Organic Syntheses

Preparation of 1,5-Dioxaspiro[5.5]undecan-3-one

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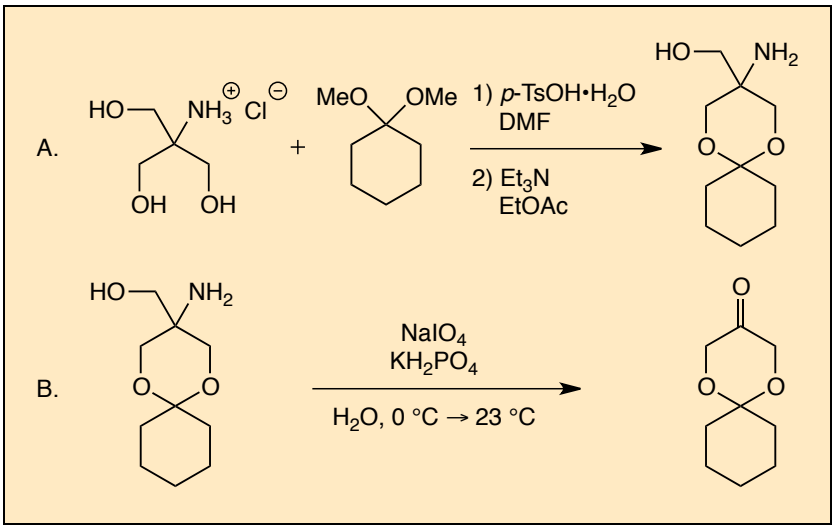

Procedure

A. *3-Amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane*. A 1-L single-necked, round-bottomed flask is equipped with an egg-shaped, Teflon®-coated magnetic stirring bar (3.5 cm x 1.5 cm), capped with a rubber septum, flame-dried under vacuum, and cooled under an argon atmosphere (Note 1). After cooling to ambient temperature (21–23 °C), to the flask is added anhydrous *N*,*N*-dimethylformamide (DMF, 365 mL, 0.78 M) via

cannula. Subsequently, tris(hydroxymethyl)aminomethane hydrochloride (45.0 g, 286 mmol, 1.00 equiv) (Note 2 and 3) is added in a single portion as white crystalline solid. The reaction vessel is immediately resealed with a rubber septum under inert atmosphere and stirring is commenced (Figure 1). To this white suspension is added 1,1-dimethoxycyclohexane (50.0 mL, 47.4 g, 329 mmol, 1.15 equiv) via syringe in one portion (Note 4). Lastly, to the off-white slurry is added *para*-toluenesulfonic acid monohydrate (*p*-TsOH•H_2O, 1.63 g, 8.57 mmol, 0.03 equiv) as a solid in one

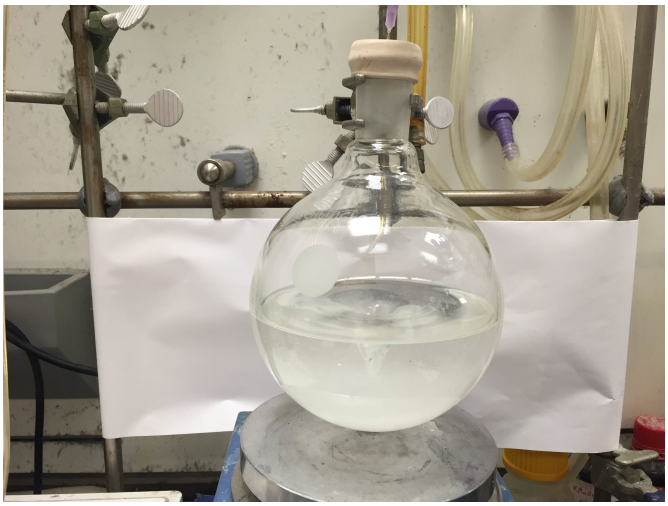

Figure 1. Heterogeneous Reaction Mixture at Initiation of Transketalization

portion quickly, immediately replacing the rubber septum to maintain an inert atmosphere. After stirring for 18 h at ambient temperature, the off-white heterogeneous reaction mixture becomes a completely homogenous, pale yellow solution (Figure 2, Note 5). The reaction flask is then placed in an oil bath and the rubber septum is replaced with a short path distillation head with a hollow water-jacketed column 6.0 cm in length, equipped with a thermometer and a 500-mL single-necked, round-bottomed receiving flask being cooled in an ice-water bath (Figure 3, Note 6). The volatiles are distilled off under high vacuum with heating (Note 7) and vigorous stirring (Note 8) to furnish an extremely viscous off-white semi-solid (Figure 4).

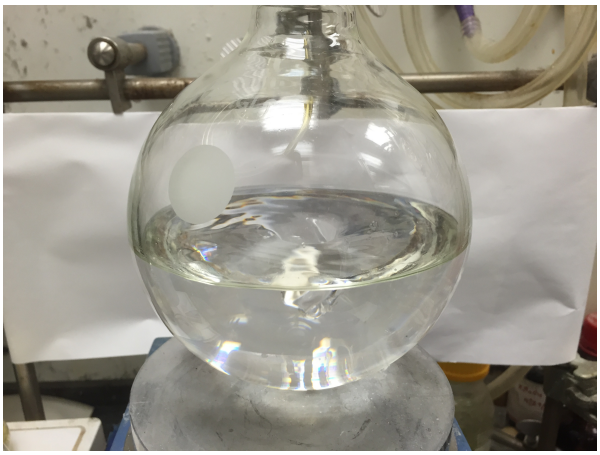

Figure 2. Homogeneous Reaction Mixture at Completion of Transketalization

Figure 3. Distillation Apparatus Before Introduction of Heating and Cooling Baths (Baths Omitted for Visual Clarity)

This residue is triturated with diethyl ether (700 mL), resulting in the precipitation of a white solid (Note 9). The heterogeneous suspension is

then filtered through a medium porosity sintered glass funnel (Note 10). The solid is then washed with a single 100 mL portion of ethyl acetate. The lumpy white solid is then briefly dried for 2–3 min by pulling air through the sintered glass funnel and then ground into a fine powder using a mortar and pestle (Note 11). Once thoroughly ground, the white solid is triturated with three 100 mL portions of ethyl acetate in a medium porosity sintered glass funnel (Note 10). The resultant white powder is dried under high vacuum (23 °C, 0.40 mmHg) for 12 h to afford an amorphous white solid (63 g).

