Cascade Cyclization via a 4-exo-dig-Cyclocarbopalladation for an Easy Access to New Polycyclic Structures

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Received 23 September 2003

Abstract: The 5-exo-dig-cyclocarbopalladation is a known reaction although the functionality present on the substrates used is generally limited. This reaction was performed on our original substrates propargylic diols 2a–c and 3a–c gave encouraging results. Once the analogs α-bromopropargylic diols were used, the 4-exo-dig-cyclocarbopalladation turns out to be a new possible way to prepare bicyclic compounds containing a strained 1,2-cyclobutane-diol. This process is associated with a Stille cross-coupling that can be achieved in some cases by a 6π-electrocyclization. This reaction sequence can thus achieve an increase in structural complexity from readily available starting materials, in a one-pot operation.

Key words: 4-exo-dig-cyclocarbopalladation, cyclobutene, 5-exo-dig-cyclocarbopalladation, palladium, cascade cyclization, Stille-reaction, 6π-electrocyclization

Introduction

The synthesis of highly functionalized polycyclic compounds required the development of reactions catalyzed by transition metals. In particular, cyclocarbopalladation has emerged as a potentially general and versatile synthetic method for the preparation of complex polycyclic systems in a one-pot operation. Palladium catalyzed multistep cascades are especially noteworthy in terms of atom economy, stereocontrol, and overall efficiency. Moreover, they can be used to form carbon-carbon bonds that would be much more difficult or impossible to make by conventional organic reagent alone. Since the pioneering independent studies of Mizoroki,1 Heck and Nolley,2 followed by their development in the 1980’s by Grigg3–5 and Negishi,6,7 later by de Meijere,8,9 intramolecular cyclocarbopalladation has widely been used to generate the polycyclic framework of natural products. But the potential of this palladium catalyzed process has not yet been fully explored. In this context, we report herein our investigations in the study of an unprecedented domino reaction involving a rare 4-exo-dig-cyclocarbopalladation followed by a Stille cross-coupling. A 6π-electrocyclization can occur leading to new tricyclic structures, with an appropriate stannylated reagent. However, when faced with molecular complexity, the challenge for the chemist is also the quest of ‘simplicity’, a concept illustrated by Compain10 in a recent article as a combination of ‘simplicity’ and maximization of structural complexity. This study will show that we offer an easy access to complex polycyclic molecules resulting from readily available simple starting materials.

Preliminary Results: 5-exo-dig-Cyclocarbopalladation

In the field of cyclocarbopalladation, the 5-exo-dig-intramolecular Heck reaction is the easiest type of cyclization. It has been widely applied to the construction of five-membered rings. However, the substrates used generally do not contain much functionality. In contrast, our substrates 2a–c and 3a–c contain a propargylic diol function and the vinyl bromide, included in an aliphatic ring. Our first approach was to study the influence of the propargylic diol function on the course of the palladocatalyzed reaction. Recently,11 we have presented results of an efficient 5-exo-dig-cyclocarbopalladation of several propargylic diols leading to [3.0.3], [4.0.3], [5.0.3] and [6.0.3] substituted bicyclic compounds (Figure 1). The starting diols anti-2a–c and syn-3a–c were prepared in good yields by addition of a properly protected metalated propargylic alcohols onto bromoaldehydes 1a–c (Equation 1) followed by deprotection and chromatographic separation of the anti- and syn-diastereomers.

Equation 1

Then, the reaction of interest proceeds at 90 °C in benzene in the presence of a catalytic amount of Pd(PPh₃)₄ (10 mol%) and trans-bis(tributylstannyl)ethylene. The impact
of the stereochemistry of the starting diol and the size of the ring bearing the vinyl bromide function was examined. It turns out that the anti- and syn-diols, whatever their ring size, afforded only products resulting from a preliminary 5-exo-dig-cyclocarbopalladation (Scheme 1), generally with acceptable to good yields.

