Synthesis of Carbon *E,E*-Diene Chain-Linked Dinucleotide Analogues

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Abstract: The synthesis of a dinucleotide thymidine–thymidine linked by a carbon *E,E*-diene chain is described. This dimer is synthesized by a coupling reaction between an (*E*)-vinylstannane and an (*E*)-iodovinyl partner prepared from acetylenic parents, which are both available from thymidine in six and five steps, respectively. In addition, a new efficient access to 3′-*C*-formyl thymidine is presented.

Key words: antisense agents, nucleobases, Stille reactions, alkynes, isomerizations

Antisense technology, first introduced by Stephenson and Zamecnik[1] in 1978, is a simple and elegant concept: a single-stranded oligodeoxynucleotide can bind in a specific manner, using the rules of Watson and Crick, the messenger RNA of a gene in order to inhibit its translation into protein. Antisense oligonucleotides are currently being investigated as therapeutic agents in many fields including oncology, vascular, and genetic diseases, as well as viral infections; theoretically, any diseases caused by the expression of a deleterious gene.[2] In 1998, the first antisense oligonucleotide drug, a first generation phosphorothioate oligodeoxynucleotide 21-mer (ISIS 2922) vitravene®, was commercialized for the treatment of cytomegalovirus (CMV)-induced retinis.[3] Although the antisense oligonucleotide concept is quite simple, its application has proved to be challenging; target sites, delivery, toxicity, affinity, and stability, as well as the retention of the RNase H activity, have to be integrated. Unmodified oligodeoxynucleotides are rapidly degraded under physiological conditions by nucleases. To overcome this problem, a huge effort has been made through the development of various chemical modifications to increase the stability of antisense oligonucleotides without affecting their target affinity.[4] It is clear that, although most of the modifications introduced into antisense oligonucleotides have led to an increased resistance towards nucleases, only a few have resulted in improved affinity properties.

The replacement of the phosphodiester linkage by a number of amide isomers has been previously patented[5] and then reported in the literature (Figure 1).[6,7] It was pointed out that the two amide modifications **1** and **2**, which could be regarded as structural analogues of the same *E* C–C double bond, displayed a higher affinity for an RNA target (up to 4.4 °C per modification for amide **1**) and a very good resistance towards nucleases. More recently, Rozners[8] has shown that a uridine–uridine dimer ribo analogue of dinucleotide **1** substantially stabilizes RNA–RNA duplexes (+1 °C to +2.4 °C per modification) making this amide linkage promising for small interfering RNA (siRNA).[9] However, it is surprising to note that the incorporation of the dimer **3** with an *E* C–C double bond into oligomers led to a significant decrease in the stability of the DNA–RNA duplexes (average –0.8 °C per modification).[10] In order to investigate the importance of the rigidity of the backbone, the dimer **4** with the most flexible internucleoside linkage was studied, and a drastic drop in the thermal stability of the DNA–RNA duplexes was noted (average –4.2 °C per modification).[11]

In the context of evaluating the importance of geometric parameters, we wish to report the synthesis of a dinucleotide thymidine–thymidine **5**, in which the natural phosphodiester linkage has been replaced by an *E,E*-diene chain, C-3′α to C-4′β. To the best of our knowledge, no work has been done on the synthesis and on the biological evaluation of this rigid modification **5**.

