Bradsher Cycloaddition of 4-Alkoxyisoquinolinium Salts as a Route to a Fully Functionalized B Ring of the Angucycline Antibiotics†

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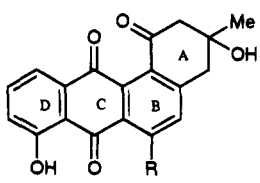
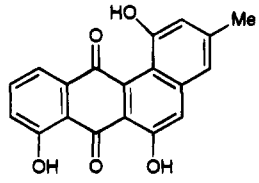
The title cycloaddition leads to a more complicated reaction manifold when there is an alkoxy group at C-4 of the isoquinoline salt. Whereas the earlier unsubstituted isoquinoline salts afforded materials from 1,4 cycloaddition, in the present examples, 1,4 and 1,3 cycloaddults are observed. Both simple and alkoxylated substrates yielded one-bond noncycloadduct materials. Careful product analysis suggests that the general mechanistic principles of the Bradsher reaction can account for all the observations in the alkoxyisoquinoline reactions. Cycloadduct **22** was carried through a short sequence to acetal **44**, the first synthetic model for the 1-acyl-*cis*-1,2-dialkoxy-1,2-dihydronaphthalene framework of the sakyomicin class of the angucycline antibiotics.

The isolation and characterization of tetrangomycin (**1**) and tetrangulol (**2**) in 1965 ushered in a novel class of natural products characterized by their intriguing chemical structures and their varied biological activities.[1] In view of the angular disposition of the A ring with respect to the remaining linear tricyclic structure of the B, C, and D components, the name "angucycline" was introduced.[2]



R=H :Tetrangomycin (**1**)
R=OH: Rabelomycin (**3**)



Tetrangulol (**2**)

Most synthetic efforts in the angucycline field have been concerned with antibiotics in which the AB ring fusion is within an aromatic ring, for example, rabelomycin **3** recently synthesized by Krohn.[3] The most challenging aspect of a total synthesis of the more complex 4a and 12b oxygenated angucyclines, represented by sakyomicin A (**4**), is the construction of the AB ring system.[4] This structural arrangement exhibits a marked propensity for rearrangement under basic, acidic, and photochemical conditions.[5] Thus far, no total synthesis of the challenging oxygenated angucyclines has appeared in the literature. Recent synthetic efforts by Danishefsky and Sulikowski on the more complex targets only highlight the sensitivity of the AB framework and the need for mild methodologies required for its assembly.[6,7] Danishefsky's approach to SF 2315A, one the simplest monooxygenated congeners, resulted in a fully aromatized product. While Sulikowski was able to quickly assemble the tetracyclic framework, the introduction of the ring junction hydroxyls proved to be complicated. We set our sights on a total synthesis of sakyomycin A which has been reported to inhibit the proliferation of the HIV in vitro.[8] Our retrosynthetic approach to the target is outlined in Scheme 1. The first stage consists in the synthesis of a precursor **5** in which the enol ether moiety is appended to the isoquinoline nucleus at C3. The linker side chain carries a tertiary hydroxyl fuctionality as the precursor to the A-ring C3 tertiary alcohol. Upon quaternization (step 1), the precursor would be activated as **6** toward an intramolecular Bradsher cycloaddition.[9]

The second and key stage (step 2) is the cycloaddition itself. Since it is known that there is a preference for exo addition in the Bradsher cycloaddition, a cis outcome of the protected 4a and 12b hydroxyls is predicted. The iminium salt **7** which is generated by the cycloaddition can be subsequently hydrolyzed to unmask the keto group of the A-ring.

The final stage (step 4) consists in functional group manipulations of **8** to unveil the free hydroxyl groups and to establish the B-ring double bond by Hoffman elimination of the amino group.

In order to lay the foundation for key step 2, the study of the *inter*molecular Bradsher cycloaddition with 4-alkoxyisoquinolinium salts was undertaken. This study resulted in the first synthesis of the 1-acyl-*cis*-1,2-dialkoxy dihydronapththalene framework of the sakyomicin family.

† Dedicated to the memory of our colleague, Prof. Samuel H. Wilen, deceased November 20, 1994.

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(2) Drautz, H.; Zähner, H.; Rohr, J.; Zeeck, A. *J. Antibiot.* **1986**, *39*, 1657.

(3) (a) Krohn, K.; Khanbabaee, K; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 99. (b) Krohn, K.; Khanbabaee, K.; Flörke, U.; Jones, P. G.; Chrapkowski, A *Liebigs Ann. Chem.* **1994**, 471.

(4) (a) Nagasawa, T.; Fukao, H.; Irie, H.; Yamada, H. *J. Antibiot.* **1984**, *37*, 693. (b) Irie, H.; Mizuno, Y.; Kouno, I.; Nagasawa, T.; Tani, Y.; Yamada, H.; Taga, T.; Osaki, K. *J. Chem. Soc., Chem. Commun.* **1983**, 174.

(5) For the rearrangements of aquayamycin see: (a) Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171. (b) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103.

(6) Gordon, M. D.; Danishefsky, S. J.; Schulte, K. G. *J. Org. Chem.* **1992**, *57*, 7052.

(7) Kim, K.; Reibenspies, J.; Sulikowski, G. *J. Org. Chem.* **1992**, *57*, 5557.

(8) Tanaka, N.; Okabe, T.; Tanaka, N.; Take, Y.; Inouye, Y.; Nakamura, S.; Nakashima, H.; Yamamoto, N. *Jpn. J. Cancer Res.* **1986**, *77*, 324.

(9) For recent papers on the Bradsher cycloaddition see (a) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falck, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 6320–6321. (b) Yin, H.; Franck, R. W.; Chen, S. I.; Quigley, G. L.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644–651.