Thus, we obtained several bicyclic compounds including a 1,2-cyclopentanediol with an exocyclic stereodefined diene function. However, once the different diols are protected as a dioxolane, the direct Stille cross-coupling seriously competes. Independently of ring size, we can distinguish the dioxolane cis-4a-c that proceeded via a cyclocarbopalladation, from the dioxolane trans-5a-c that leads to the direct Stille-product 9a-c. In the later case, the cyclocarbopalladation did not proceed due to the highly strained tricyclic derivatives that could be theoretically obtained.

In conclusion, in this preliminary approach to cyclocarbopalladation, the diol function does not disturb the course of the reaction. On the other hand, concerning the syn-configuration of the substrate, the reactivity can be finally modulated by the presence of a dioxolane. In addition, we

Biographical Sketches

Bahaâ Salem was born in France in 1976, she received her diploma in Chemical Engineering from the National School of Chemistry at Clermont-Ferrand. She defends her Ph.D. thesis in December 2003, under the supervision of Dr. Jean Suffert, at the University Louis Pasteur, Strasbourg. Her main interest is to study the mechanism of the tandem reac-
tion 4-exo-dig-cyclocarbopalladation/Stille cross-coupling and to extend its application to the synthesis of polycyclic systems.

Philippe Klotz was born in France in 1963, he received his Ph.D. degree in chemistry in 1992 from the University Louis Pasteur, Strasbourg (France) under the direction of Prof. M. Goeldner and Prof. C. Hirth (photo-
activatable probes for photoaffinity labeling). After a postdoctoral appointment with Prof. G. Just and Prof. B. Lennox (McGill University, Montreal, Canada, phospholipid syn-
thesis), he obtained a CNRS research position in 1993 at the Faculté de Pharmacie de Montpellier (Université de Montpellier I), France, in the group of Prof. J.-C. Rossi (non-pep-
tidic glutathion analogue synthesis). In 1998, he joined the laboratory of Prof. C.-G. Wermuth at the Faculté de Pharmacie de Strasbourg (ULP Strasbourg), France. He is now working under the direction of Prof. M. Hibert, in the group of Dr. J. Suffert and Dr. A. Mann. His research is fo-
cused on the development of new synthetic methods involving car-
bocyclisation catalysed by palladium, tandem or multi-component reactions for ‘reaction simplifica-
tion’, and synthesis of biologically active aza-compounds. A second in-
terest lies in the synthesis of reactive or fluorescent probes for biological receptor spanning.

Jean Suffert was born in Mulhouse (France) in 1954. He graduated from the Université Louis Pasteur, Stras-
bourg (1978) where he obtained his Ph.D. with the highest honors (1984) under the supervision of Dr A. Solla-
dié-Cavallo. He was appointed as a Chargé de Recherches at the CNRS (1982–1991). He worked as a post-
doctoral associate with Professor P. A. Wender at Stanford University (1985–1986). He moved at the Fac-
ulté de Pharmacie de Strasbourg in 1992 where he joined the group of Prof. C. G. Wermuth. He is Directeur de Recherches at the Centre National de la Recherche Scientifique (CNRS) in the Laboratoire de Pharmacochimie, Faculté de Pharmacie de Strasbourg. He is currently working on the development of new cascade reac-
tions using transition metals, the synthesis of polycyclic complex molecules and dienediyne chemistry.
have described an efficient way to prepare highly substituted bicyclic compounds that could be valuable intermediates in the syntheses of sophisticated biologically active natural or unnatural products.

An Unprecedented 4-exo-dig-Cyclocarbopalladation

Considering these encouraging results, we envisioned the possibility of a 4-exo-dig-cyclocarbopalladation, starting from α-bromopropargylic diols. The diols anti-10a–c and syn-11a–c were prepared in a large scale by addition of a protected metalated propargylic alcohol onto bromoalkenones, followed by deprotection and chromatographic separation of the two diastereomers (Equation 2).

When 10b was heated with trans-bis(tributylstannyl)ethylene and Pd(PPh₃)₄ for 6 hours, a single product was formed in 62%. It was identified as the hemiketal 12b, the structure of which was unambiguously confirmed by X-ray diffraction analysis, as a single diastereomer. In the first communication₁² of this work, we described the reaction pathway involving a cascade of three different reactions including an unusual and quite rare 4-exo-dig-cyclization, finally leading stereospecifically to masked bicyclic ketones 12b and 12c (Scheme 2).

