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A short and convenient way to produce the Taxol™ A-ring utilizing the Shapiro reaction

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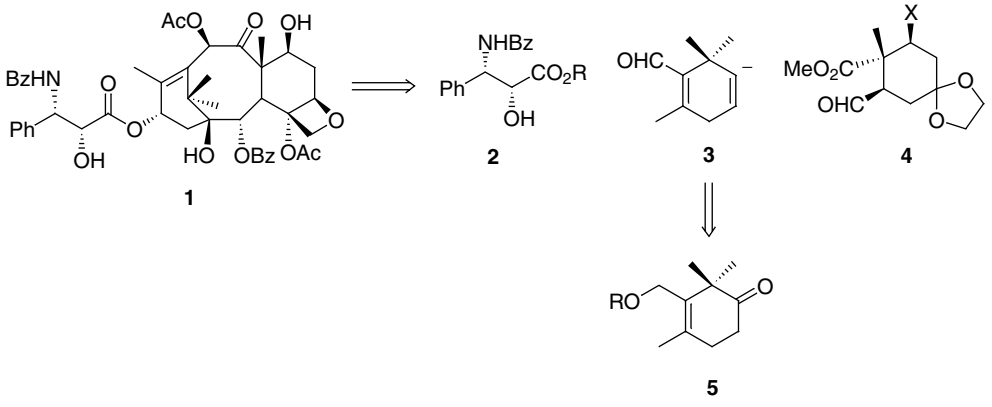
Abstract—The Shapiro reaction was utilized in an efficient route to a Taxol™ A-ring building block. Commercially available 2-methyl-1,3-cyclohexanedione was converted in three simple steps to various arenesulfonylhydrazones and then to the target molecule with the Shapiro reaction. Remarkable differences were observed in the reactivity and stability of different hydrazones and their dianions in the Shapiro reaction. This pathway is the shortest one reported to give the target molecule in good overall yield. The use of different electrophiles in the final Shapiro reaction step allows alternative ways to prepare the target alcohol. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Synthetic preparation of Taxol **1** is still under intensive investigation due to its extremely low availability from nature (bark of Pacific yew tree *Taxus brevifolia*) and growing shortage in treatment against a number of mammalian cancers.[1] Semisynthesis of Taxol™ from 10-deacetylbaccatin III, readily available from the needles of *Taxus baccata*, has provided some amelioration against lack of Taxol.[2] Several different strategies to Taxol™ A-ring fragments have been developed utilizing Diels–Alder reaction,[3] modification of cyclohexanones[4] and ene-reaction[5] as the most common methods.

Our retrosynthetic strategy for Taxol™ is shown in Scheme 1. We have earlier reported our entries to the side chain **2**[6] and the C-ring precursor **4**.[7] Compound **5** has been utilized successfully as an A-ring precursor in the total synthesis of Taxol™ by Nicolaou et al.[8]

The Shapiro reaction is an efficient way to create a new C–C bond to the carbonyl carbon of ketones simultaneously introducing a vinylic moiety into the product. In the Shapiro reaction the ketone derived hydrazone is converted to a dianion using an alkyl lithium base and then decomposed directly to the vinyl anion.[9] The vinyl anion can also be alkylated to introduce a substituent to the neighboring



Scheme 1. Retrosynthetic analysis of Taxol™ and the role of A-ring building block.

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carbon atom. The lithiated vinyl anion reacts readily with electrophiles allowing an easy entry to the final product. The use of intramolecular electrophiles allows preparation of cyclic products with high stereoselectivity.[10]

In this paper we report the shortest and simplest synthesis of a Taxol™ A-ring fragment utilizing the Shapiro reaction as the key step. The route involves only four steps and proceeds with high yields.

2. Results and discussion

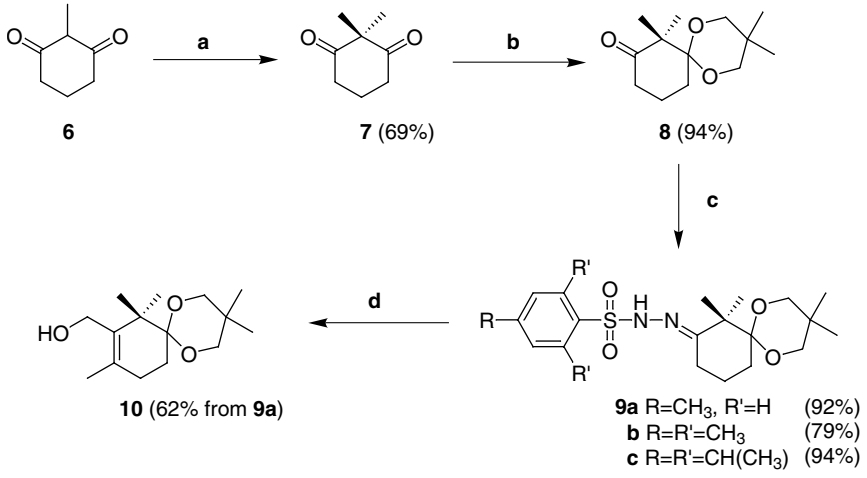
The synthesis plan for the A-ring precursor **10** is shown in Scheme 2. We have earlier reported the first two steps in a complementary and longer route to the Taxol™ A-ring block.[4d] Herein we optimized those steps and the product, monoketal **8**, was used as the starting material in the preparation of the hydrazones **9a–c**. The Shapiro reaction of **9a–c** and related hydrazones **12a–b** was investigated carefully.

