Platinum- and Acid-Catalyzed Enyne Metathesis Reactions: Mechanistic Studies and Applications to the Syntheses of Streptorubin B and Metacycloprodigiosin

Alois Fürstner,* Hauke Szillat, Barbara Gabor,† and Richard Mynott†

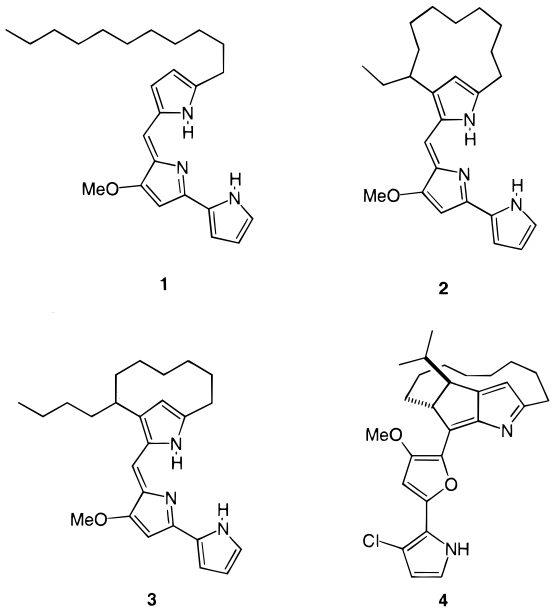
Contribution from the Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany

Received April 8, 1998

Abstract: Formal total syntheses of the antibiotics metacycloprodigiosin (**2**) and streptorubin B (**3**) are described, which are known to exhibit promising immunomodulating properties. The key step en route to their meta-bridged pyrrole core structures **5** and **7**, respectively, consists of a metathesis reaction of electron-deficient enynes catalyzed by either platinum halides, hard Lewis acids, or HBF_4. This transformation expands the pre-existing cycloalkene of the substrates by two C atoms, forges the bicyclic pyrrolophane structure of the targets, and simultaneously forms a bridgehead alkene function. The products of this skeletal rearrangement are converted into the targets by a sequence comprising (i) a stepwise reduction of their enone entity to the corresponding saturated alcohols and (ii) an aromatization of the N-tosylated dihydropyrroles **20** and **34** thus obtained via elimination of potassium sulfinate on exposure to KAPA (potassium 3-aminopropylamide). A careful analysis of the minor byproducts formed in the enyne metathesis reactions allows a mechanistic rationale to be proposed for this operationally trivial yet highly attractive transformation which involves "nonclassical" cyclopropylmethyl−homoallyl−cyclobutyl cations as key intermediates. This cationic pathway is distinctly different from mechanistic interpretations of other enyne metathesis reactions previously reported in the literature.

Introduction

The "prodiginine" antibiotics produced by a restricted group of eubacteria and actinomycetes possess a deeply red colored, characteristic pyrrolylpyrromethene chromophore which is responsible for the fairly unique history related to these natural products.[1] Although numerous reports on the antimicrobial, cytotoxic, and antimalaria activity of these compounds can be found in the literature,[2−4] clinical applications have been prevented by their rather high toxicity. Recently, however, it has been discovered that some members of this series, in particular undecylprodigiosin (**1**), inhibit T-cell proliferation at doses which are not cytotoxic.[5] Compound **1** seems to exert its immunomodulating properties with a mechanism of action which is distinctly different from that of cyclosporin A, FK-



* Corresponding author. E-mail: fuerstner@mpi-muelheim.mpg.de.
† NMR spectroscopy department.

(1) The red appearance of *Serratia marescens* and related bacteria due to the production of prodiginin-type metabolites forms the basis of the miracle of the "bleeding host", which occurred rather frequently during the Middle Ages. For a documentation of these historical aspects, see: Gaughran, E. R. L. *Trans. N. Y. Acad. Sci., Ser. II* **1969**, *31*, 3.

(2) See the following for leading references: (a) Castro, A. J. *Nature* **1967**, *213*, 903. (b) Gerber, N. N. *Crit. Rev. Microbiol*. **1974**, *3*, 469 and references therein.

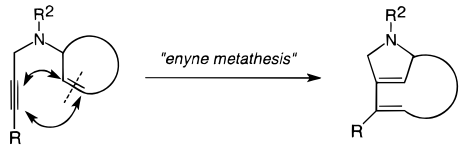
(3) For previous studies on various prodigiosines, see e.g.: (a) Hearn, W. R.; Elson, M. K.; Williams, R. H.; Medina-Castro, J. *J. Org. Chem*. **1970**, *35*, 142. (b) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett*. **1989**, 1725. (c) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc*. **1962**, *84*, 635. (d) D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513. (e) Boger, D. L.; Patel, M. *Tetrahedron Lett*. **1987**, *28*, 2499. (f) Boger, D. L.; Patel, M. *J. Org. Chem*. **1988**, *53*, 1405.

(4) For preparation and the biological evaluation of prodigiosine analogues, see e.g.: (a) Brown, D.; Griffiths, D.; Rider, M. E.; Smith, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 455. (b) Blake, A. J.; Hunter, G. A.; McNab, H. *J. Chem. Soc. Chem. Commun*. **1990**, 734. (c) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem*. **1977**, *108*, 233. (d) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem*. **1978**, *109*, 137. (e) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem*. **1977**, *108*, 285. (f) Berner, H.; Schulz, G.; Fischer, G.; Reinshagen, H. *Monatsh. Chem*. **1978**, *109*, 557. (g) Castro, A. J.; Gale, G. R.; Means, G. E.; Tertzakian, G. *J. Med. Chem*. **1967**, *10*, 29.

(5) (a) Lin, J. *Immunology Today* **1993**, *14*, 290. (b) Nakamura, A.; Nagai, K.; Ando, K.; Tamura, G. *J. Antibiot*. **1986**, *39*, 1155. (c) Tsuji, R. F.; Yamamoto, M.; Nakamura, A.; Kataoka, T.; Magae, J.; Nagai, K.; Yamasaki, M. *J. Antibiot*. **1990**, *43*, 1293. (d) Kataoka, T.; Magae, J.; Nariuchi, H.; Yamasaki, M.; Nagai, K. *J. Antibiot*. **1992**, *45*, 1303. (e) Tsuji, R. F.; Magae, J.; Yamashita, M.; Nagai, K.; Yamasaki, M. *J. Antibiot*. **1992**, *45*, 1295. (f) Kataoka, T.; Magae, J.; Kasamo, K.; Yamanishi, H.; Endo, A.; Yamasaki, M.; Nagai, K. *J. Antibiot*. **1992**, *45*, 1618. (g) Kataoka, T.; Muroi, M.; Ohkuma, S.; Waritani, T.; Magae, J.; Takatsuki, A.; Kondo, S.; Yamasaki, M.; Nagai, K. *FEBS Lett*. **1995**, *359*, 53.

S0002-7863(98)01183-4 CCC: $15.00
Published on Web 08/07/1998

Scheme 1

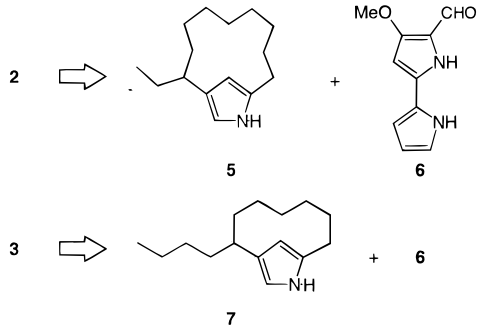


506, and rapamycin.[6] Since the availability of agents acting at different stages along the T-cell activation pathway may improve therapeutic results, the prodiginines constitute important new lead compounds in the search for supplementary drugs to prevent allograft rejection.

Most studies reported so far deal with **1** as the parent compound of this series, but preliminary results indicate that its cyclic analogues metacycloprodigiosin (**2**)[7] and streptorubin B (**3**) ("butylcycloheptylprodiginine")[8] are similarly potent immunomodulators.[9] As part of our program aiming at the preparation of physiologically active heterocycles by organometallic means,[10] we embarked on the synthesis of these challenging targets. Because of the similarities in the chromophore and the meta-bridged heterocyclic entities, compounds **2** and **3** may also be considered as close structural relatives to the cytotoxic alkaloid roseophilin (**4**), the total synthesis of which has recently been accomplished in our laboratory.[11] In the following we outline a new approach to these potentially useful immunomodulators based on a skeletal rearrangement which expands a preexisting ring by two carbon atoms and thereby forms a *m*-pyrrolophane entity.[12,13]

This overall transformation (Scheme 1) may be formally regarded as an enyne metathesis reaction. Although metathesis in general is believed to be a domain of pure organometallic chemistry,[14−17] the mechanistic information gathered so far surprisingly indicates for our cases a "cationic" rather than the anticipated "anionic" pathway.

Scheme 2



Results and Discussion

It is well established in the literature that pyrrolylpyrromethene chromophores in general are easily formed by condensations of the known aldehyde **6** with the appropriate pyrrole segment (Scheme 2).[3,4,7,18] Therefore the preparation of the core structures **5** and **7** constitutes the prime challenge en route to the title compounds. Having in mind that metal-catalyzed cycloisomerizations of enynes had previously been used to forge meta-bridged bicyclic ring systems (Scheme 1),[12,13] such a ring expansion method was envisaged as the key step for the synthesis of **5** and **7**.

Streptorubin B. A set of suitable substrates **10**−**12** was prepared as shown in Scheme 3. An ene-type reaction of cyclooctene **8** with an intermediate formed in situ from chloramine-T and elemental selenium[19] provides ready access to multigram amounts of allylamine **9**. Its N-alkylation with propargyl bromide followed by acylation of the terminal alkyne **10** thus obtained with either methyl chloroformate or butanoyl chloride delivers the electron-deficient alkynes **11** and **12**, respectively.

Unfortunately, however, we faced significant problems in applying the recorded procedures for cycloisomerization reactions to these derivatives (Scheme 4). Specifically, exposure of the acetylenic ester **11** to a mixture of the electron-deficient

(6) For a review on the biological response elicited by these immunophilins, see: Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 384.

