Angewandte Chemie International Edition

DOI: 10.1002/anie.201408637

Helicenes

π-Helicenes Truncated to a Minimum: Access Through a Domino Approach Involving Multiple Carbopalladations and a Stille Coupling**

*Bastian Milde, Markus Leibeling, Martin Pawliczek, Jörg Grunenberg, Peter G. Jones, and Daniel B. Werz**

Dedicated to Professor Armin de Meijere on the occasion of his 75th birthday

Abstract: *A novel type of π-helicenes is reported, in which the π-system is truncated to an all-s-cis all-Z oligoene chain. A domino sequence was developed, consisting of up to four consecutive carbopalladation reactions and a terminal Stille cross-coupling, to generate these entities in one step from the respective linear oligoynes. Despite the minimal π-system, very high optical rotation values were encountered for the single enantiomers. X-ray crystallography confirmed their screw-shaped structure.*

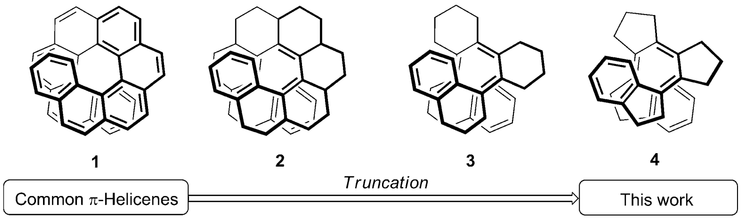


Figure 1. Proposed truncation of [9]helicene to an oligoene-based [9]helicene.

Typically, π-helicenes (e.g., **1**) consist of *ortho*-fused aromatic units. Because of steric hindrance of the terminal rings, they adopt a helical screw-shaped topology. This property makes them chiral although no asymmetric carbon atoms are present.[1,2] Symmetrical π-helicenes show a C_2 axis perpendicular to the axis of the helix. Although the first helicene, an aza[5]helicene,[3] was investigated by Meisenheimer and Witte in 1903, these compounds have lost none of their fascination. Originally treated as laboratory curiosities, they have now become model compounds for measuring the deformation of a π-system by determining and computing the activation energy for racemization.[4,5] Numerous synthetic routes,[6] some involving enantioselective transformations,[7] have been developed to access these molecular entities. Because of their helical molecular skeleton, unusual chiroptical properties are observed, such as very large values (in the range of several thousand degrees) for optical rotation.[1] An impressive demonstration that unusual π-systems can also be utilized to generate helicenes was the synthesis of angular [*n*]phenylenes, so-called heliphenes, in which alternating benzene units are fused with cyclobutadienes.[8] Recently, the field has again received much attention since novel synthetic routes to highly luminescent heterohelicenes incorporating silicon and phosphorus have been developed.[9]

Whereas almost all modern reports in this field tackle questions such as the incorporation of heteroatoms or the elongation of the conformationally distorted π-system, the idea of truncating the π-system of a helicene to its minimum (as in **3** or **4**) has not been addressed. Instead of an array of angular fused arene moieties, an oligoene chain fixed in the all-*Z* configuration should also force the system into a helical topology. However, it has often been assumed that a normal linear all-*Z* oligoene adopts a linear (all-s-*trans*) rather than a helical structure. So far, no crystal structure has shed light on this question.[10] The only way to connect the oligoene system in a helical fashion is to annulate ring systems at the side of the connecting single bonds, thus generating quadruply substituted C=C double bonds. The theoretical deconstruction of [9]helicene to an oligoene-based [9]helicene is depicted in Figure 1. These entities show the most truncated π-systems of all helicenes reported to date.

