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An Asymmetric Synthetic Approach to the A-ring of the Taxol Family of Anti-Cancer Compounds*

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Abstract: A synthetic route developed for the preparation of the A-ring of Taxol family of molecules is reported. By means of an intramolecular Diels-Alder reaction an asymmetric approach to this ring has been accomplished. Also, initial studies to prepare the A ring using an intramolecular Diels-Alder reaction have been successful.

Keywords: Taxol, cation-mediated cascade cyclisation, asymmetric Diels-Alder reaction

Introduction

The Taxol® family of molecules, exemplified by Taxol [1], and baccatin III (**Figure 1**) has commanded the attention of some of the most eminent synthetic organic research teams in the world [2]. This intense interest has been engendered by the unusual tetracyclic structure of this class of compounds, and more importantly, by the use of Taxol in cancer chemotherapy. This outstanding combination of attractive features has stimulated a huge variety of synthetic approaches directed towards the synthesis of Taxol itself, and simpler analogues which may also have desirable anti-cancer properties.

We proposed a versatile strategy for Taxol synthesis in which two major fragments are coupled at a late stage in the synthetic sequence (**Scheme 1**). Our approach is unique in that the C-3-C-4 and C-8-C-9 bonds are formed from a cyclisation precursor containing an intact D-ring.
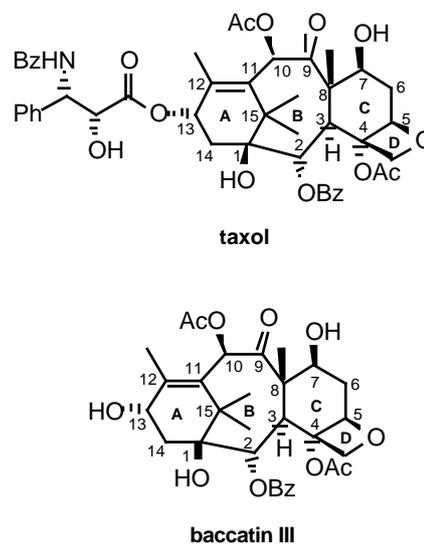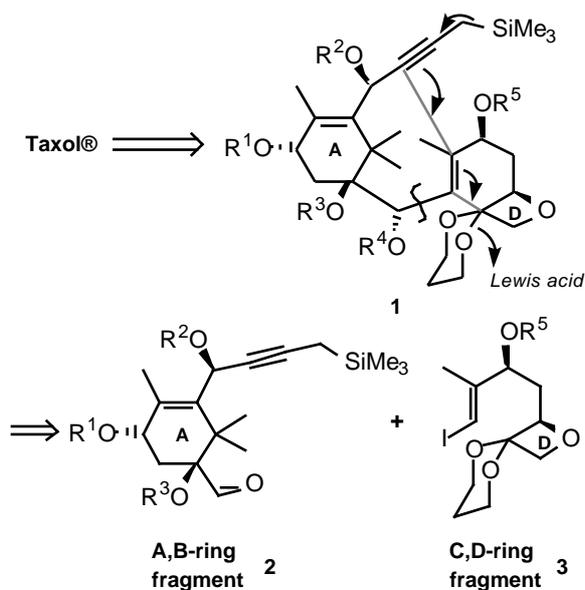

Figure 1.

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The inception of this approach is based on previously developed Diels-Alder chemistry within the Craig group [3], especially in the context of tethered intramolecular (IMDA) cycloadditions [4], and on the studies of cation-mediated intramolecular C-glycosidation processes [5]. Thus, the B- and C-rings are closed in a single step on the coupled product **1** *via* cation-mediated cascade cyclisation. This precursor **1** is obtained by coupling the A,B-ring (**2**) and the C,D-ring (**3**) fragments.
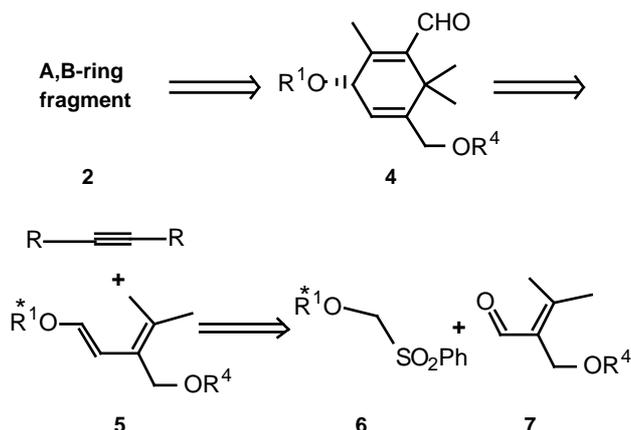

Scheme 1.

