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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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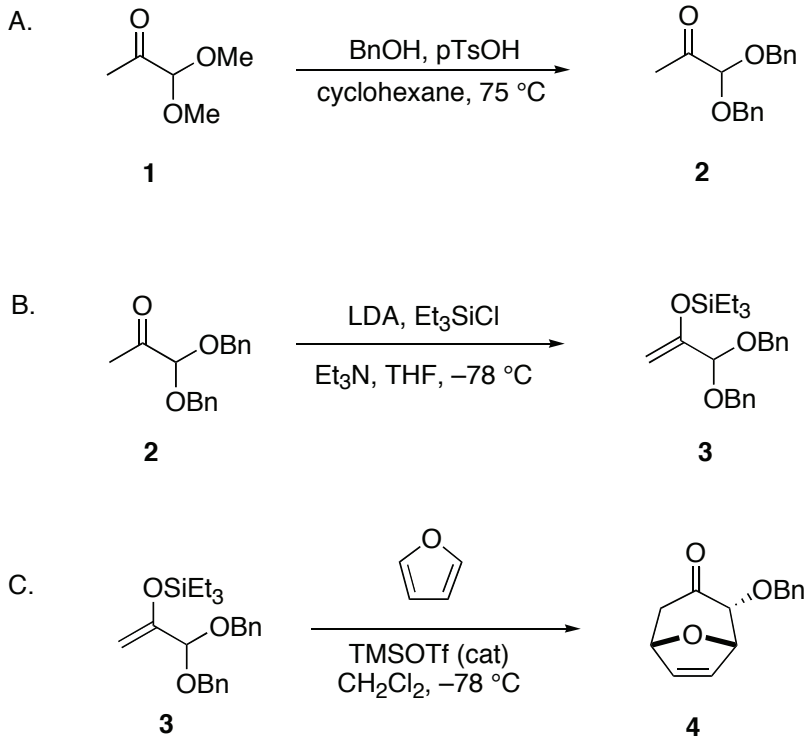
SYNTHESIS OF 2α-BENZYLOXY-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE BY [4+3] CYCLOADDITION



Submitted by María Vidal-Pascual, Carolina Martínez-Lamenca and H. M. R. Hoffmann.[1]
Checked by Timothy E. Long and Marvin J. Miller.

1. Procedure

A. 1,1-Bis(benzyloxy)propan-2-one (**2**). A one-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with pyruvic aldehyde dimethyl acetal (12.1 mL, 100 mmol) in cyclohexane (50 mL), benzyl alcohol (22.8 mL, 220 mmol) and *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol) (Note 1). The resulting mixture is heated at reflux for 2 h using a Dean–Stark separator for the removal of methanol. When the reaction is complete (approximately 2 h), approximately 8.1 mL (200 mmol) of MeOH is obtained. The reaction mixture is cooled to room temperature and washed with saturated potassium carbonate solution (25 mL) and water (20 mL). The aqueous layer is extracted twice with

cyclohexane (2 x 50 mL). The combined organic phase is dried (Na_2SO_4), filtered, evaporated and the crude black oil is purified by column chromatography using a 10-cm diameter column packed with 900 g silica gel (Note 2) and eluting with 2.1 L of MTBE/cyclohexane (1:20) to afford keto acetal **2** as a yellowish oil (22.3 g, 83%) (Note 3).

B. [1,1-(Bis-benzyloxymethyl)vinyloxy]triethylsilane (**3**) (Note 4). An LDA solution is prepared in a 250-mL, two-necked, round-bottomed flask equipped with a nitrogen inlet and nitrogen balloon, magnetic stirring bar and rubber septum by adding BuLi (1.6 M solution in hexane, 22.5 mL, 36 mmol) (Note 5) into a solution containing diisopropylamine (5.1 mL, 36 mmol) (Note 6) in THF (36 mL) (Note 7) at −78 °C (Note 8). The resulting mixture is stirred for an additional 15 min at room temperature. A separate two-necked, 250-mL round-bottomed flask is equipped with two septa and a nitrogen balloon. Dibenzyl acetal **2** (8.1 g, 30 mmol) and chloro-triethylsilane (7.5 mL, 45 mmol) (Note 9) are dissolved in THF (30 mL) under a nitrogen atmosphere. This mixture is cooled to −78 °C and the LDA solution is added by cannula over the course of 10 min. Triethylamine (18.8 mL, 135 mmol) (Note 10) was immediately added by syringe over the course of 10 min. The resulting reaction mixture is stirred for 16 h at −78 °C. Water (25 mL) is added, the cooling bath is removed, and the mixture is stirred until it reaches room temperature. The aqueous phase is extracted twice with cyclohexane. After being dried over sodium sulfate (Na_2SO_4) the organic solution is concentrated under vacuum and purified by column chromatography (6-cm diameter column, 360 g silica gel, MTBE/cyclohexane (1:100, 9 L) with 0.1% Et_3N) (Note 11) to give **3** as a yellow oil (8.9 g, 77%) (Notes 12, 13).