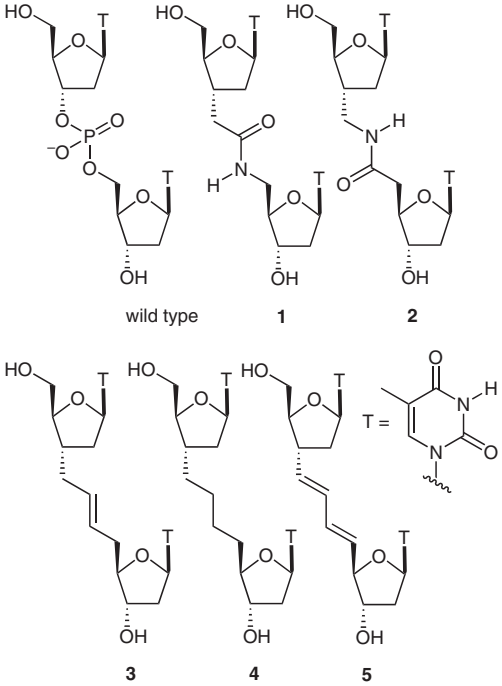

Figure 1 Dinucleotides thymidine–thymidine **1–5**

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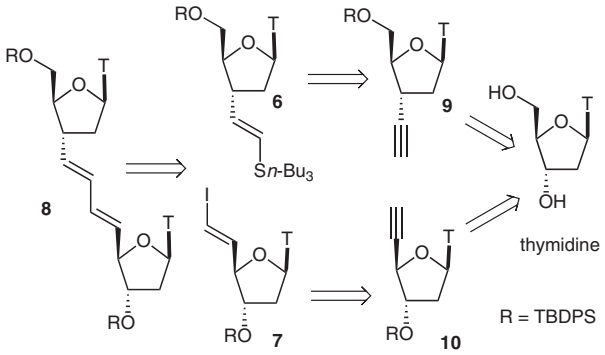
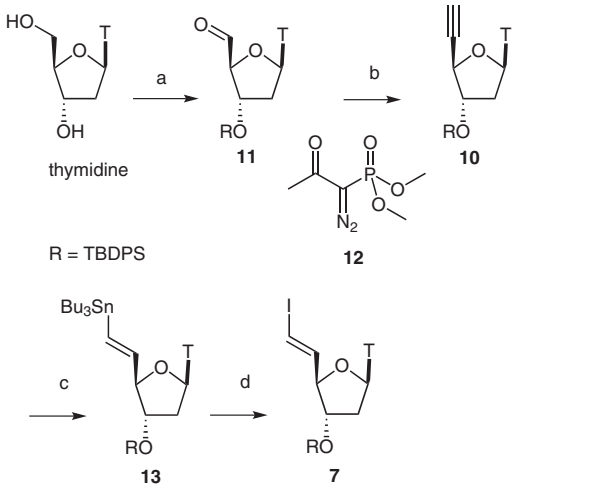
In our synthetic plan, Stille coupling turned out to be the method of choice for single C–C bond formation between the (*E*)-vinylstannane **6** and the iodovinyl **7** partners providing the diene **8** as outlined in the retrosynthetic scheme (Scheme 1). Both vinyl derivatives are easily available from their acetylenic parents **9** and **10**, which are prepared from thymidine.



Scheme 1 Retrosynthetic scheme

In previous work in this field, we have already introduced an acetylenic group into the 4′-position by a sequence developed by Bobek[12] from aldehyde **11**[11] (Scheme 2) via the corresponding dibromo olefin. Unfortunately, yields of the dehalogenation step were found to be strongly dependent on the scale of the reaction leading to serious problems for purification in multigram quantities.[13] It is worth noting that the silyl group at the 3′-position in the dibromo olefin intermediate has to be temporarily removed prior to treatment with *n*-BuLi. Prompted by this experience, we decided to explore the reactivity of dimethyl-1-diazo-2-oxopropylphosphonate (Bestmann–Ohira reagent **12**)[14] in order to develop a short and efficient protocol to prepare compound **10**.



