m). Anal. Calcd for $C_{28}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.46.

1-(4-Methoxyphenyl)cyclohexen-4-ol (10). The THP ether (11.4 g, 39.6 mmol) from the previous experiment was suspended

in 100 mL of methanol in a 250-mL flask under a N_2 atmosphere. *p*-Toluenesulfonic acid (50 mg) was added and the solution stirred at room temperature for 24 h. Product isolation was accomplished by removing the methanol in vacuo and redissolving the crude solid in $CHCl_3$. The $CHCl_3$ solution was washed with one 50-mL volume of saturated bicarbonate to remove the residual tosyl acid and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo yielded **10** (7.90 g, 97.9%) as a white solid which was of ample purity to be used in the subsequent reaction. An analytical sample was obtained by crystallization from $CHCl_3$–Et_2O: mp 124–126 °C; ^1H NMR (acetone 100 MHz) δ 7.35 (2, d, J = 9.4 Hz), 6.88 (2, d, J = 9.4 Hz), 5.95 (1, m), 4.00 (1, m), 3.82 (3, s), 2.92 (1, s), 2.74–2.10 (6, m). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44. H, 7.89. Found: C, 76.24. H, 7.89.

1-(4-Methoxyphenyl)-4-acetoxycyclohex-1-ene (11). The alcohol **10** (5.0 g, 24.5 mmol) was dissolved in 15 mL of dry pyridine, and acetic anhydride (7.5 mL, 3 equiv) was added. The product was isolated after 15 h by addition of ice to the reaction mixture. Recrystallization from methanol yielded the pure *O*-acetate **11**: 5.80 g (96.2%); mp 86 °C; IR 1715 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 7.37 (2, d, J = 10.4 Hz), 6.91 (2, d, J = 10.4 Hz), 5.97 (1, m), 5.12 (1, br m), 3.85 (3, s), 2.77–1.89 (6, m), 2.09 (3, s), ^{13}C NMR δ 171.22 ($OCOCH_3$), 159.11 (C'4), 136.00 (C1), 134.36 (C1'), 126.36 (C3', C5'), 119.53 (C2), 113.93 (C2',C6'), 69.58 (C4), 55.40 (OMe), 31.38, 27.73, 25.45 (C3, C5, C6), 21.48 ($OCOCH_3$). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.21.

1-(4-Methoxyphenyl)-4-acetoxy-*cis*-bicyclo[4.2.0]octan-7-one (13). (a) The alkene **11** (3 g, 12 mmol) in 100 mL of dry ether containing Zn–Cu couple was brought to reflux, and trichloroacetyl bromide (8.26 g) in ether (40 mL) was added dropwise over the course of 4 h while 7.5 g of the Zn–Cu couple was added in 1-g aliquots each hour. The solution was refluxed for a total of 8 h and then cooled to room temperature. The solution was filtered through Celite and then washed with cold water (2 × 30 mL). The solution was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give the crude dichlorocyclobutanone which was immediately dechlorinated in 100 mL of methanol by adding 10 g of Zn–Cu couple and 7 g of NH_4Cl. After the mixture was stirred at room temperature for 6 h, the solution was filtered and the methanol removed in vacuo to give a semisolid mass which was partitioned between $CHCl_3$ and water to remove excess NH_4Cl and $ZnCl_2$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated, yielding a crude product (4 g). GC/MS of this showed a 78:22 mixture of the 4β/4α isomers of **13**. After chromatography on an activity I Al_2O_3 column with $CHCl_3$ as the eluant, the ketone **13** (2.56 g, 73%) was obtained together with the starting alkene **11** (520 mg). The ketone, which consisted of ~95% of the 4β/isomer was distilled at 120–122 °C (0.1 mmHg): IR 1785 (C=O), 1730 cm^{-1} (C=O); ^1H NMR 4β isomer (100 MHz) δ 7.26 (2, d, J = 8.9 Hz), 6.93 (2, d, J = 8.9 Hz), 4.80 (1, br m), 3.86 (3, s), 3.73 (1, m), 3.28 (1, d, J = 16.0 Hz), 2.06 (3, s), 2.70–1.10 (6, m); ^{13}C NMR 206.43 (C7), 170.69 (acetate C=O), 158.59 (C4'), 139.71 (C1'), 127.47 (C2', C6'), 114.19 (C3', C5'), 70.70 (C4), 61.65 (C6), 59.18 (C8), 55.47 (OMe), 36.65, 35.42, 27.29, 26.50 (C1, C2, C3, C5), 21.35 ($OCOCH_3$). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.39; H, 7.05.

