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Molecular Diversity

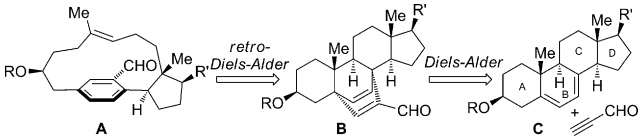
Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy**

Jean-Philippe Krieger, Gino Ricci, Dominique Lesuisse, Christophe Meyer, and Janine Cossy**

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *With the goal of synthesizing new [n]paracyclophanes, the expansion of the scope of a strategy originally disclosed by Winterfeldt et al., was investigated. This approach involves sequential Diels–Alder/retro-Diels–Alder reactions, the applications of which have been constrained so far to steroid derivatives. An efficient access to new functionalized [9]-, [10]-, and [16]paracyclophanes, including original cage architectures, was developed from readily available building blocks using thermal electrocyclization and a cycloaddition/cycloreversion sequence as the key steps.*

Paracyclophanes have found many applications in material science, supramolecular chemistry, and catalysis owing to their unique structures and physicochemical properties.[1] Despite their inherent strain, [*n*]paracyclophanes, and especially those incorporating an aryl ether, are encountered in many bioactive natural products[2] as well as in synthetic protease inhibitors.[3] The synthesis of [*n*]paracyclophanes is usually accomplished by macrocyclization of appropriately substituted aromatic compounds, leading to carbon–heteroatom or carbon–carbon bond formation within the chain.[4] These challenging reactions often require high dilution conditions and/or conformational control elements to facilitate ring-closure.[2–5] Strategies enabling the formation of [*n*]paracyclophanes from acyclic precursors by construction of the aromatic ring are also appealing.[6–9] In this context, cobalt- and rhodium-catalyzed [2+2+2]-cycloadditions of α,ω-diynes with alkynes have been developed, but the challenge is to control the regioselectivity by an appropriate selection of substrates.[7] Macrocyclizations relying on intramolecular [4+2]-cycloadditions with pyrones, followed by release of CO_2 by a retro-Diels–Alder reaction, have also been elegantly used as key steps in the synthesis of naturally occurring paracyclophanes.[9] In 1985, Winterfeldt et al. reported an interesting entry toward macrocycles **A** ("*ansa*-steroids") from steroids **C** incorporating a 1,3-diene into the B ring. The sequence relies on sequential Diels–Alder cycloaddition with propiolaldehyde/retro-Diels–Alder reaction of adduct **B**, leading to a [10]paracyclophane fused to a cyclopentane (Scheme 1).[10]



Scheme 1. Winterfeldt's approach to [10]paracyclophanes **A** from steroids **C**.

Several structurally related ansa-steroids,[11] including a library of such compounds by solid-phase synthesis using aryl ynones as dienophiles,[12] have been prepared by this strategy, and two larger [13]- and [14]paracyclophanes were also synthesized after cleavage of the five-membered ring.[11] However, only steroids have been considered as starting materials so far, thereby restricting this strategy to the preparation of [10]paracyclophanes possessing an invariable carbon framework with a trisubstituted (*E*)-olefin and limited opportunities for functionalization.

In view of recent reports on the so-called "ring-distortion reactions" to produce libraries of compounds[13] and on the interest of macrocycles in new drugs discovery,[14] this Diels–Alder/retro-Diels–Alder sequence would be a powerful strategy to access a wide variety of [*n*]paracyclophanes if its scope could be extended to 1,3-dienes other than steroid derivatives. Herein, we report the synthesis of new [*n*]paracyclophanes **D**, incorporating heteroatoms and other key structural features encountered in natural products (aryl ethers, biaryls, lactams), by a retro-Diels–Alder fragmentation of 1,4-dienes **E** arising from a Diels–Alder cycloaddition of acetylenic dienophiles with tricyclic 1,3-dienes **F**. Despite their apparent structural complexity, 1,3-dienes **F** can be easily formed by the 6π-electrocyclization[15] of trienes **G**, which in turn can be prepared by semihydrogenation of the corresponding dienynes that are readily assembled from simple building blocks such as alkenyl iodides or enol triflates **H** and cyclic ketones **I** using trimethylsilylacetylene as a lynchpin (Scheme 2).