In order to shed more light on the mechanistic course of the reaction, 10b and 10c were heated separately at 90 °C with tributylstannylethylene and Pd(PPh₃)₄. Thus, we isolated the unprecedented tricyclic compounds 13b and 13c in 35% and 62% yield, respectively. The structure of 13c was unambiguously confirmed by an X-ray diffraction analysis. To the best of our knowledge, such a cyclobutanediol derivative has never been prepared previously via a tandem 4-exo-dig-cyclocarbopalladation/Stille cross-coupling reaction. No trace of the corresponding direct Stille-product was observed in this case. Finally, the cascade reaction mechanism is described in Scheme 3. A 6π-electrocyclization occurs as the 6π-e bicyclic intermediate isolated at lower temperature is well preorganized. When the trans-bis(tributylstannyl)ethylene is used (R = SnBu₃), the reaction undergoes an opening of the strained cyclobutenediol assisted by elimination of the tributylstannyl group.

4-exo-dig-Cyclizations are unfavored according to Baldwin’s rules, and only a few examples of them are known.¹³,¹⁴ This difficulty appears mainly to be due to Dunitz–Schumaker strains (1,3-carbon-carbon interactions) that are significant in four-membered rings. However, the reaction of 10b with 1.3 equivalents of tributylstannylethylene in the presence of 10 mol% of Pd(PPh₃)₄ in benzene as the solvent at 90 °C resulted in the formation of 13b in 35% yield. As various stannylated reagents are readily available, we focused our initial studies on this reaction with the less hindered one as our model system. Thus, in an effort to optimize the yield of this unfavorable process, we examined the effect of several dif-

Equation 2
Cascade Cyclization via a 4-exo-dig-Cyclocarbopalladation

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ferent palladium catalysts, various inorganic and organic bases and the phosphine ligands. The six membered ring starting diol 10b was selected for this study because of the difficulty in generating the strained tricyclic derivative 13b. We decided first to test the most common conditions encountered in Heck and Stille couplings. The results are summarized in Table 1. The reaction of 10b can afford, in principle, three different products: the tricycle 13b, the cyclobutanediol 14b, or the direct cross-coupling derivative 15b. Among the different solvolytic conditions, benzene seems to give the best results for the 4-exo-dig-cyclocarbopalladation. Palladium(II) sources such as PdCl2(PhCN)2, PdCl2(CH3CN)2, PdCl2(AsPh3)2 were also used, unfortunately leading only to decomposition. Besides, additives could have substantial effects on reaction. For example, copper salts are known to accelerate the Stille coupling. Corey’s conditions involving CuCl advised for difficult Stille reactions was ineffective in our case. Indeed, we observed no reaction (entries 2 and 3). The catalytic system Pd(OAc)2/PPh3 is frequently used in carbopalladative processes, however, we should keep in mind that the direct Stille-coupling can be a serious competitive reaction, as with our substrate there is the possibility of forming a strained cyclobutene diol derivative.

In the presence of Pd(OAc)2 and PPh3 in benzene, we observed the exclusive formation of the Stille-product 15b in 15% yield (entry 5). When additives such as Et4NCl, silver salts or Et3N (entries 6, 7, 8, 11, 12) were used, only the Stille-product was formed with no improvement of the yield. With K2CO3 or Na2CO3 (entries 9, 10) in benzene, black palladium precipitates rapidly and decomposition of the substrate occurred. The preferred solvent for such reactions is usually CH3CN, however this did not act according to our expectations (entries 13, 14, 15). Thus, we turned our attention to catalytic systems including Pd2(dba)3 and Pd(dba)2, which are stable sources of palladium(0). The phosphines AsPh3 and TFP recommended by Farina18 for their accelerating effect on the Stille-reaction, gave a mixture of Stille-product and the bicyclic 1,2-cyclobutanediol (entries 16–26). In conclusion, this investigation led to the following standard reaction procedure: 10 mol% Pd(PPh3)4, 1.3 equivalent of stannylated reagent, in benzene as the solvent at 90 °C. Probably, optimization is limited by the ring system strain imposed by the cyclobutanediol, as a better yield was obtained with the seven-membered ring 10c.

