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A Straightforward and Versatile Synthetic Approach to 1-Azabicyclic Alkaloids

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A very straightforward route to 1-azabicyclo alkaloid scaffolds with several ring sizes is reported. The final bicyclic structures were built through a synthetic scheme that involved (i) the construction of dienic 4-piperidone systems by an imino-Diels–Alder reaction between aminotrienes and *N*-ω-vinylimines, in the presence of $Yb(OTf)_3$, and (ii) the ring-closing metathesis reaction of these cyclic dienes, under the influence of the first-generation Grubbs' Ru-complex catalyst. During this investigations, various polysubstituted azabicyclic ring skeletons, including several examples of the quinolizidine alkaloids, are reported, and their relative stereochemistry is adequately discussed.

Introduction

Indolizidine and quinolizidine skeletons can be found in many important biological natural products.[1] These nitrogen derivatives occur in plants, insects, and amphibians and exhibit notable biological activities.[2] Therefore, the stereoselective synthesis of these bicyclic skeletons has become an important goal for synthetic chemists in the recent years.

Among these derivatives, 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines, such as indolizidine 209B and quinolizidine 207I, respectively, constitute an important group that have received great attention and study (Figure 1). These types of alkaloids are isolated from skin extracts of neotropical members of tropical amphibians and ants and possess interesting features such as noncompetitive blockers for muscle-type and ganglionic nicotinic receptor channels.[3] Moreover, the 4-arylquinolizidine substructure is a characteristic structural motif present in the Lythraceae family of alkaloids. Representative lythraceous alkaloids are lasubine I, lasubine II,[4] subcosine II,[5] and the macrocycles lythrancepine[6] and vertaline[7] (Figure 1).

Because of the importance of these natural products, the synthesis of higher 1-azabicyclic analogues with various ring sizes would be of great interest (Figure 2). Despite that, very little effort has been made toward this aim, and the synthetic strategies published in the literature are in general long, describe the preparation

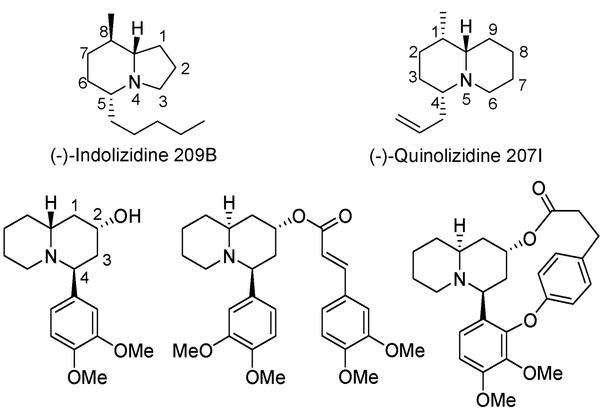

FIGURE 1. Examples of natural "izidine-type" alkaloids.

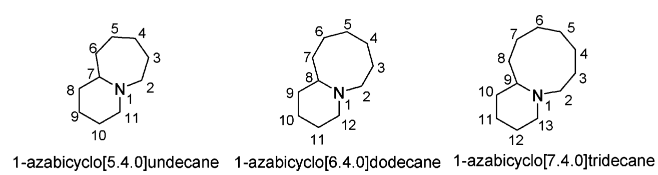

FIGURE 2. Examples of 1-azabicyclo[*x*.4.0]alkanes and conventional numbering.

(1) For reviews, see: (a) Daly, J. W.; Garraffo H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: London, U.K., 1993; Vol. 43, pp 185–288. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, Chapter 1, pp 1–161. (c) Michael, J. P. *The Alkaloids* **2001**, *55*, 91. (d) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (e) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719. (f) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. (g) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579. (h) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (i) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 571.

(2) For an example, see: Rolf, S.; Haverkamp, W.; Borggrefe, M.; Musshoff, U.; Eckardt, L.; Mergenthaler, J.; Snyders, D. J.; Pongs, O.; Speckmann, E.-J.; Breithardt, G.; Madeja, M. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 22.

(3) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213.

(4) Some recent examples of the synthesis of lasubine I and II: (a) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855. (b) Gracias, V.; Zeng, Y.; Desai, P.; Aube, J. *Org. Lett.* **2003**, *5*, 4999. (c) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (d) Davis, F.; Chao, B. *Org. Lett.* **2000**, *2*, 2623 and references therein.

(5) For an asymmetric approach to lasubine I, II and subcosine II, see: Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361.

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of slightly substituted scaffolds, and have not proven to be sufficiently general.[8]

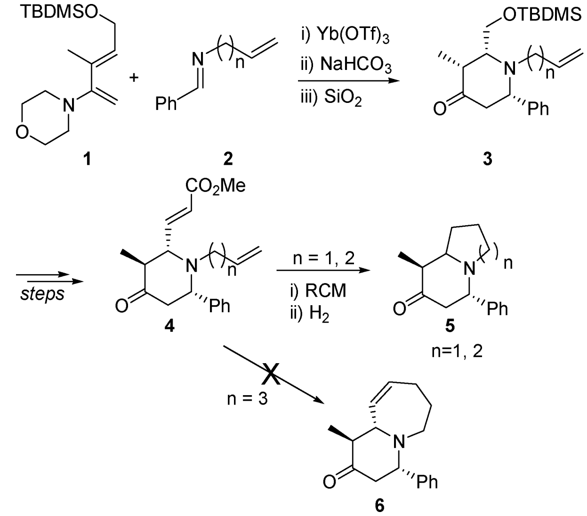
On the other hand, our research group has been working for many years in the development of synthetic applications of 2-amino-1,3-butadiene reagents. Thus, we have demonstrated that these dienes are particularly useful in imino-Diels−Alder cycloaddition with nonactivated imines.[9] This reaction furnishes, after hydrolysis of the enaminic cycloadduct, polysubstituted 4-piperidones with a high degree of stereoselectivity.[10] Moreover, we have recently implemented this process into the solid phase.[11]

As a part of our investigation on the synthetic applications of the 2-aminodienes we have described the preparation of the natural indolizidine (−)-nupharamine by derivatization of an enantiopure piperidone.[12] More recently, we disclosed a more concise and convergent route to 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines employing a synthetic strategy that required three main stages: (i) stereoselective preparation of functionalized 4-piperidones **3** from 2-amino-1,3-butadienes **1** and *N*-ω-vinylimines **2** by imino-Diels−Alder reaction, (ii) transformation of the piperidones **3** into dienes **4**, and (iii) ring-closing metathesis (RCM) of **4** to afford, after hydrogenation in an ultimate step, the bicyclic saturated indolizidine and quinolizidine skeletons **5** (Scheme 1).[13]

This methodology demonstrated its potential for the preparation of indolizidines (1-azabicyclo[4.3.0]nonanes) and quinolizidines (1-azabicyclo[4.4.0]decanes) but failed in the synthesis of 1-azabicyclo[5.4.0]undecene **6** as a result of the known prevention of the RCM process to yield a seven-membered ring from a disubstituted olefin.[14]

With this previous work in mind, we initiated a research plan aimed at the development of a new route for the synthesis of 1-azabicyclic skeletons based again on the imino-Diels−Alder/RCM sequence. Herein, we expound on our recent studies, which represent an extension and improvement of our previous work and which have resulted in a more general, straightforward, and convergent synthetic methodology for the preparation not only of indolizidine and quinolizidine frameworks but also of larger members of this class of bicyclic alkaloids, with a high degree of diversity.

