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Heck self-condensation of polycyclic haloalkenes: the case of (1*R*)-2-iodobornene

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Abstract—The unusual reactivity of a haloalkene undergoing Heck reaction behaving both as reagent and substrate (Heck donor and acceptor) is studied and discussed in detail in the case of (1*R*)-2-iodo-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ene (2-iodobornene). This enantiopure substrate allows for a rational description of the mechanism which takes into account the nature of the products and the substitution of one of the substituents (iodine and proton) at carbons 2 and 3 of the bornene skeleton. Under catalytic conditions the main products are the *syn* and *anti*-cyclotrimers, a head-to-tail dimer and an arene derived from the latter. The products of the stoichiometric reaction between palladium(0) tetrakis(triphenylphosphine) and 2-iodobornene are principally trans-Pd$(PPh_3)_2$PhI and various dimeric species. The results are rationalized in terms of a catalytic reaction which takes into account the Pd(II)–Pd(IV) oxidation state sequence. The major products in both the catalytic and stoichiometric reactions are dimeric species with formal elimination of an iodine molecule that are unprecedented in the literature for the Heck reaction. © 2001 Elsevier Science Ltd. All rights reserved.

The Heck reaction[1] is one of the fundamental reactions in organometallic chemistry and is of particular relevance at present because of its environmental friendliness. Infact, the Heck reaction involves simple olefins and, through palladium catalysis in the Pd(0)–Pd(II) oxidation states, produces non-toxic by-products, at variance with other C–C forming reactions that require tin, boron or other reagents.[2] Standard reagents for the Heck reaction are aryl or alkenyl halides (acting as Heck donors), and electron-poor alkenes (acting as Heck acceptors). The traditional mechanism for the Heck reaction requires the *syn* addition of the palladated halo-alkene or halo-arenes to the electron-deficient olefin, followed by the *syn* coplanar β-hydride-elimination and regeneration of the active palladium(0) species. In any case, in all Heck reactions so far reported, the coupling occurs with formal loss of an HI molecule.

Our interest in the Heck reaction originated from the study of cyclotrimerisation reactions of polycyclic alkenes leading to hexasubstituted benzenes.[3] In the cyclotrimerisation reaction of simple polycyclic olefins it was noticed that the Heck reaction afforded only the *anti* isomer when starting from racemic reagents, but only the *syn* cyclotrimer (albeit in lower yield and in longer reaction times) when starting with the enantiopure substrates.[3a] On these bases, it was supposed that the Heck reaction applied to the enantiopure (1*R*)-2-iodo-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ene (2-iodobornene)[4] (**1**) could generate *syn*-tribornene as the sole product. The study of the Heck cyclotrimerisation applied to this substrate could also furnish information regarding the mechanism, owing to its peculiarities which can be outlined as follows: (i) 2-iodobornene acts simultaneously as Heck donor and acceptor; (ii) polycyclic systems are more reactive than simple unsaturated systems; (iii) the 1-methyl group of the bornene moiety represents a useful stereochemical marker; (iv) 2-iodobornene is available in enantiopure form. On the other hand, the presence of the apical methyl groups in the molecular fragment entails a remarkable steric hindrance thereby reducing the reaction rate and yield with respect to analogous polycyclic alkenes.

We therefore decided to study the catalytic coupling reaction of 2-iodobornene in the presence of Pd(0) complexes. The formation of unexpected products prompted us to investigate the intermediates of the reaction, through some experiments carried out under stoichiometric conditions, in the aim of establishing a plausible mechanistic pathway and, eventually, improving the yields of the desired products.

1. Catalytic reactions

At the outset, the reaction was performed according to the protocol described by Jeffery,[5] using palladium(II) acetate (0.05 equiv.) in the presence of triphenylphosphine (0.1 equiv.), triethylamine (2.5 equiv.) and tetrabutylammonium hydrosulphate. The mixture was sealed in a

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Keywords: aromatisation; dimerisation; cyclotrimers; Heck reaction; terpenes; terpenoids.