In the last two decades, a number of carbopalladation cascades[11] have been developed to access quadruply substituted alkene moieties.[12–14] Herein, we report our investigations for the preparation of highly truncated π-helicenes based on *Z*,*Z*-diene, *Z*,*Z*,*Z*-triene, and *Z*,*Z*,*Z*,*Z*-tetraene chains that are fixed in an *all*-s-*cis* arrangement. The key to their synthesis is an approach involving multiple carbopalladations and a Stille coupling, with up to five consecutive steps

---

[*] M.Sc. B. Milde, Dr. M. Leibeling, M.Sc. M. Pawliczek,
Prof. Dr. J. Grunenberg, Prof. Dr. D. B. Werz
Technische Universität Braunschweig, Institut für Organische Chemie
Hagenring 30, 38106 Braunschweig (Germany)
E-mail: d.werz@tu-braunschweig.de
Homepage: http://www.werzlab.de
Prof. Dr. P. G. Jones
Technische Universität Braunschweig
Institut für Anorganische und Analytische Chemie
Hagenring 30, 38106 Braunschweig (Germany)

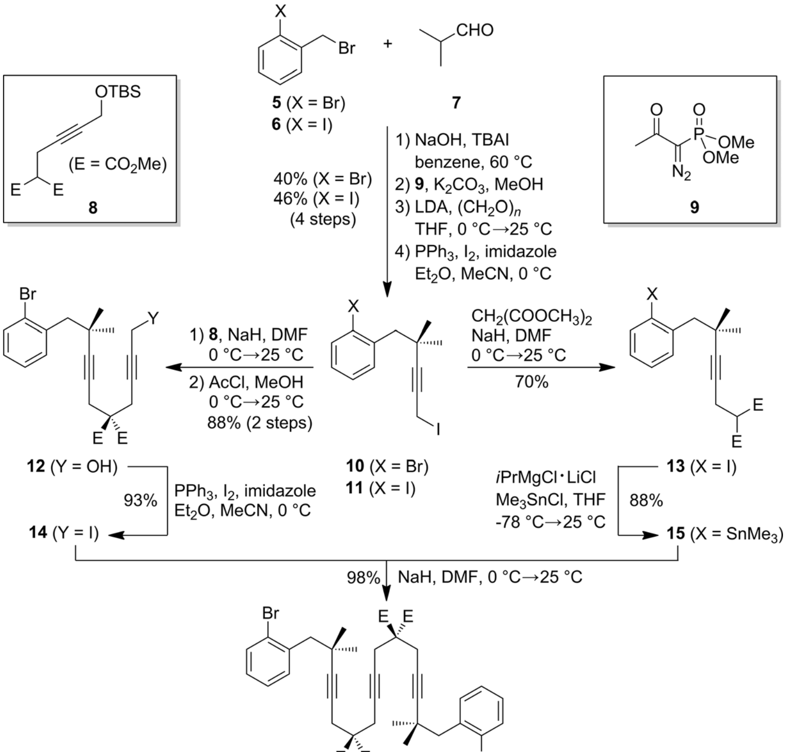
[**] We thank the German Research Foundation (DFG) and the Fonds der Chemischen Industrie. Furthermore, we are grateful to Alexander Hecht for preparative assistance, to Brigitte Brinkmann and Prof. Dr. Thomas Lindel for their support with the HPLC instrumentation, and to Prof. Dr. Nicolai Cramer (EPFL) for a gift of the chiral phospholane ligand.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408637.

in the cascade. Because of the common *syn* attack of the reactive organopalladium species on a C–C triple bond, the two residues are placed on the same side of the emerging alkene moiety. In the case of several tethered alkyne units, repetition of this process leads to the formation of a helical conjugated oligoene system in which rigidity results from the concurrent generation of ring systems between the C–C double bonds.

To test our design principle, we chose long chains equipped with C–C triple bonds at distinct distances and arene units at the termini. The first terminus consists of an aromatic ring substituted with a bromine, the second of an arene unit substituted with $SnMe_3$. With such a design, we intended to start with oxidative addition of the Pd catalyst into the C–Br bond, followed by several carbopalladation steps, and to finalize the cascade through a Stille cross-coupling reaction.