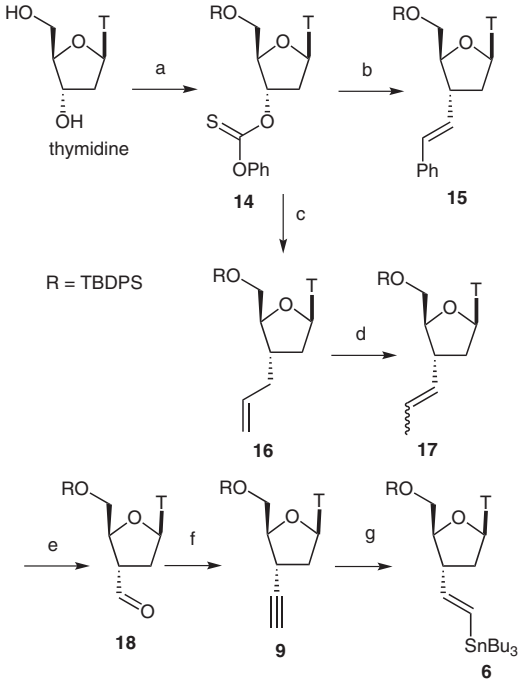
Scheme 2 *Reagents and conditions*: (a) see ref. 11, 4 steps, 35% overall yield; (b) Bestmann–Ohira reagent **12**, K_2CO_3, MeOH, r.t., 5 h, 66%; (c) $(Bu_3Sn)BuCuCNLi_2$, THF, –40 °C, 45 min, 72%; (d) I_2, CH_2Cl_2, 0 °C, 83%.

To our satisfaction, we found that the homologation of aldehyde **11** with the Bestmann–Ohira reagent **12** in methanol with K_2CO_3 at room temperature afforded, in a single step, the acetylenic derivative **10** in 70% yield after purification.

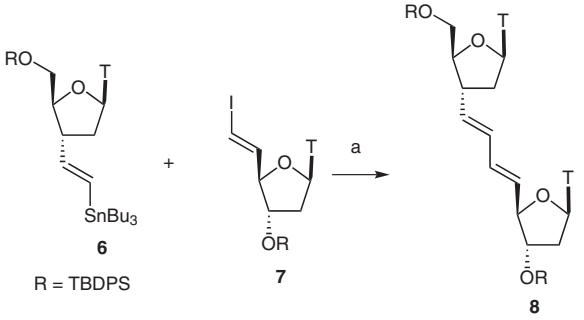
Pivotal to the success of this work was securing a stereoselective access to both (*E*)-vinylstannane partners **13** and **6**. Robins reported a particularly effective synthesis of 6′-(*E*)-vinylstannane homonucleosides by radical stannyldesulfonation of the corresponding 6′-(*E*)-tosylvinyl derivatives.[15] Although this methodology has found many applications in the multistep synthesis of nucleoside analogues, it should be pointed out that the vinylstannane homonucleosides are obtained in modest to good yields as a separable mixture of *E*- and *Z*-isomers in the range of ratios 2.8:1 to 7.3:1.[16] To the best of our knowledge, only one example of 3′-β-vinylstannane nucleoside has been described in the literature by stannyl radical addition to an ethynyl intermediate leading to the desired product as a 1:1 mixture of the *E*- and *Z*-isomers.[17] In view of this lack of stereoselectivity, we considered the stannylcupration reaction of the alkynes, which offers good regio- and stereoselectivity. Moreover, these stannylcopper reagents are compatible with various functionalities, including base-unprotected nucleosides. In fact, subsequent investigations showed that, following the work of Duchêne,[18] the treatment of **10** with the mixed stannyl cyanocuprate $(Bu_3Sn)BuCuCNLi_2$ successfully led to the formation of the desired (*E*)-vinylstannane **13** as the unique isomer in 72% yield. Finally, a classical iodine exchange was performed on the latter compound **13** to afford our first partner **7**[19] in 83% yield after purification on silica gel chromatography. As an alternative, the direct conversion of aldehyde **11** into the iodovinyl derivative **7** was investigated. A Takai reaction of the aldehyde **11** using iodoform gave the vinyl iodide **7** in low yield with no stereoselectivity.[20]