Figure 4. Semi-Solid Product After Distillation

Following trituration, this white solid (63 g) is split into two equal portions and each portion is added to a separate 1-L single-necked, round-bottomed flask equipped with an egg-shaped, Teflon®-coated magnetic stirring bar (3.5 cm x 1.5 cm) (Note 12). To each of these round-bottomed flasks is added ethyl acetate (EtOAc, 400 mL) (Note 13) and stirring commenced. To each white, heterogeneous suspension is then added triethylamine (Et_3N, 23.7 mL, 179 mmol) (Note 14) dropwise over 6 min. After 12 h, each white, heterogeneous reaction mixture is filtered through a medium porosity sintered glass funnel (Note 10), collecting the filtrate in a

1-L round-bottomed flask. For each portion, the filter cake ("Solid A") is subsequently washed with ethyl acetate (4 x 50 mL). The washes are combined with the filtrate, concentrated by rotary evaporation (23 °C, 13 mmHg), and dried under high vacuum (23 °C, 0.40 mmHg) for 12 h to afford a fluffy white solid (the free-base amino alcohol, "Solid B"). The two filter cakes (Solid A) are then combined in a 1-L single-necked, round-bottomed flask equipped with an egg-shaped, Teflon®-coated magnetic stirring bar (3.5 cm x 1.5 cm) and suspended in ethyl acetate (250 mL) with stirring. Triethylamine (18.0 mL, 129 mmol) (Note 15) is subsequently added dropwise over 3 min. The pure white suspension is stirred vigorously for 24 h and then filtered through a medium porosity sintered glass funnel (Note 10). The filter cake is then washed with ethyl acetate (4 x 75 mL). The filtrate and washes are added to the flask containing Solid B and then concentrated by rotary evaporation (23 °C, 13 mmHg) to furnish 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane (42.6 g, 74% combined yield over the two iterations, melting point: 91–92 °C) as an amorphous white solid (Notes 16 and 17).

B. *1,5-Dioxaspiro[5.5]undecan-3-one*. 3-Amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane (31.4 g, 156 mmol, 1.00 equiv) (Note 18) is added to a 2-L three-necked, round-bottomed flask equipped with an egg-shaped, Teflon®-coated magnetic stirring bar (3.5 cm x 1.5 cm) and suspended in water (520 mL). The flask is fitted with a pressure-equalizing 250-mL addition funnel capped with a rubber septum in the middle neck, a rubber septum equipped with a thermometer in one of the side necks, and capped with a rubber septum in the third neck (Figure 5). Subsequently, potassium dihydrogen phosphate (KH_2PO_4, 25.5 g, 187 mmol, 1.20 equiv) is added. Stirring is commenced and the heterogeneous white suspension is cooled in an ice-water bath (Note 19). To the resultant stirred heterogeneous reaction mixture is added a solution of sodium (meta)periodate ($NaIO_4$, 33.4 g, 156 mmol, 1.00 equiv) as a pale yellow solution in water (520 mL, 0.30 M) dropwise over 3 h through the addition funnel (Note 20). The reaction is then allowed to stir for 1.0 h before removing the ice-water bath (Note 21) and allowing the homogenous, pale yellow reaction mixture to warm slowly. The starting material is completely consumed 3.0 h after removing the cooling bath as determined by TLC (Note 22, Figure 6). Anhydrous sodium thiosulfate (24.7 g, 156 mmol, 1.00 equiv) (Note 23) is then immediately added in one portion (Note 24). The solution is allowed to stir for 20 min at which time the pale yellow homogenous reaction mixture is transferred to a 2-L separatory funnel. The aqueous reaction mixture is

extracted with dichloromethane (12 x 150 mL) (Note 25). The organic layers are combined in a 2-L Erlenmeyer flask equipped with a cylindrical, Teflon®-coated magnetic stirring bar (7.4 cm x 1.2 cm) and dried over 400 g of anhydrous sodium sulfate for 20 min with stirring. The organic solution is subsequently filtered through grade 4 filter paper and concentrated in vacuo (23 °C, 50 mmHg) and under high vacuum (23 °C, 0.4 mmHg, 20 min) to afford 1,5-dioxaspiro[5.5]undecan-3-one (25.5 g, 96% yield, boiling point: 82–88 °C, 0.60 mmHg) as a pale yellow oil (Notes 26, 27, 28, 29, and 30).

Figure 5. Oxidative Cleavage Reaction Set-up Before Cooling

Figure 6. Oxidative Cleavage After Completion Before Quenching

Notes

1. The reaction may alternatively be run under a nitrogen atmosphere with no deleterious effects.
2. Tris(hydroxymethyl)aminomethane hydrochloride (Trizma® hydrochloride, ≥99%, crystalline, Sigma-Aldrich), 1,1-dimethoxycyclohexane (99%, Sigma-Aldrich), *para*-toluenesulfonic acid monohydrate (≥98.5%, ACS reagent grade, Sigma-Aldrich), potassium dihydrogen phosphate (anhydrous, 99.8%, ACS reagent grade, Mallinckrodt), sodium (meta)periodate (≥99%, Sigma-Aldrich), anhydrous sodium thiosulfate (99%, Sigma-Aldrich), and anhydrous sodium sulfate (≥99%, granular (10-60 mesh), Macron; Submitters: ≥99%, powder, Fisher Scientific) are purchased and used as received. *N*,*N*-Dimethylformamide (DMF, ≥99.9%, HPLC grade, Sigma-Aldrich;