C. 2α-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**4**). A 250-mL, one-necked, round-bottomed flask capped with a rubber septum and equipped with a nitrogen balloon and magnetic stirring bar is charged under nitrogen atmosphere with silyl enol ether **3** (9.2 g, 24 mmol) (Note 14) and dichloromethane (25 mL) (Note 15). The mixture is cooled to −78 °C, and furan (1.8 mL, 24 mmol) (Note 16) is added by syringe. After 15 min at −78 °C, TMSOTf (0.46 mL, 2.4 mmol) is added by syringe (Note 17). The mixture is stirred for 30 min at −78 °C and then a saturated solution of sodium bicarbonate (25 mL) is added. The cooling bath is removed and the flask is shaken thoroughly until the mixture reaches room temperature. The

aqueous layer is extracted with dichloromethane (3 × 25 mL) and the combined organic phase is dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product is purified by column chromatography (5-cm diameter column, 250 g silica gel, MTBE/cyclohexane (1:3)) giving cycloadduct **4** as a colorless oil (3.72 g, 70%) (Note 18). On storage in the freezer at –25 °C, the product crystallizes from *tert*-butyl methyl ether to give a white solid (2.87 g, 54%) mp 64−65 °C (Notes 19-20).

2. Notes

1. Pyruvic aldehyde dimethyl acetal was purchased from Acros Organics. Benzyl alcohol was purchased from Lancaster. *p*-Toluenesulfonic acid was purchased from Aldrich.

2. Silica gel (230-400 mesh) was obtained from Macherey Nagel.

3. Spectral data for 1,1-bis(benzyloxy)propan-2-one **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3 H), 4.68 (d, J = 12 Hz, 2 H), 4.78 (d, J = 12 Hz, 2 H), 4.84 (s, 1 H), 7.41–7.45 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0, 69.2, 101.0, 127.4, 128.0, 128.5, 137.0, 203.7. EI-MS (*m/z*): 271 (5), 259 (15), 228 (10), 182 (18), 181 (100), 165 (14); HRMS (FAB) (*m/z*): calcd for $C_{17}H_{19}O_2$ (M^++1) 271.1334, observed 271.1308.

4. The preparation of [(1,1-bis(benzyloxy)methyl)vinyloxy]-triethylsilane (**3**) is appropriate for scales of 30 mmol of dibenzyl acetal or less. See Note 20 for information regarding larger scale reactions.

5. A commercial solution of 1.6 M butyllithium in hexane from Acros Organics was used.

6. Diisopropylamine was purchased from Acros and was distilled from KOH pellets and stored over solid KOH, purchased from Fisher Scientific.

7. Tetrahydrofuran supplied by Mallinckrodt is dried by distillation from sodium and benzophenone under an argon atmosphere.

8. The reaction mixture is cooled to –78 °C using dry ice-acetone bath or a cryostat.

9. Chlorotriethylsilane from both Acros Organics and Gelest, Inc. was used.

10. Triethylamine was dried and distilled from and stored over KOH pellets purchased from Fisher Scientific.

11. The checkers found that addition of triethylamine to the eluent is required to prevent decomposition of the silyl enol ether during chromatography.

12. Spectral data for [(1,1-bis(benzyloxy)methyl)-vinyloxy] triethylsilane **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.69 (q, *J* = 7.8 Hz, 6 H), 0.95 (t, *J* = 8.1 Hz, 9 H), 4.37 (d, *J* = 1.2 Hz, 1 H), 4.57 (d, *J* = 12 Hz, 2 H); 4.63 (d, *J* = 11.7 Hz, 2 H), 4.70 (s, 1 H), 4.89 (s, 1 H), 7.31–7.26 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.9, 6.7, 67.6, 92.3, 99.2, 127.5, 127.8, 128.4, 138.2, 153.8. EI-MS (*m/z*): no M^+, 279 (9), 249 (4), 248 (3), 193 (4), 187 (6), 181 (7), 159 (14), 157 (13), 115 (17), 91 (100).

