

A NOVEL APPROACH TO PERIPLANONE-B INVOLVING AN INTRAMOLECULAR DIELS-ALDER REACTION WITH  
FURAN-DIENE AND ALLENE-DIENOPHILE

Serge G. Cauwberghs and Pierre J. De Clercq<sup>1\*</sup>

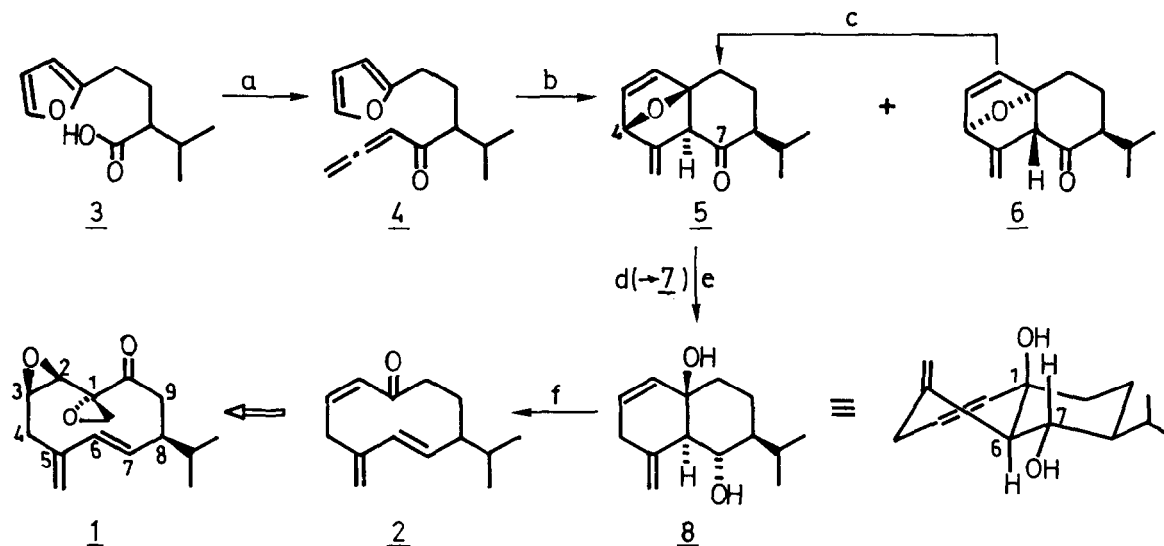
State University of Gent, Laboratory for Organic Synthesis,  
Krijgslaan, 281 (S.4), B-9000 Gent (Belgium)

**Abstract** - The 6-step sequence to trienone 2, a known intermediate for the total synthesis of periplanone-B, involves the conversion of 3 into 4 using dilithiated propadiene, the IMDA of 4 to exo-adducts 5 and 6, the conversion of 5 to diol 8 via a radical anion promoted cleavage of the oxygen bridge, and a in-situ low temperature Grob fragmentation to 2.

After the discovery in 1952 that females of the species *Periplanata americana*, the American cockroach, produce a very potent sex excitant,<sup>2</sup> two extremely active compounds, periplanones -A and -B, were isolated by Persoons, and a germacranoid structure proposed for the latter.<sup>3</sup> The unambiguous structural assignment of periplanone-B as 1 resulted from the pioneering work of Still, that culminated in the first total synthesis of ( $\pm$ )-1.<sup>4</sup> Later total syntheses of ( $\pm$ )-1 were reported by Schreiber,<sup>5</sup> Hauptmann and Walker,<sup>6</sup> Takahashi,<sup>7</sup> and of natural (-)-1 by Kitahara.<sup>8</sup> In these approaches the construction of the 10-membered ring resulted either from an oxyanion-Cope rearrangement<sup>4,5</sup> or from an alkylative cyclization.<sup>6-8</sup>

We herein describe an expeditious synthesis of racemic trienone 2, a known intermediate for the synthesis of periplanone-B.<sup>5,8</sup> The proposed route involves three key-steps: (i) the non-stereoselective IMDA reaction of furan-allene 4, (ii) the conversion of adduct 5 into diol 8, possessing the appropriate functionality and stereochemistry for (iii) eventual Grob fragmentation to trienone 2 (scheme 1). The present synthesis serves to illustrate the synthetic potential of combining both furan-diene and allene-dienophile in a intramolecular Diels-Alder reaction.<sup>9</sup> Examples of the use of furan as a diene partner in this reaction type have been scarce, despite some obvious synthetic potential.<sup>10</sup> On the other hand, allene-dienophiles are virtually unknown in IMDA reactions,<sup>11</sup> especially when furan is involved as an endocyclic diene.<sup>12,13</sup>

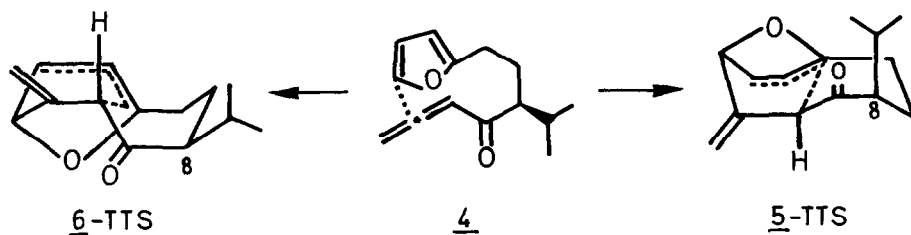
Acid 3 was obtained via alkylation of the dianion of isovaleric acid (LDA, THF, 45°C, 2 h) with 1-(2-bromoethyl)furan<sup>14</sup> (THF, rt, 12 h; 60 % yield).<sup>15,16</sup> The direct introduction of the allene moiety was successfully achieved by treatment of the lithium salt of 3 (n-BuLi, -78°C) with 5 equiv of dilithiated propadiene<sup>17</sup> in THF at rt.<sup>18</sup> Monolithiated propadiene was found unreactive under the same conditions.<sup>19</sup> Without further purification allene 4<sup>16</sup> is usually subjected to the cycloaddition.