Scheme 2.

Scheme 3. *Reagents and conditions:* a) TBDPSCl, TEA, DMAP, 0°C then rt; 90%; b) TFA, MeCN:H_2O (4:1), rt; 99%; c) Piv-Cl, TEA, DMAP, 0°C; 72%; d) PDC, mol. sieves, rt; 71%; e) $Me_2C(SeMe)Li$, -78°C to rt o/n; 99%; f) PI_3, TEA, 0°C; 56%; g) DIBAL, -78°C; 84%; h) $(COCl)_2$, DMSO, TEA, -60°C to rt; 79%.
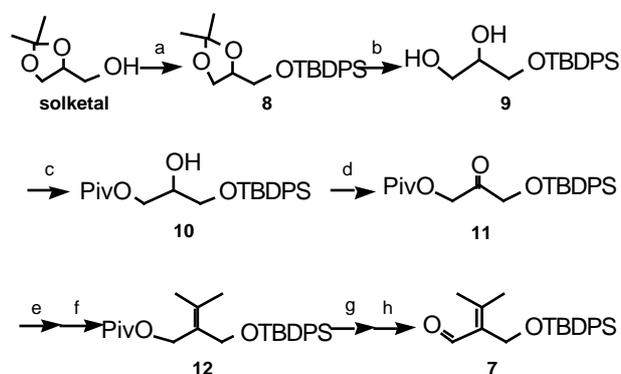
Results and Discussion

In this paper we report studies of a synthetic approach to the A-ring fragment **2**. The retrosynthetic analysis we proposed for this fragment is shown in **Scheme 2**. The side chain on C-11 of fragment **2** would be introduced by a nucleophilic addition to an aldehyde moiety existing on this carbon in the cyclohexane **4**. This intermediate would be the result of a Diels-Alder reaction between the diene **5** and a suitable dienophile. In order to accomplish an asymmetric approach to the A,B-ring fragment we proposed to prepare chiral dienes and attempt Diels-Alder reactions with relatively simple dienophiles. These asymmetric dienes **5** would be available by a Julia olefination reaction between the asymmetric sulfones **6** and the aldehyde **7**.

Therefore, the synthesis began with the preparation of the aldehyde **7** from the commercially available solketal (**Scheme 3**).

Protection of the hydroxyl group of solketal as its TBDPS derivative, followed by unmasking of the diol and subsequent protection of the primary alcohol gave the compound **10**, which was then oxidized to the ketone **11**. Nucleophilic addition of $Me_2C(SeMe)Li$ [6] to the carbonyl group of the ketone **11** followed by reductive elimination of the resulting adduct gave the isopropenyl moiety of **12**. Then, reduction of the ester and subsequent oxidation of the alcohol to the corresponding aldehyde gave the desired aldehyde **7**.

With this aldehyde in hand we examined options for the preparation of the above-mentioned chiral sulfones **6**. For this purpose, the alcohol **13** (**Scheme 4**) was considered to be an attractive starting material since it is commercially available as the racemic mixture as well as in both of the enantiomerically pure forms. Also, it would

result in a benzyl protected alcohol which can be differentiated from the alcohol already present in the molecule. Initial attempts to convert the alcohol **13** to the corresponding chloromethyl derivative by reaction with paraformaldehyde and hydrogen chloride [7] failed, so an alternative route was developed in order to prepare the sulfone **16**. Racemic sec-phenylethyl alcohol **13** was protected as the corresponding MEM-derivative [8]. Reaction of **14** with Me$_2$BBr [9] followed by addition of thiophenol gave the sulfide **15** [10]. Finally, oxidation under the usual conditions afforded the desired asymmetric sulfone **16**.
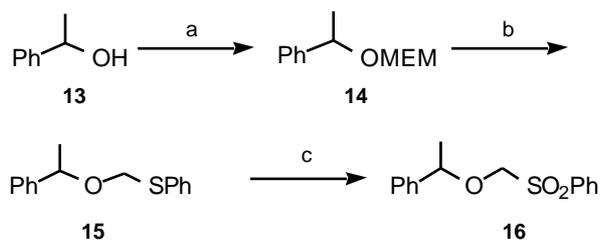
Scheme 4. *Reagents and conditions:* i) MEM-Cl, DIPEA, rt; 86%; ii) Me$_2$BBr, -78 °C, then DIPEA, PhSH, -78° °C; 99%; iii) NaOAc, AcOOH, 0 °C to rt; 96%.