SCHEME 1. Synthesis of Indolizidines and Quinolizidines



Results and Discussion

Taking into account that the RCM of terminal unsubstituted alkenes is usually more favorable, we envisioned the dienes **II** as the ideal precursors of bicyclic target **I**. The synthesis of cyclic diene **II** would be easily achieved by imino-Diels−Alder reaction of an aminotriene with general structure **III** an the proper imine **IV**. Moreover, the improved versatility of this route would permit variations on the position of the ω-vinyl substituent in both cycloaddition partners **III** and **IV**, giving rise to different ring sizes and double bond positions in the final bicyclic structure. In addition, variation in the substitution pattern on the reactants would furnish final products with a higher degree of diversity and would be suitable for the parallel synthesis of a series of these bicyclic alkaloids (Scheme 2).

Synthesis of Aminotrienes III. The first step in the synthetic route was the efficient preparation of 2-aminotrienes **III**, which could be achieved by hydroamination[15] of the corresponding terminal dienynes **V**. To the best of our knowledge, dienynes with the general structure **V** had not been previously reported, and therefore a new synthetic strategy was urgent.

The known alcohols **8** (Scheme 3) were chosen as the starting point for the preparation of a series of dienynes. Alcohols **8** were synthesized following published procedures[16] developed by the Trost research group, which consisted of the addition of trimethylsilylacetylene to a substituted propiolate **7**, in the presence of $Pd(OAc)_2$. The

(6) For references on the total syntheses of lythrancepine alkaloids: (a) Hart D.; Hong, W.; Hsu, L. *J. Org. Chem.* **1987**, *52*, 4665. (b) Hart, D., Hong, W. *J. Org. Chem.* **1985**, *50*, 3670.

(7) Total syntheses of Verltaline: (a) Shishido, K.; Tanaka, K.; Fukumoto, K. *Tetrahedron Lett.* **1983**, *24*, 2783. (b) Hart, D.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.

(8) (a) Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127. (b) Tehrani, K.; D'hooghe, M.; DeKimpe, N. *Tetrahedron* **2003**, *59*, 3099. (c) Lindemann, U.; Wulff-Molder, D.; Wessig, P. *Tetrahedron: Asymmetry* **1998**, *9*, 4459. (d) Zeng, Y.; Smith, B. T.; Hershberger, J.; Aubé, J. *J. Org. Chem.* **2003**, *68*, 8065. (e) Haddad, M.; Célérier, J. P.; Haviari, G.; Lhommet, G. *Heterocycles* **1990**, 31, 1251. (f) Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4173.

(9) For reviews, see: (a) Boger D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 2. (b) Waldmann, H. *Synthesis* **1994**, *535*. (c) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (d) Waldmann, H. *Synlett* **1995**, 133. (e) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, 190. (f) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131. (g) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (h) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435.

(10) (a) Barluenga, J.; Aznar F.; Valdés, C.; Cabal M. P. *J. Org. Chem.* **1993**, *58*, 3391. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403. (c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo J. *Chem. Eur. J.* **1996**, *2*, 805. (d) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem.* **1998**, *63*, 3918.

(11) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 3667.

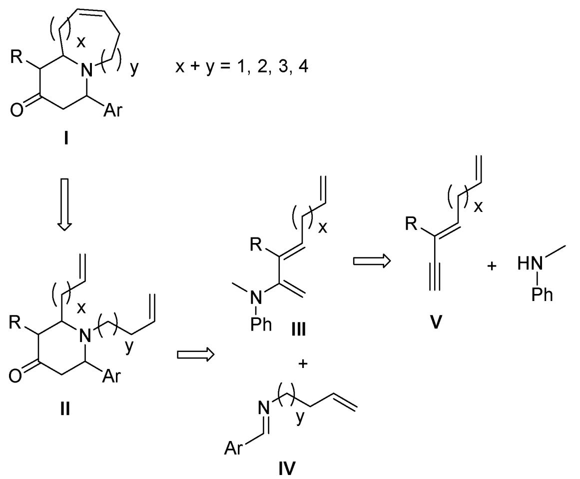
(12) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736.

(13) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 1971.

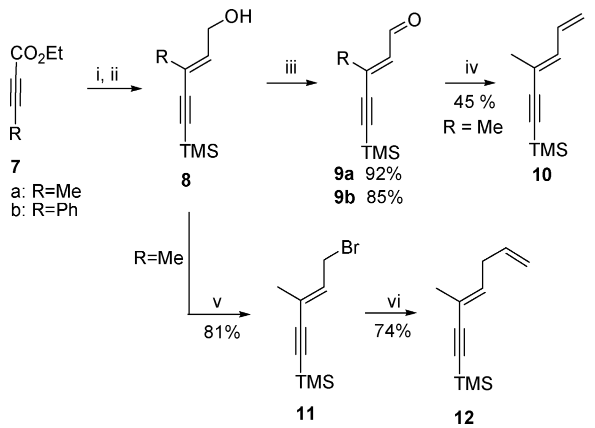
(14) For effects of olefin substitution on RCM reactions, see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(15) (a) Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1375. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M. P. *J. Org. Chem.* **1991**, *56*, 6166.

SCHEME 2. Retrosynthetic Approach to 1-Azabicyclic Skeletons I



SCHEME 3. Synthesis of Dienynes 10 and 12[a]



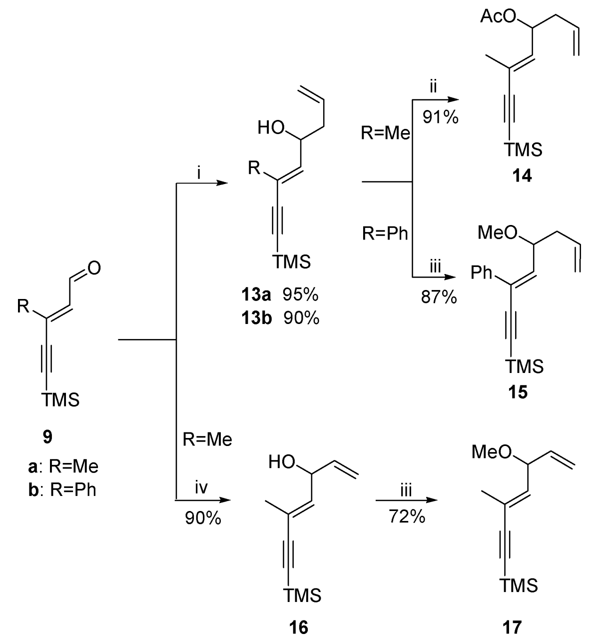
[a] (i) Trimethylsilylacetylene, $Pd(OAc)_2$, TDMPP, THF, rt; (ii) DIBAL-H, toluene, −80 °C; (iii) Dess−Martin periodinane, DCM, rt; (iv) methyltriphenylphosphorane, DCM, −40 °C; (v) CBr_4, PPh_3, CH_3CN; (vi) $Sn(CH{=}CH_2)_4$, 3 mol % $(CH_3CN)_2PdCl_2$, 1.5 mol % PPh_3, $CHCl_3$, 60 °C.

resulted unsaturated ester was then reduced with DIBAL-H to yield the enyne **8**. This protocol turned out to be very useful as it allows for the introduction of different substitution in the enyne **8** by changing the substituents in the starting ethynyl ester **7**.

Finally, alcohol **8a** was readily transformed into dienyne **10** by smooth oxidation using Dess−Martin periodinane[17] followed by Wittig olefination of aldehyde intermediate **9a**.

On the other hand, alcohols **8** served also as the starting materials for the preparation of the homologous dienyne **12** (Scheme 3), which was prepared via a Stille cross-coupling reaction of the correspondent allyl bromide **11**.[18] Compound **11** was synthesized upon treatment of alcohol **8a** with CBr_4 and PPh_3.[19] Two different vinyltin reagents were tested in the cross-coupling step: tetrabutylvinyltin and tetravinyltin, providing similar results; therefore, we chose the latter because of its lower cost. The effect of the palladium catalyst was also studied in the cross-coupling reaction, and the best results after testing different complexes were achieved with a combination of 3 mol % $(CH_3CN)_2PdCl_2$ and 1.5 mol % PPh_3. The optimized reaction conditions for the synthesis of methyl-substituted dienyne **12** are shown in Scheme 3.