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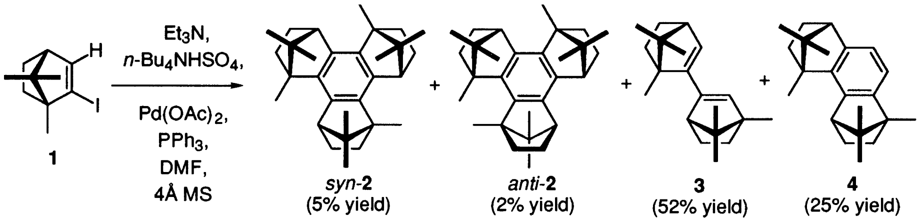


Scheme 1.

Pyrex test tube under an argon atmosphere and heated at 80–90°C until complete consumption of the starting 2-iodobornene was observed (GC monitoring). After 72 h, the reaction led to the formation of the expected *syn*-cyclotrimer **2** in quite modest yield (5%) and, surprisingly, a very small but detectable amount of the unexpected *anti*-cyclotrimer **2** (2%). The two major products of the reaction were dimer **3** (52% yield) and arene **4** (25% yield).[6] The yields of cyclotrimers were very low but in agreement with previous observation in cyclotrimerisation reactions of a similar substrate.[3d] More importantly, the ratio of the *syn* with respect to the *anti* cyclotrimer is strongly in favour of the *syn* isomer, in contrast to the ratio observed in the copper(II) nitrate-promoted cyclotrimerisation of 2-bromo-3-trimethyltinbornene which led to a 9:1 mixture of *anti* and *syn* isomers and whose yields were lowered by the protodestannylation.[3d]

Of the two dimeric species in Scheme 1, compound **3** is the apparent result of a head-to-tail coupling followed by hydrodeiodination. At this stage, it seemed to us that **3** was a quenched intermediate in the path to the trimers **2**. With the aim of promoting formation of the cyclotrimers with respect to dimer **3** and arene **4**, the reaction of Scheme 1 was carried out under slightly different reaction conditions. In one experiment, the iodide **1** was slowly added to the catalyst over 24 h with a syringe-pump, in order to determine the effect of the concentration of the substrate with respect to the catalyst. This procedure lowered the amount of dimer **3** and increased the formation of the arene **4**, with no substantial difference in the yields of the trimers, suggesting that the stability of the intermediates is not a crucial parameter and that concentrated solutions and higher amounts of catalyst play a beneficial effect in the yields of coupled products.

The formation of the arene **4** was rather puzzling. In an early hypothesis, **4** was proposed to result from dimer **3** via a double coupling with an ethene residue. Since no sources of C_2 fragments could be envisioned in the reaction mixture except for the triethylamine, the latter was substituted with amines bearing residues other than ethyl groups (i.e. *N*-methylmorpholine and 1,8-diazabicyclo[2.2.2]-octane). In agreement with this speculation, with these bases no **4** was detected in the mixtures. As a confirmation, when diisopropylethylamine was used as the base, large amounts of **4** were obtained. The results are summarized in the Table 1. Inorganic bases like sodium hydrocarbonate or potassium carbonate were revealed to be ineffective even after prolonged reaction times.

Table 1.

Entry	Base	Time[a] (h)	*syn*-**2** (%)	*anti*-**2** (%)	**3** (%)	**4** (%)
1	Et_3N	72	5	2	52	25
2	$EtN(i\text{-}Pr)_2$	48	1	Traces	65	33
3	NMM	48	4	4	84	–
4[b]	DABCO	72	–	–	90	–

[a] Required for complete consumption of the reagent.

[b] The reaction was performed with $n\text{-}Bu_4NBr$ in place of $n\text{-}Bu_4NHSO_4$.