For the synthesis of the starting materials, we employed a repetitive approach, with elongation of the chain through nucleophilic substitutions of malonate derivatives with functionalized propargylic iodides (Scheme 1). Key intermediates **10** and **11** were obtained through a four-step sequence using benzyl bromide derivatives **5** and **6**, respectively, together with 2-methylpropanal (**7**). The triple bond in **10**/**11** was generated with the Bestmann–Ohira reagent **9**, starting from the corresponding carbaldehyde.[15] The bromine-containing congener **10** was elongated through attachment of **8**[16] to the respective propargylic iodide, whereas the iodine-substituted analogue **11** was reacted with dimethylmalonate. Iodine–magnesium exchange paved the way for the attachment of the stannyl group to furnish **15**. Finally **14** and **15** were coupled to afford substrate **16a**. This compound consists of a 16-atom linear carbon chain with three embedded alkyne moieties between the terminal arene residues. Analogous compounds (see Table 1), with either a different substitution pattern or with two and four triple bonds, were obtained in a similar manner (see the Supporting Information).



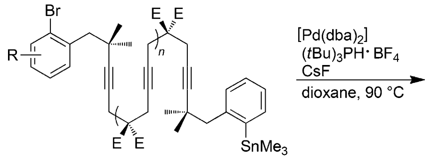
Scheme 1. Synthesis of domino precursor **16a**.

With compound **16a** in hand, we performed the anticipated domino process. We were delighted to observe that common conditions for Stille-type reactions[17] were applicable to drive this cascade, which consists of three subsequent carbopalladations and the terminal Stille cross-coupling, to completion. Indeed, with compound **16a** as starting material, the desired oligoene system was obtained in 93% yield (Table 1, entry 2). The complex $[Pd(dba)_2]$ (dba = dibenzylideneacetone) was employed as the precatalyst and Fu's salt[18] was used to liberate the highly sterically encumbered tris(*tert*-butyl)phosphine to act as the ligand. CsF proved to be beneficial to activate the stannyl group.[17] Careful inspection of the ^{13}C NMR data for the domino product revealed a C_2-symmetric structure with three quaternary olefinic carbon atoms. The helical structure was unequivocally confirmed through analysis of the ^{1}H NMR spectrum; the chiral axis renders the geminal methyl groups diastereotopic, thus resulting in different chemical shifts.

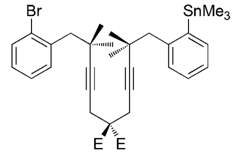
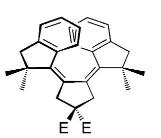
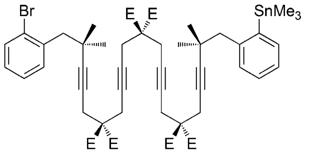
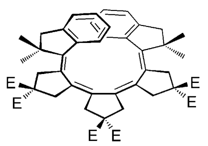
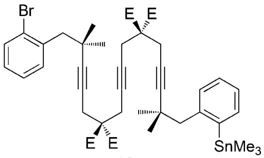
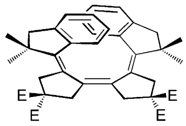
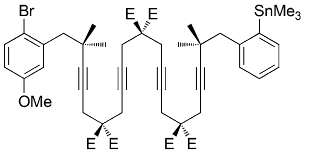
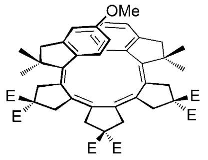
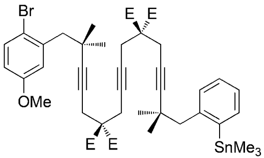
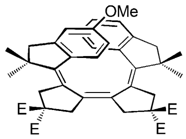
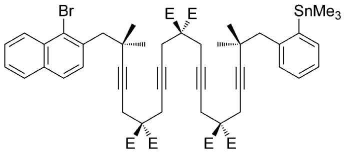
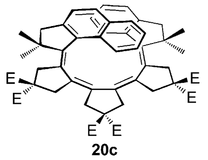
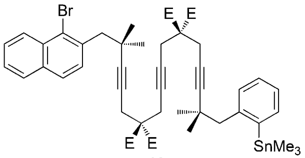
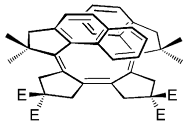
To explore the scope of this domino cascade, the reaction conditions were then applied to a range of substrates (**16**–**18**) with two, three, or four triple bonds embedded in the chain between the arene moieties (Table 1). In all cases, the respective all-*Z* oligoenes (**19**–**21**) were obtained. The synthetic route to the precursors enabled us to generate several derivatives. Since the modification of the arene residue used for oxidative addition proved to be easier than modification of the stannyl-substituted arene, we concentrated our efforts on the former aromatic ring. Instead of a simple phenyl moiety, methoxyphenyl (entries 3 and 6) and naphthyl (entries 4 and 7) moieties were also utilized. The quadruple domino sequences consisting of three consecutive carbopalladations and a terminating Stille coupling gave excellent yields in the range of 89–93%, whereas the yields for the quintuple domino reaction resulting in a *Z*,*Z*,*Z*,*Z*-tetraene ranged between 57 and 72% (entries 5, 6, and 7).