Study of the Influence of Different Parameters

Next, we explored the scope and limitations of this novel route to 1,2-cyclobutanediols, by examining the influence of different structural parameters of the substrate on the course of the palladium induced cascade reaction (Figure 2). In a former paper,19 we have presented several bicyclic compounds containing a 1,2-cyclobutanediol, starting from analogs of the anti 10a–c and syn 11a–c propargylic diols. In the majority of the cases, we observe the exclusive cyclocarbopalladation coupling. Various stannylated reagents were used, some of them allowed a 6e-disrotatory cyclization process to take place, thus leading to tricyclic structures bearing a strained cyclobutene ring fused with two other rings.

Figure 2
In average, the yields are good considering the molecular complexity obtained in a one-pot operation from readily available starting materials.

First, the size of the ring bearing the vinyl bromide function was considered. In general, the seven-membered ring 18 displayed better yields, compared to the five- and six-membered rings. We noticed that in the case of the five-membered ring, the reaction proceeded only via an exclusive direct Stille coupling, decomposition also occurred thus lowering the yield (Table 2). This can be explained by the ring strain induced by the cyclobutanediol when attached to a smaller ring. However, geometry is not the only limiting factor of this 4-exo-dig-carbopalladation. The stereochemistry of the diol is also important by directing the triple bond more or less in the proximity of the vinyl bromide. Thus, the experiments on the syn-pro-

Table 1  Screen of Catalytic System for the Formation of Tricyclic System

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Additives</th>
<th>Yield/Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(Ph3)_4</td>
<td>–</td>
<td>PhH</td>
<td>–</td>
<td>35% (13b)</td>
</tr>
<tr>
<td>2</td>
<td>Pd(Ph3)_4</td>
<td>–</td>
<td>PhH</td>
<td>CuCl</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd(Ph3)_4</td>
<td>–</td>
<td>DMSO</td>
<td>CuCl</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>Herrmann Cat.</td>
<td></td>
<td>PhH</td>
<td>–</td>
<td>18% (15b)</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>–</td>
<td>15% (15b)</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>Et_4NCl</td>
<td>18% (15b)</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>Ag_2CO_3</td>
<td>10% (15b)</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>AgNO_3</td>
<td>9% (15b)</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>K_2CO_3</td>
<td>Decomp.</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>Na_2CO_3</td>
<td>Decomp.</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>NEt_3</td>
<td>20% (15b)</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>DMF</td>
<td>NEt_3</td>
<td>trace (15b)</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>CH_3CN</td>
<td>NEt_3</td>
<td>15% (15b)</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>CH_3CN</td>
<td>Ag_2CO_3</td>
<td>no reaction</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)_2</td>
<td>PPh3</td>
<td>CH_3CN</td>
<td>TiOAc</td>
<td>no reaction</td>
</tr>
<tr>
<td>16</td>
<td>Pd_(dba)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>–</td>
<td>14% (14b/15b, 50:50)</td>
</tr>
<tr>
<td>17</td>
<td>Pd_(dba)_2</td>
<td>TFP</td>
<td>THF</td>
<td>–</td>
<td>13% (14b/15b, 52:48)</td>
</tr>
<tr>
<td>18</td>
<td>Pd_(dba)_2</td>
<td>TFP</td>
<td>Cyclohexane</td>
<td>–</td>
<td>Decomp.</td>
</tr>
<tr>
<td>19</td>
<td>Pd_(dba)_2</td>
<td>TFP</td>
<td>THF</td>
<td>HNEt_2</td>
<td>44% (15b)</td>
</tr>
<tr>
<td>20</td>
<td>Pd_(dba)_2</td>
<td>t-BuP</td>
<td>PhH</td>
<td>–</td>
<td>Decomp.</td>
</tr>
<tr>
<td>21</td>
<td>Pd_(dba)_2</td>
<td>o(biphenyl)t-BuP</td>
<td>PhH</td>
<td>–</td>
<td>Decomp.</td>
</tr>
<tr>
<td>22</td>
<td>Pd_(dba)_2</td>
<td>AsPh_3</td>
<td>DMF</td>
<td>Cul</td>
<td>no reaction</td>
</tr>
<tr>
<td>23</td>
<td>Pd_(dba)_2</td>
<td>PPh3</td>
<td>PhH</td>
<td>–</td>
<td>16% (14b/15b, 34:66)</td>
</tr>
<tr>
<td>24</td>
<td>Pd_(dba)_2</td>
<td>TFP</td>
<td>PhH</td>
<td>–</td>
<td>25% (14b/15b, 35:65)</td>
</tr>
<tr>
<td>25</td>
<td>Pd_(dba)_2</td>
<td>AsPh_3</td>
<td>PhH</td>
<td>–</td>
<td>40% (14b/15b, 32:68)</td>
</tr>
<tr>
<td>26</td>
<td>Pd_(dba)_2</td>
<td>Xanthonos</td>
<td>PhH</td>
<td>–</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
pargylic diol 11b showed a versatile reactivity: a mixture of the Stille product and cyclobutanediol derivatives was obtained (Table 2). Consequently, we continued preferentially to work with the anti-diol.