In the field of modified nucleosides, the 3′-*C*-formyl nucleosides, like the thymidine derivative **18**, have been used as key intermediates in the synthesis of various 3′-C-branched chain nucleosides (Scheme 3).[21] A short and stereoselective approach to the compound **18** has previously been reported by De Mesmaeker et al.[22] based on a Barton–McCombie-type radical addition–elimination. In this reaction, the 3′-C-center radical, generated from 3′-*O*-(phenyloxy)thiocarbonyl]-2′-deoxynucleoside **14**, reacted on β-tributylstannylstyrene to give **15** followed by oxidative cleavage of the double bond. Nevertheless, as noted by us and other authors, this free-radical introduction of the β-styrene residue to prepare **15** was found to be tricky. For no apparent explanation, the yield was not always reproducible (in our experience, 25–65%) and a significant amount of the corresponding 2′,3′-dideoxynucleoside was formed. In searching for an alternative method, we made use of a recently reported efficient allyl to propenyl isomerization[23] using Grubbs second-generation catalyst and the ready synthetic availability of the 3′-*C*-allyl[24] intermediate **16** from **14**. We thus achieved an access to this

key aldehyde **18** with reproducible yield. The 3′-*C*-allyl thymidine **16** at a concentration of 0.07 M was heated in methanol at 60 °C for 12 hours with 10 mol% of Grubbs catalyst to afford, after removal of the solvent and direct purification of the crude mixture on silica gel, the propenyl derivative **17** in 95% yield (*E*/*Z* ratio = 4:1). This latter compound **17** was converted in 60–65% yield to the desired aldehyde **18** via a standard one-pot OsO_4/$NaIO_4$-mediated oxidative cleavage of the double bond. At this point, following the success of the former sequence to prepare **13**, the same chemical transformations were carried out on the aldehyde **18** to give the (*E*)-vinylstannane **6**[25] in 52% overall yield.



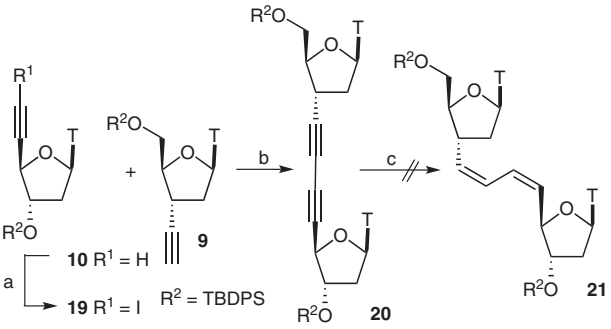
Scheme 3 *Reagents and conditions*: (a) see ref. 22, 2 steps, 85% overall yield; (b) see ref. 22, 25–65%; (c) Bu_3Sn-allyl, AIBN, PhH, reflux, 12 h, 85%; (d) Grubbs second-generation catalyst (10 mol%, 0.07 M), MeOH, 60 °C, 12 h, 95%; (e) 4-NMO, OsO_4, dioxane–H_2O, r.t., 3 h then $NaIO_4$, r.t., 4 h 65%; (f) Bestmann–Ohira reagent **12**, K_2CO_3, MeOH, r.t., 5 h, 76%; (g) $(Bu_3Sn)BuCuCNLi_2$, THF, –40 °C, 45 min, 68%.



Scheme 4 *Reagents and conditions*: (a) $Pd(PPh_3)_4$, THF, 60 °C, 4 h, 52%.

At this stage, we were ready to set up the Stille coupling[26] as outlined in Scheme 4. The Pd-catalyzed coupling gave the *E*,*E*-diene **8**[27] as a single isomer in 52% yield.

In order to evaluate the influence of the geometry of the double bonds on DNA–RNA duplexes, it was thought interesting to prepare the *Z*,*Z*-diene isomer. It seemed that the simplest strategy to reach the *Z*,*Z*-diene **21** would be to prepare the diyne from the previous alkyne partners by a C–C coupling reaction to afford the asymmetrical diynes[28] followed by a stereoselective reduction. The iodoalkyne **19** was prepared from acetylenic **10** using a standard procedure.[29] Then, Pd-mediated coupling of the alkyne **9** with the iodoalkyne **19** using Schreiber's protocol[30] afforded the diyne **20**[31,32] in 35–40% yield. To our disappointment, the stereoselective reduction with Zn/Cu following Boland's procedure[33,34] to afford the corresponding *Z*,*Z*-diene **21** failed (Scheme 5). This reaction was investigated under a variety of conditions, giving invariably a complex mixture, which did not appear to contain the desired diene **21**.