Unfortunately, the nature of the active catalytic species is not clear and efforts to perform this transformation enantioselectively have so far been in vain. We tried to apply (+)-BINAP in the hope of favoring one of the two possible helicities of the product, but without any success. Then a chiral phospolane, which mimics the tris(*tert*-butyl)ligand, was used;[19] however, only poor enantiomeric ratios of 55:45 were obtained. Since we were interested in the values for the optical rotation, we relied on preparative HPLC to separate the single enantiomers of two model compounds (**19a** and

Table 1: Scope of the domino multiple carbopalladation/Stille approach



16, 17, 18 (n = 1, 2, 0) **19, 20, 21** (n = 1, 2, 0)

Entry	Substrate	Domino Product	Yield[b] [%]	Entry	Substrate	Domino Product	Yield[b] [%]
1[c]	 **18**	 **21**	89	5[d,e]	 **17a**	 **20a**	72
2	 **16a**	 **19a**	93	6[d,e]	 **17b**	 **20b**	68
3	 **16b**	 **19b**	89	7[d,f]	 **17c**	 **20c**	57
4[d]	 **16c**	 **19c**	92				

[a] Reaction conditions: **16**, **17**, or **18** (1.0 equiv), catalyst (10 mol%), ligand (20 mol%), CsF (2.2 equiv), dioxane (20 mM), reaction time of 2.5 h. [b] Yield of isolated product based on oligoyne. [c] Reaction time: 9 h at 60 °C. [d] Catalyst (20 mol%), ligand (40 mol%). [e] Reaction time: 17 h at 60 °C. [f] Reaction time: 46 h at 50 °C.

20a) differing in the length of the oligoene chain. A Chiralpak IA column with n-heptane/ethanol as the solvent mixture proved to be ideally suited for this purpose. With the single enantiomers in hand, values for optical rotation were determined. Huge values for the specific rotation were measured (triene **19a**: 1380°; tetraene **20a**: 1490°). For a better comparison of the two helicenes differing in length and mass, the molar rotation, a substance parameter that is independent of the molecular weight, was calculated (**19a**: 9006°; **20a**: 12441°). To structurally assign the different enantiomers, UV CD spectra were recorded and compared with the results of a computational study (Figure 2).[20–22]

Additionally, single crystals of two oligoene-based helicenes (**19a** and **20b**) could be obtained (Figure 3).[23,24] In the triene-based helicene **19a**, the two indane moieties are stacked on top of each other (ca. 1.4 turns), whereas the tetraene-based congener **20b** reveals about 1.8 turns per molecule. The terminal carbon atoms of the triene unit in **19a** are separated by 3.6 Å. The helical topology of all three structures can be traced back to large torsion angles at the C–C single bonds between the alkene units, ranging from 13–57°. The C–C double bonds are only slightly twisted to a maximum of 11°. The bond lengths are not affected at all by this distortion. For **19a**, we also determined the racemization barrier through a kinetic analysis of its racemization at 110 °C