In our planned strategy, the first task was to secure an efficient access to tricyclic 1,3-dienes **F**. A Sonogashira coupling between 2-iodocycloalkenones **1a** or **1b** and enyne

[*] J.-P. Krieger, Dr. C. Meyer, Prof. J. Cossy
Laboratory of Organic Chemistry, ESPCI ParisTech, CNRS
10 rue Vauquelin 75231 Paris Cedex 05 (France)
E-mail: christophe.meyer@espci.fr
janine.cossy@espci.fr
Dr. D. Lesuisse
R&D Sanofi
1 Avenue Pierre Brossolette 91385 Chilly-Mazarin Cedex (France)
Dr. G. Ricci
Sanofi Process Development
45 Chemin de Mételine BP15, 04210 Sisteron Cedex (France)

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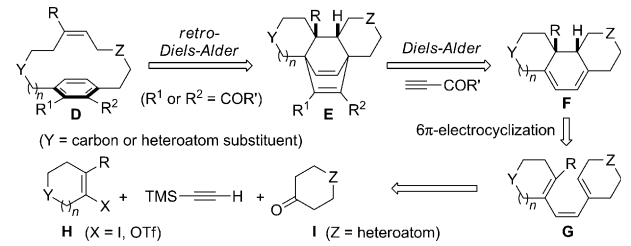
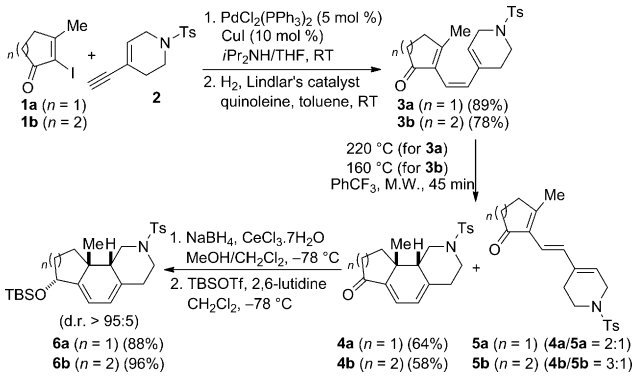


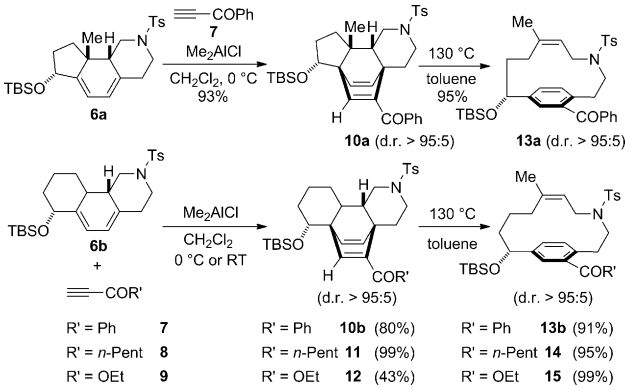
Scheme 2. Retrosynthetic analysis of structurally diverse functionalized [*n*]paracyclophanes from readily available building blocks.

2, followed by semihydrogenation of the resulting dienynes, afforded trienes **3a** (89%) and **3b** (78%), respectively, possessing an internal (*Z*)-olefin. After some experimentation, the most satisfactory conditions found to achieve the 6π-electrocyclization of **3a** involved heating in trifluorotoluene under microwave irradiation (220°C, 45 min). A mixture of the tricyclic dienone **4a** and triene **5a**, resulting from the isomerization of the internal olefin, was produced (**4a**/**5a** = 2:1), from which **4a** was isolated in 64% yield. In the case of triene **3b**, a mixture of dienone **4b** and the isomerized triene **5b** was obtained with an optimal ratio reached at 160°C (**4b**/**5b** = 3:1) and no improvement at higher temperatures. Dienone **4b** was isolated in 58% yield, whereas triene **5b** (21%) could be recycled by photochemical isomerization into **3b**.[16] Dienones **4a** and **4b** were reduced with high diastereoselectivity and the resulting alcohols were protected as silyl ethers to afford the tricyclic 1,3-dienes **6a** (88%) and **6b** (96%) (Scheme 3).