Methylation of commercially available 2-methyl-1,3-cyclohexanedione **6** was carried out with K_2CO_3/CH_3I in acetone.[11] The product mixture contained 85% of the desired **7** and 15% of 3-methoxy-2-methyl-cyclohex-2-enone as the side product (ratios based on GC analysis). The crystalline side product was filtered off and recycled to the enol form of the starting material **6** by treatment with 2 M HCl in CH_2Cl_2. Diketone **7** was isolated in 99% purity when CH_2Cl_2 was used as the solvent in the extraction. If toluene was used instead of CH_2Cl_2 the product had to be distilled (103–104°C; 13 mmHg) in order to obtain sufficient purity. Dimethylation of cyclohexane-1,3-dione directly to **7** was also attempted but the yield was rather low (40%) and more side products were observed.

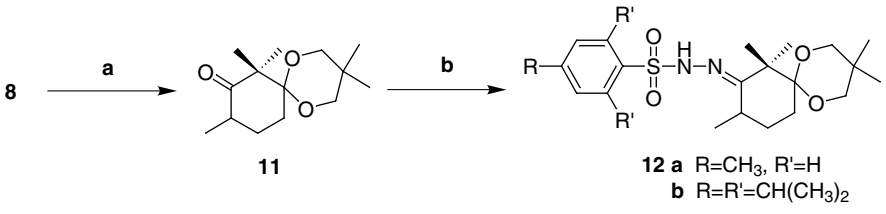
Selective monoketalization of pure 2,2-dimethyl-1,3-cyclohexadione **7** was achieved by treatment with 2,2-dimethyl-1,3-propanediol and 1 mol% of *p*-TsOH in CH_2Cl_2 with azeotropic removal of water.[12] Traces of two side products were observed but no diketalized dione.

In the beginning of this work, we wanted to study the reactivity of different electrophiles in the Shapiro reaction. The aim was to use tosyl **12a** and trisylhydrazone **12b** (Scheme 3) as model compounds. Ketone **8** was first converted (LDA/CH_3I) to the methylated ketone **11** in 66% yield. However, preparation of the arylsulfonylhydrazones from ketone **11** proved to be impossible or extremely slow. No product was observed in the case of **12b** and only traces of product was formed in the case of **12a** even after 24 h. The steric hindrance caused by the methyl groups in the α-position obviously retards the reaction. With HCl as acid catalyst, only deketalization of **11** was observed.

We decided to use sterically less hindered hydrazones **9a–c** (of ketone **8**) as model compounds (Scheme 2) in order to uncover the limitations in the Shapiro reaction. Additionally, the use of hydrazones **9a–c** instead of hydrazones **12a–b** provides one step shorter reaction pathway. All stable hydrazones **9a–c** were prepared in excellent yields. Typically hydrazones are prepared under concentrated conditions so that all starting material and reagent hardly



Scheme 2. Synthesis of Taxol™ A-ring block via tosylhydrazone **9a**. *Reagents and conditions*: (a) K_2CO_3, CH_3I, acetone, rfx, 8 h; (b) CH_2Cl_2, $Me_2C(CH_2OH)_2$, *p*-TsOH×H_2O, CH_2Cl_2, rfx, 7 h; (c) EtOH (THF in **9b**), hydrazide, +40°C 16 min, then rt 6 h; (d) THF, −50°C, *n*-BuLi, 30 min, CH_3I, 30 min, *n*-BuLi, from −50°C to rt, 25 min, paraformaldehyde, 30 min.