(7) (a) Wasserman, H. H.; Rodgers, G. C.; Keith, D. D. *J. Am. Chem. Soc*. **1969**, *91*, 1263. (b) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc*. **1969**, *91*, 1264. (c) Wasserman, H. H.; Keith, D. D.; Rodgers, G. C.. *Tetrahedron* **1976**, *32*, 1855. (d) Wasserman, H. H.; Gosselink, E.; Keith, D. D.; Nadelson, J.; Sykes, R. J. *Tetrahedron* **1976**, *32*, 1863. (e) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *Tetrahedron* **1976**, *32*, 1867.

(8) For the elucidation of the correct structure of streptorubin B, see: (a) Laatsch, H.; Kellner, M.; Weyland, H. *J. Antibiot*. **1991**, *44*, 187. (b) Gerber, N.; McInnes, A. G.; Smith, D. G.; Walter, J. A.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem*. **1978**, *56*, 1155. (c) Tsao, S. W.; Rudd, B. A. M.; He, X. G.; Chang, C. J.; Floss, H. G. *J. Antibiot.* **1985**, *38*, 128.

(9) (a) Magae, J.; Miller, M.; Nagai, K.; Shearer, G. M. *J. Antibiot*. **1996**, *49*, 86. (b) Abe, F.; Morimoto, M.; Shibuya, K.; Yamazaki, M.; Nishigori, T.; Saito, S.; Shimada, N. *Jpn. Kokai Tokkyo Koho* JP 02,250,828 [90,250,828], Oct 8, 1990. *Chem. Abstr*. **1991,** *114*, 108967g.

(10) (a) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem*. **1995**, *60*, 6637. (b) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem*. **1994**, *59*, 5215. (c) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329. (d) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773. (e) Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber*. **1994**, *127*, 1125. (f) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2442.

(11) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1997**, *119*, 2944. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1998**, *120*, 2817.

(12) (a) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc*. **1991**, *113*, 1850. (b) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824. (c) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem*. **1993**, *105*, 1130. (d) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc*. **1993**, *115*, 5294.

(13) (a) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (b) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc*. **1994**, *116*, 6049.

(14) For general reviews on metathesis reactions, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446−452. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036.

(15) For intramolecular enyne metathesis reactions with various catalysts, see: (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (b) Kinoshita, A.; Mori, M. *J. Org. Chem*. **1996**, *61*, 8356. (c) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem*. **1996**, *61*, 1073. (d) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1995**, *14*, 5062. (e) Watanuki, S.; Mori, M. *Organometallics* **1995**, *14*, 5054. (f) Sivavec, T. M.; Katz, T. J.; Chiang, M. Y.; Yang, G. X. Q. *Organometallics* **1989**, *8*, 1620. (g) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 10603. (h) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A. *Chem. Commun*. **1997**, 1375.

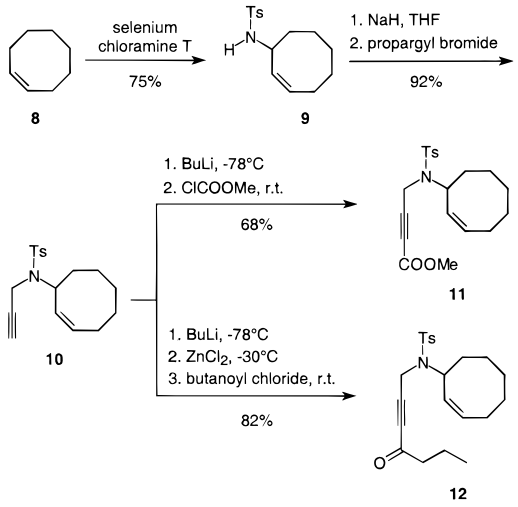
(16) For studies on metathesis reactions from our laboratory, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (c) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, 7005. (d) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746. (e) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (f) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130. (g) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2466. (h) Fürstner, A.; Müller, T. *J. Org. Chem*. **1998**, *63*, 424. (i) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun*. **1998**, 1315.

(17) For a review on the more common ene-type cycloisomerizations of enynes, see: Trost, B. M. *Acc. Chem. Res*. **1990**, *23*, 34.

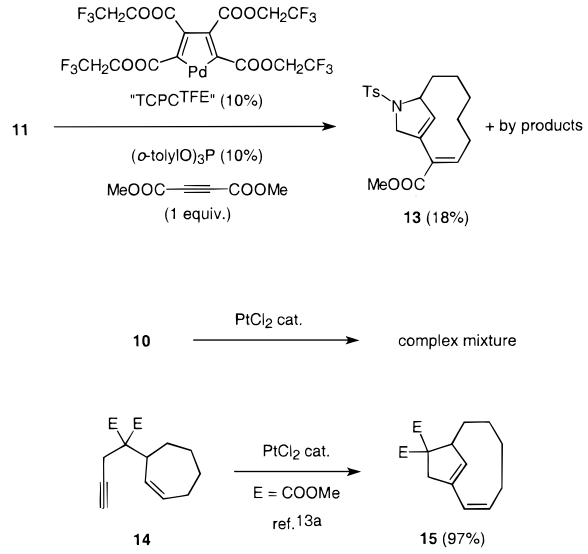
(18) It is interesting to note that this condensation of **5** and **6** mimics the biosynthesis of metacycloprodigiosin (and related prodiginine antibiotics); in contrast, however, our approach to **5** differs completely from the biosynthetic one, which involves an oxidative cyclization of a polyacetate derived alkyl side chain leading to the formation of the medium sized ring entity, cf. ref 8b and the following papers for leading references: (a) Wasserman, H. H.; Shaw, C. K.; Sykes, R. J.; Cushley, R. J. *Tetrahedron Lett*. **1974**, 2787. (b) Wasserman, H. H.; Sykes, R. J.; Peverada, P.; Shaw, C. K.; Cushley, R. J.; Lipsky, S. R. *J. Am. Chem. Soc*. **1973**, *95*, 6874.

(19) Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M. O.; Jones, N. D.; Schwartzendruber, J. K. *Bull. Chem. Soc. Jpn*. **1989**, *62*, 1167.

Scheme 3



Scheme 4



palladole complex TCPC^{TFE} (10 mol %),[12] tris(*o*-tolyl phosphite) (10 mol %), and dimethyl acetylenedicarboxylate (1 equiv) led to rather poor results in our hands. Similarly, attempted isomerization of the *terminal* alkyne **10** by means of $PtCl_2$ afforded a rather complex mixture despite the seemingly close analogy to an example previously reported in the literature (**14** → **15**).[13a]

In view of these failures, we were surprised to find that enynes **11** and **12** *bearing electron-withdrawing substituents* on the alkyne entity cleanly afford the ring-expanded products **13** and **16**, respectively, in good to excellent yields on treatment with catalytic amounts of PtX_n (X = Cl, Br; n = 2, 4) in toluene as the preferred solvent (Scheme 5, Table 1).[20]

The net increase in structural complexity achieved by these amazingly simple and highly reliable transformations is quite appealing. Because of their "low-tech" character, the platinum-catalyzed reactions favorably contrast with the multicomponent system comprising TCPC^{TFE}, tris(*o*-tolylphosphite) (both of which are commercially not available), and stoichiometric amounts of dimethyl acetylenedicarboxylate previously described for similar purposes.[12] The platinum-catalyzed reactions

(20) In contrast to PtX_n (X = Cl, Br; n = 2, 4), the following platinum compounds have been found to be inactive: $PtCl_2$(COD), $PtCl_2(PhCN)_2$, PtO_2, $H_2Pt(OH)_6$, $Pt(acac)_2$, $Pt_2(dba)_3$, and $K_2[PtCl_6]$.

Scheme 5

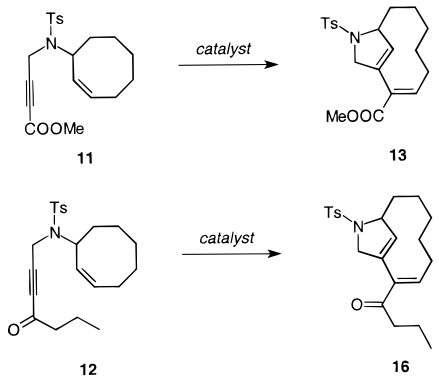
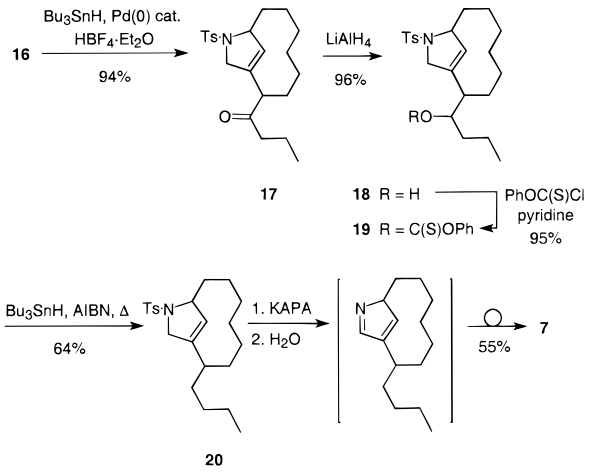


Table 1. Skeletal Reorganizations of Electron-Deficient Enynes Catalyzed by Platinum Salts[a]

entry	substrate	catalyst	T (°C)	t (h)	product (yield)
1	**11**	$PtCl_2$ (4%)	80	8	**13** (67%)
2	**11**	$PtCl_2$ (10%)	20	36	**13** (78%)
3	**11**	$PtCl_4$ (10%)	20	72	**13** (85%)
4	**11**	$PtBr_4$ (10%)	20	86	**13** (95%)[b]
5	**12**	$PtCl_2$ (5%)	50	66	**16** (79%)[c]
6	**12**	$PtCl_4$ (5%)	20	64	**16** (74%)

[a] All reactions have been performed in toluene as the solvent. Isolated yields, unless otherwise stated. [b] GC yield. [c] Minor byproducts isolated: **21** (1%), **22** (1%), **23** + **25** (2%), **24** (5%). Cf. text.

Scheme 6



directly scale-up: thus, the skeletal reorganization of **12** into **16** has been carried out with 3.2−7.5 g of the starting material without compromising the yield. However, these runs allowed us to isolate some very minor byproducts which might have been overlooked in experiments on a smaller scale, but which encode important mechanistic information (vide infra).