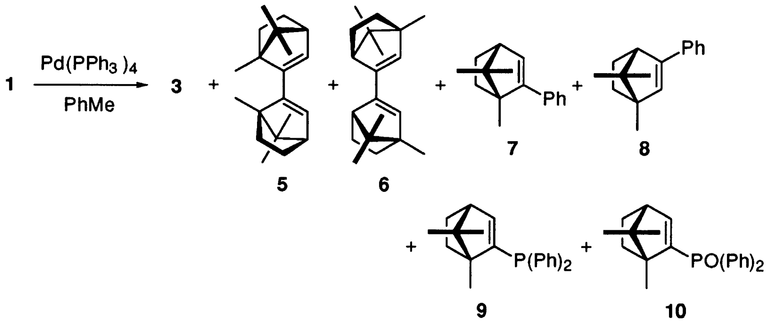
Other bornene derivatives were employed in this Heck reaction (e.g. 2-bromobornene[4,6a] and bornene-2-triflate[6b]). The former reacted according to the standard Jeffery protocol[5] to furnish an equimolar amount of trimers in an overall 8% yield and traces of **3** and **4**, according to a 72% conversion. The triflate proved more reluctant, being unreactive at temperatures lower than 90°C, while it decomposed to several unidentified by-products at higher temperatures.

In order to get more information on the unexpected formation of the cyclotrimer *anti*-**2**, the diene **3** and the arene **4** in the Heck reaction of 2-iodobornene, a stoichiometric study was undertaken.

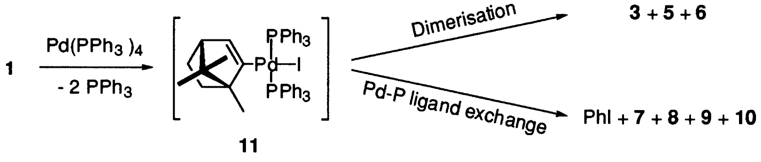
2. Stoichiometric reactions

The stoichiometric reaction between 2-iodobornene and palladium(0)tetrakistriphenylphosphine[7] was carried out in the absence of added base in order to ensure the possibility of isolating intermediate species.[8] Thus, 2-iodobornene (**1**) was heated in dry toluene with $Pd(PPh_3)_4$ until complete dissolution was observed (2 h); upon cooling to room temperature an orange solid was obtained which was collected by filtration. Spectroscopic analysis (^1H- and ^{31}P NMR) revealed the latter to be *trans*-$Pd(PPh_3)_2PhI$ complex,[9] which accounted for nearly 60% of the original amount of palladium. The mother liquors were released from the rest of the palladium species by filtration through a short silica gel column, eluting with diethyl ether. The eluant was analysed by GC-MS and by comparison with authentic samples, and turned out to be composed, except for minor amounts of triphenylphosphine oxide and phenyliodide, of the set of products illustrated in Scheme 2.

The products can been divided into three main groups of compounds: (a) dimeric products **3**, **5** and **6**; (b) aromatic derivatives **7** and **8**; (c) phosphorous derivatives **9** and **10**. Except for the dimer **3** (ca. 32% yield), all the other products



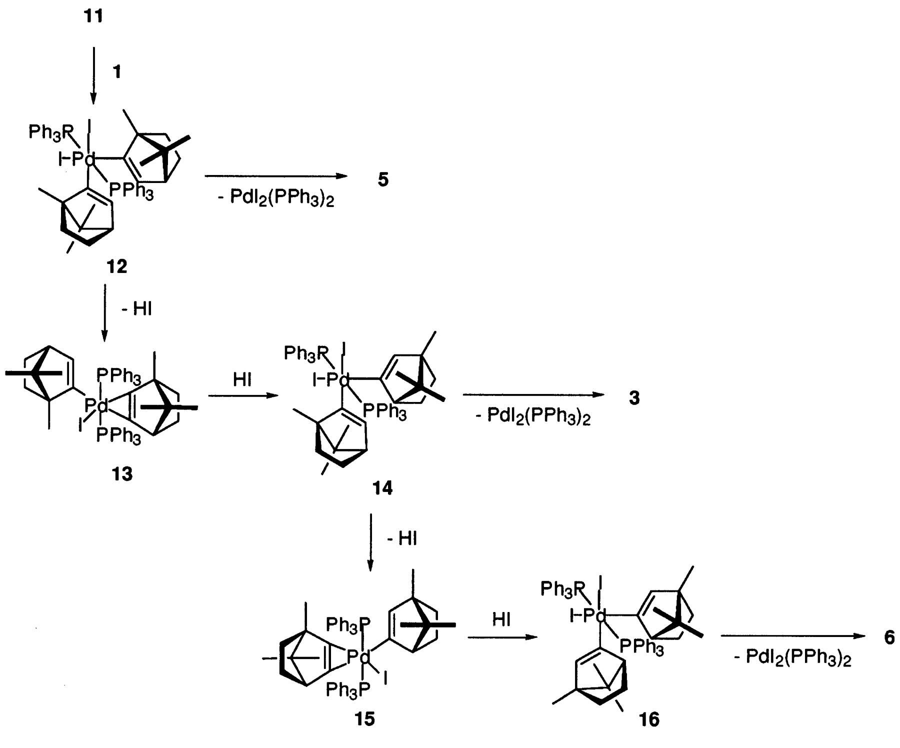
Scheme 2.