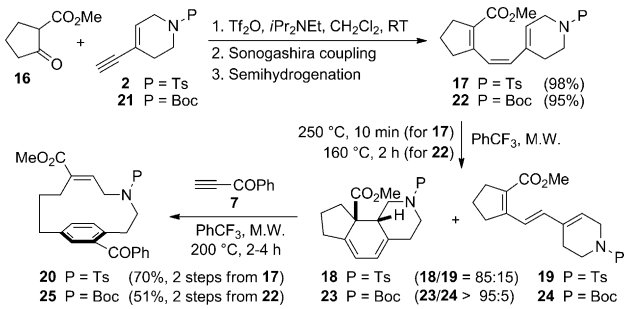
Scheme 3. Synthesis of tricyclic 1,3-dienes **6a** and **6b**. M.W. = microwave irradiation.

The Diels–Alder cycloaddition of **6a** and **6b** with ynone **7** was achieved in the presence of Me_2AlCl,[12] and the 1,4-dienes **10a** (93%) and **10b** (80%) were respectively obtained in a highly regio- and diastereoselective manner. The [4+2]-cycloaddition occurs on the less-hindered (convex) face of the tricyclic system of dienes **6a** and **6b**, which differ from steroids by the *cis* relationship between the angular methyl group and hydrogen atom, and the ynone substituent preferentially occupies a distal position from the methyl group. The Diels–Alder reaction between ynone **8** and diene **6b** afforded the 1,4-diene **11** in high yield (99%). Methyl propiolate **9** could also be used as dienophile, but the 1,4-diene **12** was isolated in modest yield (43%) owing to competitive elimination of TBSOH. The 1,4-dienes **10a**, **10b**, **11**, and **12** smoothly underwent fragmentation by retro-Diels–Alder reaction (toluene, 130°C) to afford the [9]paracyclophane **13a** (95%) and the [10]paracyclophanes **13b** (91%), **14** (95%), and **15** (99%), respectively, possessing a trisubstituted (*Z*)-alkene (Scheme 4).



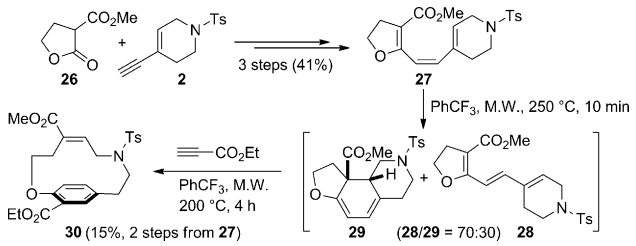
Scheme 4. Synthesis of [9]- and [10]paracyclophanes from **6a** and **6b**.

To take advantage of precursors different from steroids, the angular methyl substituent (R = Me) in tricyclic dienes **F** was replaced by an ester moiety (R = CO_2Me), as this would lead to [*n*]paracyclophanes **D** functionalized by a Michael acceptor. The Sonogashira coupling of the enol triflate derived from **16** with enyne **2**, followed by semihydrogenation, afforded triene **17** (98%). Upon heating (250°C, 10 min), triene **17** led to a mixture of the tricyclic diene **18** and the isomerized triene **19** (**18**/**19** = 85:15).[17] The difficult separation of these compounds was unnecessary, as addition of ynone **7** and subsequent heating (200°C, 4 h) afforded the [9]paracyclophane **20** in 70% overall yield by a Diels–Alder/retro-Diels–Alder sequence. As the initial [4+2]-cycloaddition of diene **18** with ynone **7** could be achieved under thermal conditions, the sequence was investigated with triene **22** in which the nitrogen atom is substituted by a Boc group, which was found to be incompatible with the Lewis acid promoted cycloaddition.[18] The electrocyclization of **22** leading to 1,3-diene **23** could be achieved at a lower temperature (160°C, 2 h), and in this case the (*E*)-isomer **24** was not observed as a by-product. Subsequent heating with ynone **7** (200°C, 2 h) delivered the [9]paracyclophane **25** (51%) (Scheme 5).



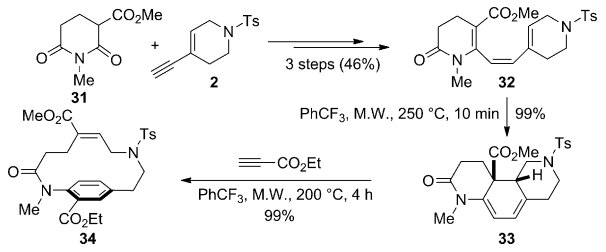
Scheme 5. Synthesis of the [9]paracyclophanes **20** and **25**.