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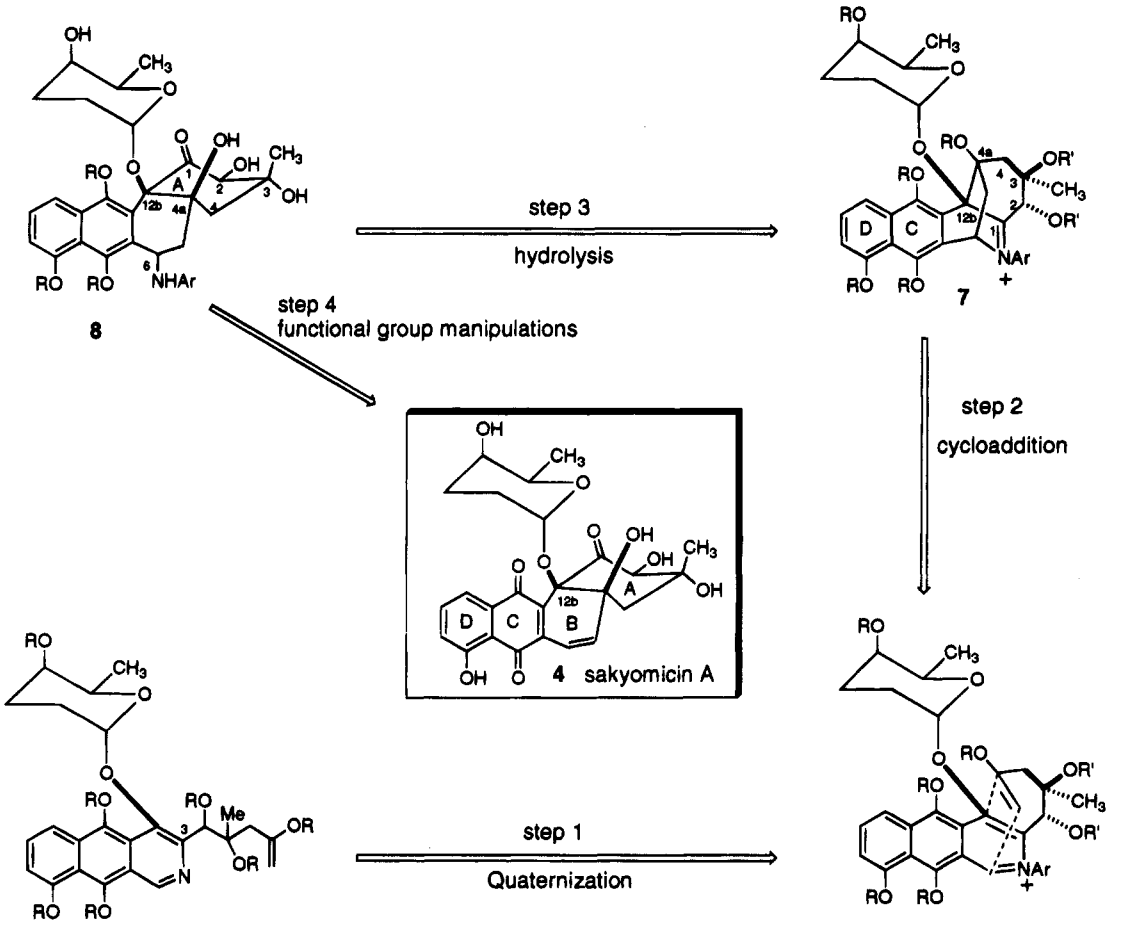
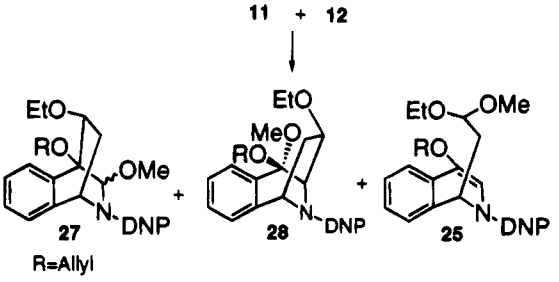
Scheme 1. Sakyomycin A Retrosynthesis



Scheme 2. Cycloaddition of Ethyl Vinyl Ether to Salt 11

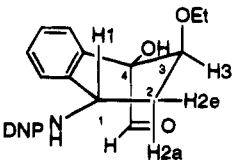


Results. Cycloadditions. Hydroxyl-protected 4-hydroxyisoquinolines were converted to their 2,4-dinitrophenyl (DNP) salts I and were then treated with dienophiles II in methanol solvent in the presence of $CaCO_3$ at room temperature to produce cycloadducts III and IV and in some cases, "one-bond" products V.[10] The results for the cycloadditions are summarized in Table 1.

Scheme 2, which depicts the addition of ethyl vinyl ether **12** to 2-(2,4-dinitrophenyl)-4-(allyloxy)isoquinolinium salt **11**, illustrates the observed product distribution before chromatographic separation over silica gel. It should be noted that tricyclic aminal **27** and ketal **28** are the precursors, respectively, to aldehyde **19** and ketone **23**.

The cycloaddition of THP vinyl ether **29** to isoquinolinium salt **11** (Scheme 3) resulted predominantly in the formation of one-bond products **30** and **31**. Conjugated enone **31** arises from isomerization of the initially formed unconjugated species **30**. The presence of the anticipated cycloadduct **32** was ascertained by inspection of the NMR spectrum of the reaction mixture.[11]

Structural Assignments. The ^1H NMR for **17** is representative of all the tetralin aldehydes obtained. It displays, a sharp singlet resonance at 9.82 ppm corresponding to the aldehyde proton.



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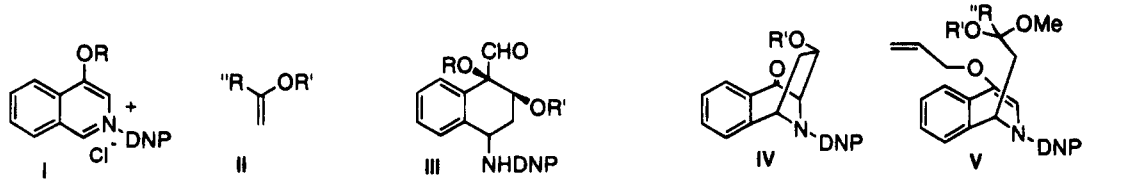
The appearance at 8.88 ppm of a broad doublet for the NH proton proved to be quite diagnostic in the characterization of the amino aldehydes synthesized in this study. By comparison, the NH resonance is conspicuously absent in the structures assigned to the one-bond V and 1,3 products IV. Inspection of the coupling constants in the tetralin allowed us to assign the relative stereochemistry of the four groups on the cyclohexene ring. The doublet of doublets at 4.09 ppm corresponding to H3 exhibits two small coupling constants (2.1 and 7.6 Hz) to the methylene group protons (H2a and H2e). The magnitude of the "*J*" values points to an equatorial arrangement of H3. The ethoxy group is therefore

(10) The synthesis of the alkoxy isoquinolines as well as their salts is described in the supporting information.

(11) The THP vinyl ether **29** was obtained via the coupling of α-lithio tetrahydropyranyl vinyl ether (D'Angelo, J. *Bull. Soc. Chim. Fr.* **1969**, *1*, 181) with 3-bromo-2-methylpropene.

Table 1. Cycloaddition of 4-Alkoxyisoquinolinium Salts



a. R=CO_2Et: **9**	R'=Et, R"=H: **12**	R=H, R'=Et: **17** (44%)	R'=Et: **23** (21%)	----------
b. **9**	R'=TBDMS, R"=H: **13**	----------	----------	----------
c. R=Ac: **10**	**12**	----------	**23** (24%)	----------
d. R=Allyl: **11**	**12**	R=Allyl, R'=Et: **19** (18%)	**23** (11%)	R'=Et, R"=H: **25** (9%)
e. **11**	R'=MOM, R"=H: **14**	R=Allyl, R'=MOM:**20** (47%)	----------	----------
f. **11**	R'=THP, R"=H: **15**	R=Allyl, R'=THP: **21** (51%)	----------	----------
g* **11**	**13**	R=Allyl, R'=TBDMS: **22** (95%)	R'=TBDMS:**24****	----------
h. **11**	R'=R"= Me: **16**	----------	----------	R'=R"=Me : **26** (95%)***
i. **11**	(see scheme 3)			

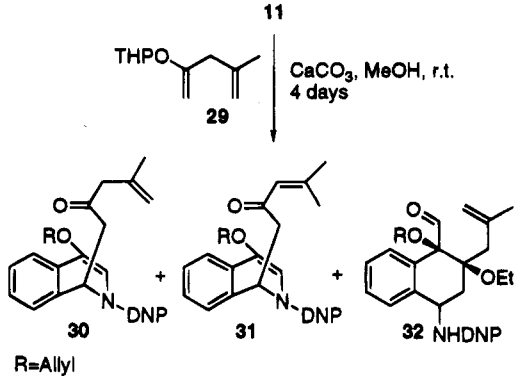
Reactions were worked up by filtration, evaporation of the solvent and chromatography over silica gel.

* Standard work up but the crude rather than exposed to chromatography was treated with TsOH/H_2O/THF.

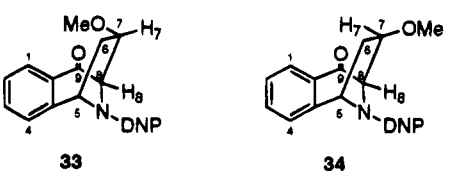
** Observed only when the standard work up was applied.