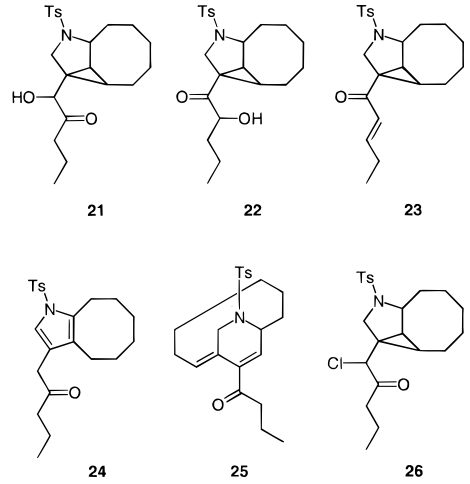
With significant amounts of **16** in hand, we focused our attention on its conversion into the pyrrolophane core **7** of streptorubin B. This requires a formal isomerization of the double bonds and a reduction of the carbonyl group. However, these seemingly trivial transformations turned out to be more delicate than anticipated and were best achieved along the following lines (Scheme 6): treatment of **16** with Bu_3SnH in the presence of catalytic amounts of $Pd(PPh_3)_4$ under acidic conditions converts the enone into the respective ketone **17**.[21] The latter is then reduced with $LiAlH_4$ to afford alcohol **18** in

(21) For precedence, see ref 16d and the following: (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (b) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.

good yield. As it turned out that any conditions giving rise to a cation at the −OR bearing carbon atom must be strictly avoided since they result in undesirable ring-expansion processes (vide infra), we took recourse to a method involving free radicals for the deoxygenation of this derivative. Specifically, alcohol **18** was converted into thionocarbonate **19**, which delivered dihydropyrrole **20** on exposure to Bu_3SnH and AIBN at 75 °C.[22] Treatment of **20** with a base as strong as KAPA (potassium 3-aminopropylamide) results both in the aromatization of the five-membered ring and its concomitant deprotection via the elimination of potassium sulfinate and a reorganization of the double bonds as indicated.[23,24] This completes our synthesis of the core structure **7** of streptorubin B, which is obtained in only nine steps starting from cyclooctene with an overall yield of ≈16%. Compound **7** can then be converted into the antibiotic upon condensation with the heterocyclic side chain **6** by following literature methods.[3,4,7,18]

An interesting feature in the NMR spectrum of compound **7** is the high upfield shift of the central H atom of the ansa chain ($\delta = -1.88$ ppm) which is obviously held within the anisotropy cone of the pyrrole ring by the rigidity of the tether.[25] At elevated temperatures or upon keeping the solution at ambient temperature for extended periods of time, however, a second high-field signal at $\delta = -1.83$ ppm starts to appear which is attributed to another diastereoisomer of **7** formed by a ring flip. Coalescence, however, could not be reached and the barrier for ring inversion must therefore be considerable, in any case >17.5 kcal·mol^{-1}.[26] Relevant parts of the spectra depicting this amazing phenomenon are given in the Supporting Information. This spectroscopic property also indicates that compound **7** contains an element of planar chirality in addition to its chiral center.[27] Nevertheless, this product has been obtained as a single diastereoisomer independent of whether the synthesis is carried through with a mixture of the diastereomers of its precursors **17**−**20** or with the major isomers thereof in pure form. However, since very similar retention times renders their chromatographic separations tedious and lead to a significant loss of material, this stereochemical convergence greatly simplifies our approach.

Mechanistic Rationale for the Enyne Metathesis. As mentioned above, it was possible to isolate some minor byproducts **21** (1%), **22** (1%), **23** + **25** (2%), and **24** (5%) in addition to the desired ring-expanded derivative **16** (79%) when the platinum-catalyzed enyne metathesis reaction was carried out on a multigram scale. The structures of these rather unconventional polycyclics have been unambiguously established by means of extensive 2D NMR spectroscopy at 600 MHz, as they may well shed light on the mechanism of the platinum-catalyzed skeletal rearrangement. A complete analysis of their spectroscopic data is given in the Supporting Information.



Previous studies on the mechanism of the closely related $TCPC^{TFE}$-catalyzed cycloisomerizations suggest that a Pd(II) ⇌ Pd(IV) manifold involving spiropalladacycles accounts for the observed results.[12] These intermediates might undergo reductive elimination to cyclobutene derivatives which readily reopen to the final product due to the release of ring strain (Scheme 7). A similar catalytic cycle based on Pt(II) ⇌ Pt(IV) species has been proposed for enyne reorganization reactions catalyzed by $(PPh_3)_2Pt(OAc)_2$ and trifluoroacetic acid.[12b]

However, such a scenario does not easily explain our results. Therefore we are tempted to suggest an alternative mechanism which accommodates all preparative data gathered so far and allows some predictions which can be probed experimentally. The formation of the desired compound **16** and of all byproducts **21**−**25** can be rationalized by assuming a type of "nonclassical" homoallyl−cyclopropylmethyl−cyclobutyl cation as the reactive intermediate (Scheme 8).[28] Triggered by the coordination of the platinum cation onto the triple bond of the substrate,[29] such a species represented by the canonical forms **A**, **B**, **C**, and **D** may evolve (Scheme 9). Eventual trapping of the mesomeric structure **A** by traces of moisture in the solvent results in the formation of product **21**, its enediol tautomer **22**, and the elimination product thereof **23**. If the nonclassical cation is depicted in its homoallyl form **B**, this translates into the pyrrole derivative **24** as shown in Scheme 9. The complementary form **C** of this intermediate will lead to the formation of the *p*-tetrahydropyridinophane structure **25**. Finally, the mesomeric form **D** feeds the major pathway delivering the ring-expanded metathesis product **16**.

This scenario has a few important implications. The crucial "nonclassical" cation-type intermediate is believed to originate from a π-complexation of the alkyne entity onto the platinum salt.[29] Alternatively, one may envisage the formation of a similar species by coordination of a Lewis acid onto the adjacent carbonyl group or even upon its simple protonation (Scheme 10). In fact, we noticed that a set of strong Lewis and Brønsted

(22) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc*. **1983**, *105*, 4059.

(23) For the preparation of KAPA, see: Brown, C. A.; Jadhav, P. K. *Org. Synth*. **1987**, *65*, 224.

(24) (a) Very little precedence is known for the aromatization of dihydropyrroles on treatment with bases. For an example using *t*-BuOK, see: Terry, W. G.; Jackson, A. H.; Kenner, G. W.; Kornis, G. *J. Chem. Soc*. **1965**, 4389. (b) For a timely review on pyrrole chemistry, see: Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R. R., Ed.; Thieme: Stuttgart, Germany, 1994; Vol. E 6a, Part 1, pp 556−798.

(25) The NMR spectrum of streptorubin B shows the same effect, cf. ref 8a.

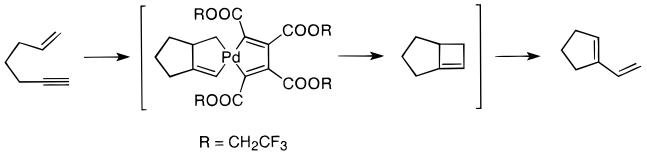
(26) For pertinent studies on related meta-bridged phane structures describing similarly high barriers for the ring flip. see: (a) Hirano, S.; Hiyama, T.; Fujita, S.; Kawaguti, T.; Hayashi, Y.; Nozaki, H. *Tetrahedron* **1974**, *30*, 2633. (b) Nozaki, H.; Koyama, T.; Mori, T. *Tetrahedron* **1969**, *25*, 5357.

(27) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, 2nd ed.; Wiley: New York, 1994; p 1166.

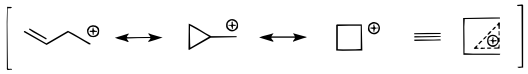
(28) For comprehensive discussions. see: (a) Vogel, P. *Carbocation Chemistry*; Elsevier: Amsterdam, 1985; p 349−358. (b) Klunder, A. J. H.; Zwanenburg, B. In *Houben-Weyl, Methoden der Organischen Chemie*; de Meijere, A., Ed.; Thieme: Stuttgart, Germany, 1997; Vol. E17c, p 2419. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992 and references cited therein.

(29) It is well established that Pt(II)−alkyne complexes show reactivity patterns characteristic for carbocations, especially when bearing electron-withdrawing substituents. For a review, see: Chisholm, M. H.; Clark, H. C. *Acc. Chem. Res.* **1973**, *6*, 202.

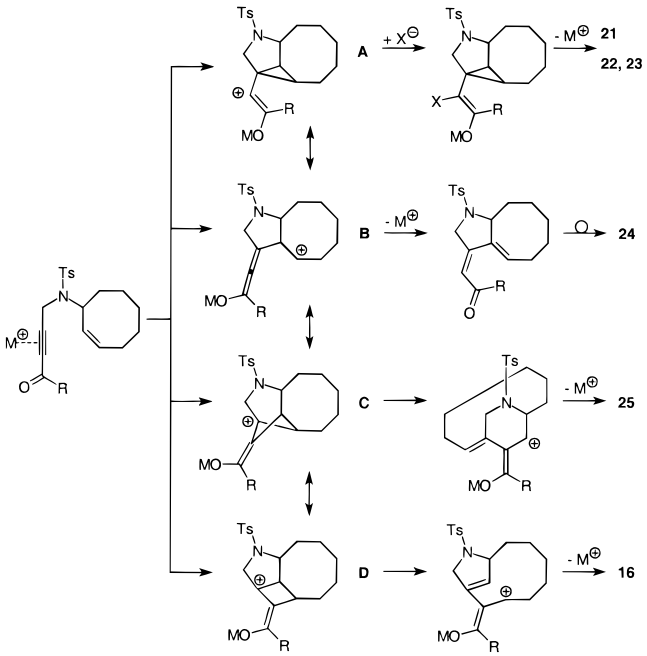
Scheme 7



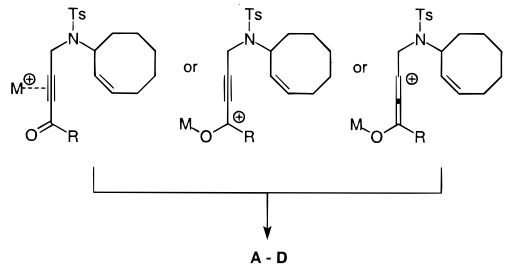
Scheme 8



Scheme 9



Scheme 10



acids consistently afford the cyclo-rearranged product **16** from **12** in reasonable to good yields, with $BF_3{\cdot}Et_2O$ being the best initiator in terms of yield and reaction rate. The results of this screening are summarized in Table 2. Less acidic salts such as $NiCl_2$, $PdCl_2$, $CoCl_2$, $RhCl_3$, $CrCl_2$, and $MnCl_2{\cdot}4H_2O$, in contrast, turned out to be catalytically inactive. These results further corroborate the mechanistic rationale outlined above.