The preparation of [*n*]paracyclophanes incorporating aryl ethers was then investigated. Triene **27** slowly isomerized into the (*E*)-isomer **28** upon standing at RT, and brief heating at high temperature (250 °C, 10 min) produced a mixture of the tricyclic 1,3-diene **29** and the isomeric triene **28** as the major product (**28**/**29** = 70:30), which could not be readily separated. Nevertheless, the resulting mixture was treated with an excess of ethyl propiolate to achieve the [4+2]-cycloaddition with the electron-rich 1,3-diene **29** (200 °C, 4 h) and subsequent retro-Diels–Alder reaction delivered the [9]paracyclophane **30** (15 %, two steps from **27**). Although the yield is low, the synthesis of the macrocyclic ether **30** has been achieved in only five steps from lactone **26** using three sequential thermal processes without intermediate purifications (Scheme 6).



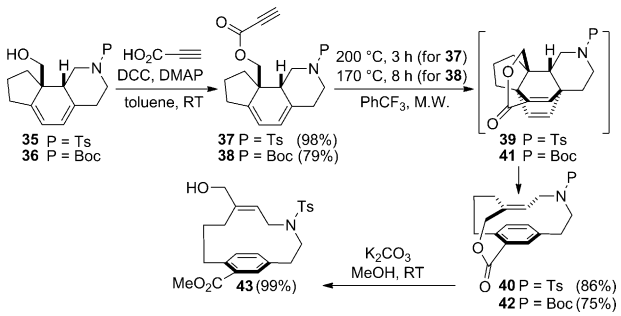
Scheme 6. Synthesis of the [9]paracyclophane **30**.

The synthesis of macrolactam **34** is a remarkable illustration of the efficiency of the sequence. The electrocyclization of triene **32** into the tricyclic 1,3-diene **33** (250 °C, 10 min) proceeded in almost quantitative yield, which is probably due to the methyl substituent on the nitrogen atom of the amide moiety that favors the reactive *s-cis* conformation. Subsequent Diels–Alder cycloaddition of dienamide **33** with ethyl propiolate, followed by retro-Diels–Alder reaction (200 °C, 4 h), led to the [10]paracyclophane macrolactam **34** in 99 % yield (Scheme 7).



Scheme 7. Synthesis of the [10]paracyclophane **34**.

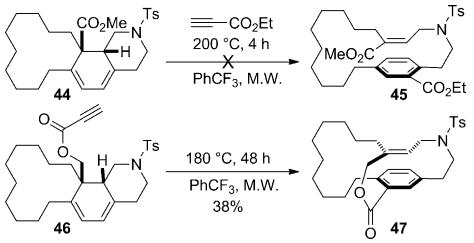
The Diels–Alder cycloaddition of the dienol ether **29** and dienamide **33** with ethyl propiolate proceeded efficiently owing to the electron-rich character of these polarized 1,3-dienes. The regioselectivity, which is opposite to that observed for tricyclic dienes **18** and **23**, can be understood on the basis of an electronic control which overrides the unfavorable steric repulsion between the two ester moieties. To alter the regioselectivity of the [4+2]-cycloaddition of acetylenic dienophiles with tricyclic dienes **F** lacking a donor heteroatom substituent, intramolecular Diels–Alder cycloadditions were developed. Dienes **35** and **36** possessing an angular hydroxymethyl group were esterified with propiolic acid to afford propiolates **37** (98 %) and **38** (79 %). Upon heating (200 °C, 3 h), ynoate **37** underwent an efficient intramolecular Diels–Alder reaction leading to 1,4-diene **39**; the fragmentation of this diene by retro-Diels–Alder reaction delivered the cage [9]paracyclophane **40** (86 %). For the *N*-Boc substituted 1,3-diene **38**, the same transformation was carried out at lower temperature to avoid thermal cleavage of the Boc group (170 °C, 8 h) and the analogous [9]paracyclophane **42** was obtained (75 %). Methanolysis of lactone **40** led to the [9]paracyclophane **43** (99 %), thereby highlighting the interest of the intramolecular version to alter the regioselectivity of the Diels–Alder reaction of tricyclic dienes **F** devoid of a heteroatom substituent (Scheme 8).