*** Crude yield.

Scheme 3. Entry i of Table 1

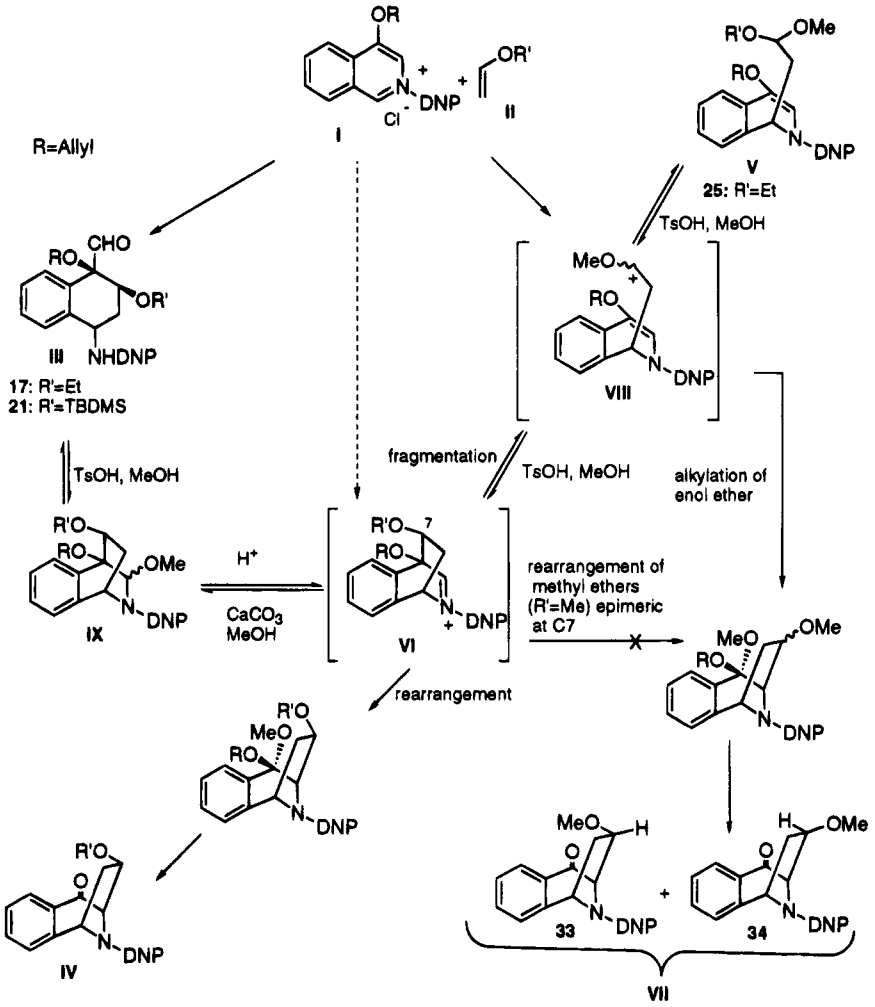


assigned to the axial position. The benzylic proton, H1, which appears as a doublet of doublets exhibits a large coupling constant (12.9 Hz) indicative of an axial−axial interaction. The assignment of an equatorial orientation to the amino group follows logically from the axial orientation of the benzylic proton. A consideration of the mechanism of the Bradsher cycloaddition shows that the aldehyde and amino groups arise from the cleavage of the C−N bond in an intermediate iminium species VI (Scheme 4) so that the two groups per force are cis. On the basis, therefore, of the axial orientation of the benzylic proton H1, the aldehyde group was assigned an axial orientation. The hydroxyl group at C4 must therefore be equatorial and is cis to the axially orientated ethoxy group at C-3. This result demonstrates that the cis introduction of the alkoxy functionalities by the carbon−carbon bond forming Bradsher reaction validates the basic tenet of our approach to the angucyclines. The diastereotopic methylene protons, H2a and H2e, were distinguished on the basis of their chemical shifts. The more shielded resonance was assigned to the axial proton. This distinction was further supported by the two small coupling constants (5.1 and 7.5 Hz) exhibited by the downfield signal. The chemical shifts and coupling constants arguments that led to the structural and stereochemical characterization of the hydroxy product proved to be remarkably consistent in the tetralin series synthesized in this study. In addition to the ^{1}H NMR data, the infrared spectral analysis was unequivocal in determining the presence and absence of the NH stretching frequency. The band at 3300 cm^{-1} which appears in the spectra of the 1,4-adducts was absent in the spectra of the 1,3-adducts. The 1,4-adducts displayed an aldehyde band at 1730 cm^{-1}. On the other hand, the carbonyl of the 1,3-adducts appears at 1700 cm^{-1}, as would be expected for conjugated ketones. The assignment of configuration of **23** and all the 1,3-adducts in this series was aided by the availability of both **33** and **34** from a different series of experiments to be described below. Thus H7 in the NMR spectrum of **33** appears at 4.63 ppm whereas the corresponding H7 resonance of isomer **34** is shifted upfield, appearing at 4.08 ppm.



The upfield shift is indicative of a stereochemical arrangement which positions H7 in the shielding cone of the carbonyl. Therefore we assign the methoxy 1,3 adduct *endo*-7-methoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**33**) with the methoxy group oriented toward the phenyl ring and in an anti arrangement with the C8−N bond. The stereochemical assignment was confirmed by comparing the coupling constants obtained by molecular mechanics

Scheme 4. Mechanism of the Bradsher Reaction of 4-Alkoxyisoquinolinium Salts



calculations on the two structures with the experimentally derived values. Of particular significance is the coupling constant between H7 and H8. The experimentally observed value is 11.7 Hz for the endo isomer **33** with a calculated value of 8.1 Hz. On the other hand the corresponding values in the exo **34** series are 0.0 Hz (experimental) and 1.5 Hz (calculated). The relative trend corroborates the stereochemical arrangement which was assigned on the basis of the chemical shift of H7 in the two series.

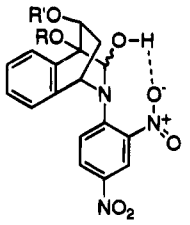
One-bond product **25** was identified by the presence of a vinyl singlet at 5.1 ppm. The presence of the dihydroisoquinoline ring was ascertained by the absence of an NH resonance as well as a characteristic upfield shift of the H2 proton of the 2,4-dinitrophenyl group. This upfield shift is also observed in the 1,3 adduct and is evidence that no C–N bond breaking has taken place. Furthermore, in the one-bond product, the diastereotopic protons α to the acetal carbon appear at nearly the same chemical shift. This is indicative of free rotation about the C–C bond since the chemical shift difference between the two protons is significant when they are constrained into the 1,4 or 1,3 rings.

Reversals and Rearrangements. Scheme 4 summarizes the range of interconversions that were observed upon treatment of type III materials, (exemplified by compounds **17** and **21**) and type V adducts (exemplified by **25**) with acid.