Submitters: ≥99.8%, ACS reagent grade, Mallinckrodt) is degassed with argon and purified by passage through two columns of molecular sieves (9 cm x 60 cm) under argon. Triethylamine (≥99.5%, EMD; Submitters: ≥99%, Sigma-Aldrich) is degassed with argon and purified by passage through two columns of molecular sieves (9 cm x 60 cm) under argon (Submitters: triethylamine distilled from calcium hydride prior to use). Water is distilled and purified with a Barnstead NANOpure Infinity UV/UF system and had a pH of ca. 7 (Submitters: water pH between 5 and 6). Diethyl ether (≥99%, anhydrous, ACS reagent grade, Fisher Scientific; Submitters: ≥99%, ACS reagent grade, EMD), ethyl acetate (≥99.5%, ACS reagent grade, Sigma-Aldrich; Submitters: ≥99.5%, ACS reagent grade, EMD), and dichloromethane (≥99.5%, ACS reagent grade, Sigma-Aldrich; Submitters: ≥99.5%, ACS reagent grade, EMD) are purchased and used as received without needing to remove dissolved gasses or water from the solvent. For the purpose of purity analysis, dimethyl fumarate (TraceCERT® certified reference material, Sigma-Aldrich) is used as an internal standard.

3. Crystalline tris(hydroxymethyl)aminomethane hydrochloride used for this procedure from Sigma-Aldrich arrived with some large chunks of material mixed in with fine white crystals. These large chunks are broken up prior to use, using a mortar and pestle if necessary, to ensure efficient transketalization since the material is not fully soluble in the *N*,*N*-dimethylformamide reaction solvent.
4. Varying the rate of addition of 1,1-dimethoxycyclohexane to the reaction flask has provided no noticeable effect on the yield of the reaction or the purity of the 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane.
5. Extended reaction times up to 30 h have shown no deleterious effects on the overall yield or purity of 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane.
6. The internal temperature of the receiving flask is not monitored, however, the temperature of the surrounding ice-water bath is between 3 °C and 5 °C.
7. Reaction flask is initially placed under vacuum CAREFULLY since at ambient temperature (21–23 °C) under reduced pressure (>1 mmHg), the methanol byproduct from the transketalization will boil vigorously. Only after all of the methanol has been distilled off is the reaction flask heated to facilitate the distillation of the *N*,*N*-dimethylformamide. Typically, the oil bath is heated to between 50 °C to 65 °C depending on

the high vacuum manifold pressure, resulting in the distillation of the *N*,*N*-dimethylformamide at an indicated temperature range from 35 °C to 39 °C in the distillation head.

8. Vigorous stirring is necessary to ensure full removal of the volatiles by distillation. Without vigorous stirring, the pale yellow semi-solid resulting from the distillation process will trap *N*,*N*-dimethylformamide which can lead to the contamination of the aminoalcohol product.
9. This step is *critical* to achieving optimal yield. The trituration process will take some time as the semi-solid pale yellow gel that results from the distillation process hardens when cooled to ambient temperature. The semi-solid should be manually ground and triturated until no pale yellow semi-solid remains either on the walls of the flask or suspended in solution.
10. A medium porosity sintered glass funnel refers to a sintered glass funnel with 10–15 μm sintered glass mesh.
11. In order to ensure complete removal of *N*,*N*-dimethylformamide and *para*-toluenesulfonic acid, the white solid must be ground as finely as possible. If these impurities remain, however, they will not affect the subsequent reactions and can be separated from 1,5-dioxaspiro[5.5]undecan-3-one by filtration through silica gel (see Note 30).
12. No precautions are taken to exclude either water or air from the reaction flask. The flask is neither dried prior to use nor placed under an inert atmosphere. The product has been split into two portions to allow for more vigorous and efficient stirring of the heterogeneous reaction mixture.
13. Assuming quantitative yield after the first step of the crude amorphous white solid intermediate, this volume of ethyl acetate corresponds to a concentration of 0.36 M. As a reminder, the ethyl acetate used as the solvent for this step is purchased and used as received without the need to remove dissolved gasses or water from the solvent.
14. Assuming quantitative yield after the first step of the crude amorphous white solid intermediate, 1.25 equivalents of triethylamine are added.
15. Since the majority of the 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane is isolated after the first free base procedure and filtration, a large excess of triethylamine is added here to help drive any remaining hydrochloride salt of 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane to the desired product. Smaller amounts of triethylamine may be used here, however, this will result in a slightly

reduced isolated yield of 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane.

16. *3-Amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane*: R_f = 0.17 (1:4 methanol:dichloromethane eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36–1.45 (*m*, 2H), 1.45–1.60 (*m*, 4H), 1.68–1.81 (*m*, 4H), 2.01 (*bs*, 2H), 2.04 (*bs*, 1H), 3.48 (*s*, 2H), 3.52 (*d*, J = 11.9 Hz, 2H), 3.79 (*d*, J = 11.9 Hz, 2H), ^{13}C NMR (101 MHz, $CDCl_3$) δ: 22.6, 25.7, 31.1, 33.8, 50.5, 64.7, 66.4, 98.6. IR (film): 3350, 3294, 2938, 2860, 1619, 1449, 1331, 1285, 1255, 1160, 1110, 1087, 918 cm^{-1}. HRMS (MM: ESI-APCI) *m*/*z* calcd for $C_{10}H_{20}NO_3$ $[M+H]^+$: 202.1438, found 202.1431; Elemental anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96; O, 23.85, found: C, 59.67; H, 9.62; N, 6.86; O, 23.85. The product is indefinitely stable at ambient temperature stored under an inert atmosphere (argon or nitrogen).
17. A second run on half-scale provided 21.2 g (74%) of the product.
18. Only a portion of the 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane from Step A is advanced for ease in using glassware no larger than 2-L in volume.
19. The internal temperature of the reaction mixture is measured between 2 °C and 3 °C after cooling.
20. The internal temperature of the reaction mixture during addition ranges between 1 °C and 3 °C.
21. The internal temperature of the reaction mixture is between 0 °C and 1 °C.
22. Progress of the reaction can be monitored by TLC analysis on silica gel using 20% methanol in dichloromethane eluent with visualization by potassium permanganate. The aminoalcohol starting material has an R_f = 0.17 and the ketone product has an R_f = 0.90. At the time of the reaction quench, 3.0 h after removing the reaction vessel from the cooling bath, the internal temperature is between 16 °C and 17 °C.
23. The internal temperature of the reaction warms to between 18 °C and 19 °C after the addition of anhydrous sodium thiosulfate. Alternatively, sodium thiosulfate pentahydrate may also be used without any deleterious effects on the overall efficacy of the described transformation.
24. This portion of the procedure is mildly *time sensitive*. Stirring overnight should be avoided, as prolonged exposure of 1,5-dioxaspiro[5.5]undecan-3-one to the reaction conditions will result in decomposition by ketal cleavage, as evidenced by the presence of

cyclohexanone, which can be observed in the ^{1}H NMR spectrum of the product.