An another point that seems to be essential is the presence of the diol function. First, the anti-diol 10b was protected as a dioxolane. In the presence of the different stannylated reagents, the bicyclic systems are always obtained in acceptable yields. The proximity of the triple bond with the reactive site, induced by the dioxolane cis, seems to prevail on the ring strains in the final products. Then, we
turn our attention to examine the role of each of the hydroxyl groups (Table 2).

The tertiary alcohol 18 and propargylic alcohol 19 derivatives were easily prepared racemically. Applying the same standard reaction conditions, it clearly appeared that the propargylic hydroxyl group controls the feasibility of the 4-exo-dig-cyclocarbopalladation. However, the yields are limited by the formation of the Stille-product, resulting in lower values than those for the analogous propargylic diol substrate 10b. In contrast, the tertiary diol 18 underwent predominantly a direct Stille cross-coupling. Therefore, to favor the 4-exo-dig-cyclocarbopalladation, the presence of these two oxygen atoms is necessary.

The substitution of the triple bond was varied (Table 3). With the unprotected triple bond, black palladium rapidly precipitates and decomposition occurred. With a terminal methyl group, the substrate proceeded through a 4-exo-dig-cyclocarbopalladation without achieving the final 6π-electrocyclization, as was the case in the presence of a trimethylsilyl group. We noticed an isomerization of the diene function in product 21c probably assisted by palladium and the vinyltributylstannane. In the presence of different stannylated agents, the diol 21 displayed low yields. Indeed, decomposition of the substrate in these standard conditions appeared to be important. In addition, changing the terminal silyl group from the trimethylsilyl to the triethylsilyl group did not optimize the reaction. On the contrary, its reactivity is more versatile. The trimethylsilyl group was introduced to prevent the decomposition of the precursor and to enhance the yield.

<table>
<thead>
<tr>
<th>Table 3 The Effect of Varying Triple Bond Substitution</th>
</tr>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Starting compounds</strong></td>
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</tr>
<tr>
<td><strong>20</strong></td>
</tr>
<tr>
<td><strong>21</strong></td>
</tr>
<tr>
<td><strong>10b</strong></td>
</tr>
<tr>
<td><strong>23</strong></td>
</tr>
</tbody>
</table>

The yields for the products are given in percentages. The diene function in 21c isomers probably assisted by palladium and the vinyltributylstannane. In the presence of different stannylated agents, the diol 21 displayed low yields. Indeed, decomposition of the substrate in these standard conditions appeared to be important. In addition, changing the terminal silyl group from the trimethylsilyl to the triethylsilyl group did not optimize the reaction. On the contrary, its reactivity is more versatile. The trimethylsilyl group was introduced to prevent the decomposition of the precursor and to enhance the yield.
lysilyl group turned out to be the most appropriate protection of the triple bond, which may be due to electronic reasons.