We assume that acid catalyzes cyclization of type III and type V structures to the intermediate iminium ion type VI which is the pivotal intermediate leading to the desired tetralin materials in the Bradsher cycloaddition. To be discussed are two factors which influence the partition of ion VI to the array of products observed: (i) the solvent, and (ii) the R'O vinyl ether dienophile. There is a third factor, the RO group on the isoquinoline heterodiene which could be influential, but our conditions of $CaCO_3$–MeOH slowly cleave the acetate and carbonate groups of entries a–c in Table 1. Thus we cannot be certain to what extent the type IV product stems from rearrangement of type VI or from a dipolar cycloaddition of a betaine as reported earlier by Katritzky.[12] We also assume that a fourth factor, the quaternizing group on the nitrogen would be influential, but this has not been varied in our work. The effect of solvent is quite striking. Thus, exposure of any material (with the exception of the 1,3-adducts which remain unaffected under the conditions) in the manifold to aqueous acid conditions leads to aldehyde type III, whereas when anhydrous methanol or trimethyl orthoformate are the solvents, we obtain fragmentation products type VII and rearrangement product type IV. It should be noted that the stereoisomeric rearrangement products type VII (**33** and **34**) are not the results of the direct rearrangement of a cycloadduct of type VI, but are only observed when a type V

(12) (a) Dennis, N.; Katritzky, A. R.; Parton, S. K. *Chem. Pharm. Bull.* **1975**, *23*, 2899. This paper describes the chemistry of the 2,4-dinitrophenyl betaine. (b) Dennis, N.; Katritzky, A. R.; Takeuchi, Y. *J. Chem. Soc., Perkin 1* **1972**, 2054. This paper describes the chemistry of the *N*-methyl betaine.

acetal (directly subjected to the reaction conditions or generated in situ from an aldehyde of type III) is equilibrated with MeOH. One option for the equilibrated acetal is to recyclize to a pair of stereoisomeric iminium salts (OMe C7 epimers of type VI), which then rearrange to type VII. A second option allows the equilibrated acetal to alkylate its enolic double bond to form a type VII adduct directly from an intermediate of type VIII. We account for the solvent effect by examining the two different solvent adducts of the type VI iminium salt, namely tricyclic derivatives **35** and **36**.



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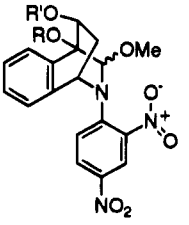

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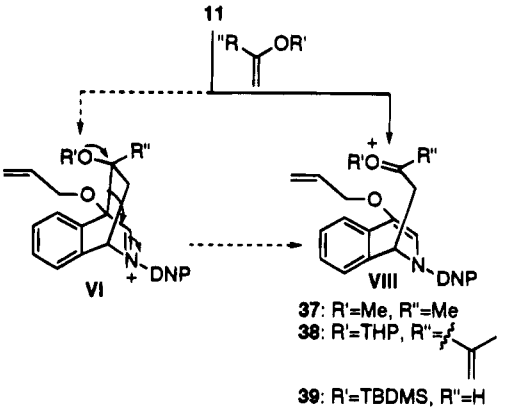
The water adduct **35** can form a hydrogen bond with the *o*-nitro group which will facilitate proton transfer and ring opening to the observed aldehyde. On the other hand, in methanol the nitro group can only crowd the methyl ether of the adduct **36** and lead to a facile elimination to the iminium species which then undergoes a semipinacolic rearrangement to the type IV series and/or fragmentation to the type VII species. The effect of the ether dienophile blocking group is evident in the ethyl case which is associated with the highest yields of 1-bond and 1,3-adducts. The product distribution may be explained by the greater electron-donating ability of the ethyl group which induces rearrangement and fragmentation of the iminium salt type VI much faster than in the cases where the ether is THP, MOM, or TBDMS. An alternative explanation for the observed product ratio invokes the increased stability of the intermediate oxonium ion in the ethyl case. The demonstration of the existence in the 4-alkoxyisoquinolinium series of a reversal pathway for III to VI and then to V via VIII for the Bradsher cycloaddition manifold leads to interesting retrospective considerations on the general two-step mechanism proposed earlier.[13] Thus, the earlier hypothesis stated that an intermediate of type VIII must be the initial reaction product of an isoquinolinium salt I and a vinyl ether II. It was postulated that ion VIII was then captured by two competing pathways, cycloadduct formation (type III) or acetal formation (type V). Our results are consistent with the two-step mechanism since we now demonstrate unequivocally that a "cycloadduct" species, VI, can fragment to VIII. This fragmentation step is the microscopic reversal of the postulated second step of the two-step forward reaction.

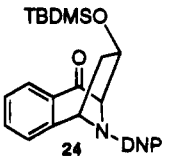
The cycloaddition of branched vinyl ethers results mainly in the isolation of one-bond products (Table 1: entries h and i). The cycloaddition proceeds (Scheme 5), in a stepwise fashion through the intermediacy of a one-bond oxonium ion of type VIII. The alternative concerted pathway involves a less stable tricyclic iminium ion of type VI. Such an imminium ion if generated would rapidly fragment to VIII since this process leads to more stable carbocations (**37** and **38**) than observed in the fragmentation of adducts of unsubstituted vinyl ethers which leads to cations such as **39**.

(13) Gupta, R. B.; Franck, R. W. J. *Am. Chem. Soc.* **1987**, *109*, 5393.

Scheme 5. Cycloaddition of Branched Vinyl Ethers



Synthesis of a Model of the BC Rings of Sakyomicin A. The sequence (Scheme 6) begins with aldehyde **22** described above. In the most difficult step of the scheme, the aldehyde was protected as its dimethyl acetal **40**, obtained in yields of 25–33% by treatment with *p*-toluenesulfonic acid in trimethyl orthoformate. The low yields are due to the competing retro-Bradsher process described above. The 1,3-adduct **24** and its associated ketal **41** arising from such a reversal were isolated in 10 and 46% yields, respectively. On standing, ketal **41** slowly converts to ketone **24**.



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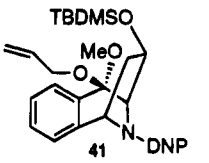

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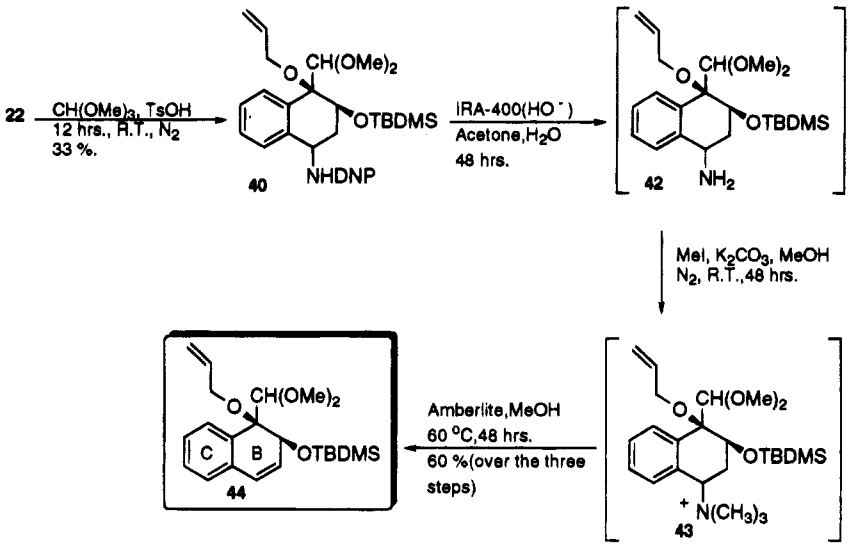
The disappearance of the aldehyde peak and the presence of the singlet resonance for the acetal proton provided evidence for the formation of dimethyl acetal **40**.