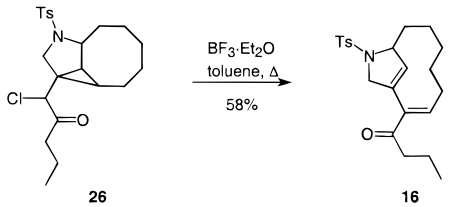
Quite interestingly, the use of $AlCl_3$ provides significant amounts of the cyclopropyl derivative **26** (41%) in addition to product **16** (39%). One may explain the formation of this compound if the assumed cationic intermediate is trapped in its mesomeric form **A** by a chloride anion internally delivered by the aluminum salt. With **26** in hand, it was also possible to probe another important aspect of the proposed mechanism. Regeneration of a cationic species by cleavage of the C−Cl bond on treatment of **26** with $BF_3{\cdot}Et_2O$ converts this cyclopropyl derivative into the ring-expanded product **16** in 58% yield

Table 2. Acid-Promoted Skeletal Rearrangements of Enyne **12**[a]

entry	catalyst	*T* (°C)	*t* (h)	product (yield)
1	$BF_3{\cdot}Et_2O$ (1.1 equiv)	20	46	**16** (63%), **25** (6%)
2	$BF_3{\cdot}Et_2O$ (5%)	80	120	**16** (64%)
3	HBF_4	50	8	**16** (57%)
4	$SnCl_4$ (10%)	20	46	**16** (52%)[b]
5	$AlCl_3$ (20%)	20	3	**16** (39%), **26** (41%)
6	$TiCl_4$ (10%)	20	40	**16** (31%)[b]
7	$ZnCl_2$ (2 equiv)	110	66	**16** (54%)[b]

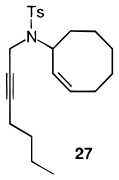
[a] All reactions have been performed in toluene as the solvent. Isolated yields, unless otherwise stated. [b] GC yield.

Scheme 11



(Scheme 11). This outcome strongly supports the notions (i) that compounds **21**−**26** constitute real byproducts derived from the metathesis reaction and do not originate from independent pathways and (ii) that the major ring expanded compound **16** and the minor byproducts **21**−**26** are likely interconnected via cationic intermediates.

A final aspect concerns the substitution pattern of the enyne substrates. As has been mentioned above, the presence of an electron-withdrawing group on the alkyne moiety turned out to be a key to successful platinum- or acid-catalyzed cycloisomerization reactions. Schemes 9 and 10 readily explain the eminent role of this substituent which intervenes as enol or enolate and may thus provide part of the driving force for the productive enyne metathesis. In accordance with this view, neither the terminal alkyne **10** nor substrate **27** containing an electronically unbiased internal alkyne group underwent proper rearrangements on exposure to $PtCl_n$ ($n = 2, 4$).



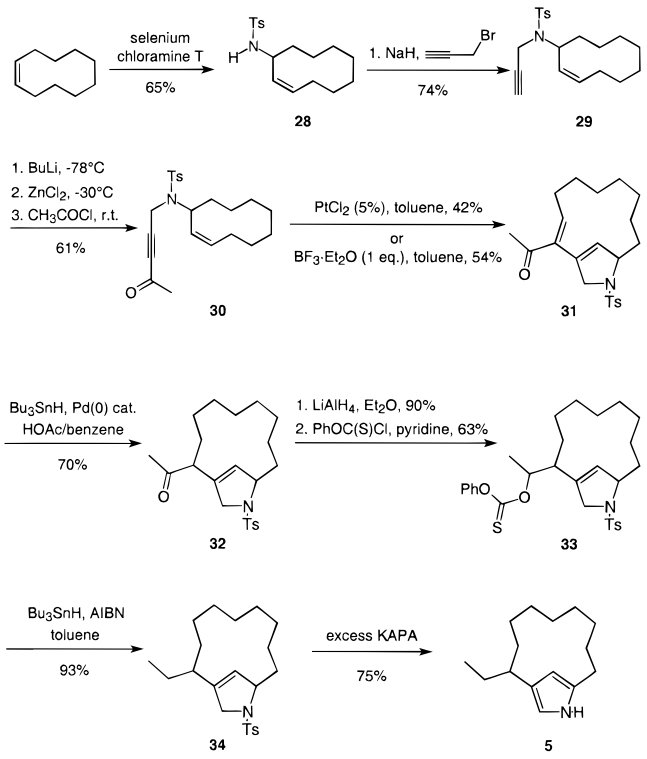
Although definite proof of the proposed mechanism must await further investigations, the data gathered so far provide a consistent picture favoring cationic rather than metallacylic intermediates. However, we emphasize that other metal-catalyzed cycloisomerization reactions of terminal enyne substrates previously reported in the literature[12,13,30] may occur along pathways which are distinctly different from the one operative in our case.

Formal Total Synthesis of Metacycloprodigiosin. In closely following the route leading to the streptorubin B core (vide supra), we were also able to prepare the *m*-pyrrolophane **5** (Scheme 12). This completes a formal total synthesis of the alkaloid metacycloprodigiosin **2**, as compound **5** had already served as a key intermediate in previous approaches to this promising immunosuppressive target.[7]

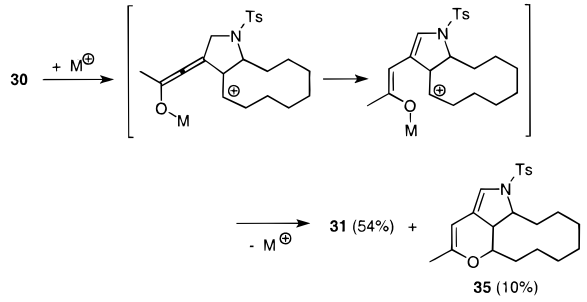
The synthesis of the required enyne **30** comprises an ene-type reaction of cyclodecene with an intermediate formed in

(30) For another example of enyne transformations induced by Pt(IV), see: Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567.

Scheme 12



Scheme 13

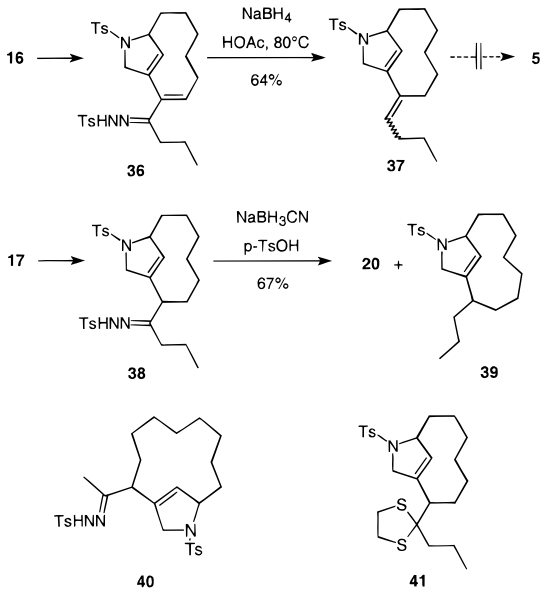


situ from chloramine-T and elemental selenium[19] and a subsequent N-alkylation of allylamine **28** with propargyl bromide, followed by an acylation of the resulting terminal alkyne **29** with acetyl chloride. In line with the results summarized above, the skeletal reorganization of **30** can be achieved in reasonable yields on a fairly large scale with either $BF_3{\cdot}Et_2O$ or $PtCl_2$ as initiators. In addition to the desired ring-expanded compound **31**, a minor byproduct formed was identified as the fairly labile tricyclic enol ether **35**. Its formation is very well in line with a cationic scenario analogous to the one shown in Scheme 13, giving further credence to the notion that the carbonyl group plays an active role in such enyne metatheses (vide supra). The full analysis of the spectroscopic data of **35** is given in the Supporting Information.

Conversion of **31** into thionocarbonate **33** by two reduction processes and a subsequent acylation with PhOC(S)Cl, followed by a radical deoxygenation[22] of this compound, leads to dihydropyrrole **34**. This product is aromatized and deprotected in one pot on exposure to KAPA,[23] delivering pyrrole **5** as a known key component for the synthesis of metacycloprodigiosin **2** in ≈5% overall yield starting from cyclodecene.

Alternative Syntheses of 5 and 7: Ring Expansion. Although the stepwise conversion of **16** and **31** into pyrrolophanes **7** and **5**, respectively, is highly satisfactory in preparative terms, we briefly investigated alternative and possibly even shorter routes. Specifically, ketone **16** was converted into the corresponding tosylhydrazone **36**,[31] which on treatment with $NaBH_4$ in HOAc[32] afforded diene **37** (E:Z = 1:4) (Scheme 14);[33] however, we could not find appropriate conditions for its conversion into pyrrole **5** via isomerization of the double bonds.

Scheme 14



Strategies other than the radical path for the deoxygenation of the ketone groups in the cycloisomerization products have also been briefly investigated. Specifically, ketone **17** was converted into tosylhydrazone **38**, which was reduced with $NaBH_3CN$ in the presence of *p*-TsOH.[34] However, the careful analysis of the NMR spectra of the crude product shows that the acidic and rather forcing conditions led to a mixture of the desired compound **20** and the ring-expanded pyrrolophane **39** that cannot be separated by flash chromatography. The same problem was encountered with tosylhydrazone **40**, leading to a mixture of **34** and a ring-expanded byproduct. In close analogy, attempted desulfurization of dithioacetal **41** with Raney Ni resulted in an unselective conversion. These results are deemed to reflect the high propensity of such strained carbon skeletons for Wagner−Meerwein-type skeletal rearrangements. In view of this unfavorable bias, we did not pursue these approaches any further.