SCHEME 4. Synthesis of Oxy-Substituted Dienynes[a]



[a] (i) Allylmagnesium bromide, THF, 0 °C; (ii) Ac_2O, pyridine, rt; (iii) MeI, KOH, reflux; (iv) vinylmagnesium bromide, THF, 0 °C.

An alternative method, suitable for synthesizing functionalized dienynes, involves the addition of ω-vinyl Grignard reagents to aldehydes **9**. Thus, the reaction between conjugated aldehydes **9** and allylmagnesium bromide afforded allyllic alcohols **13**, which were subsequently protected as acetate **14** and methyl ether **15** (Scheme 4). On the other hand, to demonstrate the versatility of this approach, dienyne **17** was prepared by a similar procedure, by addition of vinylmagnesium bromide to aldehyde **9a** followed by methylation of the resulting alcohol **16**. It is noteworthy that the present methodology would allow for the straightforward preparation of larger alkyl chain dienynes, by exposing aldehydes **9** to longer chain ω-vinylmagnesium halides in a similar manner as described above.

With a series of structurally diverse dienynes in hand we studied the hydroamination of the triple bond in order to synthesize the required 2-aminotrienes **III**. Mercury-catalyzed hydroamination of the triple bond represents a very efficient method for the synthesis of 2-amino-1,3-butadiene derivatives but implies the existence of a

(16) (a) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *117*, 698. (b) Trost, B. M.; McIntosh, M. *Tetrahedron Lett.* **1997**, *38*, 3207.

(17) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Herlem, D.; Khuong-Huu, F.; Kende, A. S. *Tetrahedron Lett.* **1993**, *34*, 5587.

(18) (a) Stille, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Kosugui, M.; Miyajima, Y.; Nakanishi, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3383. (c) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840. (d) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.

(19) (a) Lee, J. B.; Downie, I. M. *Tetrahedron* **1967**, *23*, 359. (b) Friederang A. W.; Tarbell, D. S. *J. Org. Chem.* **1968**, *33*, 3797. (c) Kim, S.; Lee, J.; Lee, T.; Park, H.-G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703.

SCHEME 5. Synthesis of Aminotrienes 18

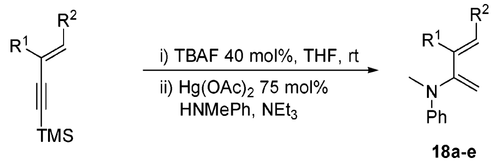
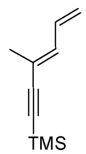
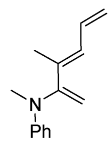
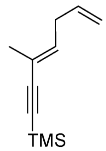
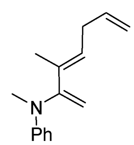
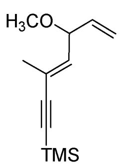
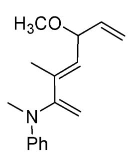
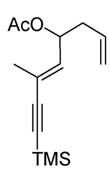
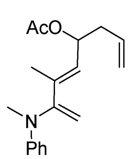
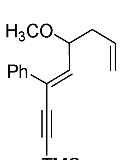
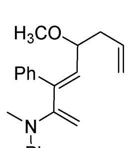


TABLE 1. Aminotrienes 18 Prepared from Scheme 5

Dienyne	Aminotriene	Yield %
 **10**	 **18a**	56[a]
 **12**	 **18b**	52[a]
 **17**	 **18c**	48[b]
 **14**	 **18d**	47[b]
 **15**	 **18e**	48[b]

[a] Hydroamination carried out at room temperature. [b] Hydroamination carried out at THF reflux.

terminal alkyne.[20] However, the procedures outlined above afforded trimethylsilylated species that should be desilylated. The deprotection step resulted in a very inefficient process in some cases, as a result of the volatility of the resulting terminal alkynes. To avoid this problem, a one-pot procedure of deprotection followed by hydroamination was devised. Thus, the dienynes were exposed to a minimized quantity of 40 mol % TBAF in THF, and after tracing the transformation until completion by TLC, the standard protocol for the hydroamination with *N*-methylaniline was followed in the same reaction flask. Finally, isolation following published procedures gave the desired aminotrienes **18** in a comparable yield with the two-step process (Scheme 5, Table 1).

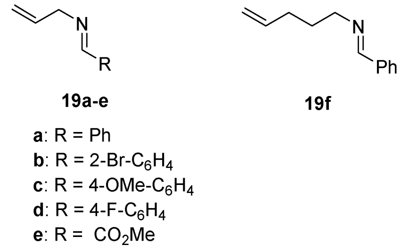
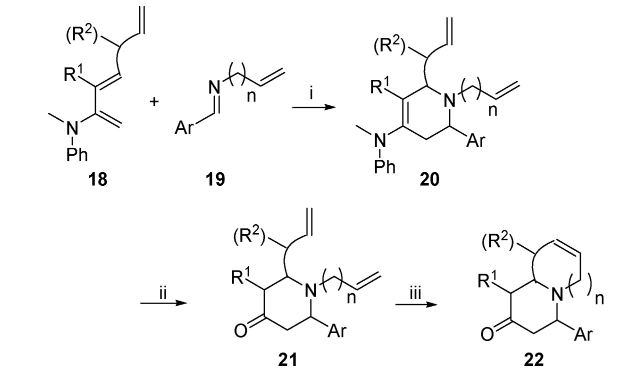


FIGURE 3. Imines **19** prepared.

SCHEME 6. Synthesis of 1-Azabicyclic Alkaloids 22 through the Cycloaddition−RCM Sequence[a]



[a] (i) 20 mol % $Yb(OTf)_3$, THF, rt; (ii) 2% TFA/DCM, rt; (iii) 3.5 mol % $Cl_2(PCy_3)_2Ru{=}CHPh$, 10^{-2} M, DCM, 40 °C.

Under the standard conditions discussed previously, dienynes **10**, **12**, **14**, **15**, and **17** were transformed into the correspondent aminotrienes **18** with moderate yields. Although the hydroamination of dienynes **10** and **12** occurred at room temperature, in the case of the preparation of **18c**−**e** the reaction temperature had to be increased to THF reflux to reach completion.

Imine Synthesis. Imine formation was achieved from correspondent aldehydes and amines employing trimethylorthoformate as dehydrating agent.[21] The synthesized imines include examples derived from electron-donating as well as electron-withdrawing aromatics and also from ethyl glyoxylate (Figure 3).[22]

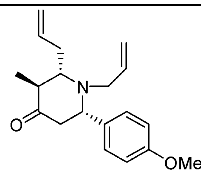
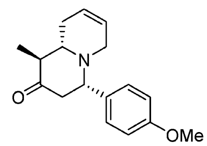
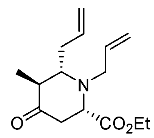
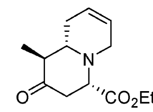
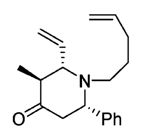
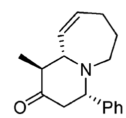
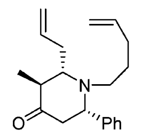
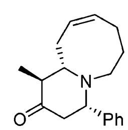
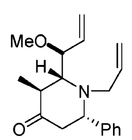
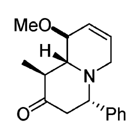
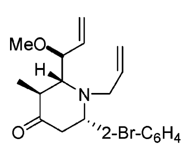
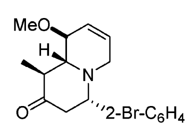
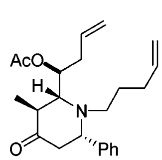
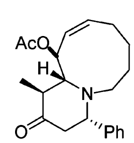
Imino-Diels−Alder and RCM Reactions. The general procedure to access the bicyclic scaffolds is depicted in Scheme 6. The imino-Diels−Alder reaction between aminotrienes **18** and imines **19** consisted of a modified

(20) Barluenga, J.; Aznar, F.; Liz, R.; Rodes, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1087.