Scheme 5 *Reagents and conditions*: (a) NIS, $AgNO_3$, acetone, r.t., 45 min, 92%; (b) $Pd_2(dba)_3$, CuI, $(furyl)_3P$, PhH, r.t., 20 min, 38%; (c) $Zn/CuSO_4$, $AgNO_3$, MeOH–H_2O.

In conclusion, we have developed a concise and stereoselective route to a dinucleotide thymidine–thymidine linked by a carbon *E*,*E*-diene chain. We also hope that the new access to 3′-*C*-formyl thymidine **18** reported herein will find synthetic applications in the field of modified nucleosides. The extension of this pathway to other diene linkages from acetylenic partners via (*Z*)-vinyliodide is in progress, as well as the incorporation of this backbone into oligonucleotides for biological evaluations.

Acknowledgment

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(19) **Selected Physicochemical Data for Compound 7**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 9 H, *t*-Bu), 1.82–1.92 (m, 1 H, $H_{2''}$), 1.89 (s, 3 H, CH_3), 2.39 (ddd, 1 H, *J* = 10.0, 6.5, 3.0 Hz, $H_{2'}$), 4.20 (ddd, 1 H, *J* = 10.0, 3.0 Hz, $H_{3'}$), 4.24 (m, 1 H, $H_{4'}$), 6.23 (br s, 2 H, $H_{5'}$ and $H_{6'}$), 6.34 (dd, 1 H, *J* = 6.5 Hz, $H_{1'}$), 6.93 (d, 1 H, *J* = 1.0 Hz, H_6), 7.38–7.50 (m, 6 H, H_{ar}), 7.59–7.67 (m, 4 H, H_{ar}), 9.28 (br s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6 (CH_3, CH_3), 18.9 (C, *t*-Bu), 26.8 (CH_3, *t*-Bu), 39.6 (CH, $C_{2'}$), 75.4 (CH, $C_{3'}$), 80.7 (CH, $C_{6'}$), 84.8 (CH, $C_{1'}$), 88.2 (CH, $C_{4'}$), 111.3 (C, C_5), 127.9, 128.0 (CH, C_{ar}), 130.2 (CH, C_{ar}), 132.7 (C, C_{ar}), 134.9 (CH, C_6), 135.6, 135.8 (CH, C_{ar}), 142.1 (CH, $C_{5'}$), 150.2 (C, C=O), 163.6 (C, C=O) ppm. MS (CI/NH_3): *m/z* ($C_{27}H_{31}I\,N_2O_4Si$) = 620 [M + NH_4^+], 603 [M + H^+].

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(25) **Selected Physicochemical Data for Compound 6**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70–0.80 (15 H, 3 CH_3 and 3 CH_2, CH_3 and CH_2 *n*-Bu), 1.02 (s, 9 H, 3 CH_3, *t*-Bu), 1.10–1.27 (m, 6 H, 3 CH_2, *n*-Bu), 1.38 (m, 6 H, 3 CH_2, *n*-Bu), 2.26 (m, 1 H, $H_{2'}$), 2.40 (m, 1 H, $H_{2'}$), 2.40 (s, 3 H, CH_3), 3.14 (m, 1 H, $H_{3'}$), 3.75–3.86 (m, 2 H, $H_{4'}$ and $H_{5'}$), 4.11 (m, 1 H, $H_{5'}$), 5.76 (dd, 1 H, *J* = 7.0, 19.0 Hz, $H_{3''}$), 6.15 (d, 1 H, *J* = 19.0 Hz, $H_{3'''}$), 6.16 (dd, 1 H, *J* = 3.0, 7.0 Hz, $H_{1'}$), 7.22–7.49 (m, 6 H, H_{ar}), 7.66 (s, 1 H, H_6), 7.62–7.84 (m, 4 H, H_{ar}), 9.50 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.4 (CH_2, *n*-Bu), 11.9 (CH_3, CH_3), 13.6 (CH_3, *n*-Bu), 19.4 (C, *t*-Bu), 27.1 (CH_3, *t*-Bu), 27.4 (CH_2, *n*-Bu), 29.0 (CH_2, *n*-Bu), 39.3 (CH_2, $C_{2'}$), 45.0 (CH, $C_{3'}$), 62.5 (CH_2, $C_{5'}$), 84.7 (CH, $C_{1'}$), 85.6 (CH, $C_{4'}$), 110.5 (C, C_5), 127.8 (CH, C_{ar}), 129.8 (CH, C_{ar}), 132.5 (CH, $C_{3'''}$), 132.8, 133.3 (C, C_{ar}), 135.2, 135.4 (CH, C_{ar}), 135.6 (CH, C_6), 145.5 (CH, $C_{3''}$), 150.5 (C=O), 164.2 (C=O) ppm. ESI-HRMS: *m/z* [M + H^+] calcd for $C_{40}H_{61}N_2O_4SiSn$ [M(^{119}Sn) + H]$^+$: 780.3433; found: 780.3431.