The 2,4-dinitrophenyl group was removed by treatment of the acetal with amberlite resin in moist acetone to yield benzylic amine **42**. In an attempt to avoid what was assumed to be products of acetone self-condensation, the reaction was carried out in methylene chloride, but only starting material could be detected by TLC after prolonged stirring under these conditions. The amine obtained could not be purified by chromatography over silica gel as it decomposed during the process. Therefore the crude amino acetal **42**, which displays no 2,4-dinitrophenyl protons in its ^{1}H NMR spectrum, was exhaustively methylated (methyl iodide, K_2CO_3, methanol, room temperature, 48 h), and the resulting ammonium salt **43** was deaminated (Amberlite, MeOH, 3 days) to generate alkene **44** in 60% yield over the three steps. The elimination product was easily identified by the presence of the vinylic protons in the ^{1}H NMR spectrum. This simple sequence (six steps from a 4-alkoxyisoquinoline) is the first construction of the 1-acyl-*cis*-1,2-dialkoxy-1,2- dihydronaphthalene framework of the sakyomicin family.[14]

(14) The parent *cis*-1,2-dihydroxy-1,2-dihydronaphthalene has been synthesized via fermentation of napthalene with *P. putida*: Allen, C. C. R.; Boyd, D. R.; Dalton, H.;Sharma, N. D.; Ranagan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1995**, 117–118 and references therein.

Scheme 6. Synthesis of the BC Ring Model of the Angucyclines



Experimental Section

NMR spectra were recorded on a GE QE 300 (300 MHz) instrument with $CDCl_3$ or CD_3OD as solvent. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotomer. High resolution mass spectra were obtained from the Pennsylvania State University Mass Spectrometry Facility. Thin-layer chromatography was done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and short/long-wave ultraviolet light was used to visualize the spots. Chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merk). Solvents were purified and dried by using standard procedures. All experiments were done under an inert atmosphere of nitrogen or argon.

Cycloaddition of Ethyl Vinyl Ether (12) to 2-(2,4-Dinitrophenyl)-4-acetoxyisoquinolinium Chloride (10). Synthesis of 23. Ethyl vinyl ether (1 mL, 10.5 mmol) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-acetoxyisoquinolinium chloride (50 mg, 0.1 mmol, 1 equiv) and $CaCO_3$ (51 mg, 0.5 mmol, 5 equiv) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 4 days. The crude reaction mixture was filtered over Celite using methylene chloride to give a reddish material following the removal of the solvent *in vacuo*. The crude material was purified by radial chromatography to give the 1,3 adduct *endo*-7-ethoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**23**) as the only characterizable product in 24% yield (12 mg). ^1H NMR, IR, and HRMS have been reported.[15] ^{13}CMR (75 MHz, $CDCl_3$) δ 192.5, 144.9, 144.1, 139.6, 138.4, 134.8, 129.8, 128.6, 128.3, 127.3, 125.1, 123.0, 119.8, 76.9, 71.0, 66.6, 62.2, 39.1, 14.8.

Cycloaddition of Ethyl Vinyl Ether (12) to 2-(2,4-Dinitrophenyl)-4-(ethoxycarbonyl)isoquinolinium Chloride (9). Synthesis of 17. Ethyl vinyl ether (82 μL, 0.9 mmol, 4 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyl)isoquinolinium chloride (90 mg, 0.2 mmol, 1 equiv) and $CaCO_3$ (86 mg, 4 equiv) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The reaction mixture was filtered over Celite, using methylene chloride. A reddish material (124.9 mg) was obtained following the removal of the solvent *in vacuo*. The crude product was subjected to radial chromatography (2 mm chromatotron plate. The sample was loaded with CH_2Cl_2 and eluted with 10% EtOAc/petroleum ether). The first fraction consisted of 50.4 mg (66% yield) of the 1,3 adduct endo-7-ethoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**23**). The second band (17.2 mg) was identified as hydroxy aldehyde **17** (19% yield). **17**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 9.19 (d, J = 2.6 Hz, 1H, 2,4-DNP), 8.83 (broad d, J = 7.8 Hz, 1H, NH), 8.33 (dd, J = 2.4 Hz, J = 9.5 Hz, 2,4-DNP), 7.43–7.31 (m, 4H, phenyl), 7.08 (d, J = 9.5 Hz, 1H, 2,4-DNP), 5.19 (dd, J = 7.6 Hz, J = 12.9 Hz, 1H, C*H*NHAr), 4.04 (dd, J = 2.12 Hz, J = 7.6 Hz, 1H, C*H*OEt), 3.79–3.72 (m, 1H, OCH_2Me), 3.60–3.53 (m, 1H, OCH_2Me), 2.59 (ddd, J = 5.1 Hz, J = 7.5 Hz, J = 13.4 Hz, 1H), 2.59 (m,1H),1.57 (broad s, 1H, OH), 1.23 (t, 3H, Me). ^{13}CMR (75 MHz, $CDCl_3$) δ 199.1, 147.5, 136.7, 135.1, 134.3, 131.0, 130.6, 129.7, 129.5, 127.6, 124.9, 124.5, 114.0, 78.2, 73.8, 66.0, 49.6, 29.7, 15.4. LRMS calcd for $C_{19}H_{19}N_3O_7$ 401.01, found M − 29 (−CHO) 372.25, M − 74 (OEt + CHO) 327.10.

Cycloaddition of Ethyl Vinyl Ether (12) to 2-(2,4-Dinitrophenyl)-4-(allyloxy)isoquinolinium Chloride (11). Synthesis of 19 and 25. Ethyl vinyl ether (37.2 mg, 49 μL, 0.5 mmol, 4 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy) isoquinolinium chloride (**11**) (50 mg, 0.13 mmol, 1 equiv) and $CaCO_3$ (52 mg, 0.5 mmol, 4 equiv) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude reaction mixture was filtered over Celite using methylene chloride to give a reddish material (69.8 mg) following the removal of the solvent *in vacuo*. A portion of the crude product (32 mg) was subjected to radial chromatography (1 mm chromatotron plate; eluent: 25% CH_2Cl_2/petroleum ether). The isolated fractions required further purification. The expected aldehyde **19** was isolated in a combined yield of 40%. The 1,3 adduct *endo*-7-ethoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**23**) and the one-bond product **25** were obtained in 24% and 19% yields, respectively. The yields are adjusted for the total weight of the crude reaction mixture. **19**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H, CHO), 9.21 (d, J = 2.6 Hz,1H, 2,4-DNP), 8.83 (d, J = 8.5 Hz, 1H, NHDNP), 8.31 (dd, J = 9.5 Hz, J = 2.6 Hz, 1H, 2,4-DNP), 7.63 (d, J = 7.6 Hz, 1H, phenyl), 7.63 (d, J = 7.6 Hz, 1H, phenyl), 7.47–7.31 (m,2H, phenyl), 7.02 (d, J = 9.6 Hz, 1H, 2,4-DNP), 6.05–5.92 (m, 1H, internal vinyl), 5.36 (dd, J = 17.2 Hz, J = 1.5 Hz, 1H, trans terminal vinyl), 5.22 (dd, J = 10.52 Hz, J = 1.4 Hz, 1H, cis terminal vinyl), 5.32–5.27 (ddd, overlapping the cis terminal vinyl proton, 1H, C*H*NHAr), 4.29 (dd, J = 6.1 Hz, J = 2.1 Hz, 1H, CHOEt), 4.17–4.14 (ddd, 2H, allylic methylene), 3.84–3.74 (m, 1H, OCH_2Me), 3.65–3.55 (m, 1H, OCH_2Me), 2.68 (dt, J = 4.5 Hz, J = 10.4 Hz, 1H), 2.29 (ddd, J = 2.1 Hz, J = 10.0 Hz, J = 13.8 Hz, 1H). ^{13}CMR (75 MHz, $CDCl_3$) δ 198.7, 147.9, 136.9, 134.6 (two peaks), 131.8, 131.0, 130.6, 129.6, 129.5, 129.0, 126.8, 124.6, 116.8, 113.9, 82.5, 74.3, 66.6, 65.8, 49.0, 31.7, 15.4. IR (CCl_4): 3340, 3100, 2960, 2920, 1730, 1600, 1580, 1420, 1330, 1250 cm^{-1}.