Once the aldehyde **7** and the sulfone **16** had been successfully prepared the next step in our synthesis was to couple these two fragments in a Julia-type olefination reaction (**Scheme 5**). This initially gave the diastereomeric mixture of adducts **17**, which were subjected to reductive cleavage of the sulfone and benzoate groups [11] to afford the desired diene **18** [12] as an E:Z mixture in a ratio of 9 to 1.
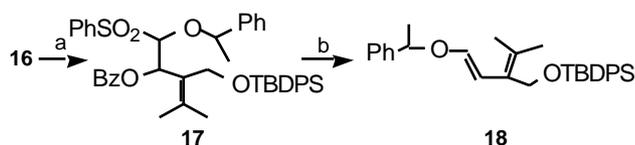
Scheme 5. *Reagents and conditions:* a) BuLi, -78 °C, then aldehyde **7**, -78 °C, then BzCl, -78 °C to rt; 88%; b) SmI$_2$, THF, DMPU, rt; 90%.

Thus, we had achieved the synthesis of the first chiral diene which would be used to investigate the asymmetric intermolecular Diels-Alder approach. To test the asymmetric induction of this diene **18**, and, at the same time, avoid problems of regioselectivity in the reaction, the dimethyl ester of the acetylenedicarboxylic acid was chosen as a dienophile. The intermolecular Diels-Alder reaction was carried out at 140°C for 67 hours and afforded, in 80% yield, a mixture of diastereoisomers in a ratio of 7 to 3 (**Scheme 6**). This result proved the asymmetric induction of the diene was possible. It was impossible, however, to assign both diastereoisomers since

they were inseparable by chromatogaphy. Fortunately, we found that reduction of the mixture of adducts **19** [13] to the mixture of lactones **20** [14] enabled easy separation of both diastereoisomers by flash chromatography. The major isomer was obtained as a crystalline solid, and X-ray analysis allowed us to unequivocally assign both compounds. Major **20**, and therefore major **19** had the *R**, *R**configuration.
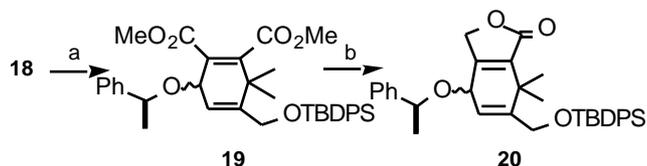
Scheme 6. *Reagents and conditions:* a) 2.5 M in PhMe, DMAD, 140 °C, 67h; 80%; b) LiAlH(i-Bu)$_2$(n-Bu), THF-hexane, -30 °C o/n; 40%.

After this encouraging Diels-Alder reaction, we explored the possibility of improving the asymmetric induction of the reaction by preparing a more hindered diene and one that was more electron-rich. Both dienes (**22** and **24**) were prepared following the synthetic route previously developed (**Scheme 7**). The diene **22** was synthesised in a comparable yield to the **18**, whereas the sulfone **23** proved to be very sensitive and it was not possible to obtain the diene **24** as a pure compound in order to carry out the Diels-Alder reaction.
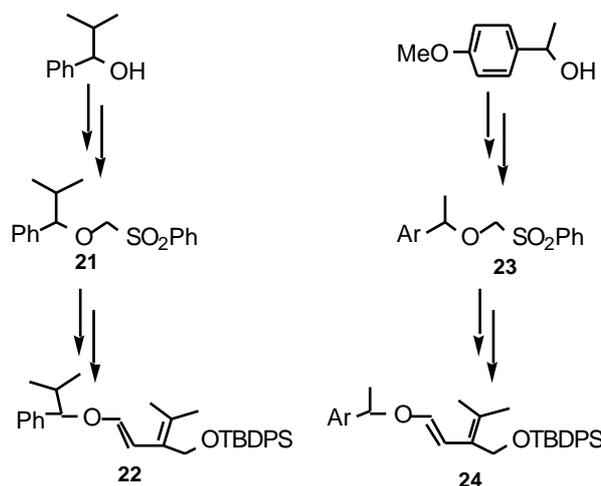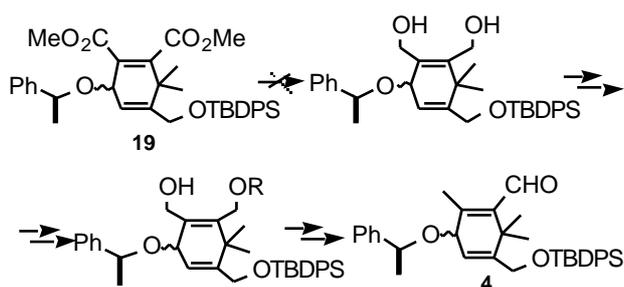