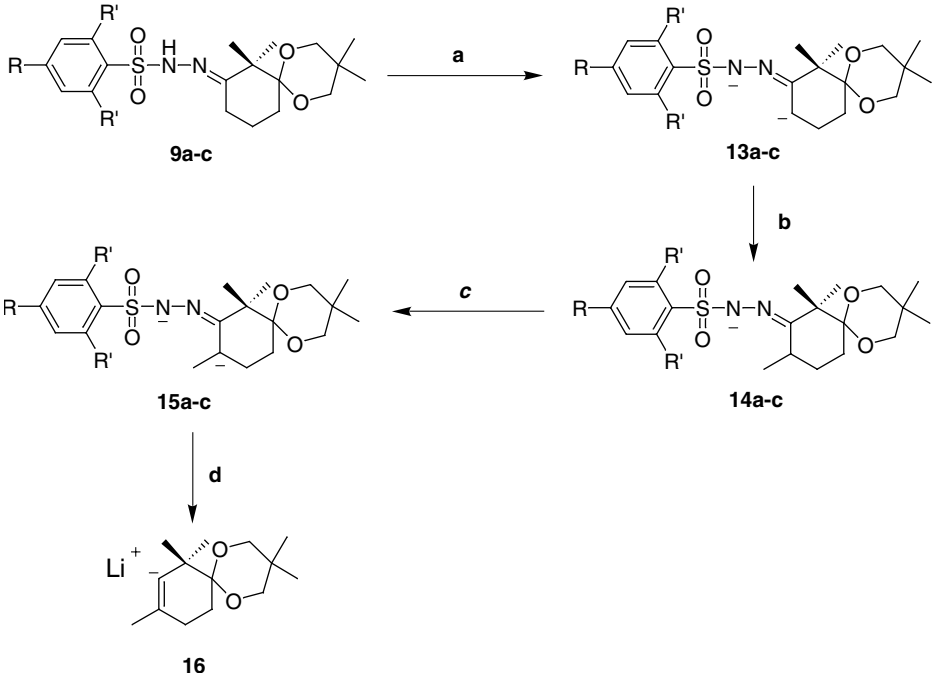
Scheme 3. *Reagents and conditions*: (a) LDA, THF, −78°C, CH_3I, 0°C then rt; (b) hydrazide, EtOH, (HCl).

dissolve in the solvent.[13] Also a small excess of hydrazine (105–110 mol%) is usually required to run the reaction to completion. If the ketone used is sterically hindered, addition of a catalytic amount of HCl, refluxing the reaction mixture and longer reaction time are sometimes needed.[14] Here, under optimized reaction conditions to prepare **9a–c**, the reaction mixture is first heated up to +30 to +40°C until complete dissolution is achieved and then allowed to react at room temperature (too high reaction temperatures caused partial decomposition of the product even at +50°C). The use of acid catalyst was not necessary. Absolute EtOH was found to be the best solvent in the preparation of tosylhydrazone **9a** and trisylhydrazone **9c** allowing a spontaneous crystallization of the hydrazones from the reaction mixture. The preparation of **9a** was carried out also in THF and MeOH successfully but in lower yields. Additionally, the reaction was slightly slower and the hydrazone did not crystallize out from the reaction mixture. Mesitylhydrazone **9b** was prepared only in THF. Differences in the stabilities of hydrazones **9a–c** during storage were also observed. Tosylhydrazone **9a** seems to be very stable and can be stored at +4°C for a few years under argon. Trisylhydrazone **9c** decomposed partly under similar conditions giving yellowish color in a few months. The stability of mesitylhydrazone **9b** during the storage was close to that of tosylhydrazone **9a**.

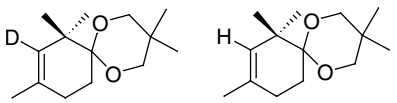
Detailed description of the Shapiro reaction is described in Scheme 4. Hydrazone **9** was first treated with 220 mol% of *n*-BuLi in order to prepare dianion **13**. The first hydrogen removed is the one located on nitrogen and this monoanion is usually colorless. Addition of another equivalent of butyl lithium gives a beautiful deep red color. The dianion was methylated quantitatively to **14** with CH_3I at −50°C (internal temperature). The second addition of *n*-BuLi at −50°C gives dianion **15** which can be observed as a slightly orange color. When this dianion is heated to room temperature it slowly decomposes to vinyl anion **16**. The decomposition can be easily observed as the formation of small bubbles when N_2 is liberated. An electrophile must be added immediately when the gas formation has ceased especially if THF is used as the solvent in order to avoid possible protonation of vinyl anion **16** by THF.

The strength of the used alkyl lithium base in the Shapiro reaction is also crucial.[15] Stronger bases like *t*-BuLi are sometimes required in the deprotonation. In our case the formation of dianion **15** from **14** can be carried out easily with *n*-BuLi. However, *t*-BuLi gave similar results.

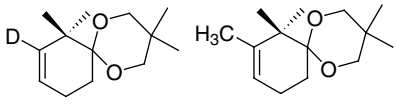
We initially studied the Shapiro reaction with trisylhydrazone **9c** which was treated with *t*-BuLi at −78°C in THF and formation of the first dianion **13c** was observed as a red color (Scheme 4). The dianion of trisylhydrazone was found to be too labile even at −78°C and decomposition was observed. Methylation of the dianion was carried out at −78°C as well as the preparation of the second dianion **15c**, followed by heating to 0°C and quenching by D_2O. In the product mixture there was only 7.5% of compound **17** where methylation proceeded successfully at the α-carbon and then decomposed to vinyl anion and captured with deuterium. The main product was **19** (57% of product mixture) which indicates that the dianion had not reacted with CH_3I at all but decomposed to vinyl anion and was trapped later with deuterium. The presence of product **20** was a clear evidence of premature decomposition of dianion **13c** to its vinyl anion. N_2 evolution was also observed already at −45°C which indicates the decomposition of the dianion to the vinyl anion.