25. Washes of the aqueous layer with dichloromethane should be followed by TLC analysis on silica gel (20% diethyl ether in hexanes eluent, *p*-anisaldehyde stain, R_f = 0.38) to ensure the product has been completely extracted. The product is persistent in the aqueous layer, and remains visible by TLC until the twelfth extraction.
26. *1,5-Dioxaspiro[5.5]undecan-3-one*: R_f = 0.90 (1:4 methanol: dichloromethane eluent) and 0.38 (1:4 diethyl ether:hexanes eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.49 (*m*, 2H), 1.55–1.64 (*m*, 4H), 1.70–1.77 (*m*, 4H), 4.18 (*s*, 4H), ^{13}C NMR (101 MHz, $CDCl_3$) δ: 22.8, 25.2, 32.5, 66.5, 99.8, 208.0; IR (film): 2938, 2863, 1751, 1448, 1435, 1425, 1369, 1338, 1281, 1264, 1239, 1201, 1162, 1146, 1118, 1079, 1058, 1028, 922, 847, 825 cm^{-1}; HRMS calcd for $C_9H_{15}O_3$ $[M+H]^+$: 171.1016, found 171.1008; Elemental anal. calcd for $C_9H_{14}O_3$: C 63.51, H 8.29, O 28.20, found C 63.53, H 8.49, O 27.98; Quantitative NMR Analysis: title compound (20.4 mg) with dimethylfumarate standard (19.7 mg) in $CDCl_3$, 100.0% pure (see ^{1}H NMR spectrum below). The product may be stored at –20 °C under an inert atmosphere (argon or nitrogen) for >3 months, however, prolonged storage or storage at higher temperature will result in slow decomposition by ketal cleavage.
27. A second run on half-scale provided 12.7 (96%) of the product.
28. After storage overnight in a freezer at –20 °C as a neat oil, 1,5-dioxaspiro[5.5]undecan-3-one solidifies to become a tan solid that does not melt upon warming back to ambient temperature (ca. 23 °C). Melting point of this tan solid: 28–30 °C.
29. Residual dichloromethane can be challenging to remove from the title compound. To aid in the removal of this impurity, the dioxanone product can be diluted with pentane (ca. 1.5 mL pentane/g of dioxanone) and then concentrated in vacuo (23 °C, 13 mmHg) and under high vacuum (23 °C, 0.40 mmHg, 5 min). After repeating this procedure two additional times, the removal of residual dichloromethane will be complete.
30. The procedure, as written, will afford the title compound in analytically pure form. Neither column chromatography nor distillation are necessary. However, if traces of *N*,*N*-dimethylformamide or *para*-toluenesulfonic acid from Step A remain with 1,5-dioxaspiro[5.5]undecan-3-one after aqueous work-up, the impure product may be filtered through a pad of silica gel (5 cm diameter, 3 cm

depth) in a medium porosity sintered glass funnel (see Note 10) as a solution in dichloromethane (200 mL), rinsing the silica gel with dichloromethane (100 mL) after filtration. This procedure typically provides 1,5-dioxaspiro[5.5]undecan-3-one in a slightly reduced isolated yield from 3-amino-3-(hydroxymethyl)-1,5-dioxaspiro-[5.5]undecane. Attempts to purify 1,5-dioxaspiro[5.5]undecan-3-one by either short-path distillation or bulb-to-bulb distillation (82–88 °C, 0.60–0.70 mmHg) result in partial decomposition of the dioxanone product by ketal cleavage and contamination of the distilled product with cyclohexanone.

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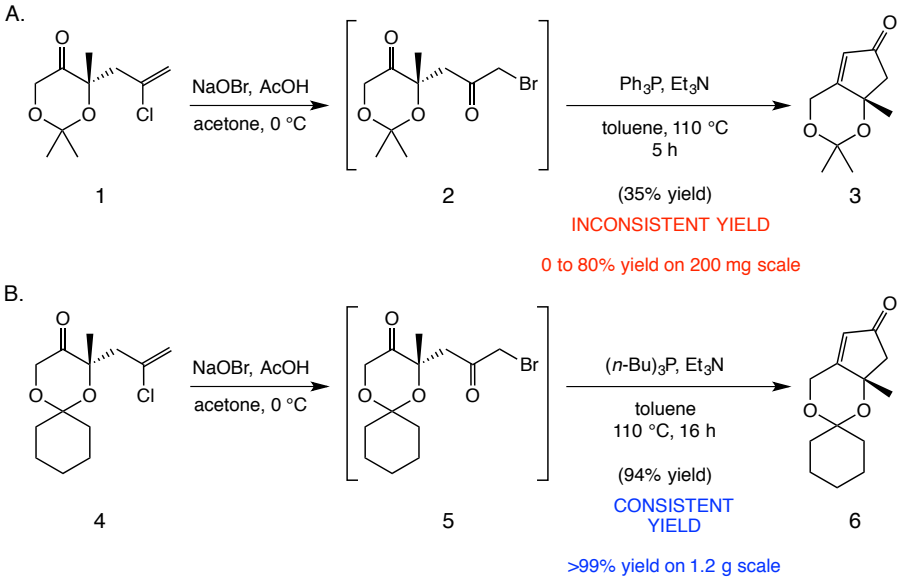
Discussion

The procedure for the synthesis of 1,5-dioxaspiro[5.5]undecan-3-one is based on our previous report[2] and was originally adapted from the work of Forbes[3] and inspired by the work of Majewski,[4] Hoppe,[5] and Enders[6] on the synthesis of related ketodioxanone scaffolds. Using the procedure described herein, the synthesis of the analogous diethyl ketal product has been accomplished using 3,3-dimethoxypentane in place of 1,1-dimethoxycyclohexane.[7] This modification provided the corresponding ketodioxanone in a comparable yield to 1,5-dioxaspiro[5.5]undecan-3-one.