<sup>a</sup> 5 eq  $\text{Li}_2\text{C}_3\text{H}_2$  (from allene : 2 eq  $n\text{-BuLi}$ ,  $-55^\circ\text{C}$ , 2 h), THF, rt, 10 min; <sup>b</sup> benzene,  $80^\circ\text{C}$ , 12 h (65 % from 3); <sup>c</sup> mesitylene,  $164^\circ\text{C}$ , 24 h to 5:6, ratio 2:1; <sup>d</sup>  $\text{Li}$ , liq.  $\text{NH}_3$ ,  $\text{NH}_4\text{Cl}$ ,  $-78^\circ\text{C}$  (42 %); <sup>e</sup> LiDDB radical anion, THF,  $-50^\circ\text{C}$ ; aniline (68 %); <sup>f</sup> 2 eq  $n\text{-BuLi}$ ,  $-30^\circ\text{C}$ , 30 min; 3 eq triflic anhydride, ether,  $-20^\circ\text{C}$ , 15 min (38 %).

Scheme 1

In view of the prior results obtained in this IMDA-type,<sup>13</sup> the cycloaddition of 4 is expected to proceed irreversibly under normal thermal conditions,<sup>20</sup> and to yield adducts of the exo-type (i.e., trans-oriented angular H and oxygen bridge). The transition states leading to the two exo-adducts 5 and 6, in which the asynchronicity of the Diels-Alder reaction is reflected and wherein the pseudo 10-membered ring would adopt a boat-chair-boat conformation, reveal that the eventual outcome of the cycloaddition would be primarily dictated by the orientation of the isopropyl group (scheme 2).<sup>21</sup> Since force field calculations have shown that there is no relevant difference in conformational energy between an equatorial and axial group at this position (cf. C-8) in a BCB-form,<sup>22</sup> the reaction is not expected to be stereoselective. This is borne out by the experiment : both at rt ( $\text{CH}_2\text{Cl}_2$ , 3 days) and in refluxing benzene (12 h; 90 % conversion after 3 h), the cycloaddition of 4 leads to a similar mixture consisting of the two expected exo-adducts 5 and 6,<sup>16</sup> and one endo-adduct with undefined stereochemistry, in a ratio 5:4:1, respectively (65 % combined yield from 3).<sup>23</sup>



Scheme 2

Under thermodynamic control, the more stable adduct 5 with equatorial isopropyl group is expected to predominate. Not surprisingly, the less stable isomer 6 was found reluctant to cyclorevert under thermal conditions.<sup>20</sup> Reflux in mesitylene (N<sub>2</sub>, 164°C) for 24 h was found necessary for obtaining an equilibrium mixture of 5 and 6 ratio 2:1, respectively.

The conversion of adduct 5 into diol 8 involves two steps : (i) the reduction of the carbonyl into alcohol 7<sup>16</sup> with the equatorial orientation at C-7 (Li, liq. NH<sub>3</sub>, NH<sub>4</sub>Cl, -78°C; 42 % yield next to 45 % starting material); (ii) the selective reductive cleavage of the oxygen bridge at C-4 using lithium di-*tert*-butylbiphenyl radical anion (THF, -50°C; 68 % of 8.<sup>24</sup> Quite to our surprise, the unsaturated diol 8 could be readily purified by column chromatography on neutral aluminum oxide and HPLC.<sup>16</sup>

Derivative 8 possesses the necessary features for Grob fragmentation to trienone 2 with the required (E)-6,7-bond, i.e., the antiperiplanar orientation of the eventual leaving group at C-7 to the 1,6-fusion bond of the *trans*-decalin system.<sup>25</sup> Treatment of the dilithium salt of 8 (*n*-BuLi, -30°C, ether, 30 min) with trifluoromethanesulfonic anhydride (3 eq) readily led at -20°C to the desired 2 (44 % isolated after chromatography on aluminum oxide, followed by HPLC), next to starting material (25 %). Comparison of the spectral data of 2<sup>16</sup> with those reported for (-)-2 fully corroborated its structure.<sup>8</sup>

Although several steps need further optimization, some features of the above sequence, in which no protective groups were used, are noteworthy : the direct introduction of the allene moiety on acid 3 using dilithiated propadiene, the use of lithium radical anion (LiDBB) for effecting the selective cleavage of the oxygen bridge in 7, and, finally, the in situ low temperature Grob fragmentation of 8 into trienone 2. Also, the brevity of the route (6 steps from isovaleric acid) further exemplifies the synthetic potential of the IMDA reaction using the combination of furan-diene and allene-dienophile.

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