(21) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

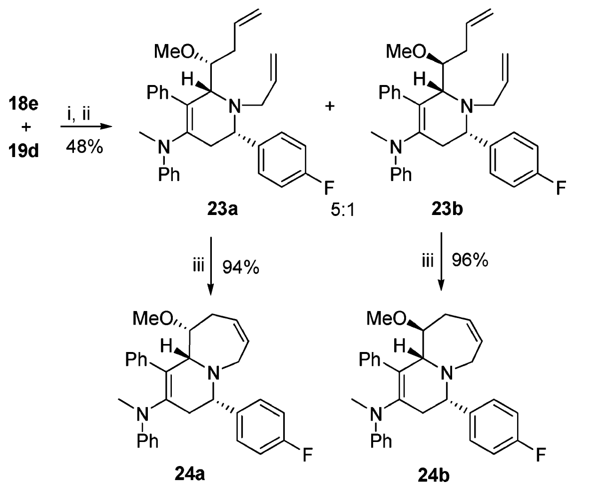
(22) Our study did not include *C*-alkyl-substituted imines, because usually these systems provide poor results in the imino-Diels−Alder reactions with 2-aminodienes.

TABLE 2. Cycloaddition Reactions of Dienes 18 and Imines 19 and RCM of the Resulting Cyclic Dienes; Synthesis of Structurally Diverse Bicyclic Frameworks 22

Entry	Triene	Imine	Cycloaddition Product	Yield[a] %	RCM Product	Yield[a] %
1	**18b**	**19c**	 **21a**	55	 **22a**	95
2	**18b**	**19e**	 **21b**	45	 **22b**	97
3	**18a**	**19f**	 **21c**	45	 **22c**	95
4	**18b**	**19f**	 **21d**	52	 **22d**	97
5	**18c**	**19a**	 **21e**	51[b]	 **22e**	93[b]
6	**18c**	**19b**	 **21f**	55[b]	 **22f**	97[c]
7	**18d**	**19f**	 **21g**	50[b]	 **22g**	95[b]

[a] After chromatographic purification. [b] Product obtained as a 5:1 mixture of diastereoisomers. [c] Yield of the reaction. Both diastereoisomers were subsequently separated.

SCHEME 7. Synthesis of Enamine-Containing Azabicycles[a]



[a] (i) 20 mol % $Yb(OTf)_3$, THF, rt; (ii) 2% TFA/DCM, rt; (iii) 3.5 mol % $(PCy_3)_2Cl_2Ru{=}CHPh$, 10^{-2} M, DCM, 40 °C.

method to that reported previously.[13] The correspondent imine was exposed to an equimolecular amount of the aminotriene in the presence of 20 mol % $Yb(OTf)_3$. Then, to prevent problems during purification, crude enaminic cycloadducts **20** were hydrolyzed with TFA 2% in DCM to give dienic 4-piperidones **21** in moderate yields. These new dienes **21** were treated with Grubbs' first-generation catalyst to afford the desired azabicycles **22** in nearly quantitative yields. The results of both cycloaddition and RCM reactions are represented in Table 2.

The cycloaddition reaction under the conditions described above proceeded with total diastereoselectivity when dienes **18a** and **18b** were employed, to afford the adducts **21a**−**d**, which bear the substituents in positions 2 and 6 in a *cis* relationship (entries 1−4). The diastereoisomer obtained corresponds to an *endo* approach of the substituent attached at the carbon atom of the imine in a formal [4 + 2] cycloaddition, a general trend in the aza-Diels−Alder reactions of 2-amino-1,3-butadienes.[10] The dienic 4-piperidones subjected to the RCM process with the Grubbs' first-generation Ru-complex as catalyst afforded unsaturated bicyclic structures in nearly quantitative yields. Thus, substituted unsaturated quinolizidines **22a** and **22b** were obtained with total diastereoselectivity from aminotriene **18b** and *N*-allylimines **19c** and **19e**, respectively, after the cycloaddition-RCM sequence (entries 1 and 2).

Different combinations of dienes and imines allow for the construction of various bicyclic frameworks. For instance, 1-azabicyclo[5.4.0]undecene **22c** could be accessed with total diastereoselectivity and very high yield from aminotriene **18a** and imine **19f** after RCM of the dienic 4-piperidone **21c** (entry 3). The 1-azabicyclo-[6.4.0]dodecene **22d** homologous was formed following the identical method starting from aminotriene **18b** and imine **19f** (entry 4).

On the other hand, the use of methoxy-substituted 2-aminotriene **18c** would lead to bicyclic structures with an additional stereocenter. However, the cycloaddition reaction with *N*-allylimines **19a,b** gave rise to a mixture of two diasteromeric cycloadducts in a 5:1 relationship as a result of the moderate facial diastereoselectivity of the process. Nevertheless, the mixture of diastereoisomers was subjected to the RCM conditions to furnish the expected unsaturated quinolizidines **22e** and **22f** with very high yield (entries 5 and 6).

Interestingly, the choice of acetoxy-substituted aminotriene **18d** permitted the synthesis of 4-piperidone **21g**, isolated again as a 5:1 mixture of diastereoisomers. This underwent ring closure to 1-azabicyclo[7.4.0]tridecene **22g**, which features the piperidone fused to a nine-membered ring, with quantitative yield (entry 7).

In the context of constructing large rings by RCM,[23] concentration of reactants must be taken into account. It is known that in the formation of macrocycles by RCM, secondary dimerization products are often isolated,[24] it being necessary to employ high dilute solutions. However, we obtained the desired compounds with no byproducts using a concentration of 10^{-2} M in all cases. Additionally, as Grubbs' first-generation carbene is reported to be moderately thermally unstable,[25] the catalyst had to be added in two portions to reach completion of the reaction. Optimized cyclization conditions were 3.5 mol % Grubbs' catalyst, 40 °C, DCM, 8 h.

As shown in Table 2, a variety of imines can be employed in the cycloaddition-RCM process. Noticeably, the overall yields showed no dependence on the imine nature, with similar values in all cases. Interestingly, the use of imino ester **19e** allows for the preparation of bicyclic derivatives of the α-amino acid pipecolic acid[26] and may also permit further elaboration of the side chain (entry 2).

It must be mentioned that the stereochemical integrity of the stereocenters remained unaltered during the transformation of dienic compounds to bicyclic systems. The sterochemistry of all of the products was deduced by ^{1}H NMR and qualitative NOESY experiments.

On the other hand, the reaction of phenyl-substituted aminotriene **18e** with imine **19d** afforded a 5:1 mixture of diasteromeric enamines **23a** and **23b**, which unlike the previous examples did not undergo hydrolysis of the enamine moiety under the standard conditions (2% TFA/DCM). Despite that, we decided to perform further with the enamine. Both isomers reacted successfully with Grubbs' catalyst to provide bicyclic enamines **24a** and **24b**, respectively, in quantitative yield (Scheme 7). Interestingly, the presence of the enamine functionality did not diminish the activity of the Grubbs' catalyst, which performed equally efficiently.[27] This remarkable result opens the door to the preparation of diverse amine-substituted bicyclic structures, simply by employing different secondary amines in the aminodiene synthesis.

Conclusion

In summary, we have described the general preparation of polysubstitued 1-azabicycloalkenes by a imino-

(23) For a review on the preparation of medium-sized rings by RCM, see: Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(24) See the following for preparation of macrocycles by RCM: (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürtsner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.

(25) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

(26) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Tetrahedron Lett.* **2002**, *43*, 8159.