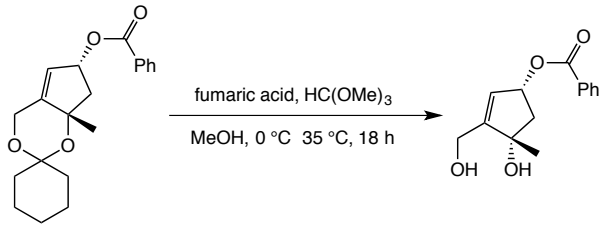


Scheme 1. Effect of Ketal Identity on Oxidative α-Bromination

The title compound has been previously synthesized by another method.[8] It has been employed successfully as a nucleophile in palladium-catalyzed enantioselective allylic alkylation[2] as well as stereoselective aldol condensation.[9] As a synthetic building block, 1,5-dioxaspiro[5.5]undecan-3-one offers the advantage of a ketal that is significantly more stable to acidic

reaction conditions in comparison to the acetonide and diethylketal orthologues. For example, exposure of acetonide **1** to acidic oxidative α-bromination conditions furnished α-bromoketone **2** in widely variable yields, most typically between 0% and 20% (Scheme 1.A).[2] Although the conversion of α-bromoketone **2** to cyclopentenone **3** was accomplished, the labile nature of the acetonide contributed to the diminished yield.

Alternatively, employment of cyclohexyl ketal analog **4** enabled consistent quantitative conversion to α-bromoketone **5** on gram scale (Scheme 1.B).[2] Under optimized reaction conditions, α-bromoketone **5** was converted to cyclopentenone **6** in excellent yield. Although the comparatively robust cyclohexyl ketal had enabled the efficient formation of the cyclopentenone scaffold (e.g. **6**), the protecting group was easily removed from benzoyl ester **7** under relatively mild acidic transketalization conditions to provide diol **8** in 97% yield (Scheme 2).



7 (97% yield) **8**

Scheme 2. Removal of Cyclohexyl Ketal Under Mild Acidic Conditions

Ketal orthologues of the title compound have been studied more extensively than the title compound itself, showing the utility of ketodioxanones as nucleophiles in enantioselective palladium-catalyzed allylic alkylations,[2,10] diastereoselective alkylations,[6,11] α,α′-annulations,[12] and organocatalyic stereoselective aldol condensations.[13] The products of these transformations have been successfully applied to the synthesis of a variety of simple and complex carbohydrates[13b,f,g,k] and biologically active natural products.[10a,c,11 a–b,12a,13a,c–d,h,14]

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Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States. stoltz@caltech.edu; Ph. (626) 395-6064; Fax (626) 395-8436. The authors wish to thank the NIH NIH-NIGMS (R01M080269—01), Amgen, and Caltech for financial support. R.A.C. gratefully acknowledges the support of this work provided by a fellowship from the National Cancer Institute of the National Institutes of Health under Award Number F31A17435. B.P.P. thanks the NSF for a predoctoral fellowship. B.I.E. thanks the Caltech Summer Undergraduate Research Fellowship (SURF) office for funding.

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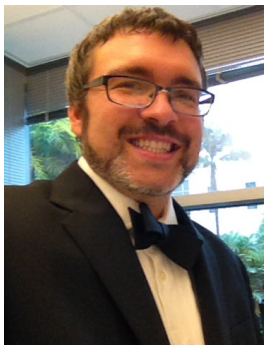
Appendix
Chemical Abstracts Nomenclature (Registry Number)

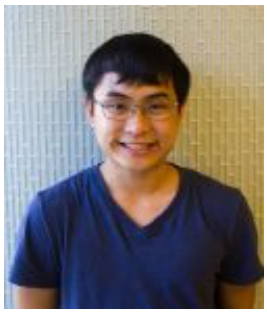
Tris(hydroxymethyl)aminomethane hydrochloride: 1,3-Propanediol, 2-amino-2-(hydroxymethyl)-, hydrochloride (1:1); (1185-53-1)
1,1-Dimethoxycyclohexane: Cyclohexane, 1,1-dimethoxy-; (933-40-4)
para-Toluenesulfonic acid monohydrate: Benzenesulfonic acid, 4-methyl-, hydrate (1:1); (6192-52-5)
Triethylamine: Ethanamine, *N*,*N*-diethyl-; (121-44-8)
3-Amino-3-hydroxymethyl-1,5-dioxaspiro[5.5]undecane: 1,5-dioxaspiro[5.5]undecane-3-methanol, 3-amino-; (5452-79-9)
Dihydrogen potassium phosphate: Phosphoric acid, potassium salt (1:1); (7778-77-0)
Sodium (meta)periodate: Periodic acid (HIO_4), sodium salt (1:1); (7790-28-5)
1,5-Dioxaspiro[5.5]undecan-3-one; (158632-48-5)

Robert A. Craig II was born in Philadelphia, PA and received his B.S. degree from Davidson College in 2010. He earned his Ph.D. in 2015 from the laboratories of Professor Brian M. Stoltz, at the California Institute of Technology as an NIH predoctoral fellow, focusing on total synthetic efforts toward the polycyclic norcembranoid natural products. In the fall of 2015, he joined the laboratories of Professor Justin Du Bois at Stanford University where he is currently an NIH postdoctoral fellow. His research interests focus on the synthesis and utility of bioactive small molecules to address pertinent biological questions.