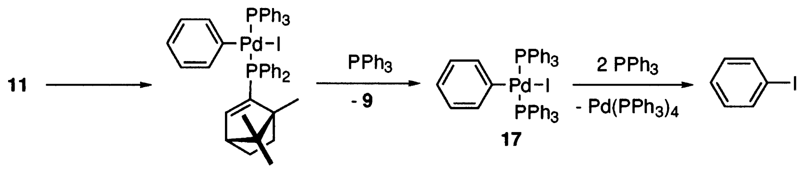
Scheme 3.

were formed in close-to-trace amounts and in similar proportions. According to the accepted knowledge of palladium reactions, all products arise from a single common Pd(II) intermediate **11** derived by oxidative addition of Pd(0) to the vinyliodide as illustrated in Scheme 3.

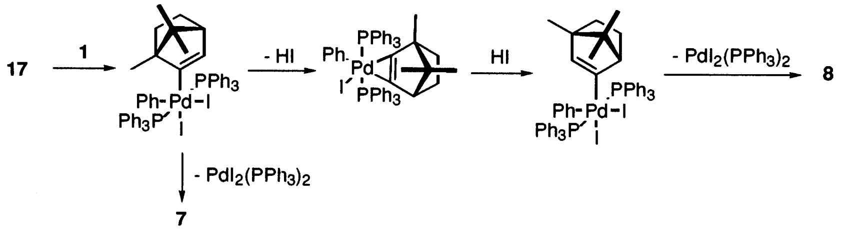
The formation of the dimers can be rationalised as shown in Scheme 4. Upon reaction of **11** with a second molecule of **1**, a palladium(IV) species **12** is formed and this is suggested as the manifold for the presence of all the dimers. The intermediacy of the palladium(IV) has been postulated in a number of palladium-mediated reactions.[10] The cine products **5** and **6** are suggested as the result of a migration of the vinyl carbon of the bornene residue through the palladacyclopropanes **13** and **15** leading respectively to the intermediates **14** and **16** arising from an acid–base reaction mediated by PPh_3 as the base. The palladium(IV) oxidation state accounts for the high acidity of the vinyl proton and the derived reactivity with the modestly basic



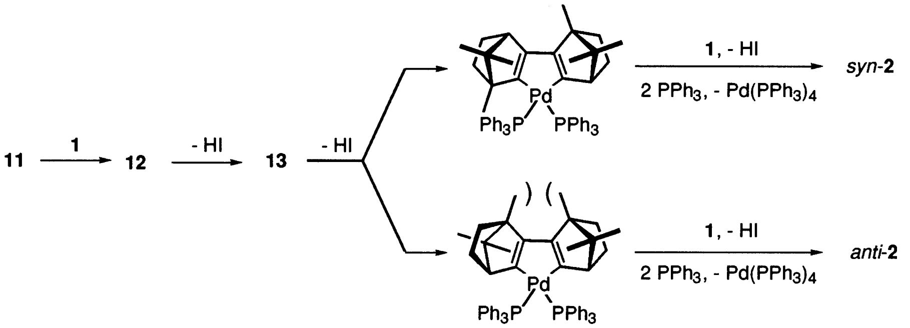
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

PPh_3. More stable platinacyclopropanes have been detected and isolated in several cases.[11]

The exchange of a group from a phosphorus ligand onto the palladium to the palladium centre is a known reaction,[12] to such an extent that it has been suggested as a synthetically viable procedure.[12a] This reaction accounts for all the products observed in our stoichiometric reaction. For example, iodobenzene is supposed to arise from the reaction shown in Scheme 5.