25: ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 2.6 Hz, 1H, 2,4-DNP), 8.30 (dd, J = 2.7 Hz, J = 9.5 Hz, 1H, 2,4-DNP), 7.66 (J = 1.1 Hz, J = 7.7 Hz, 1H, phenyl), 7.60 (d, J = 9.6 Hz, 1H, 2,4-DNP), 7.37 (dt, J = 1.1 Hz, J = 7.7 Hz, 1H, phenyl), 7.30 (dt, J = 1.4 Hz, J = 7.7 Hz, 1H, phenyl), 7.04 (d, J = 7.6

(15) Reference 13.

Hz, 1H, Phenyl), 6.14–6.01 (m, 1H, internal vinyl), 5.46 (dd, J = 1.4 Hz, J = 17 Hz, trans terminal vinyl), 5.33 (dd, J = 1.3 Hz, J = 10.6 Hz, 1H, cis terminal vinyl), 5.17 (t, 1H), 5.11 (s, J = 1.0 Hz, 1H), 4.45–4.30 (m: AB quartet + dd, 3H), 3.80–3.72 (m.1H, CH_2Me), 3.59–3.48 (m, 1H, CH_2Me), 3.29 (s, 3H,-OMe), 2.26–2.15 (m, 2H), 1.32 (t, J = 7 Hz, 3H, Me). HRMS calcd for $C_{23}H_{25}N_3O_7$ 455.1662, found 455.1703.

Cycloaddition of *tert*-Butyldimethylsilyl Vinyl Ether (13) to 2-(2,4-Dinitrophenyl)-4-(allyloxy)isoquinolinium Chloride (11). Synthesis of 22. *tert*-Butyldimethylsilyl vinyl ether (122.3 mg, 155 μL, 0.77 mmol, 4 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy)isoquinolinium chloride (**11**) (75 mg, 0.19 mmol, 1 equiv) and $CaCO_3$ (77.4 mg, 0.77 mmol, 4 equiv) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The reaction mixture was filtered over Celite, using methylene chloride, to give a reddish material upon evaporation of the solvent under reduced pressure. The crude material was dissolved in 4 mL of THF/H_2O (1:1) and, following the addition of 5 mg of TsOH, was stirred at room temperature for two days. The crude mixture was diluted with EtOAc and washed with a saturated sodium bicarbonate solution. The combined EtOAc extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Upon drying *in vacuo*, 100 mg (quantitative yield) of pure aldehyde **22** (purity ascertained by ^{1}H NMR) was obtained. **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H, CHO), 9.21 (d, J = 2.7 Hz, 1H, 2,4-DNP), 8.78 (d, J = 8.3 Hz, 1H, NH), 8.32 (dd, J = 9.5 Hz, J = 2.6 Hz, 1H, 2,4-DNP), 7.52–7.26 (m, 4H, phenyl), 7.06 (d, J = 9.6 Hz, 1H, 2,4-DNP), 6.00–5.91 (m, 1H, internal vinyl), 5.30 (dd, J = 17.3 Hz, J = 1.6 Hz, 1H, trans terminal vinyl), 5.20 (dd, J = 10.5 Hz, J = 1.5 Hz, 1H, cis terminal vinyl), 5.32 (ddd overlapping the resonance of the trans vinyl proton, 1H, C*H*NHAr), 4.67 (dd, J = 7.3 Hz, J = 2.6 Hz, 1H, C*H*OTBDMS), 4.16 (d, J = 5.2 Hz, 2H, alylic CH_2), 2.54 (ddd, J = 5.3 Hz, J = 7.3 Hz, J = 13.6 Hz, 1H), 2.29 (ddd, J = 2.7 Hz, J = 8.4 Hz, J = 13.6 Hz, 1H), 0.89 (s, 9H, *tert*-butyl), 0.11 (s,6H, $SiMe_2$). ^{13}CMR (75 MHz, $CDCl_3$) δ 199.98, 147.68, 136.41, 134.72, 131.94, 130.75, 130.64, 130.53, 129.67, 128.89, 127.49, 124.66, 124.44, 116.46, 113.86, 83.24, 68.72, 66.78, 49.40, 35.07, 25.79, 18.01. IR (CCl_4): 3330, 3110, 2930, 2830, 1730, 1620, 1590, 1510, 1430 cm^{-1}, 1340, 1030 cm^{-1}. HRMS calcd for $C_{26}H_{33}N_3O_7Si$ 527.2089, found M − 29 (−CHO) 498.2038.

Cycloaddition of Methoxymethyl Vinyl ether (14) to 2-(2,4-Dinitrophenyl)-4-(allyloxy)isoquinolinium Chloride (11). Methoxymethyl vinyl ether (113 mg, 1.28 mmol, 8.5 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy)isoquinolinium chloride (59 mg, 0.15 mmol, 1 equiv) and $CaCO_3$ (128 mg, 1.28 mmol, 8.5 equiv) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude reaction mixture was filtered over Celite using methylene chloride to give a reddish material which was subjected to radial chromatography (2 mm silica gel chromatotron plate; the crude product was loaded using acetone and eluted with a 35–100% CH_2Cl_2/petroleum ether mixture). The fastest moving band, eluting with 80% CH_2Cl_2/petroleum ether, was identified as a mixture of one-bond products (8.5 mg). The desired aldehyde **20** (32 mg) was eluted off the plate with pure CH_2Cl_2 in 47% yields. **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H, CHO), 9.19 (d, J = 2.7 Hz, 1H, 2,4-DNP), 8.81 (d, J = 8.3 Hz, 1H, NHAr), 8.31 (dd, J = 9.5 Hz, J = 2.6 Hz, 1H, 2,4-DNP), 7.65 (d, J = 7.3 Hz, 1H, phenyl), 7.51–7.36 (m, 3H, phenyl), 7.13 (d, J = 9.6 Hz, 1H, 2,4-DNP), 6.02–5.91 (m, 1H, internal vinyl), 5.35 (dd, J = 17.2 Hz, J = 1.6 Hz, trans terminal vinyl), 5.22 (dd, J = 10.5 Hz, J = 1.4 Hz, 1H, cis terminal vinyl), 5.35–5.29 (ddd, overlapping the trans vinyl resonance, 1H), 4.83 (AB quartet, J = 6.9 Hz, 2H, acetal), 4.56 (dd, J = 6.3 Hz, J = 2.2 Hz, 1H, CH-OMOM), 4.14 (ddt, J = 1.4 Hz, J = 5.3 Hz, J = 12.3 Hz, 2H, allylic CH_2), 3.45 (s, 3H, OCH_3), 2.80 (dt, J = 6.1 Hz, J = 13.9 Hz, 1H), 2.29 (ddd, J = 2.3 Hz, J = 9.7 Hz, J = 13.8 Hz, 1H).