Scheme 4. Detailed steps of Shapiro reaction from hydrazones to vinyl anion **16**. *Reagents and reaction conditions*: (a) *n*-BuLi (220 mol%), THF, −55°C, 30 min; (b) CH_3I (250 mol%), −50°C, 30 min; (c) *n*-BuLi (400 mol%), THF, −50°C, 30 min; (d) rt, 25 min.



17 **18**



19 **20**

The final proof of the premature decomposition of the dianion of **9c** was obtained when dianion **13c** was prepared at −78°C and quenched after 45 min with D_2O. Both deuterated trisylhydrazone **21** (85%) and deuterated vinyl anion **19** (15%) were observed in the product mixture (Scheme 5). At higher temperature (−48°C) and shorter stirring before quench (15 min) the product mixture contained 96% of **19** with H/D ratio 22:78.

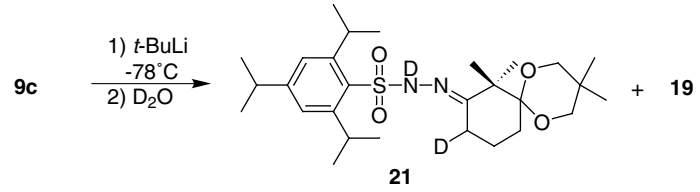
Mesitylhydrazone **9b** was assumed to be a better choice because a possible deprotonation of aromatic *ortho*-protons is avoided and the vinyl anion could be stable enough for methylation. Also the decomposition of dianion **15b** could be fast enough in order to avoid protonation of **16** by the solvent. The reaction proceeded as described in Scheme 4. Methylation was complete but the step **15b→16** was slow and the vinyl anion was protonated by THF.

Tosylhydrazone **9a** proved to be the best choice. Steps **9a→14a** (Scheme 4) were carried out uneventfully. After formation of the second dianion **15a** the solution was warmed to room temperature. The decomposition (evolution of N_2) was complete in 25 min. A shorter reaction time or lower decomposition temperature gives a significant amount of hydrazone as a side product. Paraformaldehyde (10 mol equiv.) was added to give allylic alcohol **10** in 62% isolated yield. Protonated vinyl anion was still obtained as a side product (<10%). Immediate protonation of vinyl anion **16** can occur either by reaction with the solvent[16] or due to the MeOH liberated during monomerization of paraformaldehyde. Thus, other forms of formaldehyde were also investigated. Gaseous formaldehyde was generated from paraformaldehyde by heating at 130°C and then led into the reaction with an argon flow.[17] This method gave 28% isolated yield of **10** at best. The use of excess 1,3,5-trioxane in THF gave 22% isolated yield.

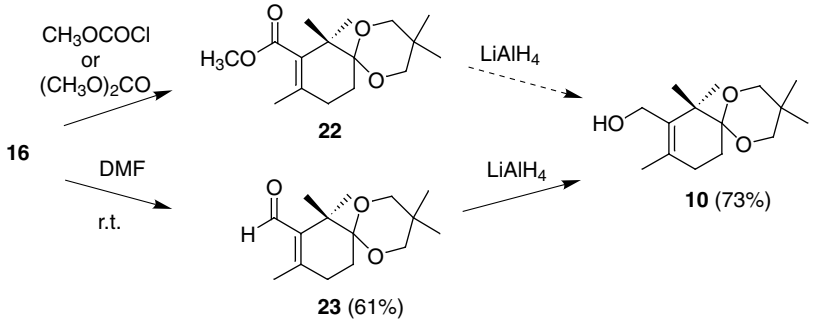
These results with Shapiro reaction of **9a–c** are in accordance with the results reported by Shapiro et al. originally. They observed that the *ortho*-position of the aromatic ring of tosylhydrazones can be deprotonated with strong alkyllithium bases to give a trianion. Vinyl anions related to **16** have also been reported to be basic enough to deprotonate the aromatic *ortho*-position.[18] The problem of vagrant deprotonation could be overcome by using 300–400 mol% of BuLi in the preparation of dianions. However, we observed no difference in the product distribution when the amount of used BuLi was varied from 220 to 400 mol%. Furthermore, dianions of tosylhydrazones decompose extremely slowly to the vinyl anion as compared to the corresponding trisylhydrazones.[19] Therefore decomposition of the dianion should be fast and the electrophile should be added immediately after complete decomposition of dianion.

