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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-cyclohexanediol 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 cyclohexanones4 and ene-reaction5 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 and the C-ring precursor 4.6 Compound 5 has been utilized successfully as an A-ring precursor in the total synthesis of Taxol™ by Nicolaou et al.5

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.7 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.

Keywords: Shapiro reaction; Taxol; shortest synthetic pathway.
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.\footnote{10}

In this paper we report the shortest and simplest synthesis of a Taxol\textsuperscript{TM} 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\textsuperscript{TM} A-ring block.\footnote{11} 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-cyclohexanedicarboxylic acid 6 was carried out with K\textsubscript{2}CO\textsubscript{3}/MeI in acetone.\footnote{11} The product mixture contained 85% of the desired 7 and 15% of 3-methoxy-2-methyl-cyclohexene-2-carboxylic acid 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\textsubscript{2}Cl\textsubscript{2}. Diketone 7 was isolated in 99% purity when CH\textsubscript{2}Cl\textsubscript{2} was used as the solvent in the extraction. If toluene was used instead of CH\textsubscript{2}Cl\textsubscript{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-cyclohexanediol 7 was achieved by treatment with 2,2-dimethyl-1,3-propanediol and 1 mol% of p-TsOH in CH\textsubscript{2}Cl\textsubscript{2} with azeotropic removal of water.\footnote{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\textsubscript{3}I) 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](image)

**Scheme 2.** Synthesis of Taxol\textsuperscript{TM} A-ring block via tosylhydrazone 9a. *Reagents and conditions:* (a) K\textsubscript{2}CO\textsubscript{3}, CH\textsubscript{3}I, acetone, rfx, 8 h; (b) CH\textsubscript{2}Cl\textsubscript{2}, Me\textsubscript{2}N-C(\textsubscript{3}H\textsubscript{5}OH\textsubscript{2}), p-TsOH\textsubscript{H}2O, CH\textsubscript{2}Cl\textsubscript{2}, rfx, 7 h; (c) EtOH (THF in 9b), hydrazide, +4°C 16 min, then rt 6 h; (d) THF, −50°C, n-BuLi, 30 min, CH\textsubscript{3}I, 30 min, n-BuLi, from −50°C to rt, 25 min, paraformaldehyde, 30 min.

![Scheme 3](image)

**Scheme 3.** *Reagents and conditions:* (a) LDA, THF, −78°C, CH\textsubscript{3}I, 0°C then rt; (b) hydrazide, EtOH, (HCl).
dissolve in the solvent. 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. 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. Hydrazine 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 CH₃I 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 N₂ 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. 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 D₂O. 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 CH₃I 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. N₂ evolution was also observed already at −45°C which indicates the decomposition of the dianion to the vinyl anion.
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 D₂O. Both deuterated trislydrazine 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.

Mesityldrazine 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.

Tosylhydrazine 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 N₂) was complete in 25 min. A shorter reaction time or lower decomposition temperature gives a significant amount of hydrazine as a side product. Parafomaldehyde (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 solvent16 or due to the MeOH liberated during monomerization of para-aldehyde. 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 alkylthium 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 trislydrazones.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)
aldehyde 23 was obtained in 61% isolated yield. Aldehyde 23 was easily reduced to alcohol 10 with LiAlH₄ 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. 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 Et₂O were investigated. However, methylation (13a—14a) was incomplete in these experiments. Also, TMEDA/hexane was impracticable here because of strong salt formation between CH₃I and TMEDA.