Scheme 8. Synthesis of the cage [9]paracyclophanes **40** and **42**.

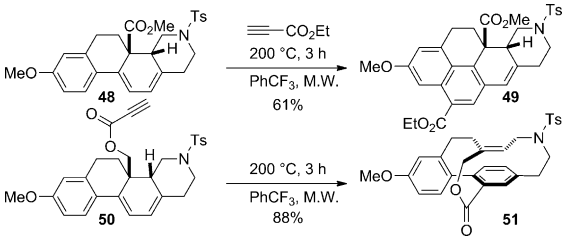
The use of sequential intramolecular Diels–Alder cycloaddition/retro-Diels–Alder reaction also enables access to other paracyclophanes from 1,3-dienes that did not provide satisfactory results in the related intermolecular processes. Whereas the [16]paracyclophane **45** could not be obtained by an intermolecular reaction between diene **44** and ethyl propiolate, the intramolecular Diels–Alder cycloaddition of ynoate **46** occurred slowly (200 °C, 3 h, 50 % conversion), which was probably due to the conformational flexibility of the twelve-membered ring that hampers the approach of the ynoate and the 1,3-diene. As competitive decomposition was observed, the temperature was decreased and a longer reaction time was used (180 °C, 48 h) to ensure complete conversion and the cage [16]paracyclophane **47** was isolated in 38 % yield (Scheme 9).

Another illustration is the reactivity of diene **48** which underwent a thermal dehydrogenative styryl-Diels–Alder



Scheme 9. Synthesis of the cage [16]paracyclophane **47**.

cycloaddition[19] with ethyl propiolate leading after aromatization to the pentacyclic compound **49** (61%), whereas ynoate **50** underwent a smooth intramolecular Diels–Alder cycloaddition followed by a retro-Diels–Alder fragmentation producing the cage [10]paracyclophane **51** (88%) with a biaryl subunit (Scheme 10).



Scheme 10. Synthesis of the cage [10]paracyclophane **51**.

In conclusion, we have developed an efficient access to new [*n*]paracyclophanes by a ring-distortion strategy capitalizing on sequential Diels–Alder/retro-Diels–Alder reactions, the applications of which had previously been constrained to steroid derivatives. The scope of this strategy has been significantly expanded, as illustrated by the preparation of functionalized [*n*]paracyclophanes incorporating heteroatoms and structural features such as aryl ethers, biaryl subunits, or lactams, as well as original cage paracyclophanes, which should be useful scaffolds for diversity-oriented synthesis.

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[1] a) *Cyclophane Chemistry*: *Synthesis Structures and Reactions* (Ed.: F. Vögtle), Wiley, Chichester, **1993**; b) *Modern Cyclophane Chemistry* (Eds.: R. Gleiter, H. Hopf), Wiley-VCH, Weinheim, **2004**.

[2] T. Gulder, P. S. Baran, *Nat. Prod. Rep.* **2012**, *29*, 899 – 934.

[3] a) P. Ettmayer, A. Billich, P. Hecht, B. Rosenwirth, H. Gstach, *J. Med. Chem.* **1996**, *39*, 3291 – 3299; b) C. P. Decicco, Y. Song, D. A. Evans, *Org. Lett.* **2001**, *3*, 1029 – 1032; c) M. P. Glenn, L. K. Pattenden, R. C. Reid, D. P. Tyssen, J. D. A. Tyndall, C. J. Birch, D. P. Fairlie, *J. Med. Chem.* **2002**, *45*, 371 – 381; d) C. C. Mak, A. Brik, D. L. Lerner, J. H. Elder, G. M. Morris, A. J. Olson, C.-H. Wong, *Bioorg. Med. Chem.* **2003**, *11*, 2025 – 2040.

[4] a) L. A. Wessjohann, E. Ruijter, *Top. Curr. Chem.* **2005**, *243*, 137 – 184; b) J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, 1949 – 1964.

[5] For illustrating references on the synthesis of paracyclophanes by ring-closing metathesis, see: a) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773 – 775; b) Y. El-Azizi, A. Schmitzer, S. K. Collins, *Angew. Chem.* **2006**, *118*, 982 – 987; *Angew. Chem. Int. Ed.* **2006**, *45*, 968 – 973; c) P. Bolduc, A. Jacques, S. K. Collins, *J. Am. Chem. Soc.* **2010**, *132*, 12790 – 12791; d) K. Mori, K. Ohmori, K. Suzuki, *Angew. Chem.* **2009**, *121*, 5748 – 5751; *Angew. Chem. Int. Ed.* **2009**, *48*, 5638 – 5641.