Summary and Outlook

In summary, it was possible to convert cyclooctene or cyclodecene in only nine high-yielding operations into *m*-pyrrolophanes **7** and **5**, respectively, which are key building blocks for the synthesis of the immunomodulating prodiginine antibiotics and analogues thereof. The pivotal step consists of a skeletal reorganization of enyne derivatives catalyzed either by PtX_n (X = Cl, Br; n = 2, 4) or by simple Lewis or Brønsted acids. This operationally trivial transformation results in a significant increase in molecular complexity and allows to valorize bulk chemicals. Specifically, it expands the preexisting ring, forges a functionalized bicyclic skeleton, and simulta-

(31) The constitution of this compound was assured by X-ray crystallography; details will be published separately.

(32) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299.

(33) The stereochemistry was unambiguously assigned by NOE experiments.

(34) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

neously fashions a bridgehead alkene. Formally resembling an enyne metathesis process, the reaction likely proceeds along a cationic rather than an anionic pathway. Further studies on this and related transformations are currently in progress.

Experimental Section

General Procedures. All reactions were carried out under Ar using Schlenk techniques. *CAUTION*: Drying of commercial chloramine-T is best achieved by storing it for several days under reduced pressure in an exsiccator charged with P_4O_{10}. Drying at elevated temperatures in vacuo is hazardous and may lead to vigorous explosions! $PtCl_2$ (98%), $PtCl_4$ (99.99%), $PtBr_2$ (98%), and $PtBr_4$ (99.9%) (Aldrich) as well as all other commercially available reagents (Aldrich, Fluka) were used as received. The solvents were dried by distillation over the following drying agents and were transferred under Ar: Et_2O (Na/K), CH_2Cl_2 (P_4O_{10}), THF (Mg−anthracene), toluene (Na/K), DMF (Desmodur, dibutyltin dilaurate). Flash chromatography was performed with Merck silica gel 60 (230−400 mesh) using hexanes/ethyl acetate in the proportions indicated as the eluent. For the instrumentation used and the spectra formats, see the Supporting Information. Elemental analyses: Dornis & Kolbe, Mülheim.

***N*-Cyclooct-2-enyl-4-methylbenzenesulfonamide (9).** A suspension of dry selenium powder (4.145 g, 52.5 mmol, dried at 80 °C, 10^{-2} bar for 1 h) and anhydrous chloroamine-T (22.744 g, 100 mmol, dehydrated in an exsiccator over P_4O_{10}) in CH_2Cl_2 (200 mL) was stirred for 17 h at room temperature. Cyclooctene (6.612 g, 7.8 mL, 60 mmol) was then added dropwise over a period of 2 h to the white-gray slurry, and stirring was continued for 14 h. The dark-green suspension was concentrated in vacuo, and the residue was dissolved in a mixture of ethyl acetate/diethyl ether (1:1) (600 mL) and 1 M NaOH/saturated NaCl (2:1) (350 mL). After stirring for 0.5 h, the red two-phase system was filtered through a plug of Celite 545. The orange organic layer of the filtrate was washed with alkaline brine solution (as mentioned above, 2 × 250 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in acetone (100 mL) and refluxed for 5 min with activated charcoal (150 mg). The mixture was cooled to room temperature and filtered through a short pad of Celite 545 covered with a layer of activated charcoal. Removal of the solvent led to a yellow solid, which was recrystallized from ethyl acetate/hexane (25 mL/200 mL) to give sulfonamide **9** (9.980 g, 75%) as colorless crystals: mp 122−123 °C; R_f 0.54 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (AA′XX′, 2H), 7.27 (AA′XX′, 2H), 5.53 (dt, 1H, J = 10.6, 8.1, 1.4 Hz), 5.15 (dd, 1H, J = 10.6, 8.0 Hz), 4.95 (m, 1H), 4.18 (m, 1H), 2.42 (s, 3H), 2.02 (dt, 2H, J = 8.1, 3.7 Hz), 1.79−1.22 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.0, 137.9, 131.2, 130.0, 129.4, 127.1, 51.4, 36.9, 29.0, 26.6, 26.2, 24.1, 21.5. Anal. Calcd for $C_{15}H_{21}NSO_2$ (279.40): C, 64.48; H, 7.58; N, 5.01; S, 11.45. Found: C, 64.43; H, 7.65; N, 4.90; S, 11.52.

***N*-Cyclooct-2-enyl-4-methyl-*N*-prop-2-ynylbenzenesulfonamide (10).** Sulfonamide **9** (6.870 g, 24.6 mmol) was added in portions at 0 °C to a stirred suspension of NaH (649 mg, 27.0 mmol) in THF (400 mL). After stirring the mixture for 0.5 h at ambient temperature, propargyl bromide (a commercial 80% solution in toluene; 8.216 mL, 8.775 g, 73.8 mmol) was added to the white slurry and stirring was continued for 11 h at 60 °C. The beige suspension was carefully quenched at 0 °C with chilled water (300 mL). The aqueous layer was extracted with ethyl acetate (3 × 200 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate, 5:1) afforded enyne **10** as a yellow syrup (7.234 g, 93%): R_f 0.54 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.25 (AA′XX′, 2H), 5.60 (m, 2H, J = 6.7 Hz), 4.83 (dt, 1H, J = 9.7, 6.8 Hz), 4.16 (dd, 1H, J = 18.6, 2.5 Hz), 4.08 (dd, 1H, J = 18.5, 2.5 Hz), 2.40 (s, 3H), 2.25−2.04 (m, 2H), 2.16 (t, 1H, J = 2.5 Hz), 1.79−1.17 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.1, 137.6, 130.4, 129.2, 128.0, 127.5, 80.0, 72.5, 55.7, 34.3, 33.0, 28.9, 26.2, 26.0, 24.5, 21.5. Anal. Calcd for $C_{18}H_{23}NSO_2$ (317.45): C, 68.10; H, 7.30; N, 4.41; S, 10.08; Found: C, 67.88; H, 7.27; N, 4.35; S, 10.02.

***N*-Cyclooct-2-enyl-4-methyl-*N*-(4-oxohept-2-ynyl)benzenesulfonamide (12).** A solution of compound **10** (600 mg, 1.89 mmol) in 20 mL of THF/hexane (1:1) was cooled to −78 °C prior to adding *n*-BuLi (1.6 M in hexane; 1.2 mL, 1.9 mmol). After being stirred for 15 min at that temperature, the mixture was warmed to −30 °C and a solution of anhydrous $ZnCl_2$ (252 mg, 1.85 mmol, previously dehydrated with $SOCl_2$ under reflux) in THF (3 mL) was rapidly introduced, causing a characteristic color change from red to yellow. After 15 min, *n*-butanoyl chloride (200 μL, 204 mg, 1.91 mmol) was added slowly at +10 °C via cannula and the mixture was allowed to warm overnight to room temperature. The orange solution was quenched with saturated aqueous NH_4Cl (50 mL) and diluted with ethyl acetate (50 mL), the aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with aqueous saturated NH_4Cl (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography of the residue (hexanes/ethyl acetate, 10:1) provided enyne **12** (588 mg, 82%) as an amorphous solid: mp 85−86 °C, R_f 0.25 (hexanes/ethyl acetate, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.27 (AA′XX′, 2H), 5.67 (dt, 1H, J = 10.7, 7.7, 1.1 Hz), 5.49 (dd, 1H, J = 10.7, 8.1 Hz), 4.87 (vq, 1H, J = 8.0 Hz), 4.32 (d, 1H, J = 19.2 Hz), 4.25 (d, 1H, J = 19.2 Hz), 2.41 (s, 3H), 2.35 (t, 2H, J = 4.4 Hz), 2.22−2.09 (m, 2H), 1.78−1.25 (m, 8H), 1.59 (q, 2H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.1, 143.4, 137.3, 130.8, 129.4, 127.4, 87.6, 83.0, 55.7, 47.0, 34.3, 33.0, 28.7, 26.2, 25.9, 24.4, 21.4, 17.2, 13.4. Anal. Calcd for $C_{22}H_{29}NSO_3$ (387.54): C, 68.18; H, 7.54; N, 3.61; S, 8.27. Found: C, 68.28; H, 7.49; N, 3.59; S, 8.48.

Representative Procedure for Platinum-Catalyzed Enyne Metatheses. Synthesis of 1-[10-(Toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-2-yl]butan-1-one (16). To a solution of substrate **12** (3.320 g, 8.57 mmol) in toluene (400 mL) was added $PtCl_2$ (114 mg, 0.43 mmol, 5 mol %). The yellow-beige colloidal solution was warmed to 50 °C for 60 h. The solvent was removed in vacuo and the residue purified by flash chromatography (hexanes/ethyl acetate, 8:1 → 6:1) to give compound **16** as a bright-yellow solid (2.619 g, 79%). In addition to the desired metathesis product **16**, four fractions containing minor byproducts have been isolated: **21** (20 mg, 1%), **22** (20 mg, 1%), a mixture of **23** + **25** (55 mg, ≈2%), and **24** (182 mg, 5%). A full analysis of the NMR data of these compounds allowing the unambiguous assignment of their structures is compiled in the Supporting Information. Data of product **16**: mp 72−73 °C, R_f 0.33 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (AA′XX′, 2H), 7.29 (AA′XX′, 2H), 6.88 (dd, 1H, J = 8.4, 6.9 Hz), 5.31 (dt, 1H, J = 2.2, 1.7 Hz), 4.73 (m, 1H), 4.35 (dt, 1H, J = 14.4, 2.2 Hz), 4.24 (ddd, 1H, J = 14.4, 4.8, 1.6 Hz), 2.42 (1H, dt, J = 16.5, 7.4 Hz), 2.39 (s, 3H), 2.30 (m, 1H), 2.32 (dt, 1H, J = 16.5, 7.4 Hz), 2.23 (m, 1H), 2.07 (dtd, 1H, J = 14.7, 7.0, 4.1 Hz), 1.64−1.40 (m, 6H), 1.51 (sext., 2H, J = 7.4 Hz), 1.14 (m, 1H), 0.83 (t, 3H, J = 7.4 Hz), ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 145.6, 143.4, 138.6, 135.2, 132.6, 131.6, 129.8, 127.2, 67.3, 58.5, 40.4, 35.3, 28.5, 27.5, 25.5, 21.5, 19.1, 17.7, 13.7. Anal. Calcd for $C_{22}H_{29}NSO_3$ (387.54): C, 68.18; H, 7.54; N, 3.61; S, 8.27. Found: C, 68.13; H, 7.56; N, 3.63; S, 8.31.