(27) For an example of participation of β-carboline and isoquinoline enamines in RCM processes, see: Evans, P.; Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 3967.

Diels–Alder/RCM sequence in a highly concise and convergent manner. The process can be carried out with a variety of aminotrienes and imines to provide the bicyclic structures carrying different substituents. Moreover, by variation of both cycloaddition partners, bicyclic frameworks featuring a piperidine ring fused to a ring of various sizes (six- to nine membered) can be accessed with a high degree of diversity and through a common and very short synthetic route. Therefore, the strategy described herein represents a very versatile approach to 1-azabicyclic skeletons which could be adapted to parallel synthesis. The implementation of this methodology into the solid phase, and the development of an enantioselective version are our current goals in this area, and our progress will be reported in due course.

Experimental Section

General Methods. The same experimental techniques were used as previously reported.[13] The starting materials were obtained following literature procedures: imines **19a–f**,[21] *N*-pent-4-en-1-amine,[28] and enynes **8a** and **8b**.[16]

General Procedure for the Dess–Martin Oxidation of Allylic Alcohols 8a and 8b. A solution of the correspondent enyne (3 mmol) in de DCM (5 mL) was treated at room temperature with a solution of Dess–Martin periodinane (8.5 g, 15% in DCM, 3 mmol). After stirring for 1 h, the resulting mixture was poured into an Erlenmeyer flask containing ether (50 mL), and NaOH 3 N (10 mL) was added. After 15 min of stirring, the aqueous phase was extracted with ether (20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated cautiously at room temperature under reduced pressure. The oil obtained is essentially pure aldehyde that can be further purified by distillation under 8 mbar vacuum.

(*E*)-3-Methyl-5-(trimethylsilyl)pent-2-en-4-ynal 9a. Prepared from alcohol **8a**. Obtained as a colorless liquid, 92% yield: bp 70 °C (8 mbar), $R_f = 0.15$ (Hex/EtOAc 20:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 10.05 (d; $J = 8.0$; 1H), 6.25 (dq; $J = 8.0$, $^4J = 1.4$; 1H), 2.31 (d; $^4J = 1.4$; 1H), 0.26 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 190.3 (C), 140.1 (C), 134.1 (CH), 105.6 (C), 105.0 (C), 18.3 (CH_3), −0.4 (CH_3). HRMS (EI) calcd for $C_9H_{14}OSi$-CH_3: 151.0574, found 151.0574.

Wittig Methylenation of Aldehyde 9a. Trimethyl((*E*)-3-methylhexa-3,5-dien-1-ynyl)silane 10. To a suspension of triphenylphosphonium bromide (3 g, 8.5 mmol) in toluene (20 mL) was added $NaNH_2$ (1 g, 25 mmol), and the resulting mixture was stirred overnight. The solution was filtered under N_2, and the filtrate was concentrated under high vacuum to obtain methylentriphenylphosphorane as a yellow crystalline solid (2.1 g, 7.3 mmol, 85%). This ylide was dissolved in THF (10 mL) and was added dropwise to a −50 °C solution of aldehyde **9a** (800 mg, 4.9 mmol) in THF (10 mL). After the mixture stirred for 10 min, water (0.2 mL) was added, and the temperature was allowed to reach room temperature. Then, the solution was dried over anhydrous Na_2SO_4 and cautiously concentrated under reduced pressure without heating. Purification by column chromatography (silica gel, eluent Hex/ether 10:1) afforded dienyne **10** as a colorless oil in 45% yield: $R_f = 0.60$ (Hex) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.65–6.52 (m; 1H), 6.42 (d; $^3J = 11.2$; 1H), 5.27 (d; $^3J_{trans} = 17.8$; 1H), 5.16 (d; $^3J_{cis} = 9.1$; 1H), 1.88 (s, 3H), 0.22 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 137.1 (CH), 132.2 (CH), 119.5 (C), 119.2 (CH_2), 108.6 (C), 93.7 (C), 17.4 (CH_3), 0.0 (CH_3). HRMS (EI) calcd for $C_{10}H_{16}Si$: 164.1016, found 164.1012.

Preparation of Allylic Bromide 11. ((*E*)-5-Bromo-3-methylpent-3-en-1-ynyl)trimethylsilane 11. To a solution of alcohol **8a** (3 mmol) in CH_3CN (15 mL) was added PPh_3 (1.2 g, 4.5 mmol), and the resulting mixture was cooled to 0 °C. Then CBr_4 (1.5 g, 4.5 mmol) was added in little portions, and the suspension was stirred for 1 h. After this period of time, CH_3CN was evaporated under reduced pressure. Purification by column chromatography (silica gel, hexanes) afforded dienyne **11** as a colorless oil in 81% yield: bp 60 °C (0.1 mmHg), $R_f = 0.42$ (Hex) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.16 (tq; $^3J = 8.5$, $^4J = 1.5$; 1H), 4.02 (d; $^3J = 8.5$; 2H), 1.92 (d; $^4J = 1.5$; 3H), 0.25 (s: 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 132.3 (CH), 124.1 (C), 106.7 (C), 94.7 (C), 27.3 (CH_2), 16.9 (CH_3), −0.1 (CH_3). HRMS (EI) calcd for $C_9H_{15}BrSi$: 230.0130, found 230.0130.

Stille Cross-Coupling of Allylic Bromide 11. Preparation of the Dienyne Trimethyl ((*E*)-3-Methylhepta-3,6-dien-1-ynyl)silane 12. PPh_3 (23 mg, 0.09 mmol, 1.5 mol %) was added to a pressure Schlenk containing a solution of $(CH_3CN)_2PdCl_2$ (45 mg, 0.18 mmol, 3 mol %) in chloroform (30 mL). The resulting mixture was stirred until a homogeneous solution was formed. Then, allylic bromide **11** (1.4 g, 6 mmol) and tetravinyltin (1.3 g, 6 mmol) were added, and the resulting mixture was heated to 60 °C for 2 h. TBME (50 mL) was added, and the solution was washed with aqueous KF 10% (4 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexanes) afforded dienyne **12** as a colorless oil in 74% yield: $R_f = 0.43$ (Hex) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.91–5.77 (m; 1H), 5.72 (t; $^3J = 7.4$; 1H), 5.09 (d; $^3J_{trans} = 17.6$; 1H), 5.01 (d; $^3J_{cis} = 10.1$; 1H), 3.09 (t; $^3J = 7.1$; 2H), 1.85 (s; 3H), 0.22 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 136.1 (CH), 136.0 (CH), 119.0 (C), 115.1 (CH_2), 104.3 (C), 97.9 (C), 35.1 (CH_2), 22.8 (CH_3), 0.1(CH_3). HRMS (EI) calcd for $C_{11}H_{18}Si$: 178.1178, found 178.1177.

General Procedure for the Addition of Grignard Reagents to Aldehydes 9a and 9b. To a solution of the aldehyde (5.4 mmol) in ether (20 mL) cooled to 0 °C was added dropwise the correspondent Grignard reagent (vinylmagnesium bromide or allylmagnesium bromide) (6.5 mL, 1 M solution in THF, 6.5 mmol). The resulting mixture was stirred for 10 min at 0 °C. Then, a saturated aqueous solution of NH_4Cl (5 mL) was added, and the aqueous mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by column chromatography.

(*E*)-5-Methyl-7-(trimethylsilyl)hepta-1,4-dien-6-yn-3-ol 16. Prepared from conjugated aldehyde **9a**. Obtained as a colorless oil in 90% yield: $R_f = 0.13$ (Hex/EtOAc 10:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.84 (d; $^3J = 6.8$; 1H), 5.82–5.77 (m; 1H), 5.25 (d; $^3J = 17.3$; 1H), 5.12 (d; $^3J = 10.3$; 1H), 4.86 (t; $^3J = 7.1$; 1H), 1.85 (s; 3H), 0.32 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 138.2 (CH), 138.1 (CH), 120.1 (C), 115.2 (CH_2), 107.2 (C), 92.3 (C), 69.5 (CH), 17.5 (CH_3), −0.1 (CH_3). HRMS (EI): calcd for $C_{11}H_{18}OSi$-CH_3: 179.0887, found 179.0888.