[6] For the synthesis of small-sized [*n*]paracyclophanes ($n = 6 – 8$) by construction of the aromatic ring from cyclic precursors, see: V. V. Kane, W. H. De Wolf, F. Bickelhaupt, *Tetrahedron* **1994**, *50*, 4575 – 4622.

[7] a) L. V. R. Boñaga, H.-C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo, B. E. Maryanoff, *J. Am. Chem. Soc.* **2005**, *127*, 3473 – 3485; b) K. Tanaka, K. Toyoda, A. Wada, K. Shirasaka, M. Hirano, *Chem. Eur. J.* **2005**, *11*, 1145 – 1156; c) K. Tanaka, H. Sagae, K. Toyoda, K. Noguchi, *Eur. J. Org. Chem.* **2006**, 3575 – 3581; d) T. Araki, K. Noguchi, K. Tanaka, *Angew. Chem.* **2013**, *125*, 5727 – 5731; *Angew. Chem. Int. Ed.* **2013**, *52*, 5617 – 5621.

[8] For other reactions such as the Pd-catalyzed benzannulation of conjugated bis(enynes), see: a) S. Saito, M. M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 3970 – 3971; for the benzannulation of Fischer carbene complexes, see: b) H. Wang, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **2000**, *122*, 9862 – 9863.

[9] a) P. S. Baran, N. Z. Burns, *J. Am. Chem. Soc.* **2006**, *128*, 3908 – 3909; b) P. Zhao, C. M. Beaudry, *Org. Lett.* **2013**, *15*, 402 – 405.

[10] D. Schomburg, M. Thielmann, E. Winterfeldt, *Tetrahedron Lett.* **1985**, *26*, 1705 – 1706.

[11] S. Bäurle, T. Blume, A. Mengel, C. Parchmann, W. Skuballa, S. Bäsler, M. Schäfer, D. Sülzle, H.-P. Wrona-Metzinger, *Angew. Chem.* **2003**, *115*, 4091 – 4094; *Angew. Chem. Int. Ed.* **2003**, *42*, 3961 – 3964.

[12] N. Kumar, M. Kiuchi, J. A. Tallarico, S. L. Schreiber, *Org. Lett.* **2005**, *7*, 2535 – 2538.

[13] a) R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood, Jr., M. F. Richter, P. J. Hergenrother, *Nat. Chem.* **2013**, *5*, 195 – 202; b) R. J. Rafferty, R. H. Hicklin, K. A. Maloof, P. J. Hergenrother, *Angew. Chem.* **2014**, *126*, 224 – 228; *Angew. Chem. Int. Ed.* **2014**, *53*, 220 – 224.

[14] a) F. Giordanetto, J. Kihlberg, *J. Med. Chem.* **2014**, *57*, 278 – 295; b) J. Mallinson, I. Collins, *Future Med. Chem.* **2012**, *4*, 1409 – 1438; c) E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608 – 624.

[15] a) W. H. Okamura, A. R. de Lera, *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, London, **1991**, pp. 699 – 750, Chap. 6.2; b) L. M. Bishop, R. E. Roberson, R. G. Bergman, D. Trauner, *Synthesis* **2010**, 2233 – 2244.

[16] Photochemical isomerization of **5b** (hv (Hg lamp), MeCN, RT, 1 h) led to a mixture of **3b**/**5b** in a 95:5 ratio.

[17] Isomerization of trienes **G** generally proceeded at lower temperatures than the 6π-electrocyclization. To rapidly reach the desired temperature in the microwave reactor, the reaction was generally carried out in a silicon carbide vial; see the Supporting Information.

[18] The *N*-Boc substituted analogue of **6a** did not undergo cycloaddition with ynone **7** in the presence of Me_2AlCl and led to a complex mixture of products.

[19] a) T. Wagner-Jauregg, *Synthesis* **1980**, 769 – 798; b) L. S. Kocsis, E. Benedetti, K. M. Brummond, *Org. Lett.* **2012**, *14*, 4430 – 4433.