(b) The 4-hydroxycyclohexene **10** (500 mg) in dry ether (50 mL) was stirred with activated zinc (1.5 g) under an N_2 atmosphere while trichloroacetyl bromide (3 mL) in ether (7 mL) was added slowly. The solution was refluxed for 30 min. The usual workup gave an oil which showed carbonyl absorptions at 1805 and 1759 cm^{-1}. GC/MS analysis showed two major peaks corresponding to compounds containing dichloroacetyl and trichloroacetyl groups. Reduction of this product in refluxing methanol (30 mL) with Zn (6 g) and NH_4Cl (3 g) for 3 h afforded a crude product which exhibited strong CO bonds at 1780 and 1730 cm^{-1}. Preparative layer chromatography of the crude material on silica gel in $CHCl_3$–5% MeOH gave the pure *cis*-bicyclo[4.2.0]octanone derivative **13** (330 mg, 56%). The spectral properties were identical with the compound prepared by procedure a.

***N*-Methyl-3a-(4-methoxyphenyl)-6β-acetoxy-*cis*-octahydroindol-2-one (14).** A solution of ketone **13** (2.16 g, 7.5 mmol) in freshly distilled pyridine (25 mL) containing 30 3A molecular sieves and *N*-methylhydroxylamine hydrochloride (2.5 g, 4 equiv) was stirred for 3 days under a N_2 atmosphere at room temperature. The solution was then cooled to 0 °C and *p*-toluenesulfonyl chloride (7.14 g, 5 equiv) was added in 1-g aliquots with continued stirring for 15 h, after which 1.5 mL of H_2O was added. After being stirred overnight, the solution was filtered and the solvent removed under vacuum, yielding a dark brown oil. The crude product was chromatographed on 300 g of silica gel with 50:50 v/v ether/hexane as the eluant to give *N*-methylhydroxylamine–*p*-toluenesulfonamide, unreacted ketone **13** (864 mg, 40%), and the *N*-methyllactam (1.07 g, 45%). An analytical sample of the lactam **14** was obtained by vacuum distillation at 170 °C (0.07 mmHg): IR (1730 (C=O), 1695 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 7.31 (2, d, J = 8.9 Hz), 6.95 (2, d, J = 8.9 Hz), 4.80 (1, m), 4.15 (1, m) 3.91 (3, s), 3.02 (3, s) 2.54 (2, s), 2.20–1.60 (6, m), 2.10 (3, s); ^{13}C NMR 174.08 (C2), 170.83 (acetate C=O), 158.5 (C4'), 135.48 (C1'), 127.66 (C2', C6'), 114.32 (C3', C5'), 69.14 (C4'), 63.08 (C7a), 55.40 (OMe), 47.89 (NMe), 42.12 (C3a), 33.20 (C7), 29.82, 27.21 (C5, C6), 21.29 ($OCOCH_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.35; H, 7.33 N, 4.17.

***N*-Methyl-3a-(4-methoxyphenyl)-6β-hydroxy-*cis*-octahydroindol-2-one (15).** The *O*-acetylindolone **14** (250 mg, 0.78 mmol) was dissolved in 20 mL of methanol under N_2, anhydrous K_2CO_3 (500 mg, 5 equiv) was added in one portion, and the reaction mixture was stirred at room temperature for 3 h. The usual workup gave the lactam alcohol **15** (204 mg, 94%) as an oil: IR 3600 (sharp), 3420 (br, OH), 1680 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 7.21 (2, d, J = 8.5 Hz), 6.80 (2, d, J = 8.5 Hz), 4.08 (1, t), 3.78 (3, s), 3.65 (1, m), 2.79 (3, s), 2.42 (2, s), 2.35–1.10 (6, m); ^{13}C NMR δ 174.31 (C2), 158.15 (C4'), 135.59 (C1'), 127.60 (C2', C6'), 114.02 (C3', C5'), 65.68 (C4), 63.28 (C7a), 55.22 (OMe), 47.82 (NMe), 42.10 (C3a), 33.65 (C3), 33.20 (C4), 30.99 (C7), 27.09 (C3); calcd $C_{16}H_{21}NO_3$ m/e 275.1521 (M^+), found m/e 275.1524 (M^+).