1-[10-(Toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodec-1(12)en-2-yl]butan-1-one (17). To a solution of compound **16** (1000 mg, 2.58 mmol), $HBF_4 \cdot Et_2O$ (418 μL, 460 mg, 2.84 mmol), and $Pd(PPh_3)_4$ (60 mg, 0.052 mmol, 2 mol %) was added *n*-Bu_3SnH (1.74 mL, 1.877 mg, 6.45 mmol) dropwise via cannula within 10 min, and the resulting yellow solution was stirred for 20 h at ambient temperature. For workup, the solvent was evaporated and the residue purified by flash chromatography (hexanes 300 mL, then hexanes/ethyl acetate, 10:1 → 6:1) to afford enone **17** (940 mg, 94%) as a colorless solid: mp 91−92 °C, R_f 0.39 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (AA′XX′, 2H), 7.29 (AA′XX′, 2H), 5.49 (dt, 1H, J = 1.8 Hz), 4.69 (m, 1H), 4.20 (ddd, 1H, J = 14.9, 4.7, 0.7 Hz), 4.00 (dt, 1H, J = 15.0, 2.3 Hz); 3.28 (dd, 1 H, J = 10.2, 3.2 Hz), 2.41 (s, 3H), 2.27 (dt, 2H, J = 7.1, 4.8 Hz), 2.09 (dtd, 1H, J = 18.1, 6.4, 2.5 Hz), 1.90−1.00 (m, 11H), 1.50 (q, 2H, J = 7.3 Hz), 0.82 (t, 3H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.9, 143.2, 134.9, 134.8, 129.6, 127.4, 126.8, 65.5, 55.3, 55.0, 43.7, 34.0, 28.8, 28.3, 24.1, 23.2, 22.0, 21.5, 16.9, 13.6. Anal. Calcd for $C_{22}H_{31}NSO_3$ (389.56): C, 67.83; H, 8.02; N, 3.60; Found: C, 67.84; H, 7.94; N, 3.63.

1-[10-(Toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodec-1(12)-en-2-yl]butan-1-ol (18). To a suspension of $LiAlH_4$ (64 mg, 1.69 mmol)

in Et_2O (10 mL) was added dropwise a solution of ketone **17** (940 mg, 2.41 mmol) in Et_2O (30 mL) at 0 °C over a period of 1 h. Stirring was continued for 4 h, the reaction mixture was carefully quenched at 0 °C by slowly adding water (5 mL) followed by a few drops of aqueous 10% HCl in order to dissolve the precipitated salts. The mixture was diluted with water (100 mL) and ethyl acetate (100 mL), the aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate, 5:1) of the residue afforded alcohol **18** as a colorless oil (906 mg, 96%): R_f 0.23 (hexanes/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (AA′XX′, 2H), 7.29 (AA′XX′, 2H), 5.37 (dt, 1H, J = 1.8 Hz), 4.63 (m, 1H), 4.21 (m, 2H), 3.47 (m, 1H), 2.40 (s, 3H), 2.17 (m, 1H), 2.03 (m, 1H, J = 5.9, 2.4 Hz), 1.67 (m, 3H), 1.45−1.07 (m, 13H), 0.85 (t, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.1, 137.7, 134.9, 129.6, 127.3, 125.9, 73.2, 65.1, 55.7, 49.1, 37.8, 34.1, 29.5, 29.1, 24.1, 23.9, 22.2, 21.4, 18.6, 14.0. Anal. Calcd for $C_{22}H_{33}NSO_3$: C, 67.48; H, 8.49; N, 3.58. Found: C, 67.53; H, 8.48; N, 3.52.

Thiocarbonic Acid *O*-Phenyl Ester *O*-{1-[10-(Toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodec-1(12)-en-2-yl]butyl} Ester (19). To a solution of alcohol **18** (746 mg, 1.91 mmol) in CH_2Cl_2 (20 mL) were added PhOC(S)Cl (462 μL, 452 mg, 5.72 mmol) and pyridine (527 μL, 658 mg, 3.81 mmol) via cannula at 0 °C. After 36 h of stirring at room temperature and a standard workup comprising a flash chromatography (hexanes/ethyl acetate, 15:1 → 10:1), product **19** was obtained as a colorless solid (951 mg, 95%): mp 55−56 °C, R_f 0.46 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (AA′XX′, 2H), 7.40−7.19 (m, 5H), 6.93 (AA′XX′, 2H), 5.35 (dt, 1H, J = 1.8 Hz), 5.30 (dt, 1H, J = 5.0 Hz), 4.59 (m, 1H), 4.02 (m, 2H, J = 1.9 Hz), 2.44 (m, 1H), 2.31 (s, 3H), 2.10−0.99 (m, 16H), 0.77 (t, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.5, 153.1, 143.2, 136.1, 134.8, 129.7, 129.5, 127.4, 127.3, 126.6, 121.7, 86.5, 65.3, 55.5, 46.6, 34.4, 34.2, 29.1, 29.0, 24.2, 24.1, 22.2, 21.4, 18.1, 14.0.

2-Butyl-10-(toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodec-1(12)-ene (20). To a solution of substrate **19** (951 mg, 1.80 mmol) in toluene (25 mL) were added AIBN (60 mg, 0.36 mmol, 20 mol %) and *n*-Bu_3SnH (969 μL, 1.049 g, 3.60 mmol). The mixture was stirred at 75 °C for 5 h and concentrated in vacuo, and the residue was purified by flash chromatography (hexanes (300 mL), then hexanes/ethyl acetate, 20:1 → 17:1) to deliver dihydropyrrole **20** as a colorless oil (435 mg, 64%): R_f 0.65 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (AA′XX′, 2H), 7.22 (AA′XX′, 2H), 5.16 (dt, 1H, J = 3.5, 1.8 Hz), 4.60 (m, 1H), 4.04 (m, 1H), 3.90 (dt, 1H, J = 14.3, 2.0 Hz), 2.34 (s, 3H), 1.96 (m, 2H), 1.62 (m, 3H), 1.29−0.83 (m, 14H), 0.74 (t, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 140.2, 135.0, 129.6, 127.3, 123.9, 66.0, 54.5, 42.9, 34.1, 32.9, 32.9, 30.2, 29.4, 24.0, 23.7, 22.6, 22.3, 21.5, 14.0. Anal. Calcd for $C_{22}H_{33}NSO_2$ (375.58): C, 70.36; H, 8.86; N, 3.73. Found: C, 70.29; H 8.86; N, 3.68.

2-Butyl-10-azabicyclo[7.2.1]dodeca-1(11),9(12)diene (7). 1,3-Diaminopropane (35 mL) was added to KH (374 mg, 9.3 mmol) at room temperature. After the mixture was stirred for 3 h, a yellow colloidal solution was obtained. The KAPA reagent thus formed was added dropwise over a period of 1 h at −15 °C to a solution of dihydropyrrole **20** (350 mg, 0.93 mmol) in 1,3-diaminopropane (15 mL). After the mixture was stirred for 3 h at that temperature, the resulting red solution was slowly poured into chilled water (300 mL). A standard extractive workup with ethyl acetate afforded a crude yellow liquid which was chromatographed on a short plug of silica with hexane/ethyl acetate (10:1) as the eluent, providing pyrrole **7** as a colorless solid (111 mg, 55%): mp 84−85 °C, R_f 0.77 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.76 (bs, 1H), 6.43 (t, 1H, J = 1.9 Hz), 6.17 (t, 1H, J = 1.9 Hz), 2.64 (ddd, 1H, J = 10.8, 4.6, 2.1 Hz), 2.41 (m, 2H, J = 4.7 Hz), 1.76−1.60 (m, 5H), 1.42−1.30 (m, 3H), 1.48 (m, 2H), 0.98−0.85 (m, 3H), 0.91 (t, 3H, J = 7.2 Hz), 0.71 (m, 1H, J = 6.8 Hz), 0.51 (dt, 1H, J = 12.9, 10.8 Hz), −1.88 (m, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 132.8, 130.2, 115.0, 112.0, 42.1, 41.6, 33.9, 32.9, 30.7, 30.4, 30.1, 29.7, 27.1, 23.4, 14.3. Anal. Calcd for $C_{15}H_{25}N$ (219.37): C, 82.13; H, 11.49; N 6.38. Found: C, 82.21; H, 11.38; N, 6.25.

Tosylhydrazone 36. To a suspension of compound **16** (150 mg, 0.387 mmol) in EtOH (3 mL) was added $TsNHNH_2$ (86 mg, 0.464 mmol). The suspension was refluxed for 2 h, and the resulting clear solution was cooled and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 4:1) to give tosylhydrazone **36** as a colorless solid (144 mg, 67%): mp 152−153 °C; R_f 0.23 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (AA′XX′, 2H), 7.63 (m, 1H), 7.34 (m, 4H), 7.07 (AA′XX′, 2H), 6.11 (t, 1H, J = 7.6 Hz), 5.01 (d, 1H, J = 1.2 Hz), 4.66 (m, 1H), 4.47 (dt, 1H, J = 13.9, 2.3 Hz), 4.19 (ddd, 1H, J = 13.8, 4.8, 1.3 Hz), 2.36 (s, 3H), 2.30 (m, 2H), 2.23 (s, 3H), 2.16 (t, 2H, J = 8.2 Hz), 1.93 (m, 1H), 1.64−1.11 (m, 9H), 0.83 (t, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.3, 143.8, 143.4, 136.7, 136.0, 135.3, 135.0, 133.5, 130.2, 129.6, 129.1, 127.9, 127.0, 66.8, 58.9, 34.9, 28.1, 27.8, 27.0, 24.7, 21.6, 21.3, 19.4, 18.0, 14.0. Anal. Calcd for $C_{27}H_{37}N_3S_2O_4$ (387.54): C, 62.67; H, 6.71; N, 7.56; S, 11.54. Found: C, 62.62; H, 6.75; N, 7.61; S, 11.65.