A few additional experiments with carefully dried electrophiles were conducted to find out whether the protonation was caused by the solvent (THF) or by moisture. The reaction of benzylchloromethylether with **16** to the BOM protected alcohol **10** was unsuccessful. Methylchloroformate and dimethylcarbonate were also examined to create an ester functionality which could be reduced to the target compound, alcohol **10**. However, the yield of **22** was very low with both electrophiles and again, protonated vinyl anion was obtained as the main product.

When DMF was employed as the electrophile (Scheme 6)



Scheme 5.



Scheme 6.

aldehyde **23** was obtained in 61% isolated yield. Aldehyde **23** was easily reduced to alcohol **10** with $LiAlH_4$ in THF in 73% isolated yield. The reactivity of *N*,*N*-disubstituted amides with alkyl lithium compounds is known to be very high giving fast reaction and good yields.[20] Thus, due to the high reactivity of the amide, protonation of **16** by THF does not occur in significant amounts.

To avoid protonation of **16** by THF, DME and Et_2O were investigated. However, methylation (**13a→14a**) was incomplete in these experiments. Also, TMEDA/hexane was impracticable here because of strong salt formation between CH_3I and TMEDA.[21]

3. Conclusions

Taxol™ A-ring building block **10** was synthesized with a novel and short method consisting of only four steps with high 38% overall yield. Tosylhydrazone **9a** was found to be the best of the studied arylhydrazones in Shapiro reaction allowing the formation of stable dianions and complete methylation. Evidence of the possible effect of steric hindrance was observed in the preparation and reactivity of hydrazones. Protonation of the vinyl anion by THF remained problematic to some extent giving always some protonated vinyl anion. This can be minimized with rapid decomposition of dianion **15a** at room temperature followed by immediate addition of the electrophile. The Shapiro reaction as the final step allows the use of different electrophiles and thus the formation of various different functionalities to the final compound.

4. Experimental

4.1. General

All solvents used were dry and distilled immediately before use. Merck silica gel 60F (230–400 mesh) plates were used in TLC analyses. The TLC plates were stained with 1% phosphomolybdic acid in ethanol. NMR spectra were measured on Bruker AM 200 and Bruker DPX-400 instruments in $CDCl_3$ with TMS as internal reference. Gas chromatography was preformed on Perkin–Elmer Model with OV-1701 column. Mass spectra were recorded on Kratos MS80 RF Autoconsole. IR spectra were measured with Perkin–Elmer Spectrum One instrument. All melting points were measured with a digital Gallenkamp GMB (capillary) apparatus.

4.1.1. 2,2-Dimethyl-1,3-cyclohexanedione (7). Acetone (300 ml), 2-methyl-1,3-cyclohexanedione (50.5 g; 400 mmol) **6**, K_2CO_3 (110.57 g; 800 mmol) and CH_3I (62.3 ml; 1000 mmol) were placed into the reaction vessel and refluxed for 8 h with vigorous stirring to avoid K_2CO_3 hardening on the walls. Acetone was evaporated, 200 ml of CH_2Cl_2 was added and evaporated to dryness to remove acetone traces. The product mixture was dissolved in CH_2Cl_2 (400 ml) and extracted with 600 ml of water. The water phase was washed with 100 ml of CH_2Cl_2. The combined organic phase was stirred with 200 ml of 2 M HCl for 4 h at room temperature and the enol form of the starting material was observed as a white precipitation. The reaction mixture was filtered, CH_2Cl_2 was evaporated, the residue taken up in toluene (300 ml) and stirred with 20 ml of 2 M HCl for 2 h. The toluene phase was separated and the water phase was washed with toluene. The toluene phases were combined, dried over Na_2SO_4, filtered and evaporated to dryness. The oily product was cooled and it crystallized out as a white powder. Yield 38.54 g (69%), purity>98% (GC). TLC (MTBE/Hex, 80:20) R_f=0.25. Mp 39–40°C. IR (in KBr): 2977, 2940, 2876, 1732, 1702. ^{1}H NMR (200 MHz) δ 2.70 (t, 4H, ^3J=6.8 Hz), 1.85–2.03 (m, 2H), 1.31 (s, 6H, 2×CH3). ^{13}C NMR (60 MHz) δ 210.4, 61.6, 37.3, 22.1, 17.9. Calcd for $C_8H_{12}O_2$: C 68.55, H 8.64; Found C 68.34, H 8.46.