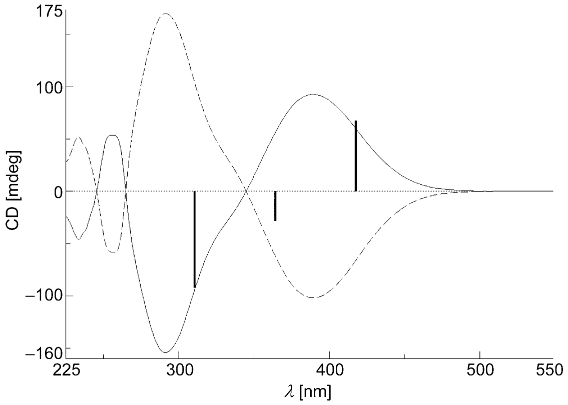


Figure 2. CD spectrum of the two enantiomers of **19a**. The solid line indicates the (P)-(+)-enantiomer, whereas the dashed line shows the (M)-(−)-enantiomer. Black bars indicate the position and rotational strengths of electronic excitations calculated with B3LYP for the (P)-(+)-enantiomer.[21,22]

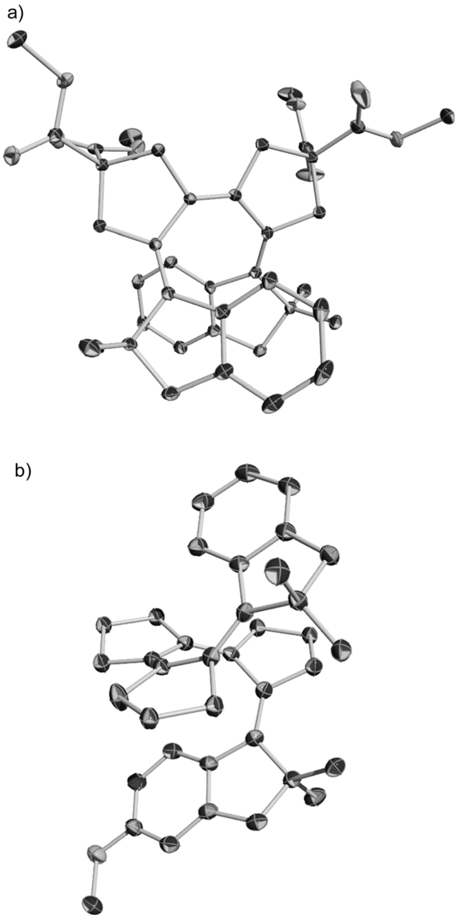


Figure 3. a) Molecular structure of **19a** (top view; H atoms are omitted for the sake of clarity); b) molecular structure of **20b** (side view; H atoms as well as ester groups and a second independent molecule are omitted for the sake of clarity). Thermal ellipsoids are shown at 50% probability level, oxygen atoms are depicted in grey.[24]

and found an activation energy of 28.1 $\mathrm{kcal\,mol^{-1}}$ (see the Supporting Information).

In summary, we have designed a novel type of π-helicenes whose scaffold is based on an *all*-s-*cis* all-*Z* oligoene chain. In these structures, the common π-system of helicenes, which consists of extended arene units, is truncated to a minimum. The key transformation to access the helical oligoene is a domino approach involving multiple carbopalladations and a Stille cross-coupling, which affords the desired compounds in yields ranging from 57 to 93%. X-ray crystallography revealed their screw-shaped topology. Despite the truncation of the π-system, very large optical rotation values were measured for the single helical enantiomers, which could be assigned by comparison of their CD spectra with quantum chemical calculations.