Scheme 7.

When the diene **22** was subjected to the same Diels-Alder conditions as above (**Scheme 8**) the desired mixture of diastereoisomers **25** (7:3) were obtained. Unfortunately,

no improvement in the selectivity of the reaction was observed and a considerable amount of material was lost due to the lower reactivity of this more hindered diene. Therefore, subsequent studies on the manipulation of the diesters were carried out using the initial mixture **19**.
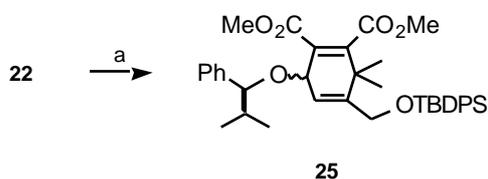

Scheme 8. *Reagents and conditions:* a) 2.5 M in PhMe, DMAD, 140°C, 67h; 49%.

In order to obtain the above mentioned aldehyde **4** differentiation of the two ester groups in compound **19** was neccesary (**Scheme 9**). The possibility of reducing both ester groups to the corresponding diol and then selectively protecting one of them was investigated. However, after trying several reductions under varying conditions the diol could not be obtained. The only case of differentiation of the two ester groups observed was in the formation of the lactones **20** (**Scheme 6**).
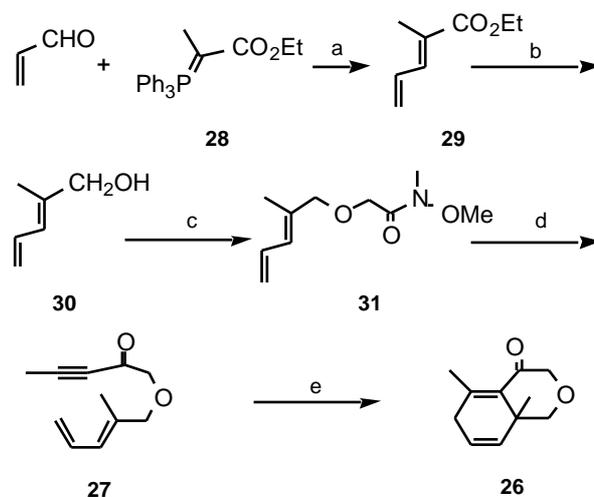

Scheme 9.

During the investigation of the selective ester reduction, we began to explore the preparation of the A,B-ring fragment *via* an intramolecular Diels-Alder reaction (IMDA). We initially considered a relatively simple A,B-ring fragment **26**, that could be obtained by an intramolecular Diels-Alder reaction from **27** (**Scheme 10**).
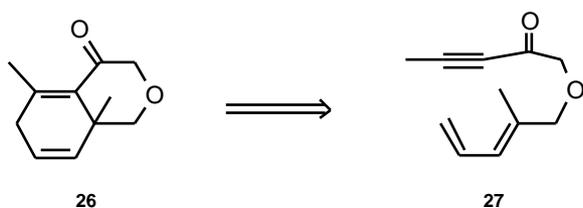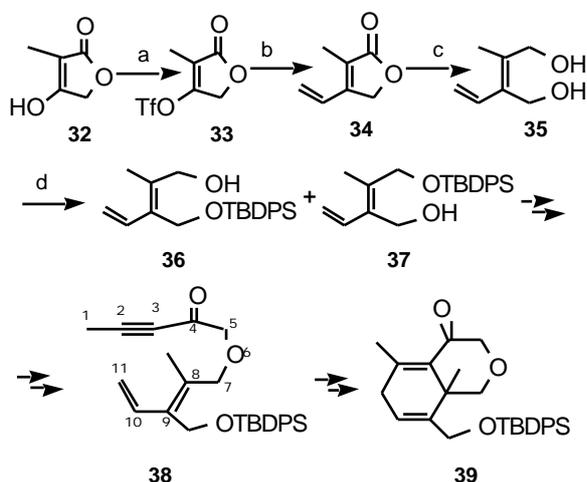

Scheme 10.