Russell C. Smith hails from central IL where he received his B.S. degree in chemistry from Illinois Wesleyan University in 2004 under the guidance of Professor Ram Mohan. His Ph.D. was earned from the University of Illinois Urbana-Champaign in 2010 under the supervision of Professor Scott E. Denmark, investigating the transmetalation step of arylsilanolate cross-coupling reactions. Post-doctoral studies were conducted at the California Institute of Technology with Professor Brian Stoltz on the total synthesis of ineleganolide. Following his educational studies, he joined the staff at Janssen Research and Development working as a medicinal chemist in Immunology.

Beau P. Pritchett received his B.S. degree in Chemistry and B.S.E. degree in Chemical Engineering from Tulane University in 2012. In the fall of 2012, he joined the laboratories of Professor Brian M. Stoltz at Caltech where he has pursued his Ph.D. as an NSF predoctoral fellow. His research interests include chemical synthesis, reaction design, and their applications in natural product synthesis and human medicine.



Benzi I. Estipona moved from Marion, Iowa to join the Class of 2017 at Caltech. He is currently a sophomore majoring in chemistry, and hopes to pursue a career in organometallic chemistry. He currently works as an undergraduate researcher during the summer and academic school year under the mentorship of Professor Brian M. Stoltz. His research is currently focused on the enantioselective total synthesis of the natural product eucomic acid and its glycosylated derivatives.

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the labs of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey labs he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is a Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

Marcel Weiss was born in Stuttgart, Germany in 1985. He received his Diploma (2010) and his Ph.D. (2015) in Chemistry from the University of Stuttgart where he worked in the group of Professor René Peters on the cooperation of carbophilic Lewis acids in bimetallic catalysts. He then joined the group of Professor Mohammad Movassaghi at the Massachusetts Institute of Technology where his research is currently focused on the total synthesis of complex natural products.
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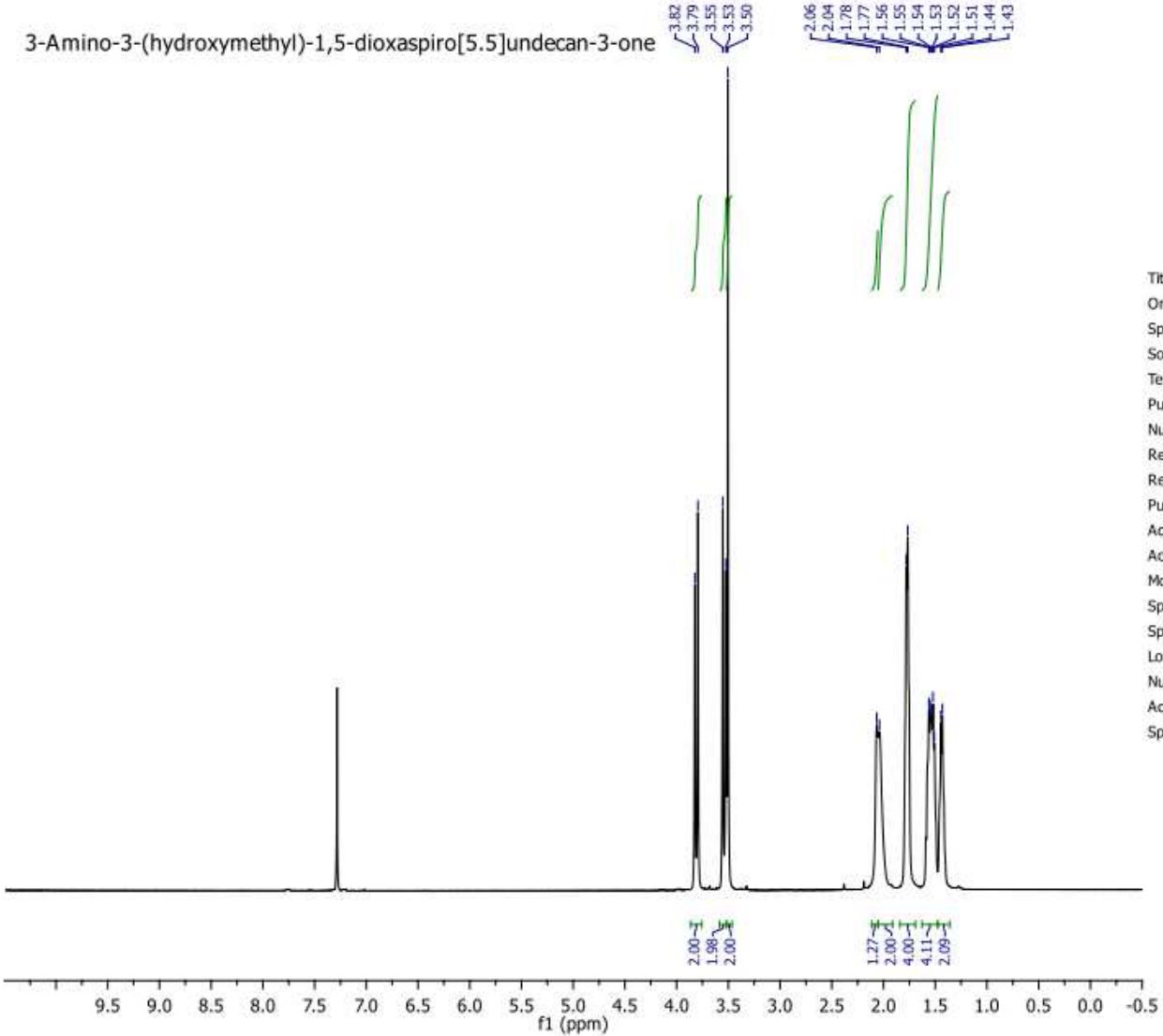
3-Amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecan-3-one