General Procedure for the Protection of Alcohols 13b and 16 as Methyl Ethers. To a flask containing the correspondent alcohol (3 mmol) was added MeI (4 mL). To the resulting mixture was added powdered KOH (0.5 g), and the suspension was heated to reflux with stirring for 1 h. Then, HCl 2 N (5 mL) and ether (10 mL) were added. The layers were separated, and the aqueous phase was extracted with ether (4 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was generally pure enough for most purpose.

((*E*)-5-Methoxyhepta-3-methyl-3,6-dien-1-ynyl)trimethylsilane 17. Prepared from alcohol **16**. Obtained as a colorless oil in 72% yield: $R_f = 0.43$ (Hex/EtOAc 10:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.84 (d; $^3J = 7.1$; 1H), 5.82–5.69 (m; 1H), 5.28 (dd; $^3J = 17.0$, $^2J = 1.5$; 1H), 5.22 (dd; $^3J = 10.5$, $^2J = 1.5$; 1H), 4.37 (t; $^3J = 7.8$; 1H), 3.31 (s; 3H), 1.85 (d; $^4J = 1.4$; 1H), 0.21 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 136.9 (CH),

(28) (a) Jacobson, M. A.; Williard, P. G. *J. Org. Chem.* **2002**, *67*, 3915. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

136.1 (CH), 121.1 (C), 116.7 (CH_2), 107.2 (C), 92.1 (C), 78.6 (CH_3), 55.8 (CH), 17.7 (CH_3), −0.1 (CH_3). HRMS (EI) calcd for $C_{12}H_{20}OSi$-CH_3: 193.1043, found 193.1037.

Acetylation of Alcohol 13a. (*E*)-6-Methyl-8-(trimethylsilyl)octa-1,5-dien-7-yn-4-yl Acetate 14. To a solution of alcohol **13a** (900 mg, 4.5 mmol) in pyridine (3 mL) and acetic anhydride (500 mg, 5 mmol) were added. After the resulting mixture stirred for 4 h, TBME (20 mL) was added, and the organic layer was washed with HCl 1 N (4 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford acetate **14** pure enough for the next transformation. This compound was obtained as a colorless oil in 91% yield: R_f = 0.32 (Hex/EtOAc 20:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 5.78 (d; ^3J = 9.4; 1H), 5.75−5.63 (m; 1H), 5.57−5.45 (m; 2H), 5.15−5.07 (m; 2H), 2.41−2.30 (m; 2H), 2.05 (s; 3H), 1.85 (s; 3H), 0.28 (s; 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 170.0 (C), 135.0 (CH), 132.5 (CH), 122.1 (C), 118.2 (CH_2), 106.9 (C), 92.6 (C), 69.7 (CH), 38.6 (CH_2), 21.0 (CH), 17.9 (CH_3), −0.2 (CH_3). HRMS (EI) calcd for $C_{14}H_{22}O_2Si$: 250.1389, found 250.1395.

General Procedure for Preparation of Aminotrienes 18. One-Pot Deprotection and Hydroamination of Silylated Dienynes 10, 12a, 14, 15, and 17. A modified procedure from that previously published[15b] was employed. To a solution of correspondent silylated enyne (3 mmol) in THF (20 mL) was added TBAF (1.2 mmol, 40 mol %), and the resulting mixture was stirred for 10 min. Then, $Hg(OAc)_2$ (2.25 mmol, 75 mol %) was added, and stirring was continued for an additional 5 min. The reaction mixture was then treated with NEt_3 (0.8 mL, 600 mg, 6 mmol). After an additional 5 min, *N*-methylaniline (300 mg, 3 mmol) was added, and the reaction mixture was heated to gently reflux overnight in the case of dienynes **14**, **15**, and **17** and at room temperature in the case of dienynes **10** and **12**. Subsequently, the reaction mixture was concentrated under vacuum. The flask was filled with dry nitrogen, and 30 mL of dry hexanes was added to the mixture. After the suspension was stirred and shaken for 30 min, the solution was filtered under a dry atmosphere, and the solid was washed with additional dry hexanes (2 × 10 mL). The filtrates were combined and concentrated under vacuum to afford the correspondent essentially pure aminotriene **18** as a yellowish oil.

***N*-Methyl-*N*-((*E*)-3-methylhexa-1,3,5-trien-2-yl)benzeneamine 18a.** Prepared from dienyne **10**. Obtained as a yellowish oil in 56% yield: ^1H NMR ($CDCl_3$, 300 MHz): 7.31−7.22 (m; 3H), 6.85−6.73 (m; 2H), 6.70−6.60 (m; 1H), 6.49 (d; J = 11.4; 1H), 5.27 (d; $^3J_{trans}$ = 16.8; 1H), 5.18 (d; $^3J_{cis}$ = 11.7; 1H), 5.13 (s; 1H), 4.90 (s; 1H), 3.15 (s; 3H), 1.93 (s; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 155.9 (C), 149.2 (C), 134.1 (C), 133.2 (CH), 128.7 (CH), 122.4 (CH), 118.5 (CH_2), 118.2 (CH_2), 116.3 (CH), 105.8 (CH_2), 39.8 (CH_3), 14.4 (CH_3). HRMS (EI) calcd for $C_{14}H_{17}N$: 199.1355, found 199.1349.

General Procedure for the Imino-Diels−Alder Reaction. Preparation of Dienic Piperidines 21. To a solution of $Yb(OTf)_3$ (55 mg, 0.1 mol, 20 mol %) in THF (10 mL) was added dropwise the correspondent imine **19** (0.50 mmol), and the resulting mixture was stirred for 10 min. Subsequently, a solution of correspondent aminotriene **18** (0.50 mmol) in THF (5 mL) was added, and the reaction mixture stirred overnight. Then, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a brown oil. The reaction crude was dissolved in 2% TFA/DCM (5 mL), and the solution was stirred for 15 min. The reaction mixture was then poured over a saturated aqueous solution of $NaHCO_3$ (sat) (10 mL). The resulting mixture was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a pale brown oil. The crude was purified by column chromatography, affording the cycloaddition products as pale yellow oils.

(2*S,3*S**,6*S**)-*N*,2-Diallyl-3-methyl-6-(4-methoxyphenyl)-piperidin-4-one 21a.** Prepared from aminotriene **18b** and imine **19c**. Obtained as a pale yellow oil in 55% yield: R_f = 0.38 (Hex/EtOAc 5:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 7.45−7.33 (m; 3H), 6.92−7.03 (m; 2H), 6.21−6.07 (m; 1H), 5.93−5.81 (m; 1H), 5.23−5.06 (m; 4H), 3.91 (s; 3H), 4.12−4.02 (m; 1H), 3.40 (dd; $^3J_{gem}$ = 15.6, $^3J_{ax-eq}$ = 6.8; 1H), 3.18 (dd; ^3J = 16.2, ^3J = 5.7; 1H), 2.81−2.63 (m; 3H), 2.42 (dd; $^3J_{ax-ax}$ = 13.4, $^3J_{ax-eq}$ = 3.4; 1H), 2.35−2.29 (m; 1H), 1.02 (d; ^3J = 6.0; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 210.7 (C), 158.5 (C), 133.2 (C), 131.2 (CH), 128.4 (CH), 118.5 (CH_2), 117.9 (CH_2), 114.2 (CH), 113.9 (CH), 64.6 (CH_3), 64.1 (CH), 60.8 (CH), 50.9 (CH_2), 46.6 (CH_2), 33.8 (CH_2), 15.6 (CH), 11.0 (CH_3). HRMS (EI) calcd for $C_{19}H_{25}NO_2$: 299.1879, found 299.1876.