To prepare tethered molecule **27** we developed the synthetic route shown (**Scheme 11**). This route starts with a Wittig reaction between acrolein and the commercially available phosphorane **28**. Reduction of the resulting unsaturated ester **29** afforded the alcohol **30**. Coupling between this alcohol and *N*-methoxy-*N*-methyl-2-chloro acetamide [15] gave the corresponding adduct **31**, which was converted into the aforementioned molecule **27** by Grignard addition. When a solution of **27** in toluene was heated at 162°C for 72 hours the expected Diels-Alder adduct **26** [16] was obtained. Unfortunately, this tethered molecule **27** was not very reactive and the IMDA adduct was obtained in only 5% yield, with remaining unreacted starting material.
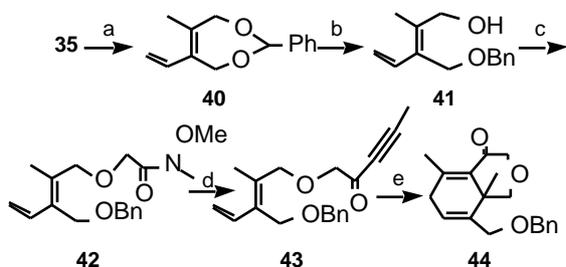

Scheme 11. *Reagents and conditions:* a) CH_2Cl_2, reflux; 70%; b) DIBAL, -78°C; 91%; c) NaH, Bu_4NI, *N*-methoxy-*N*-methyl-2-chloro acetamide, DMF, rt; 60%; d) 1-propynyl magnesium bromide, -78°C; 82%; e) PhMe, 162°C, 72h; 5%.

Previous studies have shown that when a side-chain is present on the diene C-3 in analogous intermolecular Diels-Alder reactions the reaction rate of the diene is significantly increased [17]. Therefore, in order to improve the yield of the IMDA reaction and at the same time introduce functionality that has to be present in the A-ring we decided to prepare the molecule **38**, starting from the already known 2-methyltetronic acid **32** [18] (**Scheme 12**). The corresponding triflate **33** [19] was coupled with tributyl(vinyl)tin to give **34** [20] which was reduced [21] to the corresponding diol **35**. We now intended to protect the hydroxyl group at C-9' and then apply the chemistry we had already developed in the previous scheme to the unprotected hydroxyl moiety. Initial studies using TBDPSCl as the protecting group gave a 1:1 mixture of the monoprotected alcohols, inseparable by chromatography. However, we found that after selective oxidation of **36**, from the regioisomeric mixture of

monoprotected diols, the separation was possible. The corresponding aldehyde was reduced to the alcohol and the sequence carried out only with the desired compound **36**. Unfortunately, in the basic medium of the alkylation reaction the protecting group exchanged from one hydroxyl group to the other, regenerating the regioisomeric mixture.

Scheme 12. *Reagents and conditions:* a) triflic anhydride, DIPEA, CH$_2$Cl$_2$, -78°C; 92%; b) tributyl(vinyl)tin, Pd(PPh$_3$)$_4$, THF, reflux; 91%; c) DIBAL, Bz, 0°C then rt; 60%; d) NaH, TBDPSCl, THF, 0°C then rt; 50%.

Scheme 13. *Reagents and conditions:* a) PhCHO, p-TsOH, Bz, reflux; 93%; b) DIBAL, toluene, 0°C then rt; 91%; c) NaH, Bu$_4$NI, *N*-methoxy-*N*-methyl-2-chloro acetamide, DMF, rt; 74%; d) 1-Propynyl magnesium bromide, -78°C; 45%; e) PhMe, 166°C, 100 h; 5%

Eventually, the protection of the diol as the corresponding benzylidene acetal gave **40** in 93% yield (**Scheme 13**). Fortunately, we found that the reduction of this acetal using DIBAL was selective; only the desired alcohol **41** was obtained in 91% yield. Coupling between this alcohol and *N*-methoxy-*N*-methyl-2-chloro acetamide

employing the conditions used previously gave compound **42**. Addition of 1-propynyl magnesium bromide gave **43** in only 45% yield. Substantial decomposition was observed. Only a few attempts of the intramolecular Diels-Alder reaction have been carried out so far. Nevertheless, after heating a solution of **43** in toluene at 166°C for 100 h the desired Diels-Alder adduct **44** [22] was obtained.