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(27) **Selected Physicochemical Data for Compound 8**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H, *t*-Bu), 1.10 (s, 9 H, *t*-Bu), 1.58 (s, 3 H, CH_{3A}), 1.86 (s, 3 H, CH_{3B}), 2.44–2.19 (m, 4 H, $H_{2'A}$ and $H_{2'B}$), 3.18–3.02 (tdd, 1 H, *J* = 8.0, 8.0, 8.0 Hz, $H_{3'A}$), 3.79 (m, 1 H, $H_{4'A}$), 3.75 (dd, part A of an AB system, 1 H, *J* = 12.0, 3.0 Hz, $H_{5'A}$), 4.13–4.03 (dd, part B of an AB system, 1 H, *J* = 12.0, 3.0 Hz, $H_{5'A}$), 4.22–4.14 (1 H, dt, *J* = 6.0, 3.0 Hz, $H_{4'B}$), 4.42–4.33 (dd, 1 H, *J* = 7.0, 4.0 Hz, $H_{3'B}$), 5.34–5.21 (m, 1 H, H_d), 5.52–5.38 (m, 1 H, H_a), 6.05–5.90 (2 dd, 2 H, *J* = 8.0 Hz, H_b and H_c), 6.19–6.09 (dd, 1 H, *J* = 4.0, 7.0 Hz, $H_{1'A}$), 6.40–6.30 (dd, 1 H, *J* = 7.0 Hz, $H_{1'B}$), 7.00 (s, 1 H, H_{6B}), 7.49–7.27 (m, 12 H, H_{ar}), 7.51

(s, 1 H, H_{6A}), 7.75–7.56 (m, 8 H, H_{ar}), 8.87–8.80 (2 br s, 2 H, 2 NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_3, CH_{3A}), 12.3 (CH_3, CH_{3B}), 19.0 (C, *t*-Bu), 19.4 (C, *t*-Bu), 26.8 (CH_3, *t*-Bu), 27.0 (CH_3, *t*-Bu), 39.4 (CH_2, $C_{2'A}$), 40.0 (CH_2, $C_{2'B}$), 40.7 (CH, $C_{3'A}$), 62. 8 (CH_2, $C_{5'A}$), 76.5 (CH, $C_{4'B}$), 84.8 (CH, $C_{1'A}$), 85.1 (CH, $C_{1'B}$), 85.6 (CH, $C_{3'B}$), 86.8 (CH, $C_{4'A}$), 110.7 (C, C_{5A} or C_{5B}), 111.1 (C, C_{5A} or C_{5B}), 128.0 (CH, CH_{ar}), 129.2 (CH, C_d), 130.1 (CH, CH_{ar}), 131.5 (CH, C_b and C_c), 132.3 (C, C_{ar}), 132.6 (CH, C_a), 133.2 (C, C_{ar}), 135.4, 135.5, 135.8, 135.9 (CH, CH_{ar}, C_{6A} and C_{6B}), 150.3 (C, C=O), 163.6 (C, C=O) ppm. The letter A refers to the upper moiety of the dimer **8**. ESI-HRMS: *m/z* [M + Na^+] calcd for $C_{55}H_{64}N_4O_8Si_2Na$: 987.4160; found: 987.4162.