Received: August 28, 2014
Revised: November 7, 2014

Keywords: carbopalladation · domino reaction · helicenes

---

[1] Reviews: a) A. Urbano, *Angew. Chem. Int. Ed.* **2003**, *42*, 3986; *Angew. Chem.* **2003**, *115*, 4116; b) Y. Shen, C.-F. Chen, *Chem. Rev.* **2012**, *112*, 1463; c) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 968; d) M. Gingras, G. Felix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007.

[2] a) F. Vögtle, *Fascinating Molecules in Organic Chemistry*, Wiley, New York, **1992**; b) H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**; c) A. Rajca, M. Miyasaka in *Functional Organic Materials*: *Syntheses*, *Strategies and Applications* (Eds.: T. J. J. Müller, U. H. F. Bunz), Wiley-VCH, Weinheim, **2007**.

[3] J. Meisenheimer, K. Witte, *Chem. Ber.* **1903**, *36*, 4153.

[4] R. H. Martin, M. J. Marchant, *Tetrahedron Lett.* **1972**, *13*, 3707.

[5] a) S. Grimme, S. D. Peyerimhoff, *Chem. Phys.* **1996**, *204*, 411; b) R. H. Janke, G. Haufe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc.* **1996**, *118*, 6031.

[6] Selected examples: a) M. S. Newman, D. Lednicer, *J. Am. Chem. Soc.* **1956**, *78*, 4765; b) R. H. Martin, M.-J. Marchant, M. Baes, *Helv. Chim. Acta* **1971**, *54*, 358; c) N. D. Willmore, L. Liu, T. J. Katz, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1093; *Angew. Chem.* **1992**, *104*, 1081; d) Y. Shen, H.-Y. Lu, C.-F. Chen, *Angew. Chem. Int. Ed.* **2014**, *53*, 4648; *Angew. Chem.* **2014**, *126*, 4736.

[7] Selected examples for access to enantioenriched π-helicenes: a) I. G. Stará, I. Starý, M. Tichy, J. Zavada, V. Hanus, *J. Am. Chem. Soc.* **1994**, *116*, 5084; b) M. C. Carreno, S. Garcia-Cerrada, A. Urbano, *J. Am. Chem. Soc.* **2001**, *123*, 7929; c) Y. Kimura, N. Fukawa, Y. Miyauchi, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2014**, *53*, 8480; *Angew. Chem.* **2014**, *126*, 8620; d) L. Kötzner, M. J. Webber, A. Martínez, C. De Fusco, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 5202; *Angew. Chem.* **2014**, *126*, 5303.

[8] S. Han, A. D. Bond, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt, G. D. Whitener, *Angew. Chem. Int. Ed.* **2002**, *41*, 3223; *Angew. Chem.* **2002**, *114*, 3357.

[9] a) K. Nakano, H. Oyama, Y. Nishimura, S. Nakasako, K. Nozaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 695; *Angew. Chem.* **2012**, *124*, 719; b) H. Oyama, K. Nakano, T. Harada, R. Kuroda, M. Naito, K. Nobusawa, K. Nozaki, *Org. Lett.* **2013**, *15*, 2104; c) S. Hashimoto, S. Nakatsuka, M. Nakamura, T. Hatakeyama, *Angew. Chem. Int. Ed.* **2014**, *53*, 14074; *Angew. Chem.* **2014**, *126*, 14298.

[10] Recently a (*Z*,*Z*,*Z*,*Z*,*Z*)-pentaene was reported; however, no crystal structure could be obtained: S. L. Drew, A. L. Lawrence, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2013**, *52*, 4221; *Angew. Chem.* **2013**, *125*, 4315.

[11] General overview: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; b) *Domino Reactions*: *Concepts for Efficient Organic Synthesis* (Ed.: L. F. Tietze), Wiley-VCH, Weinheim, **2014**.

[12] a) "Carbometallation Reactions": I. Marek, N. Chinkov, D. Banon-Tenne in *Metal Catalyzed-Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) E. Negishi, G. Wang, G. Zhu, *Top. Organomet. Chem.* **2006**, *19*, 1.