In future work we hope to convert the IMDA adduct **44** into the A,B-ring fragment and also to improve the yield of the sequence by changing the benzyloxy group for a more stable protecting group. We also aim to prepare an asymmetric analogue of **43**, which can then be used to prepare an asymmetric A,B-ring fragment **2**.

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12. Data of compound **18**: $_{max}$ (film) 3069, 3050, 1648, 1623, 1588, 1492, 1181, 1142, 1111, 1069, 759, 739 cm^{-1}; $_H$ (300 MHz) 7.64-7.24 (15H, m, Ph+Ph-Si), 6.63 (1H, d, J 12.4 Hz, H-5$_{maj}$), 5.96 (1H, d, J 12.4 Hz, H-4$_{maj}$), 5.88 (1H, d, J 6.2 Hz, H-5$_{min}$), 4.93 (1H, d, J 6.2 Hz, H-4$_{min}$), 4.77 (1H, q, J 6.5 Hz, PhC$\underline{H}$(CH$_3$)O$_{maj}$), 4.70 (1H, q, J 6.5 Hz, PhC$\underline{H}$(CH$_3$)O$_{min}$), 4.52 (1H, d, J 11.5 Hz, H-3'$_{min}$), 4.48 (1H, d, J 11.5 Hz, H-3'$_{min}$), 4.25 (1H, d, J 11.6 Hz, H-3$_{maj}$), 4.18 (1H, d, J 11.6 Hz, H-3'$_{maj}$), 1.68, 1.59 (2 x 3H, 2s, H-1+H-2'$_{min}$), 1.65, 1.44 (2 x 3H, 2s, H-1+H-2$_{maj}$), 1.53 (3H, d, J 6.5 Hz, PhCH(C$\underline{H}_3$)O$_{maj}$), 1.40 (3H, d, J 6.5 Hz, PhCH(C$\underline{H}_3$)O$_{min}$), 1.04 (9H, s, SiC(C$\underline{H}_3$)$_{3min}$), 0.95 (9H, s, SiC(CH$_3$)$_{3maj}$); $_C$ (75MHz) (major isomer only) 146.4 (C-5), 143.0, 135.8, 133.9, 129.5, 129.1, 128.5, 127.5, 125.9 (Ph+Ph-Si+C-2+C-3), 107.2 (C-4), 78.9 (Ph$\underline{C}$H(CH$_3$)O), 61.2 (C-3'), 26.9 (SiC($\underline{C}$H$_3$)$_3$), 23.7 (Ph$\underline{C}$H(CH$_3$)O), 20.8 (C-1+C-2'), 19.2 (Si$\underline{C}$(CH$_3$)$_3$; m/z (CI) 489 [M+NH$_4$+H]$^+$, 488 [M+NH$_4$]$^+$, 471 [M+H]$^+$, 470 M$^+$, 366, 309, 232, 215, 111, 105 (Found: [M+NH$_4$]$^+$, 488.301177. C$_{31}$H$_{38}$O$_2$Si requires [M+NH$_4$]$^+$, 488.298483).

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14. Data of compound **20**: $_{max}$ (film) 3048, 3030, 1750, 1472, 1461, 1280, 1250, 701 cm^{-1}; $_H$ (300 MHz) 7.52-7.30 (15H, m, Ph+Ph-Si), 6.05 (1H, broad s, H-5), 4.73 (1H, broad s, H-4), 4.68 (2H, s, H-3), 4.57 (1H, q, J 6.4 Hz, PhC$\underline{H}$(CH$_3$)O), 4.31 (2H, broad s, H-6'), 1.50 (3H, d, J 6.4 Hz, PhCH(C$\underline{H}_3$)O), 1.28, 1.14 (2 x 3H, 2s, H-7'+H-7''), 1.08 (9H, s, SiC(C$\underline{H}_3$)$_3$); $_C$ (75 MHz) 171.9 (C-1), 156.7, 147.5, 143.8, 135.9, 134.4, 133.6, 130.2, 129.1, 128.7, 128.4, 128.1, 126.9, 126.8 (Ph+Ph-Si+C-3a+C-7a+C-6), 118.1 (C-5), 77.9, 67.7 (C-4+Ph$\underline{C}$H(CH$_3$)$_3$), 69.7 (C-3), 61.9 (C-6'), 34.9 (C-7), 27.2 (SiC($\underline{C}$H$_3$)$_3$), 25.5, 24.7, 24.0 (C-7'+C-7''+PhCH(C$\underline{H}_3$)O), 19.7 (Si$\underline{C}$(CH$_3$)$_3$); m/z (CI) 571 [M+H+NH$_4$]$^+$, 570 [M+NH$_4$]$^+$, 553 [M+H]$^+$, 552 M$^+$, 525, 512, 510, 508, 491, 465, 461, 274, 122 (Found [M+NH$_4$]$^+$, 570.304537. C$_{35}$H$_{40}$O$_4$Si requires [M+NH$_4$]$^+$, 570.303963).