***N*-Cyclodec-2-enyl-4-methylbenzenesulfonamide (28).** A suspension of dry selenium powder (4.024 g, 51.0 mmol, dried at 80 °C, 10^{-2} bar for 1 h) and anhydrous chloramine-T (11.039 g, 49.0 mmol, dehydrated in an exsiccator over P_4O_{10}) in CH_2Cl_2 (150 mL) was stirred for 24 h at room temperature. (*Z*)-Cyclodecene (8.129 g, 9.3 mL, 59 mmol) was added dropwise over 2 h to this mixture, and stirring was continued for 16 h. Workup as described above for the preparation of sulfonamide **9** and flash chromatography (hexanes/ethyl acetate, 6:1) furnished sulfonamide **28** as colorless crystals: mp 134−135 °C; R_f 0.43 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (AA′XX′, 2H), 7.25 (AA′XX′, 2H), 5.22 (dt, 1H, J = 11.4, 4.9 Hz), 4.94 (dt, 1H, J = 11.0, 1.3 Hz), 4.64 (d, 1H, J = 7.3 Hz), 4.41 (m, 1H, J = 7.3 Hz), 2.41 (s, 3H), 2.26 (dt, 1H, J = 13.7, 5.7 Hz), 1.73 (m, 2H), 1.58−1.21 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.9, 138.2, 131.5, 129.7, 129.3, 127.2, 50.5, 35.6, 26.6, 25.6, 25.4, 24.9, 21.5, 20.7, 20.3. Anal. Calcd for $C_{17}H_{25}NSO_2$ (307.46): C, 66.41; H, 8.20; N, 4.56; S, 10.43. Found: C, 66.31; H, 8.17; N, 4.48; S, 10.59.

***N*-Cyclodec-2-enyl-4-methyl-*N*-prop-2-ynylbenzenesulfonamide (29)**. Sulfonamide **28** (4.0 g, 13.03 mmol) was added in portions at 0 °C to a stirred suspension of NaH (344 mg, 14.33 mmol) in THF (300 mL). The mixture was stirred 0.5 h at room temperature prior to the addition of propargyl bromide (commercial 80% solution in toluene; 4.35 mL, 4.648 g, 39.09 mmol). After the mixture was stirred for 22 h at 60 °C, more propargyl bromide (2.0 mL, 2.67 g, 18 mmol) was added and stirring was continued for another 20 h. Workup as described above for the preparation of enyne **10** and flash chromatography (hexanes/ethyl acetate, 10:1 → 9:1) afforded compound **29** (3.341 g, 74%) as colorless crystals: mp 122−123 °C; R_f 0.35 (hexanes/ethyl acetate 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.24 (AA′XX′, 2H), 5.51 (m, 1H), 5.38 (dd, 1H, J = 11.0, 4.4 Hz), 5.02 (ddd, 1H, J = 12.3, 10.0, 4.5 Hz), 4.11 (d, 2H, J = 2.5 Hz), 2.40 (s, 3H), 2.17 (t, 1H, J = 2.5 Hz), 1.89 (m, 2H), 1.68−1.26 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.0, 137.8, 133.0, 129.2, 127.5, 126.4, 80.2, 72.3, 53.8, 32.5, 32.4, 26.3, 25.9, 25.5, 25.3, 21.5, 20.8, 20.4. Anal. Calcd for $C_{20}H_{27}NSO_2$ (345.50): C, 69.53; H, 7.88; N, 4.05; S, 9.28. Found: C, 69.39; H, 7.85; N, 4.00; S, 9.41.

***N*-Cyclodec-2-enyl-4-methyl-*N*-(4-oxopent-2-ynyl)benzenesulfonamide (30).** To a solution of enyne **29** (1.60 g, 4.63 mmol) in 40 mL of THF/hexane (1:1) was added *n*-BuLi (1.6 M in hexane; 3.04 mL, 4.86 mmol) dropwise at −78 °C. After the mixture was stirred for 15 min at that temperature, the suspension was warmed to −30 °C and a solution of anhydrous $ZnCl_2$ (662 mg, 4.86 mmol, previously dehydrated with $SOCl_2$ at reflux) in THF (5 mL) was introduced. After another 15 min, acetyl chloride (350 μL, 4.86 mmol) was added via cannula within 5 min and stirring was continued overnight at ambient temperature. Standard extractive workup and flash chromatography (hexanes/ethyl acetate, 10:1 → 7:1) yielded product **30** (1.101 g, 61%) as colorless crystals: mp 92−93 °C; R_f 0.45 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.27 (AA′XX′, 2H), 5.44 (m, 2H), 5.07 (ddd, 1H, J = 12.0, 10.0, 4.7 Hz), 4.31 (d, 1H, J = 19.5 Hz), 4.21 (d, 1H, J = 19.5 Hz), 2.40 (s, 3H), 2.18 (s, 3H), 1.94−1.25 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.6, 143.3, 137.4, 133.4, 129.3, 127.4, 126.0, 87.9, 83.3, 53.7, 32.5, 32.2, 26.3, 25.8, 25.5, 25.2, 21.4, 20.7, 20.3. Anal. Calcd for $C_{22}H_{29}NSO_3$ (387.54): C, 68.18; H, 7.54; N, 3.61; S, 8.27. Found: C, 67.98; H, 7.58; N, 3.56; S, 8.43.

1-[12-(Toluene-4-sulfonyl)-12-azabicyclo[9.2.1]tetradeca-1(14),2-dien-2-yl]ethanone (31). Method A. A suspension of substrate **30** (300 mg, 0.774 mmol) and $PtCl_2$ (21 mg, 0.077 mmol, 10 mol %) in toluene (80 mL) was stirred for 21 h at 100 °C. Removal of the solvent in vacuo and flash chromatography (hexanes/ethyl acetate, 6:1 → 4:1) provided compound **31** as a bright-yellow oil (126 mg, 42%).

Method B. A solution of substrate **30** (1.020 g, 2.632 mmol) and $BF_3{\cdot}Et_2O$ (20 μL, 0.157 mmol, 6 mol %) in toluene (150 mL) was stirred for 22 h at ambient temperature. After this period, more $BF_3{\cdot}Et_2O$ (80 μL, 0.632 mmol, 24 mol %) was added and stirring continued for 17 h. The orange solution was then concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 7:1 → 4:1) afforded product **31** as a bright-yellow oil (551 mg, 54%): R_f 0.19 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (AA′XX′, 2H), 7.26 (AA′XX′, 2H), 6.88 (dd, 1H, J = 9.6, 7.3 Hz), 5.36 (dt, 1H, J = 2.1, 2.0 Hz), 4.53 (m, 1H), 4.40 (dt, 1H, J = 14.6, 2.2 Hz), 3.98 (ddd, 1H, J = 14.6, 2.1 Hz), 2.34 (s, 3H), 2.08 (s, 3H), 2.24−1.17 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.6, 147.5, 143.4, 137.4, 134.6, 132.7, 129.8, 129.7, 127.4, 67.5, 58.5, 32.0, 26.9, 25.9, 25.9, 25.5, 24.9, 24.4, 23.9, 21.5. Anal. Calcd for $C_{22}H_{29}NSO_3$ (387.54): C, 68.18; H, 7.54; N, 3.61. Found: C, 68.30; H, 7.58; N, 3.65.

1-[12-(Toluene-4-sulfonyl)-12-azabicyclo[9.2.1]tetradec-1(14)-en-2-yl]ethanone (32). To a solution of dienone **31** (662 mg, 1.708 mmol), glacial HOAc (108 μL, 1.879 mmol), and $Pd(PPh_3)_4$ (40 mg, 0.034 mmol, 2 mol %) in benzene was added *n*-Bu_3SnH (1.15 mL, 4.27 mmol) dropwise via cannula over 5 min. After the mixture was stirred for 3 h at ambient temperature, the solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes 300 mL, then hexanes/ethyl acetate, 10:1 → 6:1) to give product **32** (465 mg, 70%) as a colorless solid: mp 124−125 °C; R_f 0.46 and 0.42 for both diastereomers (hexanes/ethyl acetate, 4:1). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (AA′XX′, 2H), 7.22 (AA′XX′, 2H), 5.40 (dt, 1H, J = 1.9, 2.0 Hz), 4.55 (m, 1H), 4.07 (ddd, 1H, J = 14.9, 5.4, 1.9 Hz), 3.92 (dt, 1H, J = 14.9, 2.1 Hz); 3.33 (dd, 1 H, J = 10.3, 3.5 Hz), 2.33 (s, 3H), 2.17 (m, 1H), 1.76 (s, 3H), 1.72−1.48 (m, 2H), 1.42−1.03 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 143.4, 135.4, 134.6, 129.6, 129.1, 127.4, 67.3, 54.9, 53.4, 33.5, 28.0, 26.1, 26.0, 25.5, 24.4, 23.9, 23.2, 22.3, 21.4. Anal. Calcd for $C_{22}H_{31}NSO_3$ (389.56): C, 67.83; H, 8.02; N, 3.60. Found: C, 67.86; H, 7.94; N, 3.52.