4.1.2. 3,3,7,7-Tetramethyl-1,5-dioxaspiro[5,5]undecan-8-one (8).[12] Dimethyldiketone **7** (15.42 g; 110 mmol), 2,2-dimethyl-1,3-propanediol (34.37 g; 330 mmol), *p*-TsOH monohydrate (0.154 g; 1.5 mol%) and CH_2Cl_2 (220 ml) were placed into the reaction flask. This yellowish solution was refluxed for 7 h with azeotropic water removal. CH_2Cl_2 was evaporated and the product precipitated out as white crystals. The precipitate was dissolved in 250 ml of hexanes and washed first with 125 ml of 1 M $NaHCO_3$ and then water (2×125 ml). The organic phase was dried over Na_2SO_4. After filtration the solvent was evaporated and the product crystallized out as a white powder. The product was dried under high vacuum (0.15 mmHg) for 4 h. Yield 23.4 g (94%), mp 62.5–66.0°C. TLC (Hex/MTBE, 80:20) R_f=0.17. IR (KBr disk) 3385, 2983, 2959, 2872, 1708. ^{1}H NMR (400 MHz) δ 3.63 (d, 2H, ^2J=10.5 Hz), 3.34 (dd, 2H, ^2J=10.5 Hz, ^4J=1.5 Hz), 2.42 (t, 2H, ^3J=7 Hz), 2.24–2.19 (m, 2H), 1.72–1.63 (m, 2H), 1.21 (s, 6H), 1.16 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (60 MHz) δ 213.3, 101.9, 70.2, 55.4, 36.4, 29.8, 23.3, 22.3, 20.7, 19.4, 18.7.

4.1.3. 3,3,7,7-Tetramethyl-8-(tosylhydrazono)-1,5-dioxaspiro[5,5]undecane (9a). Ketone **8** (6.79 g; 30 mmol), tosylhydrazide (6.16 g; 33 mmol) and 18 ml of abs. ethanol were placed into the reaction flask. The mixture was heated for 16 min at +40°C until all solid had dissolved. The solution was stirred for 6 h at room temperature and the product crystallized out as a white precipitate. The solvent was evaporated and the solid residue was purified by means of grinding with 24 ml of cold methanol/water (80:20) solution. The precipitate was filtered, washed with 15 ml of cold methanol/water (75:25) and dried carefully to give **9a** as a white solid (10.86 g, 92%). Mp 140–144.5°C. TLC (Hex/MTBE, 80:20) R_f=0.02. IR (KBr disk): 3205, 2990, 2975, 2947, 2921, 2866, 1630. ^{1}H NMR (400 MHz) δ 7.84 (d, 2H, ^3J=8.8 Hz), 7.28 (d, 2H, ^3J=8.8 Hz), 3.55 (d, 2H, ^2J=10.5 Hz), 3.25 (dd, 2H, ^2J=10.5 Hz, ^4J=1.4 Hz), 2.42 (s, 3H), 2.26 (t, 2H, ^3J=6.8 Hz), 2.06–1.99 (m, 2H), 1.56–1.47 (m, 2H), 1.13 (s, 3H), 1.12 (s, 6H), 0.69 (s, 3H). ^{13}C NMR (60 MHz) δ 166.2, 143.6, 135.5, 129.2, 128.3, 100.7, 69.9, 49.1, 29.7, 23.3, 22.3, 22.0, 21.6, 20.9, 20.6, 19.0. Calcd for $C_{20}H_{30}O_4N_2S$: C 60.89; H 7.66; N 7.10; Found C 61.17; H 8.01; N 7.06.

4.1.4. 3,3,7,7-Tetramethyl-8-(2,4,6-trimethylbenzenehydrazono)-1,5-dioxaspiro-[5,5]undecane (9b). Ketone **8** (2.263 g; 10 mmol), 2,4,6-trimethylbenzene-sulfonylhydrazide (2.362 g; 11 mmol) and 6 ml of abs. ethanol

were placed into the reaction flask. The mixture was stirred for 40 min at +30°C and then for 3.5 h at room temperature. Ethanol was evaporated and the white precipitate was purified by means of grinding with 8 ml of methanol/water (80:20) solution. The mixture was filtered and the precipitate was washed with 2×25 ml of cold methanol/water (75:25) solution and dried carefully to give **9b** as a white solid (3.35 g, 79%). Mp 159.5–163.5°C. TLC (CH_2Cl_2/MeOH, 90:10) R_f=0.75. IR (KBr disk): 3252, 2963, 2871, 2735, 1651, 1603. ^{1}H NMR (200 MHz) δ 6.93 (s, 2H), 3.54 (d, 2H, ^2J=11.3 Hz), 3.22 (d, 2H, ^2J=11.3 Hz), 2.65 (s, 6H), 2.29 (s, 3H), 2.25–2.14 (m, 2H), 2.08–2.02 (m, 2H), 1.60–1.50 (m, 2H), 1.09 (s, 3H), 1.02 (s, 6H), 0.68 (s, 3H). ^{13}C NMR (60 MHz) δ 163.3, 142.3, 140.2, 131.5, 100.6, 69.8, 49.0, 29.7, 23.2, 22.2, 21.3, 21.0, 20.8, 20.6, 19.1. Calcd for $C_{22}H_{34}O_4N_2S$: C 62.53; H 8.11; N 6.63; Found C 62.38; H 8.10; N 6.46.