Iodobenzene itself, behaving as the substrate of the Heck reaction, is suggested to be responsible for the formation of the phenyl-substituted products **7** and **8**, as shown in Scheme 6, which include the rearrangement responsible for the cine substitution as well.

On the basis of the information gained with the stoichiometric reaction, the mechanism leading to the cyclotrimers *syn*-**2** and *anti*-**2** can be suggested as represented in Scheme 7,[13] which takes into account a reiteration of the reasoning proposed for the formation of the dimers.

In analogy with the palladium–phosphorus ligand exchange, the formation in the catalytic reaction of the arene product **4** can be justified by a palladium–nitrogen ligand exchange, which may place the required C_2 fragment in position 2 of the dimeric species **3**. Unfortunately, further support to such hypothesis is still missing.

In conclusion, in this paper we have shown a plausible mechanistic path for the Heck reaction of 2-iodobornene with itself which forms dimers and trimers. This rationalisation is based on the observations obtained in the stoichiometric reaction and on the data reported in the literature. The present findings will be used in the rational design of dimers and trimers which we plan to use as ligands for asymmetric catalysis.

3. Experimental

3.1. Typical procedure for the Heck reaction of 1

In a flame-dried Pyrex screw-capped test tube were placed in the order: 4 Å pulverised molecular sieves (1.6 g), dry DMF (4 mL), Et_3N (1.1 g, 1.5 mL, 10.0 mmol), $(n\text{-Bu})_4N\cdot HSO_4$ (1.4 g, 4.0 mmol), 2-iodobornene **1** (1.1 g, 4.0 mmol) and PPh_3 (100 mg, 0.4 mmol). The mixture was stirred under an argon atmosphere for 30 min, $Pd(OAc)_2$ (44 mg, 0.2 mmol) was added and the test tube was sealed. The mixture was stirred at rt for 30 min and heated at 80°C for 72 h. The resulting mixture was poured onto H_2O (20 mL) and extracted with pentane (4×10 mL). Combined organic layers were washed with H_2O (10 mL), dried over $MgSO_4$, concentrated in vacuum and purified by flash-chromatography (eluant pentane) to afford four main fractions.

3.1.1. First eluate: (1*R*,4*S*,5*R*,8*S*,9*S*,12*R*)-2,3,4,6,7,8,9,10,11-nonahydro-1,5,12,13,13′,14,14′,15,15′-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene *anti*-2. (12 mg, 2%) as a waxy solid; [Found: C, 89.48; H, 10.54. $C_{30}H_{42}$ requires C, 89.49; H, 10.51%]; R_f (pentane) 0.92; $[\alpha]_D^{22}=+52.0$ (c 1.2, $CHCl_3$); ν_{max}(film) 2952, 2871, 1474, 1382 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.98 (1H, d, J=4.0 Hz, CH), 2.65 (1H, d, J=3.9 Hz, CH), 2.61 (1H, d, J=3.8 Hz, CH), 2.01–1.90 (3H, m, CH_2), 1.78–1.68 (3H, m, CH_2), 1.34 (6H, s, two overlapping CH_3), 1.30 (3H, s, CH_3), 1.29–1.20 (2H, m, CH_2), 1.13–0.94 (4H, m, CH_2), 0.90 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.53 (3H, s, CH_3), 0.46 (3H, s, CH_3), 0.42 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 140.5, 140.0, 138.3, 138.1, 137.5, 136.1, 56.2, 56.1, 55.9, 53.4, 53.2, 52.2, 50.2, 49.9, 50.0, 34.0, 33.9 (two overlapping signals), 26.9, 26.6, 26.5, 20.3 (two overlapping signals), 20.2, 19.4 (two overlapping signals), 19.0, 16.7, 16.6, 14.4; m/z (EI, 70 eV) 402 (45), 374 (28), 359 (100), 109 (47), 83 (100%).