Thiocarbonic Acid *O*-Phenyl Ester *O*-{1-[12-(Toluene-4-sulfonyl)-12-azabicyclo[9.2.1]tetradec-1(14)-en-2-yl]ethyl} Ester (33). A solution of enone **32** (465 mg, 1.194 mmol) in Et_2O (15 mL) was reacted with $LiAlH_4$ (32 mg, 0.836 mmol) dissolved in Et_2O (5 mL). Standard workup followed by flash chromatography (hexanes/ethyl acetate, 6:1 → 4:1) provided two diastereomeric alcohols (420 mg, 90%) which exhibit the following physical data: mp 164−165 °C; R_f 0.36 and 0.29 (hexanes/ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (AA′XX′, 2H), 7.29 (AA′XX′, 2H), 5.34 (dt, 1H, J = 1.9, 1.8 Hz), 4.59 (m, 1H), 4.19 (m, 2H), 3.53 (v.quint, 1H), 2.40 (s, 3H), 2.22 (m, 2H), 1.53−1.14 (m, 16H), 0.96 (t, 3H, J = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.1, 134.7, 129.6, 128.4, 127.3, 69.5, 66.9, 55.2, 47.6, 33.4, 26.8, 26.0, 25.9, 25.6, 24.1, 23.3, 22.5, 21.4, 21.1; IR (KAP) 3531, 3083, 2942, 2864, 2851, 1710, 1596, 1492, 1476, 1453, 1334, 1157, 1092, 1050, 813, 668, 584 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 391 ([M$^+$] 9), 346 (100), 274 (7), 248 (10), 236 (21), 234 (32), 218 (12), 192 (27), 155 (26), 91 (52), 80 (21), 55 (9), 41 (10).

To a solution of this alcohol (diastereomeric mixture, 140 mg, 0.358 mmol) in CH_2Cl_2 (10 mL) were added PhOC(S)Cl (99 μL, 124 mg, 0.716 mmol) and pyridine (87 μL, 57 mg, 1.074 mmol) via cannula at 0 °C. After the mixture was stirred for 20 h at ambient temperature, the solvent was removed in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1 → 7:1) afforded the title compound **33** as a colorless solid (119 mg, 63%): mp 61−62 °C; R_f 0.49 (hexanes/ethyl acetate, 4:1). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (AA′XX′, 2H), 7.41 (m, 2H), 7.29 (m, 3H), 6.95 (AA′XX′, 2H), 5.31 (dt, 1H, J = 1.8, 1.9 Hz), 5.25 (dd, 1H, J = 6.2, 5.5 Hz), 4.60 (m, 1H), 4.13 (dd, 2H, J = 1.9 Hz), 2.56 (m, 1H), 2.36 (s, 3H), 2.26 (m, 1H), 1.59−1.13 (m, 15H), 0.99 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 153.0, 143.3, 136.3, 134.5, 129.7, 129.5, 129.2, 127.5, 126.5, 121.7, 83.7, 66.9, 55.4, 44.8, 33.5, 26.7, 26.0, 25.8, 25.2, 24.2, 23.1, 22.6, 21.4, 17.2.

2-Ethyl-12-(toluene-4-sulfonyl)-12-azabicyclo[9.2.1]tetradec-1(14)-ene (34). To a solution of substrate **33** (115 mg, 0.218 mmol) in toluene (5 mL) were added AIBN (7 mg, 0.044 mmol, 20 mol %) and *n*-Bu_3SnH (117 μL, 127 mg, 0.436 mmol). The solution was stirred for 4 h at 75 °C. Removal of the solvent in vacuo and flash chromatography of the residue (hexanes (300 mL), then hexanes/ethyl acetate, 20:1 → 16:1) afforded dihydropyrrole **34** as a colorless oil (76 mg, 93%): R_f 0.57 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (AA′XX′, 2H), 7.29 (AA′XX′, 2H), 5.22 (dt, 1H, J = 1.9, 1.8 Hz), 4.60 (m, 1H), 4.09 (ddd, 1H, J = 14.4, 5.2, 1.9 Hz), 3.92 (dt, 1H, J = 14.3, 1.9 Hz), 2.40 (s, 3H), 2.18 (m, 2H), 1.52−0.86 (m, 17H), 0.44 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 140.4, 134.7, 129.5, 127.3, 125.6, 67.2, 53.9, 41.6, 33.4, 30.6, 27.6, 27.2, 26.1, 26.0, 25.9, 24.2, 23.6, 22.4, 21.4, 11.7. Anal. Calcd for $C_{22}H_{33}NSO_2$ (375.58): C, 70.36; H, 8.86; N, 3.73. Found: C, 70.29; H, 8.86; N, 3.68.

2-Ethyl-12-azabicyclo[9.2.1]tetradeca-1(13),11(14)-diene (5). According to the procedure described for the preparation of pyrrole **7**, a solution of dihydropyrrole **34** (76 mg, 0.202 mmol) in 1,3-diaminopropane (2 mL) was treated with the KAPA reagent (7 mL). Compound **5** was thus obtained as a colorless solid (33 mg, 75%): R_f 0.69 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.65 (bs, 1H), 6.40 (t, 1H, J = 2.0 Hz), 5.87 (t, 1H, J = 2.0 Hz), 2.53 (m, 2H), 2.21 (m, 1H), 1.61 (m, 1H), 1.57 (m, 1H), 1.52 (m, 1H), 1.30 (m, 1H), 1.36 (m, 2H), 1.2 (m, 2H), 1.15 (m, 1H), 1.08−1.04 (m, 5H), 0.89 (t, 3H, J = 7.4 Hz), 0.49 (bs, 1H), 0.02 (bs, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 133.0, 128.9, 115.0, 106.3, 41.1, 33.5, 29.3, 29.1, 28.6, 28.0, 27.4, 26.0, 25.7, 21.9, 12.9.

***N*-Cyclooct-2-enyl-*N*-hept-2-ynyl-4-methylbenzenesulfonamide (27).** A solution of enyne **10** (718 mg, 2.262 mmol) in THF (30 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M in hexane; 1.36 mL, 2.175 mmol) was added dropwise at that temperature. After 20 min 1-butyliodide (0.78 mL, 1.249 g, 6.786 mmol) was added dropwise via cannula and stirring was continued for 0.5 h. The reaction mixture was then kept for 5 h at −30 °C prior to slowly warming to ambient temperature. After 30 h, the mixture was quenched with saturated aqueous NH_4Cl (50 mL) and diluted with ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography of the residue (hexanes/ethyl acetate, 15:1) provided enyne **27** (718 mg, 85%) as a colorless oil: R_f 0.68 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.23 (AA′XX′, 2H), 5.61 (m, 2H), 4.84 (ddd, 1H, J = 16.6, 7.2, 5.0 Hz), 4.14 (dt, 1H, J = 18.3, 2.2 Hz), 4.08 (dt, 1H, J = 18.3, 2.2 Hz), 2.40 (s, 3H), 2.23−2.00 (m, 4H), 1.80−1.20 (m, 12H), 0.86 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.2, 130.0, 129.1, 128.6, 127.7, 84.9, 75.9, 55.7, 34.5, 33.7, 30.4, 29.0, 26.3, 24.6, 21.9, 21.5, 18.3, 13.6. Anal. Calcd for $C_{22}H_{31}NSO_2$ (373.56): C, 70.74; H, 8.36; N, 3.75. Found: C, 70.63; H, 8.42; N, 3.79.

4-[Cyclooct-2-enyl(toluene-4-sulfonyl)amino]but-2-ynoic Acid Methyl Ester (11). To a solution of compound **10** (200 mg, 0.63 mmol) in THF (5 mL) was slowly added *n*-BuLi (1.6 M in hexane; 0.37 mL, 0.60 mmol) at −78 °C. After 15 min, the suspension was transferred over a period of 20 min via siphon to a solution of chloroformic acid methyl ester (119 mg, 1.26 mmol) in THF (2 mL) at −35 °C. The solution was kept at that temperature for 0.5 h and then at +10 °C for 15 min. The mixture was quenched with saturated aqueous NH_4Cl (25 mL) and diluted with ethyl acetate (20 mL), the aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue (hexanes/ethyl acetate, 8:1) gave enyne **11** (161 mg, 68%) as a colorless oil: R_f 0.48 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (AA′XX′, 2H), 7.26 (AA′XX′, 2H), 5.64 (dtd, 1H, J = 10.7, 9.0, 1.2 Hz), 5.45 (dd, 1H, J = 10.8, 8.1 Hz), 4.82 (dt, 1H, J = 7.9, 7.8 Hz), 4.29 (d, 1H, J = 19.1 Hz), 4.20 (d, 1H, J = 19.1 Hz), 3.75 (s, 3H), 2.41 (s, 3H), 2.28−2.04 (m, 2H), 1.70−1.22 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.3, 143.4, 137.1, 131.0, 129.4, 127.5, 127.4, 83.7, 75.7, 55.6, 52.6, 34.2, 32.9, 28.7, 26.2, 25.8, 24.4, 21.5.

10-(Toluene-4-sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene-2-carboxylic Acid Methyl Ester (13). To a solution of enyne **11** (280

mg, 0.746 mmol) in toluene (50 mL) was added $PtCl_4$ (24 mg, 0.071 mmol, 10 mol %) at ambient temperature. The beige suspension was stirred for 3 d at that temperature. Removal of the solvent in vacuo followed by flash chromatographic purification of the residue (hexanes/ethyl acetate, 6:1 → 4:1) afforded compound **13** (238 mg, 85%) as colorless crystals: mp 108−109 °C; R_f 0.28 (hexanes/ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (AA′XX′, 2H), 7.32 (AA′XX′, 2H), 7.07 (dd, 1H, J = 8.1, 6.1 Hz), 5.45 (dt, 1H, J = 1.9, 1.8 Hz), 4.73 (m, 1H), 4.48 (dt, 1H, J = 14.3, 2.2 Hz), 4.23 (ddd, 1H, J = 14.2, 4.9, 1.7), 3.66 (s, 3H), 2.43 (s, 3H), 2.34−2.20 (m, 2H), 2.15−2.11 (m, 1H), 1.80−1.30 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 148.3, 143.3, 135.4, 131.9, 131.6, 129.8, 129.7, 128.8, 127.3, 67.2, 51.9, 35.7, 28.9, 27.4, 26.6, 21.5, 20.4.

Acknowledgment. This paper is dedicated with deep respect to Prof. Reinhard W. Hoffmann on the occasion of his 65th birthday. Financial support of our work by the Fonds der Chemischen Industrie is gratefully acknowledged. We also thank Ms. C. Wirtz for measuring some of the NMR spectra.

Supporting Information Available: Compilation and full assignment of the NMR data of compounds **12**, **16**, **21**, **22**, **24**−**26**, and **35**, listing of the MS and IR data, and copies of the NMR spectra of all new compounds (71 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981183G