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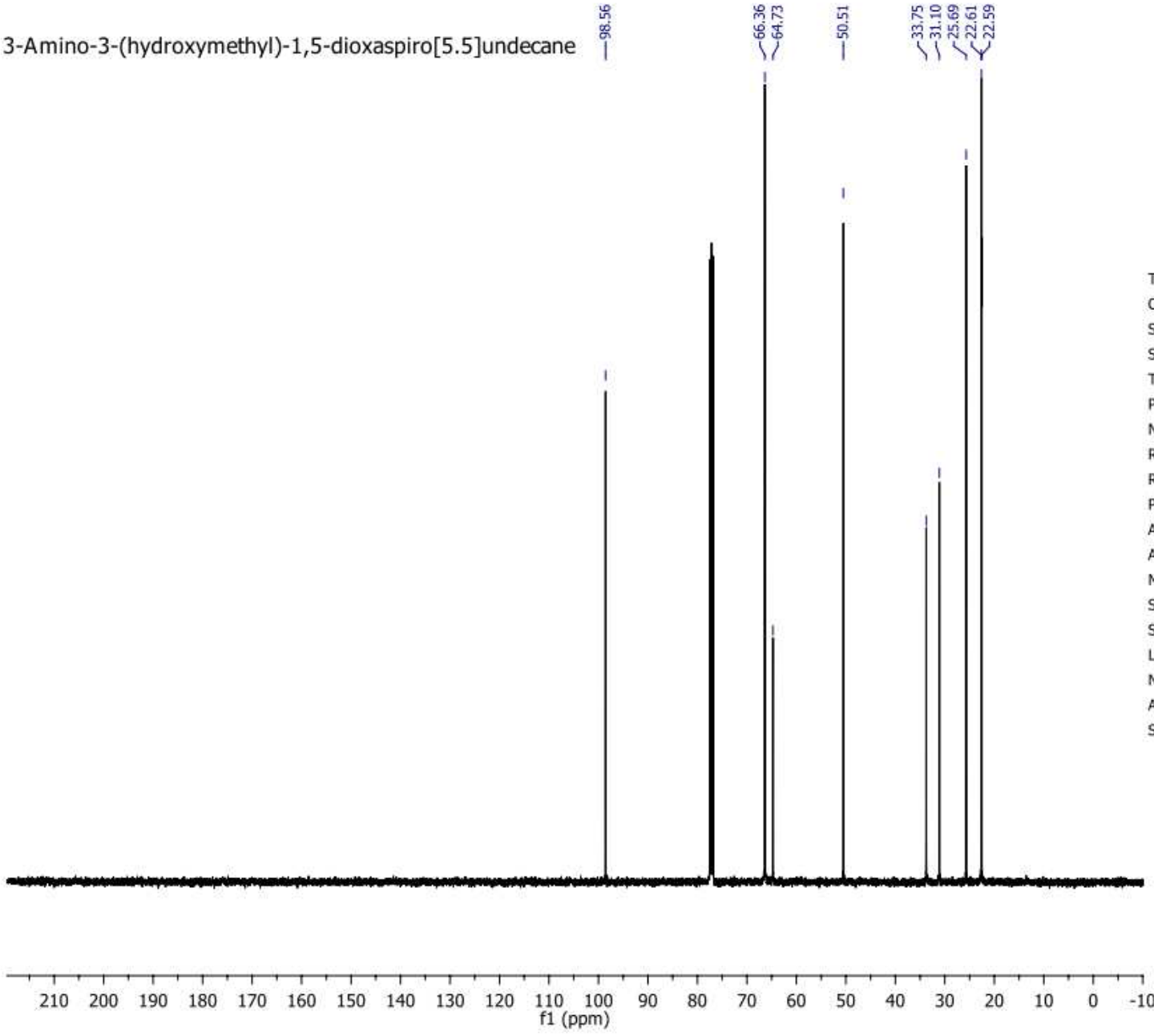
Lowest Frequency	-1535.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

3-Amino-3-(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane



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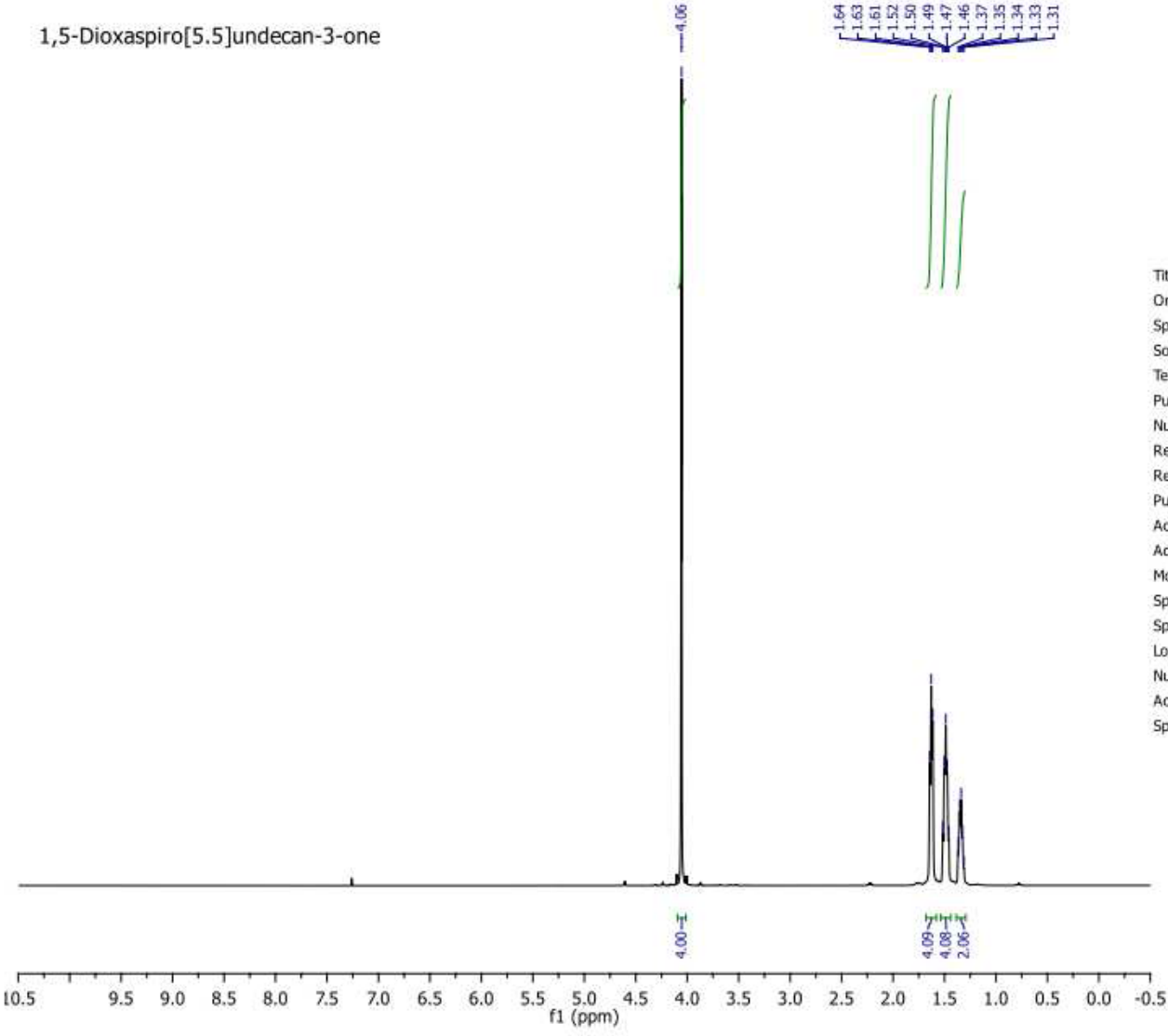
1,5-Dioxaspiro[5.5]undecan-3-one