Cycloaddition of Tetrahydropyranyl Vinyl Ether (15) to 2-(2,4-Dinitrophenyl)-4-(Allyloxy)isoquinolinium Chloride (11). Synthesis of 21. Tetrahydropyranyl vinyl ether (**15**) (21.5 mg, 0.17 mmol, 1 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy)-isoquinolinium chloride (**11**) (65 mg, 1 mmol, 1 equiv) and $CaCO_3$ (61 mg, 0.34 mmol, 2 equiv) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude reaction mixture was diluted with ethyl acetate and filtered over Celite to give a reddish material (224 mg) upon removal of the solvent under reduced pressure. The resulting mixture was subjected to radial chromatography (1 mm silica gel chromatotron plate). Elution with a 10% EtOAc/petroleum ether mixture resulted in the isolation of aldehyde **21** (42.5 mg) in 51% yield. ^{1}H NMR (300 MHz, $CDCl_3$), δ 9.56 (s, 1H, CHO), 9.19 (d, J = 2.7 Hz, 1H, 2,4-DNP), 8.82 (d, J = 8.5 Hz, 1H, NH), 8.27 (dd, J = 2.7 Hz, J = 9.6 Hz, 1H, 2,4-DNP), 7.69 (d, J = 7.2 Hz, 1H, Phenyl), 7.53–7.41 (m, 3H, phenyl), 7.37 (d, J = 9.7 Hz, 1H, 2,4-DNP), 6.04–5.91 (m, 1H, internal vinyl), 5.44 (m, 1H, C*H*NHAr), 5.41 (dd, J = 1.6 Hz, J = 17.2 Hz, 1H, trans terminal vinyl), 5.23 (dd, J = 1.3 Hz, J = 10.4 Hz, 1H, cis terminal vinyl), 4. 69 (d, J = 6.7 Hz, 1H), 4.57 (d, J = 5.2 Hz, 1H, CHOTHP), 4.12 (d, J = 5.3 Hz, 2H), 4.06–4.02 (m, 2H), 3.64–3.57 (m, 2H), 2.93 (dt, J = 5.3 Hz, J = 13.7 Hz, 1H), 2.14 (t, 1H, J = 13.1 Hz), 1.88–1.58 (m 4H). ^{13}CMR (75 MHz, $CDCl_3$) δ 197.5, 148.1, 137.6, 136.4, 134.4, 131.6. 130.8, 130.4, 129.6, 129.4, 128.8, 126.4, 124.4, 116.8, 114.7, 103.5, 82.2, 75.0, 66.3, 65.5, 49.0, 32.2, 31.8, 25.2, 21.4. IR (CCl_4): 3330, 3110, 2930, 2830, 1730, 1620, 1590, 1510, 1430, 1340, 1030 cm^{-1}. LRMS calcd for $C_{25}H_{27}N_3O_8$ 497.18, found M − 29 (−CHO) 468.25.

Cycloaddition 2-(Tetrahydropyranyloxy)-4-methyl-1,4-pentadiene (29) to 2-(2,4-Dinitrophenyl)-4-(allyloxy)-isoquinolinium Chloride (11). Synthesis of 30, 31, and 32. 2-(Tetrahydropyranyloxy)-4-methyl-1,4-pentadiene (**29**) (47.3 mg, 0.26 mmol, 2 equiv) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy)isoquinolinium chloride (**11**) (50 mg, 0.13 mmol, 1 equiv) and $CaCO_3$ (52 mg, 0.5 mmol, 4 equiv) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude reaction mixture was filtered over Celite (using methylene chloride). The material obtained upon removal of the solvent under reduced pressure was subjected to radial chromatography. One fraction, which was a mixture of products, clearly displayed the signals (CHO, NH-DNP) expected from aldehyde **32**. The amount of the aldehyde was estimated at ca. 7% yield. One-bond ketone **30** and enone **31** were isolated in 25% and 10% yield, respectively. **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 1H, DNP), 8.30 (dd, 1H, DNP), 7.55 (d, 1H, Ph), 7.35 (t, 1H, Ph), 7.26 (t, 1H, Ph), 6.90 (d, 1H, DNP), 6.20–6.00 (m, 1H, allyl internal vinyl), 5.60 (s, 1H, vinylic α-proton), 5.49 (dd, 1H, allyl trans vinyl), 5.35 (dd, 1H, allyl cis vinyl), 5.25 (s, 1H, ring vinyl), 4.97 (dd,1H, ArC*H*NDNP), 4.42 (d, AB quartet, allyl CH_2), 2.57 (m, 2H, α-CH_2) 2.19 (s, 3H, Me), 2.01 (s,3H, Me).

Cycloaddition 2-Methoxypropene (16) to 2-(2,4-Dinitrophenyl)-4-(allyloxy)isoquinolinium Chloride (11). Synthesis of 26. 2-Methoxypropene (**16**) (0.4 mL) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(allyloxy)isoquinolinium chloride (**11**) (20 mg, 0.05 mmol, 1 equiv) and $CaCO_3$ (21 mg, 0.2 mmol, 4 equiv) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude reaction mixture was diluted with methylene chloride and filtered over Celite. Upon the removal of the solvent under reduced pressure a reddish material (20 mg) which was identified as one-bond product **26** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, 1H, DNP), 8.31 (dd, 1H, DNP), 7.80 (d, 1H, Ph), 7.69 (d, 1H, Ph), 7.50–7.30 (m, 2H, Ph), 7.21 (d, 1H, DNP), 6.20–6.10 (m, 1H, allyl internal vinyl), 5.50 (dd, 1H, allyl trans vinyl), 5.39 (dd, 1H, allyl cis vinyl), 5.29 (t, 1H, AcC*H*CH_2N), 5.19 (s, 1H, ring vinyl), 4.45 (d, AB quartet, allyl CH_2), 3.29 (s, 6H, OMe_2), 1.25 (s, 3H, Me).

Synthesis of the Dimethyl Acetal (40) of Silyloxy Aldehyde 22. Silyloxy aldehyde **22** (140 mg, 0.3 mmol) was dissolved in 3 mL of trimethyl orthoformate. Following the addition of 5 mg of TsOH (0.03 mmol) the mixture was stirred at room temperature for 5 min at which point the initially yellow reaction mixture became red. The reaction was stopped after 15 min as TLC analysis (6:1 petroleum ether/ethyl acetate) revealed the disappearance of the starting material.

The reaction crude was diluted with EtOAc and washed with a saturated sodium bicarbonate solution. The organic extract was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by radial chromatography (2 mm silica gel chromatotron plate; the compound was loaded using methylene chloride and eluted with a 5% ethyl acetate/petroleum ether mixture). The mixed ketal **41** of the 1,3 adduct, *endo*-7-(*tert*-butyldimethylsilyloxy)-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-(allyloxy)-9-methoxy-5*H*-benzocyclohepten-5,8-imine (66.4 mg, 46% yield) eluted first followed by the dimethyl acetal **40** (56 mg, 33% yield). The 1,3 adduct *endo*-7-(*tert*-butyldimethylsilyloxy)-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**24**) which was eluted using a 10% ethyl acetate/petroleum ether mixture was obtained in 10% yields (12 mg). **24**: ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.62 (d, J = 2.6 Hz, 1H, 2,4-DNP), 8.13 (dd, J = 2.6 Hz, J = 9.2 Hz, 1H, 2,4-DNP), 7.95 (d, J = 7.8 Hz, 1H, phenyl), 7.53 (dt, J = 0.9 Hz, J = 7.4 Hz, 1H, phenyl), 7.38 (t, J = 7.6 Hz, 1H, phenyl), 6.95 (d, J = 9.2 Hz, 1H, 2,4-DNP), 5.06 (ddd, J = 1.9 Hz,1H), 4.80 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 7.3 Hz,1H), 3.01 (ddd, J = 6.9 Hz, J = 8.6 Hz, J = 13.0 Hz, 1H), 1.83 (dd, J = 1.9 Hz, J = 12.8 Hz, 1H), 0.73 (s, 9H, *tert*-butyl), 0.08 (s, 3H, Me), 0.03 (s, 3H, Me).^{13}CMR (75 MHz, $CDCl_3$) δ 192.5, 144.7,144.1, 139.6, 138.4, 134.6, 130.3, 128.5, 128.4, 127.1, 124.0, 123.1, 119.9, 72.3, 70.3, 62.8, 41.9, 25.5, 17.8, −5.08, −5.1. LRMS calcd for $C_{23}H_{27}N_3O_6Si$ 469.17 found M − 57 (− *tert*-butyl) 411.85, M − 282 (− TBDMS and 2,4-DNP) 187.00.