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16. Data of compound **26**: $_{max}$ (film) 3025, 1693, 1671, 1280, 1159, 1137, 1110, 966, 719 cm^{-1}; $_H$ (400 MHz) 5.73 (1H, ddd, J 9.9, 4.2, 2.6 Hz), 5.48 (1H, ddd, J 9.9, 2.6, 0.8 Hz) (H-5+H-6), 4.19 (1H, d, J 16.5 Hz, H-2), 3.98 (1H, d, J 16.5 Hz, H-2), 3.65 (1H, d, J 11.0 Hz, H-4), 3.63 (1H, d, J 11.0 Hz, H-4), 2.93 (1H, broad d, J 23.4 Hz, H-7), 2.73 (1H, broad d, J 23.4 Hz, H-7), 2.06 (3H, s), 1.21 (3H, s) (C-4a C$\underline{H}_3$+C-8 C$\underline{H}_3$); $_C$ (75 MHz) 198.8 (C-1), 143.1, 133.1 (C-8+C-8a), 130.1, 123.5 (C-5+C-6), 75.3, 75.2 (C-2+C-4), 65.8 (C-4a), 35.1 (C-7), 26.3, 20.9 (C-4a $\underline{C}$H$_3$+C-8 $\underline{C}$H$_3$); m/z (CI) 197 [M+H+NH$_4$]$^+$, 196 [M+NH$_4$]$^+$, 179 [M+H]$^+$, 178 M$^+$, 177, 163, 150, 133, 105 (Found [M+H]$^+$, 179.106865. C$_{11}$H$_{14}$O$_2$ requires [M+H]$^+$, 179.107205).

17. The presence of a substituent at the diene C-3 presumably reduces the energy difference between the unreactive transoid and reactive cisoid conformations.

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22. Data of compound **44**: $_H$ (400 MHz) 7.40-7.30 (5H, m, Ph-H), 5.83 (1H, m, H-6), 4.51 (1H, d, J 10.7 Hz, PhC$\underline{H}_2$-O), 4.48 (1H, d, J 10.7 Hz, PhC$\underline{H}_2$-O), 4.18 (1H, d, J 16.6 Hz, H-2), 4.04 (1H, d, J 11.3 Hz), 3.99 (1H, d, J 16.6 Hz, H-2), 4.01 (1H, d, J 11.7 Hz), 3.97 (1H, d, J 11.7 Hz), 3.78 (1H, d, J 11.3 Hz) (H-4+H-5'), 2.99 (1H, d, J 23.7 Hz, H-7), 2.78 (1H, dd, J 23.7, 4.6 Hz, H-7), 2.09 (3H, s), 1.30 (3H, s) (C-4a C$\underline{H}_3$+ C-8 C$\underline{H}_3$); $_C$ (75 MHz) 198.6 (C-1), 133.8 (ipso-Ph), 128.5, 127.9 (ortho +meta +para Ph), 127.9 (C-6),

74.1, 73.5, 72.2, 71.3 (C-2+C-4+C-5'+Ph$\underline{C}$H$_2$-O), 35.3 (C-7), 25.6, 21.5 (C-4a $\underline{C}$H$_3$+C-8 $\underline{C}$H$_3$); m/z (CI) 316 [M+NH$_4$]$^+$, 299 [M+H] 283, 274, 257, 242, 222, 205, 108, 91 (Found [M+NH$_4$]$^+$, 316.191447. C$_{19}$H$_{22}$O$_3$ requires [M+NH$_4$]$^+$, 316.191269).

Sample Availability: Available from MDPI.