(28) For an example of a nucleoside linked with a butadiynyl chain C-4′α/C-3′β, see: Jung, F.; Burger, A.; Biellmann, J.-F. *Org. Lett.* **2003**, *5*, 383.

(29) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

(30) Elbaum, D.; Nguyen, T. B.; Jorgensen, W. L.; Schreiber, S. L. *Tetrahedron* **1994**, *50*, 1503.

(31) To confirm the structure, this diyne was hydrogenated in MeOH in the presence of Pd/C to afford the corresponding known dimer with an alkane linkage (see ref. 11a).

(32) **Selected Physicochemical Data for Compound 20**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 9 H, *t*-Bu), 1.11 (s, 9 H, *t*-Bu), 1.62 (s, 3 H, CH_{3A}), 1.84 (s, 3 H, CH_{3B}), 1.87–2.08 (ddd, 1 H, *J* = 5.0, 9.0, 14.0 Hz, $H_{2'B}$), 2.32–2.66 (m, 3 H, $H_{2'A}$ and $H_{2'B}$), 3.42 (ddd, 1 H, *J* = 8.0, 8.0, 8.0 Hz, $H_{3'A}$), 3.83 (dd, part A of an AB system, 1 H, *J* = 2.0, 12.0 Hz, $H_{5'A}$), 4.00 (ddd, 1 H, *J* = 2.0, 7.0, 12.0 Hz, $H_{4'A}$), 4.08 (dd, part B of an AB system, 1 H, *J* = 2.0, 12.0 Hz, $H_{5'A}$), 4.53 (d, 1 H, *J* = 4.0 Hz, $H_{3'B}$), 4.67 (s, 1 H, $H_{4'B}$), 6.20 (dd, 1 H, *J* = 13.0, 6.0 Hz, $H_{1'A}$), 6.57 (dd, 1 H, *J* = 6.0, 8.0 Hz, $H_{1'B}$), 7.34–7.51 (m, 14 H, H_{ar}, H_{6A} and H_{6B}), 7.62–7.68 (m, 8 H, H_{ar}), 9.16 (br s, 1 H, NH), 9.30 (br s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_3, CH_{3A}), 12.7 (CH_3, CH_{3B}, 19.0 (C, *t*-Bu), 19.4 (C, *t*-Bu), 26.8 (CH_3, *t*-Bu), 26.9 (CH_3, *t*-Bu), 29.6 (CH, $C_{3'A}$), 38.9 (CH_2, $C_{2'A}$), 40.5 (CH_2, $C_{2'B}$), 62.5 (CH_2, $C_{5'A}$), 66.4, 72.9, 73.5, 80.0 (C, C_a, C_b, C_c and C_d), 71.9 (CH, $C_{4'B}$), 73.2 (CH, $C_{3'B}$), 84.6 (CH, $C_{1'A}$), 84.9 (CH, $C_{4'A}$), 86.7 (CH, $C_{1'B}$), 111.3 (C_{5A} and C_{5B}), 127.9, 128.0 (CH, CH_{ar}), 130.1 (CH, C_{6A} or C_{6B}), 130.2 (CH, C_{6A} or C_{6B}), 132.5, 132.6 (C, C_{ar},), 134.9 (CH, CH_{ar}), 135.3, 135.5, 135.6 (CH, CH_{ar}), 150.4 (C, C=O), 163.7 (C, C=O) ppm. The letter A refers to the upper moiety of the dimer **20**. ESI-HRMS: *m/z* [M + Na^+] calcd for $C_{55}H_{60}N_4O_8Si_2Na$: 983.3847; found: 983.3837.

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(34) For an example of stereoselective reduction of polyacetylenic compounds using this protocol, see: Solladié, G.; Adamy, M.; Colobert, F. *J. Org. Chem.* **1996**, *61*, 4369; and references cited therein.