**Conclusion**

In conclusion, preliminary work on the 5-*exo-dig*-cyclocarbopalladation showed that the diol function is compatible with the course of the palladium-catalyzed reaction. We have shown for the first time that a regiospecific 4-*exo-dig*-cyclocarbopalladation was possible and can be an efficient tool for the synthesis of complex 1,2-cyclobutanediol derivatives. The two oxygens in the *α*-bromopropargylic diols turned out to be essential to favor the 4-*exo-dig*-cyclocarbopalladation. Two other factors control the reactivity of these compounds. The trimethylsilyl group is the most appropriate substituent on the triple bond with *anti*-diol being preferred. In contrast, the *syn*-diol is more versatile and the Stille reaction turned out to be more competitive. Finally, the reaction proceeds in only two steps with a reflux condenser, under an argon atmosphere. To a solution of the substrate (100 mg, 1 equiv) in anhydrous benzene (10 mL) was added Pd(PPh₃)₄ (0.1 equiv), followed by the stannylating reagent (1.3 equiv). The reaction mixture was stirred for 1–17 h in a preheated 90 °C oil bath. The reaction was followed by TLC. Then, the reaction mixture was concentrated in vacuo and purified by flash chromatography, leading to the bicyclic cyclobutan-1,2-diol.

(1R)-1-(15S)-1-Hydroxy-3-(trimethylsilyl)prop-2-ynyl-2-(phenylethynyl)cyclopent-2-en-1-ol (16a)

**Cyclocarbopalladation of *α*-Bromopropargylic Diol; General Procedure**

The reaction is carried out in an oven-dried 25 mL flask, equipped with a reflux condenser, under an argon atmosphere. A solution of the substrate (100 mg, 1 equiv) in anhydrous benzene (10 mL) was added Pd(PPh₃)₄ (0.1 equiv), followed by the stannylating reagent (1.3 equiv). The reaction mixture was stirred for 1–17 h in a preheated 90 °C oil bath. The reaction was followed by TLC. Then, the reaction mixture was concentrated in vacuo and purified by flash chromatography, leading to the bicyclic cyclobutan-1,2-diol.

Further investigations have been performed to extend this methodology to the synthesis of more complex polycyclic systems. Encouraging new results in this field have been obtained and will be disclosed soon.

Reactions were run under an argon atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene and DMF were distilled from KOH. Crude products were purified by flash column chromatography on Merck 230–400 mesh silica gel. For some compounds, 5% Et₃N treated silica gel was used to avoid decomposition. Analytical TLC was carried out on Merck (60F-254) silica gel plates. ¹H NMR spectra were recorded at 200 MHz or 300 MHz using the residual solvent signal as an internal reference (CDCl₃, 7.27 ppm). Chemical shifts are quoted in ppm, coupling constants (*J*) are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), ap (apparent), br (broad). ¹³C NMR spectra were recorded at 50 MHz or 300 MHz using the residual solvent signal as an internal standard. Multiplicities were determined by DEPT pulse sequence and are given as follow: s = CH or CH₃, – = CH₂, C– = C. Melting points were determined with a glass capillary apparatus and are uncorrected. Mass spectral analysis were performed by Electrospray using a Mariner ESI-Tof instrument from Applied Bio-System/Perking Elmer.

**Scheme 4**

Further investigations have been performed to extend this methodology to the synthesis of more complex polycyclic systems. Encouraging new results in this field have been obtained and will be disclosed soon.

Reactions were run under an argon atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene and DMF were distilled from KOH. Crude products were purified by flash column chromatography on Merck 230–400 mesh silica gel. For some compounds, 5% Et₃N treated silica gel was used to avoid decomposition. Analytical TLC was carried out on Merck (60F-254) silica gel plates. ¹H NMR spectra were recorded at 200 MHz or 300 MHz using the residual solvent signal as an internal reference (CDCl₃, 7.27 ppm). Chemical shifts are quoted in ppm, coupling constants (*J*) are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), ap (apparent), br (broad). ¹³C NMR spectra were recorded at 50 MHz or 300 MHz using the residual solvent signal as an internal standard. Multiplicities were determined by DEPT pulse sequence and are given as follow: s = CH or CH₃, – = CH₂, C– = C. Melting points were determined with a glass capillary apparatus and are uncorrected. Mass spectral analysis were performed by Electrospray using a Mariner ESI-Tof instrument from Applied Bio-System/Perking Elmer.
2.65 (AB system, 2H, JAB = 17.4 Hz), 6.06 (t, 1H, CH vinylic on the cycle, J = 3.7 Hz), 5.37 (d, 1H, J = 1.7 Hz, Jtrans = 17.4 Hz), 5.02 (d, 1H, J = 1.7 Hz, Jcis = 10.9 Hz), 4.63 (s, 1H, CHOCH), 2.60 (br s, 2H, 2×OH), 2.31–1.51 (m, 6H), 0.12 (s, 9H, SiMe3).