[13] a) F. E. Meyer, A. de Meijere, *Synlett* **1991**, 777; b) R. Grigg, V. Loganathan, V. Sridharan, *Tetrahedron Lett.* **1996**, *37*, 3399; c) J. Suffert, B. Salem, P. Klotz, *J. Am. Chem. Soc.* **2001**, *123*, 12107; d) B. Salem, J. Suffert, *Angew. Chem. Int. Ed.* **2004**, *43*, 2826; *Angew. Chem.* **2004**, *116*, 2886; e) M. Leibeling, D. C. Koester, M. Pawliczek, S. C. Schild, D. B. Werz, *Nat. Chem. Biol.* **2010**, *6*, 199; f) M. Leibeling, B. Milde, D. Kratzert, D. Stalke, D. B. Werz, *Chem. Eur. J.* **2011**, *17*, 9888.

[14] a) J. Petrignet, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2011**, *50*, 3285; *Angew. Chem.* **2011**, *123*, 3343; b) M. Leibeling, M. Pawliczek, D. Kratzert, D. Stalke, D. B. Werz, *Org. Lett.* **2012**, *14*, 346; c) M. Leibeling, D. B. Werz, *Chem. Eur. J.* **2012**, *18*, 6138; d) L. F. Tietze, T. Hungerland, C. Eichhorst, A.

Düfert, C. Maaß, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3668; *Angew. Chem.* **2013**, *125*, 3756; e) J. Wallbaum, R. Neufeld, D. Stalke, D. B. Werz, *Angew. Chem. Int. Ed.* **2013**, *52*, 13243; *Angew. Chem.* **2013**, *125*, 13485.

[15] a) G. J. Roth, B. Liepold, S. G. Müller, H. J. Bestmann, *Synthesis* **2004**, 59; b) J. Pietruszka, A. Witt, *Synthesis* **2006**, 4266.

[16] A. Zawisza, B. Fenêt, D. Sinon, *Eur. J. Org. Chem.* **2007**, 2296.

[17] a) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **1999**, *38*, 2411; *Angew. Chem.* **1999**, *111*, 2568; b) A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343.

[18] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295.

[19] (2*S*,5*S*)-1-(*tert*-Butyl)-2,5-dimethylphospholane was employed: P. A. Donets, T. Saget, N. Cramer, *Organometallics* **2012**, *31*, 8040.

[20] In comparison with corresponding *all*-(*E*)-oligoenes, the red shift of λ_{max} is about 10 nm smaller.

[21] a) G. Bringmann, T. Bruhn, K. Maksimenka, Y. Hemberger, *Eur. J. Org. Chem.* **2009**, 2717; b) L. Goerigk, S. Grimme, *J. Phys. Chem. A* **2009**, *113*, 767.

[22] Starting with the C_1-symmetric solid-state conformation, we scanned the conformational space of the **19a** ((*P*)-(+)-enantiomer) by applying the MMFF force field (T. A. Halgren, *J. Comput. Chem.* **1996**, *17*, 490) and ended up with the C_2-symmetric global minimum conformation of the isolated molecule. In a second step, we reoptimized the structure by applying the B3LYP hybrid functional (A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648) and a standard 6-311++G(d,p) basis set. Finally, in order to get a qualitatively correct assignment of our experimental UV CD data, we computed the rotational strengths of the first three electronic transitions by applying a standard TD-DFT formalism (*Time-dependent density functional theory* (Eds.: M. A. L. Marques, C. A. Ullrich, F. Nogueira, A. Rubio, K. Burke, E. K. U. Gross), Springer, Berlin-Heidelberg, **2006**).

[23] a) T. Kottke, D. Stalke, *J. Appl. Crystallogr.* **1993**, *26*, 615; b) Bruker, SAINT V7.68A, Bruker AXS Inc., Madison (WI, USA), **2005**; c) G. M. Sheldrick, SADABS 2008/2, Göttingen, **2008**; d) G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112.

[24] CCDC 1020999 (**19a**), and 1021001 (**20b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.