Pergamon

Tetrahedron Letters 43 (2002) 8099–8101

TETRAHEDRON
LETTERS

All-(*Z*)-cyclooctadeca-1,4,7,10,13,16-hexaene: structure and first preparation via an intramolecular Wittig reaction

Sophie Guiard, Maurice Santelli and Jean-Luc Parrain*

Laboratoire de Synthèse Organique, UMR CNRS 6009, Faculté des Sciences de Saint Jérôme, 13397 Marseille, France

Received 22 July 2002; accepted 9 September 2002

Abstract—The first synthesis of all-(*Z*)-cyclooctadeca-1,4,7,10,13,16-hexaene was achieved using an intramolecular Wittig reaction as a key step. The structure was firmly established by X-ray analysis. © 2002 Elsevier Science Ltd. All rights reserved.

The concept of homoconjugation[1] enounced by Winstein attracts continuing attention because of the theoretical challenges, unique structures, and organic materials with interesting properties.[2] The term homoconjugation is used if the π-fragments are held in close proximity by one or two sp^3 centres. In this context, a wide range of cyclic compounds containing double or triple bonds have been described in the literature. For example, two compounds having a cyclic *Z*-skipped polyolefin skeleton that are 'homoconjugated' analogues of benzene and cyclooctatetraene have been synthesised: the all-(*Z*)-cyclonona-1,4,7-triene (CNT)[3] and the all-(*Z*)-cyclododeca-1,4,7,10-tetraene[4] (CDT) (Fig. 1). To the best of our knowledge, larger macrocyclic *Z*-skipped polyolefins possessing more than 12 carbon atoms have never been prepared.

Recently, we have described a new synthetic approach towards CDT via an intramolecular Wittig reaction.[5] So, we have planned to extend this methodology to the synthesis of macrocyclic polyolefins with a higher degree of insaturation. Bestmann has described the first synthesis of cycloolefin via auto-oxidation of bisphosphorane.[6] However by this methodology, the formation of strain cycles is defavourable and the reaction led to oligomers.[6,7] Based on this observation, we thought that the bisphosphorane **6** would be the appropriate precursor to cyclooctadeca-1,4,7,10,13,16-hexaene **1** (Scheme 1).

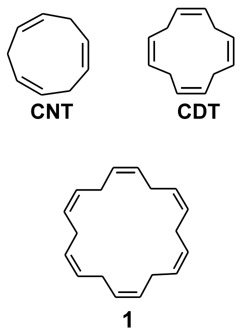
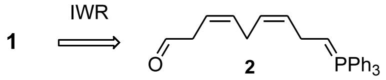


Figure 1.

In this communication, we report that cyclooctadeca-1,4,7,10,13,16-hexaene can effectively be prepared via an intramolecular Wittig reaction. Our investigation began with the preparation of the non-stabilised phosphorane aldehyde **2** under the conditions previously defined by Bestmann.[8] This compound was easily prepared via the corresponding bisphosphorane **6**. The preparation of bisphosphorane **6** is summarised in Scheme 2.

After protection of commercially available but-3-yn-1-ol **3** with dihydropyran in the presence of a catalytic amount of PPTS, protected butynol was metalled with *n*-butyllithium in THF then condensed on paraformaldehyde to give the corresponding propargyl alcohol (60% yield over two steps).[9] Reaction of alcohol and tosylchloride in the presence of potassium hydroxide in diethylether,[10] at rt, furnished the corresponding tosylate **4** in a quantitative yield. Reaction of **4** and but-3-yn-1-ol in the presence of potassium carbonate,



Scheme 1.

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* Corresponding author.

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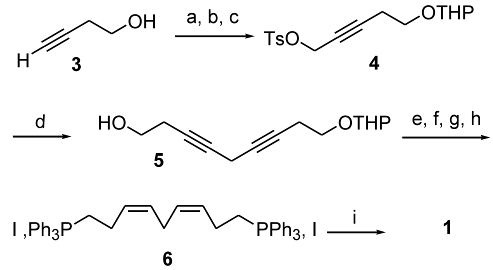
PII: S0040-4039(02)01951-2



Scheme 2. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2, (99%); (b) i. *n*-BuLi, THF, −78°C; ii. Paraformaldehyde (60%); (c) TsCl, KOH, Et_2O, rt; (97%); (d) But-3-yn-1-ol, CuI, NaI, K_2CO_3, DMF, 35°C, (82%); (e) P-2 nickel, ethylene diamine, H_2, EtOH, (80%); (f) HCl 1 M, MeOH (99%); (g) I_2, PPh_3, imidazole, THF, −10°C, then rt (81%); (h) PPh_3, CH_3CN, reflux (95%); (i) NaHMDS (2 M in THF), THF, −78 to 0°C, then O_2 (35%).