***N*-Methyl-3a-(4-methoxyphenyl)-6β-hydroxyoctahydroindole (16).** The lactam **15** in 10 mL of dry THF was added to a solution of 1 M BH_3–THF complex in THF (10 mL) at 0 °C under N_2. After the reaction mixture was allowed to come to room temperature, the solution was heated to reflux for 2 h. The reaction mixture was worked up as described previously to yield the amine **16** (95 mg, 90%) as a clear oil. An analytical sample was obtained by distillation at 122 °C (0.15 mmHg): IR 3410 cm^{-1} (OH); ^1H NMR (100 MHz) δ 7.30 (2, d, J = 8.8 Hz), 6.85 (2, d, J = 8.8 Hz), 3.92 (1, m), 2.75 (1, t), 2.35 (3, s), 2.29–1.14 (10, m), ^{13}C NMR δ 158.81 (C4'), 139.00 (C1'), 128.99 (C2', C6'), 113.80 (C3', C5'), 70.25 (C7a), 66.93 (C6), 55.34 (OMe), 54.55 (C2), 46.81 (C3a), 40.69 (C7), 40.23 (NMe), 34.89 (C3), 33.20 (C5), 33.00 (C4). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.28; H, 8.79; N, 5.18.

***N*-Methyl-3a-(4-methoxyphenyl)-*cis*-octahydroindol-6-one (17).** The amino alcohol **16** (301 mg, 1.3 mmol) in 30 mL of acetone was treated with Jones reagent (~5 mequiv/mL) at 0 °C over a 30-min period until the persistent red color of the reagent was no longer discharged. After an additional 20 min, the reaction was terminated with 1 mL of 2-propanol, and the acetone solution was decanted from the chromium salts and reduced to an oil in vacuo. The oil was partitioned between 1 N NaOH (1 mL) and ether (10 mL) and extracted with ether (3 × 50 mL). After the workup of the ether extract the ketone (326 mg, 91%) was obtained which was distilled at 120 °C (0.25 mmHg) for analysis. The IR, NMR and mass spectra of this compound were found to be identical with those reported in the literature:[9] IR 1715 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 7.23 (2, d, J = 8.8 Hz), 6.79 (2, d, J = 8.8 Hz), 3.73 (3, s), 2.89 (1, t, J = 3.2 Hz), 2.51, 2.23 (3, s), 2.48–1.85 (8 m); mass spectrum, m/e (relative intensity) 259 (45, M^+) 189 (50), 188 (88), 174 (32), 96 (78), 70 (100), 42 (47).

(±)-*O*-Methyljoubertiamine (2). The amino ketone **17** (87 mg, 0.33 mmol) in 5 mL of dry acetone was treated as described previously[8] to give (±)-*O*-methyljoubertiamine (65 mg, 71%) as a colorless oil with identical properties (IR, ^1H NMR, mass spectra) with those reported in the literature.[8,9]

Registry No. (±)-1, 82769-19-5; (±)-2, 34603-52-6; 3, 67019-46-9; (±)-4, 82732-16-9; 4 (α,α-dichlorocyclobutanone derivative, 82732-24-9; (±)-5 (isomer 1), 82732-17-0; (±)-5 (isomer 2), 82769-22-0; (±)-6 (isomer 1), 82732-18-1; (±)-6 (isomer 2), 82732-27-2; (±)-7 (isomer 1), 82732-19-2; (±)-7 (isomer 2), 82732-28-3; (±)-8, 82769-20-8; (±)-10, 66336-61-6; (±)-11, 66336-60-5; 12 (OAc = $OCOCCl_3$), 82732-25-0; 12 (OAc = $OCOCHCl_2$), 82732-26-1; (±)-13a, 82732-20-5; (±)-13b, 82769-21-9; (±)-14, 82732-21-6; (±)-15, 82732-22-7; (±)-16, 82732-

23-8; (±)-17, 70503-69-4; 1-(4-methoxyphenyl)-1-hydroxycyclohex-4-one ethylene ketal, 67019-51-6; cyclohexane-1,4-dione monoethylene ketal, 4746-97-8; 4-bromoanisole, 104-92-7; 4-(benzyloxy)cyclohexanone, 2987-06-6; 4-bromoveratrole, 2859-78-1; benzyl bromide, 100-39-0; 4-hydroxycyclohexanone ethylene ketal, 22428-87-1; *N*-methylhydroxyamine hydrochloride, 4229-44-1; 4-hydroxycyclohexaone, 13482-22-9; 4-oxocyclohexanyl 2-tetrahydropyranyl ether, 60739-53-9.