4.1.5. 3,3,7,7-Tetramethyl-8-(trisylhydrazono)-1,5-dioxaspiro[5,5]undecane (9c).[4g] Ketone **8** (4.53 g; 20 mmol), trisylhydrazide (6.27 g; 21 mmol) and THF (60 ml) were stirred for 4 h at room temperature. THF was evaporated and the white precipitate was ground with 50 ml of methanol/water (85:15) solution, filtered, washed with 50 ml of cold methanol/water (80:20), filtered again and dried carefully to give **9c** as a white solid (9.52 g, 94%). Mp 153.5–156°C. TLC (CH_2Cl_2/MeOH 90:10) R_f=0.78. IR (KBr disk): 3262, 2959, 2867, 1714, 1624, 1599, 1561. ^{1}H NMR (400 MHz) δ 7.14 (s, 2H), 4.16 (sept., 2H, ^3J=6.7 Hz), 3.37 (d, 2H, ^2J=11.6 Hz), 3.22 (d, 2H, ^2J=11.6 Hz), 2.90 (sept., 1H, ^3J=6.9 Hz), 2.21 (t, 2H, ^3J=6.8 Hz), 2.04–1.98 (m, 2H), 1.58–1.48 (m, 2H), 1.25 (d, 12H, ^3J=6.7 Hz), 1.24 (d, 6H, ^3J=6.9 Hz), 1.08 (s, 3H), 1.01 (s, 6H), 0.67 (s, 3H). ^{13}C NMR (60 MHz) δ 163.0, 152.9, 151.1, 124.0, 123.4, 100.6, 69.8, 48.9, 34.2, 29.9, 24.8, 23.6, 23.5, 23.2, 22.3, 21.5, 20.8, 20.5, 19.4, 18.9. Calcd for $C_{28}H_{46}O_4N_2S$: C 66.37; H 9.15; N 5.53; Found C 66.18; H 9.20; N 5.46.

4.1.6. 3,3,7,7,9-Pentamethyl-8-(hydroxymethyl)-1,5-dioxaspiro-[5,5]undec-8-ene (10). Tosylhydrazone **9a** (0.398 g; 1.0 mmol) was dissolved in THF (5 ml) under argon and the solution was cooled down to −55°C. *n*-BuLi (1.40 M in pentane, 2.2 mmol) was added dropwise in order to keep temperature stable and a dark red color was observed. The solution was stirred for 60 min at −50°C and CH_3I (1.8 mmol) was added dropwise giving light yellow color and small amount of white (LiI) precipitate. The solution was stirred for 30 min at −50°C and the solution turned colorless. Another *n*-BuLi (4.0 mmol) addition gave orange color. The solution was warmed up to room temperature and the dianion decomposed to its vinyl anion which was observed as a gas formation (starts even at −2°C). The solution was stirred at room temperature for 25 min in order to complete the vinyl anion formation. Paraformaldehyde (8.4 mmol) was added into the reaction in one portion to give a slightly exothermic reaction. The reaction was stirred for 60 min and the solvents were evaporated. The residue was taken up with 8 ml of hexane and washed with 8 ml of water. The organic layer was separated and the water phase was washed again with 8 ml of hexane. The hexane phases were combined and dried over Na_2SO_4, filtered and evaporated. Column chromatographic purification (Hex/MTBE, 45:55) gave 0.158 g (62%) of **10** in >98% purity (NMR). The product can be further purified by recrystallization from methanol/water (70:30). Mp 111.0–113.1°C. TLC (Hex/MTBE, 45:55) R_f=0.25. IR (KBr disk): 3532, 2975, 2958, 2930, 2901, 2870, 2729, 2700, 1660. ^{1}H NMR (400 MHz) δ 4.15 (d, 2H, J=4.1 Hz), 3.69 (d, 2H, ^2J=11.1 Hz), 3.37 (dd, 2H, ^2J=10.2 Hz, ^4J=1.4 Hz), 2.10–1.98 (m, 4H), 1.77 (s, 3H), 1.19 (s, 3H), 1.16 (s, 6H), 0.73 (s, 3H). ^{13}C NMR (100 MHz) δ 136.4, 131.7, 100.0, 70.3, 59.3, 43.7, 29.95, 29.87, 23.3, 22.5, 22.3, 19.2, 18.4. Calcd for $C_{15}H_{26}O_3$: C 70.83, H 10.30, Found C 70.72, H 10.68.