General Procedure for the RCM Reaction. To a solution of the correspondent diene **21** (0.2 mmol) in DCM (20 mL) (10^{-2} M) was added first-generation Grubbs catalyst (3 mg, 0.0035 mmol). The resulting solution was heated to gentle reflux, and stirring was continued for 4 h. Subsequently, another portion of the ruthenium catalyst was added (3 mg, 0.0035 mmol), and stirring was continued for an additional 4 h. Then, the reaction mixture was exposed to air and concentrated to afford the crude bicyclic product **22**, which was purified by flash column chromatography.

(1*S,4*S**,9*R**,9a*R**)-3,4,9,9a-Tetrahydro-9-methoxy-1-methyl-4-phenyl-1*H*-quinolizin-2(6*H*)-one 22e.** Prepared from diene **21e**. Obtained as a colorless oil in 93% yield: R_f = 0.24 (Hex/EtOAc 5:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 7.45−7.28 (m; 5H), 6.10−6.00 (m; 1H), 5.90 (ddd; ^3J = 10.2, ^3J = 5.1, J = 1.4; 1H), 3.81−3.76 (m; 1H), 3.55 (s; 3H), 3.33 (dd; $^3J_{ax-ax}$ = 12.8, $^3J_{ax-eq}$ = 2.6; 1H), 3.21−3.12 (m; 2H), 2.81 (dd; $^2J_{gem}$ = 13.1, $^3J_{ax-ax}$ = 12.8, $^3J_{eq-eq}$ = 3.8; 1H), 2.45−2.35 (m; 3H), 1.13 (d, ^3J = 6.5; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 210.2 (C), 142.1 (C), 130.2 (CH), 128.8 (CH), 127.7 (CH), 127.2 (CH), 122.0 (CH), 71.7 (CH_3), 71.1 (CH), 69.8 (CH), 56.5 (CH), 53.2 (CH_2), 50.0 (CH_2), 44.7 (CH), 10.2 (CH_3). HRMS (EI) calcd for $C_{17}H_{21}NO_2$: 271.1572, found 271.1560.

(1*S,4*S**,9*S**,9a*R**)-4-(2-Bromophenyl)-3,4,9,9a-tetrahydro-9-methoxy-1-methyl-1H-quinolizin-2(6*H*)-one 22f.** Prepared from diene **21f**. Obtained as a pale yellow oil in 97% yield: R_f = 0.23 (Hex/EtOAc 3:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 7.61−7.51 (m; 2H), 7.39−7.31 (m; 1H), 7.19−7.11 (m; 1H), 6.11−6.01 (m; 1H), 5.86 (ddd; ^3J = 9.8, ^3J = 5.2, J = 1.1; 1H), 4.81 (dd; $^3J_{ax-ax}$ = 9.6, $^3J_{ax-eq}$ = 4.9; 1H), 3.68−3.63 (m; 1H), 3.41 (s; 3H), 3.15 (dd; $^3J_{ax-ax}$ = 9.6, $^3J_{eq-eq}$ = 3.8; 1H), 3.07 (dd; $^2J_{gem}$ = 16.7; $^3J_{eq-eq}$ = 4.9; 1H), 2.73−2.58 (m; 4H), 1.25 (d; ^3J = 6.0; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 209.6 (C), 139.2 (C), 132.8 (CH), 131.1 (CH), 130.3 (CH), 129.0 (CH), 128.1 (CH), 125.0 (C), 124.0 (CH), 73.2 (CH_3), 64.9 (CH), 59.7 (CH), 56.4 (CH). 51.7 (CH_2), 48.0 (CH_2), 43.7 (CH), 9.4 (CH_3). HRMS (EI) calcd for $C_{17}H_{20}BrNO_2$: 349.0676, found 349.0675.

(1*S,4*S**,9*R**,9a*R**)-4-(2-Bromophenyl)-3,4,9,9a-tetrahydro-9-methoxy-1-methyl-1*H*-quinolizin-2(6H)-one 22*f*′.** Prepared from diene **21*f*′**. Obtained as a pale yellow oil in 97% yield: R_f = 0.28 (Hex/EtOAc 3:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 7.78 (dd; ^3J = 8.0, ^4J = 0.8; 1H), 7.54 (dd; ^3J = 7.9, ^4J = 0.7; 1H), 7.41−7.31 (m; 1H), 7.12−7.01 (m; 1H), 6.11−6.01 (m; 1H), 5.90 (ddd; ^3J = 9.8, ^3J = 5.2, J = 1.0; 1H), 4.02 (dd; $^3J_{ax-ax}$ = 12.5, $^3J_{ax-eq}$ = 3.3; 1H), 3.81−3.75 (m; 1H), 3.55 (s; 3H), 3.30−3.11 (m; 2H), 2.63−2.45 (m; 4H), 1.15 (d, ^3J = 6.1; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 209.3 (C), 140.6 (C), 132.8 (CH), 129.9 (CH), 129.0 (CH), 128.7 (CH), 128.2 (CH), 122.9 (C), 122.1 (CH), 71.6 (CH_3), 69.2 (CH), 68.0 (CH), 56.4 (CH). 52.4(CH_2), 47.9 (CH_2), 44.3 (CH), 10.0 (CH_3). HRMS (EI) calcd for $C_{17}H_{20}BrNO_2$: 349.0676, found 349.0675.

(1*S,4*S**,9a*S**)-3,4,9,9a-Tetrahydro-4-(4-methoxyphenyl)-1-methyl-1*H*-quinolizin-2(6*H*)-one 22a.** Prepared from diene **21a**. Obtained as a pale yellow oil in 95% yield: R_f = 0.16 (Hex/EtOAc 6:1) $KMnO_4$. ^1H NMR ($CDCl_3$, 300 MHz): 7.35 (d; ^3J = 8.3; 2H), 6.94 (d; ^3J = 8.3; 2H), 5.81−5.72 (m; 1H), 6.62−5.55 (m; 1H), 3.83 (s; 3H), 3.40 (dd; ^3J = 12.8, $^3J_{ax-eq}$ = 2.8; 1H), 3.15−3.05 (m, 1H), 2.89 (dd; $^3J_{ax-ax}$ =12.8, J = 12.8, 1H), 2.60−2.50 (m; 6H),1.16 (d; ^3J = 6.6; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 208.9 (C), 159.1 (C), 128.3 (CH), 124.5 (C), 123.3 (CH), 114.1 (CH), 70.3 (CH_3), 65.0 (CH), 55.3 (CH), 55.2 (C), 52.4 (CH_2), 50.1 (CH_2), 48.7 (CH), 33.3 (CH_2), 10.1 (CH_3). HRMS (EI) calcd for $C_{17}H_{21}NO_2$: 271.1567, found 271.1567.

Ethyl (1*S,4*S**,9a*S**)-2,3,4,6,9,9a-Hexahydro-1-methyl-2-oxo-1*H*-quinolizin-4-carboxylate 22b**. Prepared from diene **21b**. Obtained as a pale yellow oil in 97% yield: R_f = 0.33 (Hex/EtOAc 5:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.85−5.73 (m; 1H), 5.70−5.60 (m; 1H), 4.30 (q; ^3J = 6.4; 2H), 3.61−3.49 (m; 1H), 3.25 (dd; $^3J_{ax-ax}$ = 13.5, $^3J_{ax-eq}$ = 3.2; 1H), 3.05−2.83 (m; 3H), 2.63−2.41 (m; 4H), 1.35 (t; J = 6.4; 3H), 1.12 (d; ^3J = 6.6; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 208.7 (C), 173.5 (C), 135.8 (CH), 134.0 (CH), 64.2 (CH), 60.5 (CH_2), 60.1 (CH), 57.0 (CH_2), 46.5 (CH), 43.7 (CH_2), 36.1 (CH_2), 14.2 (CH_3), 12.0 (CH_3). HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 237.1359, found 237.1350.