Effect of Substituents on the 3-Azidobenzo-*as*-triazine/Tetrazolo[5,1-*c*]benzo-*as*-triazine/Tetrazolo[1,5-*b*]benzo-*as*-triazine Equilibrium[1]

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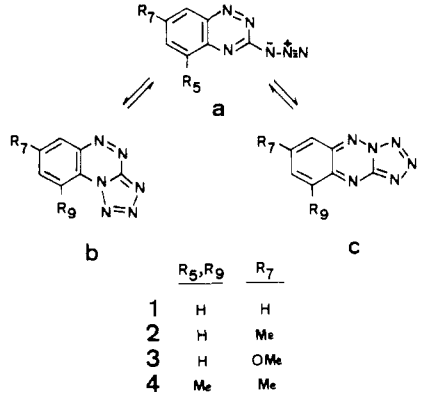
With the aim of gaining insight into the title equilibrium, some derivatives were synthesized and investigated by NMR and IR spectroscopy. The general statement that electron-donating groups and polar solvents stabilize tetrazole vs. azide forms is again confirmed. However, while the angular tetrazole tautomer **2b** is favored by a methyl group at position 7, a methoxy group at this position induces a surprising change, the linear tetrazole tautomer **3c** becoming the major one in acetone and in dimethyl sulfoxide. Likewise, **4c** predominates over **4b**, a fact that may be related to the steric hindrance between the methyl group at position 9 and the tetrazole ring in **4b**. 1-Oxido derivatives of **2a–4a** (**11a–13a**), also investigated, are true azides in chloroform, but in dimethyl sulfoxide the angular tetrazole form curiously appears to be predominant in 11 and is observed in 12 and 13 as well.

In 1973 Messmer et al. reported[2] that the product arising from the reaction of 3-hydrazinobenzo-*as*-triazine with nitrous acid, presumably 3-azidobenzo-*as*-triazine (**1a**),



	R_5,R_9	R_7
1	H	H
2	H	Me
3	H	OMe
4	Me	Me

showed no azide band in the solid state. Mainly on the basis of electronic spectra, the tetrazolo[5,1-*c*]benzo-*as*-triazine structure (angular structure **1b**) was proposed for the tetrazole form which seems to be the exclusive tautomer in the solid state and is also present in polar solvents. Taking into account that 5(and/or 6)-substituted 3-azido-*as*-triazines cyclize on N-2, affording tetrazolo-[1,5-*b*]-*as*-triazines, Paudler et al. suggested shortly afterward[3] that the tetrazolo[1,5-*b*]benzo-*as*-triazine linear structure (**1c**) should not have been ruled out by Messmer et al.[2] This group has very recently reinvestigated the problem and reached the conclusion that the structure they had proposed (**1b**) is actually predominant, both in the solid state and in Me_2SO solution, although **1a** and **1c** are also present (**1a**/**1b**/**1c** ratio equal to 25/65/10) in this solvent.[4]

With only a few ternary azide–tetrazole equilibria having been in fact observed,[5] it seemed interesting to us to study the present case in more detail, because a knowledge of the factors influencing the relative stabilization of one tetrazole tautomer vs. the other, and/or both over the azide, could be of great value in attacking the study of (or to account for the results obtained in) more complex related polyaza aromatic systems.[6] As it is well-established that electron-withdrawing substituents disfavor tetrazole forms,[5] only electron-donating groups were considered in this first approach.

Results and Discussion

The synthesis of the 7-methyl, 7-methoxy, 5,7 (or 7,9)-dimethyl derivatives of 1 (**2–4**, respectively) was first tried by means of the intramolecular cyclization[1] of the corresponding 2-(hydroxyphenyl)-1-azo-5′-tetrazolo derivatives, but only decomposition products were obtained, so that we directed our attention to a more formal step-by-step synthetic sequence.[7] Thus, heating of the ap-

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(6) For instance (naphthotetrazolotriazines), see: J. Vilarrasa and R. Granados, *J. Heterocycl. Chem.*, 11, 867 (1974).

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