sodium iodide and copper(I) iodide gave the monoprotected diynol **5** in 82% yield.[11] Semihydrogenation over Brown P-2 Ni catalyst in the presence of ethylene diamine afforded the corresponding all-(*Z*)-dienol in 80% yield.[12]

After deprotection of hydroxy group with 1 M HCl in methanol, the dienediol was iodinated with the couple triphenylphosphine/iodine in the presence of imidazole.[13] The sensitive diiodiene in the presence of triphenylphosphine yielded the bistriphenylphosphonium salt **6** which was purified by crystallisation (77% yield over three steps).

The key step of the synthesis was realised via an intramolecular Wittig reaction. The diphosphorane was generated by treatment of THF insoluble bisphosphonium salt **6** (0.025 M), at −78°C, with 2.2 equiv. of NaHMDS. As expected, oxidation reaction of phosphorane with a stream of oxygen did not furnish the all-(*Z*)-cyclonona-1,4,7-triene but the cyclooctadeca-1,4,7,10,13,16-hexaene **1** in fair yield (35% isolated), as major product with a total control of the stereochemistry of the two double bonds formed. Oligomers (15%) were also detected but easily separated by column chromatography. The cyclooctadeca-1,4,7,10,13,16-hexane **1** possesses a NMR analysis[14] similar to all-(*Z*)-cyclododeca-1,4,7,10-tetrane (CDT). After crystallisation in a mixture of cyclohexane and acetone (4/1), the structure of **1** has been confirmed by X-ray analysis[15] and MS analysis.

At the solid state, a crown conformation was found for the all-(*Z*)-cyclononatriene[16] and the all-(*Z*)-CDT.[17] On the contrary, the cyclooctadeca-1,4,7,10,13,16-hexaene **1** presents an '*S-like*'-conformation with a C_{3v} symmetry. The ORTEP drawing shows that all the double bonds exhibit a *Z* configuration demonstrating that the Wittig reaction proceeded with total stereocontrol. At the methylenic positions, it can be noted that one of the hydrogen atoms is pointing towards the molecule centre while the other hydrogen atoms are alternatively below and above the medium plan of the molecule. Finally, the core of **1** exhibits a diameter of 3.46 Å.

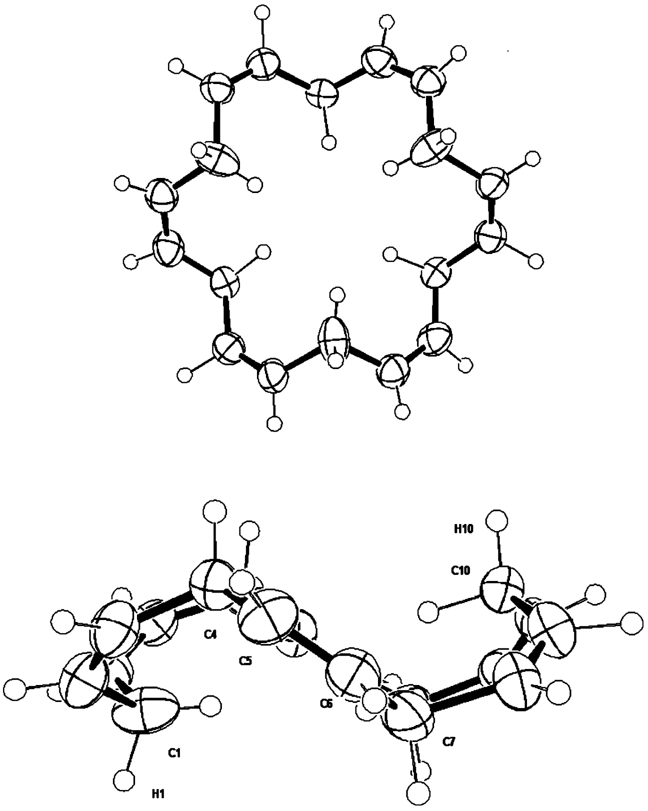
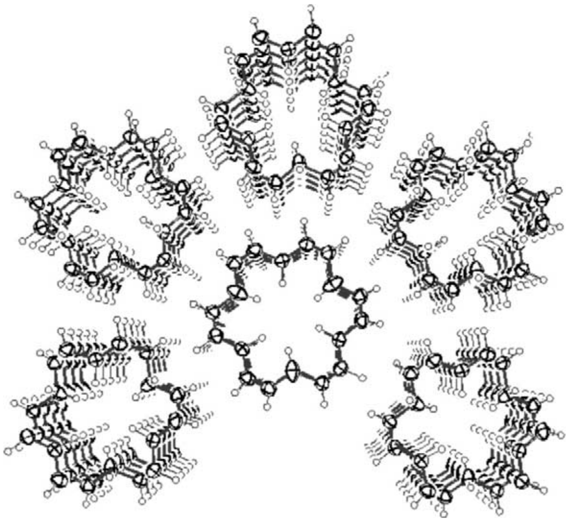