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. Tolsylhydrazone 9a was found to be the best of the studied arylhydrazones in Shapiro reaction allowing the formation of stable diazoniums 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 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 CDCl₃ with TMS as internal reference. Gas chromatography was performed on Perkin–Elmer Model with OV-1701 column. Mass spectra were recorded on Kratos MS80 RF Autoconsoles. 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, K₂CO₃ (110.57 g; 800 mmol) and CH₃I (62.3 ml; 1000 mmol) were placed into the reaction vessel and refluxed for 8 h with vigorous stirring to avoid K₂CO₃ hardening on the walls. Acetone was evaporated, 200 ml of CH₃Cl₂ was added and evaporated to dryness to remove acetone traces. The product mixture was dissolved in CH₃Cl₂ (400 ml) and extracted with 600 ml of water. The water phase was washed with 100 ml of CH₂Cl₂. 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, CH₂Cl₂ 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 Na₂SO₄, 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) Rₑ=0.25. Mp 39–40°C. IR (in KBr): 2977, 2940, 2876, 1732, 1702. ¹H NMR (200 MHz) δ 2.70 (t, 4H, =J=6.8 Hz), 1.85–2.03 (m, 2H), 1.31 (s, 6H, 2xCH₃). ¹³C NMR (60 MHz) δ 210.4, 61.6, 37.3, 22.1, 17.9. Calcd for C₈H₁₂O₂: 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). 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 CH₂Cl₂ (220 ml) were placed into the reaction flask. This yellowish solution was refluxed for 7 h with azotropic water removal. CH₂Cl₂ 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 NaHCO₃ and then water (2×125 ml). The organic phase was dried over Na₂SO₄. 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) Rₑ=0.17. IR (KBr disk): 3385, 2983, 2959, 2872, 1708. ¹H NMR (400 MHz) δ 3.63 (d, 2H, J=10.5 Hz), 3.34 (dd, 2H, J=10.5 Hz, J=1.5 Hz), 2.42 (t, 2H, J=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). ¹³C 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) Rₑ=0.02. IR (KBr disk): 3205, 2990, 2975, 2947, 2921, 2866, 1630. ¹H NMR (400 MHz) δ 7.84 (d, 2H, J=8.8 Hz), 7.28 (d, 2H, J=8.8 Hz), 3.55 (d, 2H, J=10.5 Hz), 3.25 (dd, 2H, J=10.5 Hz, J=1.4 Hz), 2.42 (s, 3H), 2.26 (t, 2H, J=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). ¹³C 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 C₂₃H₂₆O₄N₃S: C 68.09; 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-trimethylbenzene-hydrazono)-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
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) Rf 0.25. IR (KBr disk): 3532, 2975, 2958, 2930, 2901, 2870, 2729, 2700, 1660. H NMR (400 MHz) δ 4.15 (d, 2H, J=4.1 Hz), 3.69 (d, 2H, J=11.1 Hz), 3.73 (dd, 2H, J=10.2 Hz, J=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). 13C NMR (100 MHz) δ 136.4, 131.7, 100.0, 70.3, 59.3, 43.7, 29.95, 28.87, 23.3, 22.5, 22.3, 19.2, 18.4. Calc for C15H32O3: C 70.83, H 10.30, Found C 70.72, H 10.68.

4.1.7. 3,3,7,7,9-Pentamethyl-1,5-dioxo[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-ButLi (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. CH3I (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 Na2SO4, filtered and evaporated. The white precipitate was purified by recrystallization (5 ml MeOH/0.9 ml H2O). The product was washed with 4 ml of cold MeOH/H2O (70:30). Yield 0.792 g (66%). Mp 79.5—81.5°C. TLC (Hex/MTBE, 80:20) Rf 0.36. IR (KBr disk): 3407, 2960, 2929, 2867, 2785, 1714. H NMR (400 MHz) δ 3.72 (d, 1H, J=11.3 Hz), 3.52 (d, 1H, J=11.3 Hz), 3.37 (dd, 1H, J=11.3 Hz, J=2.7 Hz), 3.28 (dd, 1H, J=11.3 Hz, J=2.7 Hz), 2.76—2.68 (m, 1H), 2.64 (dt, 1H, J=12.9 Hz, J=6.4 Hz), 1.89—1.73 (m, 2H), 1.78 (dd, 1H, J=14.3 Hz, J=4.3 Hz), 1.75 (dd, 1H, J=14.3 Hz, J=4.3 Hz), 1.21 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.02 (d, 3H, J=6.40 Hz), 0.72 (s, 3H). 13C 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-dioxo[5]undecan-8-one-8-carboxaldehyde (23). Tosylhydrazide 9a (0.790 g; 2.0 mmol) was dissolved in THF (10 ml) under argon and the solution was cooled to −55°C. n-ButLi (4.4 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 CH3I (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-ButLi (4.0 mmol) addition gave orange color. The solution was warmed up to room temperature and the diion 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 Na2SO4, filtered and evaporated. 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) Rf = 0.32. IR (KBr disk) 3401, 2959, 2868, 1670, 1613. 1H NMR (400 MHz) δ 10.07 (s, 1H), 3.68 (d, 2H, J = 11.0 Hz), 3.38 (dd, 2H, J₁ = 10.5 Hz, J₂ = 1.4 Hz), 2.23 (t, 2H, J = 6.6 Hz), 2.10 (t, 2H, J = 6.6 Hz), 2.09 (s, 3H), 1.32 (s, 6H), 1.21 (s, 3H), 0.74 (s, 3H). 13C 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) calcld for M+/(C₅H₅O₂): 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 LiAlH₄ (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 H₂O 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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