3.1.2. Second eluate: (1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-2,3,4,6,7,8,10,11,12-nonahydro-1,5,9,13,13′,14,14′,15,15′-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene *syn*-2. (25 mg, 5%) as a waxy solid; [Found: C, 89.52; H, 10.49. $C_{30}H_{42}$ requires C, 89.49; H, 10.51%]; R_f (pentane) 0.84; $[\alpha]_D^{22}=+10.2$ (c 1.8, $CHCl_3$); ν_{max}(film) 2956, 2871, 1482, 1386 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.98 (3H, d, J=4.0 Hz, CH), 1.99–1.91 (3H, m, CH_2), 1.76–1.68 (3H, m, CH_2), 1.29 (9H, s, CH_3), 1.16–1.00 (6H, m, CH_2), 0.89 (9H, s, CH_3), 0.55 (9H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 138.9, 136.2, 56.0, 52.2, 49.7, 33.8, 26.1, 20.3, 19.1, 14.3; m/z (EI, 70 eV) 402 (24), 374 (32), 359 (60), 109 (65), 83 (100%).

3.1.3. Third eluate: (1*R*,1′*R*)-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-3-yl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene 3. (280 mg, 52%) as a colourless oil; [Found: C, 88.79; H, 11.21. $C_{20}H_{30}$ requires C, 88.82; H, 11.18%]; R_f (pentane) 0.78; $[\alpha]_D^{22}=-9.6$ (c 0.5, $CHCl_3$); ν_{max}(film) 2964, 2868, 1478, 1382 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.84 (1H, d, J=3.4 Hz, =CH), 5.60 (1H, s, =CH), 2.38 (1H, d, J=3.3 Hz, CH), 2.27 (1H, t, J=3.4 Hz, CH), 2.00–1.45 (8H, series of m, CH_2), 1.14 (3H, s, CH_3), 1.03 (3H, s, CH_3), 0.80 (3H, s, CH_3), 0.77 (3H, s, CH_3), 0.76 (6H, s, two overlapping CH_3); δ_C (75 MHz, $CDCl_3$) 144.4, 142.6, 131.6, 129.9, 56.6, 54.3, 53.5, 51.2, 34.2, 32.1, 31.6, 29.7, 25.9, 25.0, 22.6, 19.8, 19.2, 14.1, 13.6, 13.5; m/z (EI, 70 eV) 270 (92), 255 (83), 227 (100%).

3.1.4. Fourth eluate: (1*R*,4*S*,5*R*,8*S*)-2,3,4,6,7,8-hexahydro-1,5,11,11′,12,12′-hexamethyl-1,4:5,8-dimethanophenantrene 4. (145 mg, 25%) as a colourless oil; [Found: C, 89.72; H, 10.24. $C_{22}H_{30}$ requires C, 89.73; H, 10.27%]; R_f (pentane) 0.70; $[\alpha]_D^{22}=+11.5$ (c 1.0, $CHCl_3$); ν_{max}(film) 2952, 2864, 1478, 1386 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.82 (1H, d, J=7.0 Hz, =CH), 6.72 (1H, d, J=7.0 Hz, =CH), 3.05 (1H, d, J=4.1 Hz, CH), 2.69 (1H, d, J=3.8 Hz, CH), 2.16–1.92 (4H, m, CH_2), 1.89–1.67 (4H, m, CH_2), 1.35 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.56 (3H, s, CH_3), 0.53 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 148.7, 145.2, 142.1, 140.0, 117.0, 115.0, 57.0, 56.9, 53.3, 53.0, 51.4, 50.0, 33.5, 33.4, 26.5, 25.8, 20.2, 20.1, 19.2, 19.1, 13.9, 11.8; m/z (EI, 70 eV) 294 (44), 279 (5), 266 (21), 251 (100), 82 (84%).

Acknowledgements

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