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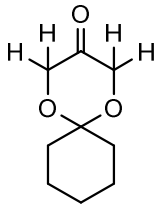
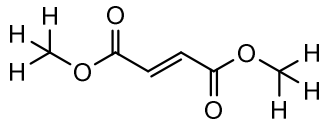
Quantitative NMR Assay



4H



6H

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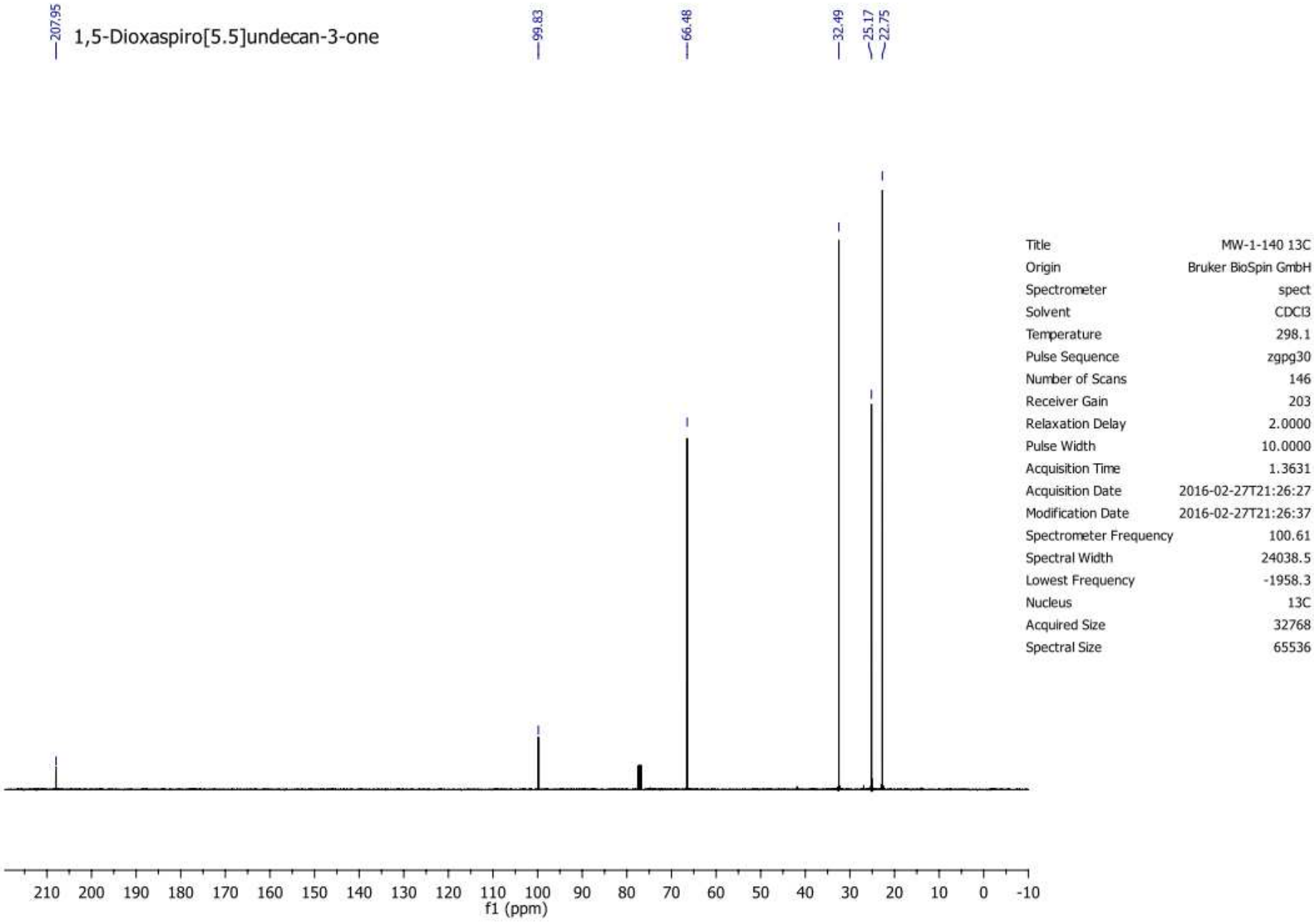
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1,5-Dioxaspiro[5.5]undecan-3-one
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Spectral Width 24038.5
Lowest Frequency -1958.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)