(7*S,8*S**,11*S**)-8-Methyl-11-phenyl-1-azabicyclo[5.4.0]undec-5-en-9-one 22c**. Prepared from diene **21c**. Obtained as a pale yellow oil in 95% yield: R_f = 0.25 (Hex/EtOAc 5:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47−7.30 (m; 5H), 5.83−5.75 (m; 1H), 5.52 (ddd; J = 11.4, 2.3, 2.1; 1H), 3.68 (dd; $^3J_{ax-ax}$ = 11.7, $^3J_{ax-eq}$ = 3.3; 1H), 3.10 (dd; ^3J = 10.5, J = 4.3; 1H), 2.91−2.62 (m; 4H), 2.60−2.49 (m; 2H), 2.19−1.92 (m; 1H), 1.56−1.40 (m; 2H), 1.12 (d; ^3J = 6.6; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 209.0 (C), 143.7 (C), 129.9 (CH), 128.7 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 72.8 (CH), 69.2 (CH), 50.7 (CH_2), 49.8 (CH), 48.8 (CH_2), 26.7 (CH_2), 23.1 (CH_2), 10.3 (CH_3). HRMS (EI) calcd for $C_{17}H_{21}NO$: 255.1618, found 255.1613.

(8*S,9*S**,12*S**)-9-Methyl-12-phenyl-1-azabicyclo[6.4.0]dodec-5-en-10-one 22d.** Prepared from diene **21d**. Obtained as a pale yellow oil in 97% yield: R_f = 0.29 (Hex/EtOAc 10:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.48−7.28 (m; 5H), 5.97−5.87 (m; 1H), 5.76−5.66 (m; 1H), 3.90 (dd; $^3J_{ax-ax}$ = 11.1, $^3J_{ax-eq}$ = 2.7; 1H), 2.71−2.51 (m; 4H), 2.38−2.22 (m; 2H), 2.22−2.11 (m; 2H), 1.91 (dd, J = 6.3, 0.7; 1H), 1.56−1.44 (m; 1H), 1.13 (d; ^3J = 6.3; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 210.8 (C), 140.6 (C), 132.6 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 69.4 (CH), 50.1 (CH_2), 46.4 (CH), 30.6 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 26.3 (CH_2), 10.8 (CH_3). HRMS (EI) calcd for $C_{18}H_{23}NO$: 269.1774, found 269.1776.

(8*S,9*R**,10*S**,13*S**)-8-Acetyl-13-phenyl-10-methyl-1-azabicyclo[7.4.0]tridec-5-en-11-one 22g**. Prepared from diene **21g**. Obtained as a colorless oil in 95% yield: R_f = 0.19 (Hex/EtOAc 6:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.51−7.29 (m; 5H), 5.62−5.48 (m; 2H), 5.00 (dt; ^3J = 10.7, 4.4; 1H), 3.95 (dd; $^3J_{ax-ax}$ = 13.1, $^3J_{ax-eq}$ = 3.1; 1H), 3.40−3.31 (m; 1H), 3.22−3.15 (m; 1H), 3.13−2.93 (m; 3H), 2.75−2.61 (m; 2H), 2.46−2.25 (m; 3H), 2.01 (s; 3H), 1.47−1.25 (m; 2H), 1,02 (d; ^3J = 6.8; 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 211.2 (C), 170.2 (C), 144.5 (C), 132.6 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 124.8 (CH), 73.2 (CH), 70.9 (C), 65.3 (CH), 63.6 (CH_2), 47.3 (CH_2), 42.7 (CH_3), 29.2 (CH_2), 28.3 (CH_2), 23.1 (CH_2), 20.7 (CH), 10.6 (CH_3). HRMS (EI) calcd for $C_{21}H_{27}NO_3$-C_4H_7: 341.1985, found 341.1986.

(*E*)-(6*R,7*S**,11*S**)-11-(4-Fluorophenyl)-6-methoxy-8-phenyl-9-(*N*-methylbenzeneamino)-1-azabicyclo[5.4.0]undec-3,8-diene 24a.** Prepared from diene **23a**. Obtained as a pale yellow oil in 94% yield: R_f = 0.26 (Hex/EtOAc 3:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.39−7.19 (m; 8H), 7.08−7.00 (m; 3H), 6.80−6.64 (m; 3H), 5.95−5.83 (m; 1H), 4.69 (dd; ^3J = 11.1, 6.0; 1H), 4.22 (dd; ^3J = 6.7, 5.6; 1H) 3.48 (dd; J = 11.1, 3.7; 1H), 3.35 (s; 3H), 3.22 (dd; J = 14.8, 5.6; 1H), 2.73 (s; 3H), 2.72−2.48 (m; 2H), 2.45−2.20 (m; 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 150.5 (C), 141.6 (C), 141.1 (C), 132.7 (C), 132.6 (C), 131.4 (CH), 130.7 (CH), 130.3 (C), 127.5 (CH), 127.3 (CH), 125.4 (CH), 124.2 (CH), 118.7 (CH), 117.5 (CH), 117.2 (CH), 115.6 (CH), 73.5 (CH), 70.5 (CH_3), 59.5 (CH), 59.4 (CH), 51.1 (CH_2), 39.5 (CH_3), 32.1 (CH_2), 31.3 (CH_2). HRMS (EI) calcd for $C_{30}H_{31}FN_2O$: 454.2415, found 454.2415.

(*E*)-(6*S,7*S**,11*S**)-11-(4-Fluorophenyl)-6-methoxy-8-phenyl-9-(*N*-methylbenzeneamino)-1-azabicyclo[5.4.0]undec-3,8-diene 24b.** Prepared from diene **23b.** Obtained as a pale yellow oil in 96% yield: R_f = 0.47 (Hex/EtOAc 3:1) $KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.38−7.19 (m; 9H), 7.05−6.93 (m; 2H), 6.75−6.69 (m; 1H), 6.60 (d; ^3J = 7.7; 2H), 5.71−5.62 (m; 1H), 5.38−5.30 (m; 1H), 4.50 (s; 1H), 4.38 (dd; ^3J = 9.4, 4.2; 1H), 3.78 (d; ^3J = 15.1; 1H), 3.45 (dd; ^3J = 6.6, 2.3; 1H) 3.18 (dd; $^2J_{gem}$ = 17.1, $^3J_{ax-eq}$ = 4.2; 1H), 3.04 (s; 3H), 2.73−2.62 (m; 2H), 2.65 (s; 3H), 2.55−2.45 (m; 1H), 2.31 (ddd; $^2J_{gem}$ = 17.1, ^3J = 9.4, 2.2; 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 147.5 (C), 139.0 (C), 138.9 (C), 134.2 (C), 129.8 (C), 129.7 (CH), 129.0 (CH), 128.2 (CH), 127.6 (C), 127.0 (CH), 126.9 (CH), 125.2 (CH), 116.7 (CH), 115.0 (CH), 114.7 (CH), 113.1 (CH), 83.9 (CH), 77.2 (CH), 67.5 (CH_3), 57.1 (CH), 56.4 (CH), 49.1 (CH_2), 37.1 (CH_3), 35.3 (CH_2), 29.9 (CH_2). HRMS (EI) calcd for $C_{30}H_{31}FN_2O$: 454.2415, found 454.2408.

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Supporting Information Available: Characterization data for compounds **9b**, **13a,b**, **15**, **18b**−**e**, **22f**, **21b**−**d**, **21f,g**, and **23a,b** and copies of the ^{13}C NMR spectra of all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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