4.1.7. 3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5,5]undecan-8-one (11). Diisopropylamine (0.79 ml; 5.4 mmol) and THF (10 ml) were placed into the reaction flask under argon and the solution was cooled down to −78°C. *n*-BuLi (5.0 mmol) was added and the solution was stirred for 30 min at −78°C and then 45 min at 0°C. Ketone **8** (1.132 g; 5.0 mmol) in THF (7 ml) was added dropwise. The solution was stirred for 30 min at 0°C. CH_3I (0.375 ml; 6.0 mmol) was added and the solution was stirred at room temperature for 30 min and quenched with 1 ml of water. THF was evaporated and the residue was taken up in 25 ml of hexanes. The organic phase was washed with 9 ml of water, the layers were separated and the organic phase was dried over Na_2SO_4, filtered and evaporated. The white precipitate was purified by recrystallization (5 ml MeOH/0.9 ml H_2O). The product was washed with 4 ml of cold MeOH/H_2O (70:30). Yield 0.792 g (66%). Mp 79.5–81.5°C. TLC (Hex/MTBE, 80:20) R_f=0.36. IR (KBr disk): 3407, 2960, 2929, 2867, 2785, 1714. ^{1}H NMR (400 MHz) δ 3.72 (d, 1H, ^2J=11.3 Hz), 3.52 (d, 1H, ^2J=11.3 Hz), 3.37 (dd, 1H, ^2J=11.3 Hz, ^4J=2.7 Hz), 3.28 (dd, 1H, ^2J=11.3 Hz, ^4J=2.7 Hz), 2.76–2.68 (m, 1H), 2.64 (dt, 1H, ^2J=12.9 Hz, ^3J=6.4 Hz), 1.89–1.73 (m, 2H), 1.78 (dd, 1H, ^2J=14.3 Hz, ^3J=4.3 Hz), 1,75 (dd, 1H, ^2J=14.3 Hz, ^3J=4.3 Hz), 1.21 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.02 (d, 3H, ^3J=6.40 Hz), 0.72 (s, 3H). ^{13}C NMR (100 MHz) δ 214.0, 102.2, 70.5, 69.7, 55.0, 39.2, 29.8, 27.8, 23.2, 22.3, 21.1, 16.3, 14.9.

4.1.8. 3,3,7,7,9-Pentamethyl-1,5-dioxaspiro-[5,5]undec-8-ene-8-carboxaldehyde (23). Tosylhydrazone **9a** (0.790 g; 2.0 mmol) was dissolved in THF (10 ml) under argon and the solution was cooled to −55°C. *n*-BuLi (4.4 mmol) was added dropwise in order to keep temperature stable and a dark red color was observed. The solution was stirred for 30 min at −50°C and CH_3I (0.250 ml; 4.0 mmol) was added dropwise giving light yellow color and small amount of white (LiI) precipitate. The solution was stirred for 30 min at −5 0°C followed with addition of *n*-BuLi (8.0 mmol) giving orange color. The solution was heated to +5°C, stirred for 5 min and heated to rt (+23°C). The solution was vigorously stirred for 25 min at rt and the decomposition of dianion to vinyl anion was observed as a gas formation. DMF (1.5 ml; 19 mmol) was added to give immediately a yellowish solution. After 30 min stirring the solvent was evaporated and the white solid residue was taken up in 15 ml of H_2O and 15 ml of hexane. The layers were separated and the water phase was washed with additional 15 ml of hexane. The combined hexane phases were dried over Na_2SO_4, with filtered and evaporated to give a yellowish oil. Column chromatography (MTBE/hexane,

40:60; 50 g of silica gel in column of 3 cm diameter) gave 0.310 g (61%) of oily **23** which slowly crystallized overnight. Mp 65–70.5°C. TLC (Hex/MTBE, 60:40) R_f=0.32. IR (KBr disk) 3401, 2959, 2868, 1670, 1613. ^{1}H NMR (400 MHz) δ 10.07 (s, 1H), 3.68 (d, 2H, ^2J=11.0 Hz), 3.38 (dd, 2H, ^2J=10.5 Hz, ^4J=1.4 Hz), 2.23 (t, 2H, ^3J=6.6 Hz), 2.10 (t, 2H, ^3J=6.6 Hz), 2.09 (s, 3H), 1.32 (s, 6H), 1.21 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (100 MHz) δ 192.3, 153.0, 139.1, 99.9, 70.3, 42.5, 32.7, 29.9, 23.2, 22.3, 21.7, 19.0, 17.8, 14.2. HRMS (EI) calcd for M+($C_{15}H_{24}O_3$): 252.1726, found 252.1733, Δ=2.8 ppm.

4.1.9. Reduction of aldehyde 23 to alcohol 10. Aldehyde **23** (0.72 g; 2.85 mmol) was dissolved in THF (10 ml) under argon. The solution was cooled to 0°C and $LiAlH_4$ (0.262 g; 6.9 mmol) was added in few portions. The reaction was stirred for 4 h at room temperature to reach the completion (monitored with TLC; Hex/EtOAc, 75:25) and was quenched at 0°C by addition of 0.7 ml (39 mmol) of H_2O at 0°C. The precipitate was filtered and washed with 5×10 ml of THF. The solvent was evaporated and the product was recrystallized from 4 ml of hexanes to give 0.530 g of white crystals.

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