40: ^{1}H NMR (300 MHz, CDCl3) δ 9.18 (d, J = 2.7 Hz, 1H, DNP), 8.78 (broad d, J = 8.2 Hz, 1H, NH-DNP), 8.28 (dd, J = 2.6 Hz, J = 9.6 Hz, 1H, DNP), 7.65 (d, J = 7.8 Hz, 1H, phenyl), 7.39 (t, J = 1.5 Hz, J = 7.5 Hz, 1H, phenyl), 7.30 (t, J = 1.3 Hz, J = 7.6 Hz, 1H, phenyl), 7.25 (d, J = 7.5 Hz, 1H, phenyl), 7.10 (d, J = 9.6 Hz, 1H, DNP), 5.92−5.81 (m, 1H, internal vinyl), 5.25 (dd, J = 1.8 Hz, J = 17.3 Hz, 1H, trans terminal vinyl), 5.21−5.12 (m, 1H, C*H*NHAr), 5.09 (dd, J = 1.8 Hz, J = 10.5 Hz, 1H, cis terminal vinyl), 4.71 (dd, J = 3.1 Hz, J = 8.2 Hz, 1H, CHOTBDMS), 4.38 (s, 1H, MeOCHOMe), 3.99 (dq, J = 5.0 Hz, J = 12.9 Hz, 2H, OCH_2-vinyl), 3.59 (s, 3H, MeO), 3.25 (s, 3H, MeO), 2.49 (ddd, J = 3.4 Hz, J = 7.4 Hz, J = 13.4 Hz, 1H), 2.15 (septet, J = 4.7 Hz, J = 8.3 Hz, J = 13 Hz, 1H), 0.90 (s, 9H, *tert*-butyl), 0.14 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$). ^{13} CMR (75 MHz, $CDCl_3$) δ 147.6, 136.8, 136.1, 136.0, 130.8, 130.2, 128.5, 128.3, 128.1, 127.0, 124.6, 114.7, 113.9, 111.9, 81.0, 68.0, 66.3, 58.1, 50.6, 36.2, 25.9, 18.1, −4.4, −4.7. HRMS calcd for $C_{28}H_{39}N_3O_8Si$ 573.2508, found M − 57 (− *tert*-butyl) 516.1816.

Synthesis of the BC Ring Model (44). The dimethyl acetal **40** (30 mg, 0.05 mmol) was dissolved in 9 mL of an acetone/water mixture (8:1), and 485 mg of Amberlite basic resin was suspended in the solution. The mixture was stirred at room temperature under nitrogen for 3 days. The disappearance of the starting material was followed by TLC (silica gel; 8:1 ethyl acetate/petroleum ether). The reaction mixture was filtered over a Celite pad, and the acetone was removed under reduced pressure. The residue was taken into ethyl acetate, washed with water and brine solution, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the viscous residue was placed *in vacuo* while heating (45 °C) with a water bath. The crude[16] amine acetal **42** (32.5 mg) was treated with 1 mL of methyl iodide and 150 mg of potassium carbonate in 1 mL of methanol. The mixture was stirred under nitrogen at room temperature for 2 days. The reaction was monitored by TLC (silica gel/ethyl acetate). The disappearance of the starting material on TLC was followed by the 2,4-dinitrophenylhydrazone test. The product does not give a positive test under these conditions but its presence was ascertained by treating the plates with ammonium molybdate. The ammonium salt gives rise to a brown spot which turns to blue upon standing. The reaction mixture was filtered over a Celite pad, and the solvent was removed under reduced pressure. To the crude ammonium salt **43** in 15 mL of MeOH was added 700 mg of Amberlite, and the mixture was refluxed for 48 h. The reaction mixture was filtered over Celite, and the solvent was removed under reduced pressure. Purification by preparative TLC (basic alumina; 4:1 hexane/ethyl acetate) afforded 11.7 mg (60% yields from the acetal **40**) of alkene **44**. **44**:^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 1H, J = 1.6 Hz, H5), 7.29 (m, 2H, H5 and H7), 7.09 (m, 1H), 6.39 (dd, 1H, J = 1.7 Hz, J = 9.8 Hz, H1), 5.99 (dd, 1H, J = 3.2 Hz, J = 9.7 Hz, H2), 5.87 (m, 1H, allyl internal vinyl), 5.24 (ddd, 1H, J = 1.9 Hz, J = 17.3 Hz, J = 3.8 Hz, allyl trans vinyl), 5.05 (ddd, 1H, J = 1.6 Hz, J = 3.5 Hz, J = 10.5 Hz, ally cis vinyl), 4.88 (dd, 1H, J = 1.8 Hz, J = 3.1 Hz, H3), 4.59 (s, 1H, acetal), 4.00 (m, 2H, allyl methylene), 3.57 (s, 3H, OMe), 3.45 (s, 3H, OMe), 0.97 (s, 9H, *tert*-butyl), 0.18 (s, 6H, $SiMe_2$). ^{13}CMR (75 MHz, $CDCl_3$) δ 134.0,131.2, 130.4 (another peak at 133.3 could also be assigned to one of the quaternary aromatic carbons),129.4, 128.0, 127.2, 126.7, 126.3, 114.4, 110.1, 80.6, 69.1, 66.3, 59.1, 57.1, 25.9, 18.1, −4.5, −3.8. HRMS calcd for $C_{22}H_{34}O_4Si$ 390.2227, found 390.2226.

Retro-Bradsher Reaction of the One-Bond Products 25. One-bond mixed acetal **25** (1mg) in 1mL of methanol was treated with 1 mg of TsOH. The mixture was stirred under nitrogen at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue taken into ethyl acetate was washed with water and brime. The ethyl acetate layer was dried over sodium sulfate and concentrated under reduced pressure. The ^{1}H NMR of the crude product revealed a 3:1 mixture of *endo*-7-ethoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**23**) and *endo*-7-methoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**33**). The ratio of *exo*-7-methoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**34**) in the mixture could not be accurately determined from the integration trace.

Bradsher Reversal of the Ethyl Vinyl Ether Adduct 19. To aldehyde **19** (5 mg) in 1 mL of methanol was added 1 mg of TsOH. The mixture was stirred at room temperature for 3 h at which point the complete disappearance of the starting material was ascertained by TLC. The solvent was removed under reduced pressure and the residue taken into ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude product revealed a 4:2:1 mixture of *endo*-7-ethoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**23**), *endo*-7-methoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**33**), and *exo*-7-methoxy-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5*H*-benzocyclohepten-5,8-imine (**34**), respectively. The ratios were determined from integration of the methoxy peaks of **33** and **34** with the methyl peak of **23**.

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Supporting Information Available: Experimental procedures and data for the ethers of 4-hydroxyisoquinoline (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) Attempts to purify the amino acetal **42** by radial chromatography over silica gel resulted in decomposition of the product.