13C NMR (50 MHz, CDCl3): δ = 137.7 (Cquat), 135.4 (+), 130.7 (+), 114.9 (–), 103.3 (Cquat), 91.8 (Cquat), 74.5 (COH), 63.8 (COH), 31.5 (–), 25.8 (–), 18.4 (–), –0.37 (SiMe3).

(1R,1aR,4aS,7hS)-7-(Trimethylsilyl)-3,4,4a,7b-tetrahydro-1H-cyclobuta[d]naphthalene-1,2dihydro-1(17d)

IR (film): 3386, 3021, 2938, 2850, 1766, 1648, 1449, 1390, 1334, 1315, 1247, 1216, 1198, 1158, 1115, 1060, 1042 cm–1.

1H NMR (200 MHz, CDCl3): δ = 6.40 (dd, 1H, J = 10.9 Hz, Jtrans = 17.4 Hz), 6.06 (t, 1H, CH vinylic on the cycle, J = 3.7 Hz), 5.37 (d, 1H, J = 1.7 Hz, Jtrans = 17.4 Hz), 5.02 (d, 1H, J = 1.7 Hz, Jcis = 10.9 Hz), 4.63 (s, 1H, CHOCH), 2.60 (br s, 2H, 2×OH), 2.25 (d, 1H, CH cis-junction, J = 7.1 Hz), 2.37–2.10 (m, 1H, CH cis-junction), 1.82–1.52 (m, 2H, JAB = 17.1 Hz), 2.50 (s, 1H, 2×OH), 2.25 (d, 1H, CH cis-junction), J = 7.1 Hz, 2.37–2.10 (m, 1H, CH cis-junction), 1.82–1.52 (m, 2H, JAB = 17.1 Hz), 2.50 (s, 1H, 2×OH), 2.25 (d, 1H, CH cis-junction), J = 7.1 Hz, 2.37–2.10 (m, 1H, CH cis-junction), 1.82–1.52 (m, 2H, JAB = 17.1 Hz), 2.50 (s, 1H, 2×OH), 2.25 (d, 1H, CH cis-junction), J = 7.1 Hz, 2.37–2.10 (m, 1H, CH cis-junction), 1.82–1.52 (m, 2H, JAB = 17.1 Hz).
(8Z)-8-[(1-Trimethylsilyl)prop-2-enylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21d) IR (FTIR, film): 3389, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1450, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

(8Z)-8-[(2-Furyl)ethylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21e) IR (FTIR, film): 3454, 3389, 3033, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1450, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

(1R,7E,8S)-7-[(1-Methyl-3-phenylprop-2-enylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21f) IR (film): 3439, 3389, 3033, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

(8Z)-8-[(1-Trimethylsilyl)prop-2-enylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21b) IR (film): 3454, 3389, 3033, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

(8Z)-8-[(1-Trimethylsilyl)prop-2-enylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21c) IR (film): 3454, 3389, 3033, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

(8Z)-8-[(1-Trimethylsilyl)prop-2-enylidene]bicyclo[4.2.0]oct-5-ene-1,8-diol (21a) IR (film): 3454, 3389, 3033, 2986, 2863, 2358, 2349, 1713, 1676, 1593, 1242, 1197, 1137, 1092, 778, 756 cm⁻¹.

References

(10) Compan, P. Actualité Chimique 2003, 4-5, 129.
(16) In presence of Pd[PPh₃]₄, the process was successfully carried out in polar solvents e.g. THF, DMF, NMP and CH₂CN.