Figure 2. ORTEP drawing of **1**.

Although **1** shows two magnetically different hydrogen atoms in the solid state (Fig. 2), **1** shows a conformational change very rapidly in solution as seen on the ^1H NMR spectrum recorded in $CDCl_3$ at 25°C.

The side view of **1** shows the unplaness of the molecule that '*S-like*'-conformation with eight central carbons in the same plan.



Another interesting feature of this compound is based on its stacking-up, which is very regular. Each molecule of cyclooctadeca-1,4,7,10,13,16-hexaene **1** is stacked up with each axial hydrogen (H_1 and H_{10}) on C_1 and C_{10}

going on the cavity formed, respectively, by C_{17}-C_{18}-C_1-C_2-C_3 and C_8-C_9-C_{10}-C_{11}-C_{12} of the following molecule. At the solid state, the stacking of **1** is similar to columnar structures. Nevertheless, the distance between the two molecules within the stack amounts to 4.47 Å. This result is incompatible with π–π stacking, which could explain the cohesion in the molecular edifice.

In summary, we have achieved the first synthesis of all-(*Z*)-cyclooctadeca-1,4,7,10,13,16-hexaene **1** using an intramolecular Wittig reaction as a key step. This compound could be an interesting precursor for the synthesis of metabolites of polyunsaturated fatty acid. Further applications of **1** are in progress and will be reported in due course.

Supplementary material

X-Ray crystal structure data (cif file) for the C18 hexaene **1** is available from the author upon request (CCDC 194074).

Acknowledgements

We thank CNRS and MESR for providing financial support, the 'conseil Régional de la Région PACA' and Isotochim chimie fine for awarding a fellowship to one of us (S.G.).

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14. Procedure for the preparation of cyclooctadeca-1,4,7,10,13,16-hexaene from bisphosphonium salt **6**: To a suspension of **6** (4.0 g, 4.44 mmol, 1 equiv.) in THF (180 mL) was added at −78°C, a 2 M THF solution of NaHMDS (6.22 mL, 12.43 mmol, 2.4 equiv.). The ylide solution was then allowed to warm to 0°C, and stirred for 1 h. The solution was cooled at −78°C and a flow of oxygen (4 mL min^{-1}) was bubbled through the solution for 4 h. After hydrolysis with satd aq. NH_4Cl, the aqueous layer was extracted with Et_2O (3×50 mL). The organic layers were washed with satd aq. NaCl, dried over $MgSO_4$ then concentrated in vacuo. Flash chromatography on silica gel (petroleum ether; $R_f = 0.37$) led to 92 mg (35%) of **1** as a white solid (mp 61°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.36–5.40 (m, 12H); 2.84–2.94 (m, 12H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.3 (12C); 26.6 (6C). MS (70 eV): 240 (M, 0.1), 131 (16), 129 (14), 119 (10), 117 (30), 115 (12), 106 (11), 105 (24), 104 (11), 93 (18), 92 (21), 91 (100), 81 (9), 80, (31), 79 (28), 77 (62), 67 (38), 66 (19), 65 (31), 55 (9), 54 (9), 53 (21), 52 (9), 51 (14), 41 (73), 39 (46).
15. Colourless crystals of **1** ($C_{18}H_{24}$) were grown from a solution of **1** in a 4/1 mixture of cyclohexane/acetone. Data collection was conducted at 298 K on a monoclinic crystal; $a = 17.001(10)$, $b = 17.001(10)$; $c = 4.474(10)$ Å; $\beta = 90(10)°$; $V = 1119.9(3)$ Å^3; space group: $R3$; $Z = 3$; $R = 0.045$; $wR = 0.051$ ($w = 1/[\sigma^2(F_o^2)+0.03F_o^2]$); GOF = 1.398; $\Delta\rho^+ = 0.1$ and $\Delta\rho^- = -0.1$ e Å^{-3}.
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