13. The submitters report that this procedure can also be used for the preparation of 3,3-bis-benzyloxy-2-trimethylsilyloxypropene by using chlorotrimethylsilane (from Acros Organics) instead of chlorotriethylsilane. In that case, the resultant trimethylsilyl enol ether cannot be purified by column chromatography due to its acid sensitivity, so the crude product is used directly in the [4+3] cycloaddition reaction (Note 20).

14. An alternative to silyl enol ether **3** as oxyallylic cation precursor is 3,3-bis-benzyloxy-2-trimethylsilyloxypropene (Notes 13, 20).

15. Commercial dichloromethane was freshly distilled from CaH_2.

16. Commercial furan (99%, stabilized with BHT) from Acros Organics was used without further purification. 2,5-Dimethylfuran (99%) from Acros Organics was used by the submitters in the unchecked [4+3] cycloaddition (85% yield of cycloadduct) following the same procedure as for furan.

17. Commercial trimethylsilyl trifluoromethanesulfonate (99%) from Acros Organics was used. Ten mole % (0.1 equiv) of TMSOTf was sufficient to catalyze the [4+3] cycloaddition.

18. The checkers observed that the oil partially solidifies to a white solid upon standing. The submitters report that residual benzyl alcohol can be removed by heating the oil at 100 °C for two hours using a Kugelrohr apparatus. The checkers did not identify the presence of benzyl alcohol by NMR analysis and did not perform the heating.

19. Spectral data for 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (d, *J* = 15.5 Hz, 1 H), 2.75 (dd, *J* = 15, 5 Hz, 1 H), 4.13 (d, *J* = 5 Hz, 1 H), 4.64 (d, *J* = 12 Hz, 1 H), 4.91 (dd, *J* = 5 ,1.5 Hz. 1 H), 4.99 (m, 2 H), 6.30 (dd, *J* = 6.5, 1.5 Hz, 1 H), 6.34 (dd, *J* = 6, 2 Hz, 1 H), 7.39–7.31 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.1,

73.7, 78.6, 80.0, 84.3, 128.1, 128.7, 132.0, 134.8, 137.8, 205.2. IR ($CHCl_3$) cm^{-1}: 1724 (very strong), 1112 (very strong), 731 (strong), 697 (strong; EI-MS (rt): 230 (6, M^+), 201 (4), 158 (38), 139 (31, M^+-Bn), 121 (10), 108 (25), 91 (100), 81 (30), 77 (14), 69 (23). Anal. Calcd for $C_{14}H_{14}O_3$: C, 72.89; H, 6.05. Found: C, 73.03; H, 6.13.

20. Alternatively, the [4+3] cycloadduct has been prepared by the submitters using inexpensive chlorotrimethylsilane (Note 13) as follows:

A two-necked, 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dibenzyl acetal **2** (27 g, 100 mmol) in anhydrous DMF (33 mL) (Dimethylformamide (DMF) is dried over powdered BaO for 2 weeks, followed by decanting and then distilling under reduced pressure.) and chlorotrimethylsilane (28.6 mL, 225 mmol) (Note 13) and heated at 75 °C. Triethylamine (38.9 mL, 280 mmol) (Note 10) is added slowly by syringe pump (60 mL/h). The reaction mixture is refluxed for 16 h at 75 °C and the reaction mixture becomes thicker and dark brown. The reaction mixture is cooled to 0 °C, washed with 30 mL of a cold saturated solution of ammonium chloride (30 mL) and water (approximately 15 mL). The aqueous phase is extracted with cyclohexane (4 x 50 mL). The combined organic phase is dried (Na_2SO_4) and the solvent removed with a rotatory evaporator. The resulting brown viscous oil is used directly in the [4+3] cycloaddition as described in procedure C.

When the 3,3-*bis*-benzyloxy-2-trimethylsilyloxypropene is used as the oxyallylic cation precursor, the yield of the [4+3] cycloadduct with furan is 41 % (two steps). The yield of the [4+3] cycloadduct with 2,5-dimethylfuran is 53 % (two steps). The procedure has been used in a reaction using 130-mmol of starting dibenzyl acetal.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

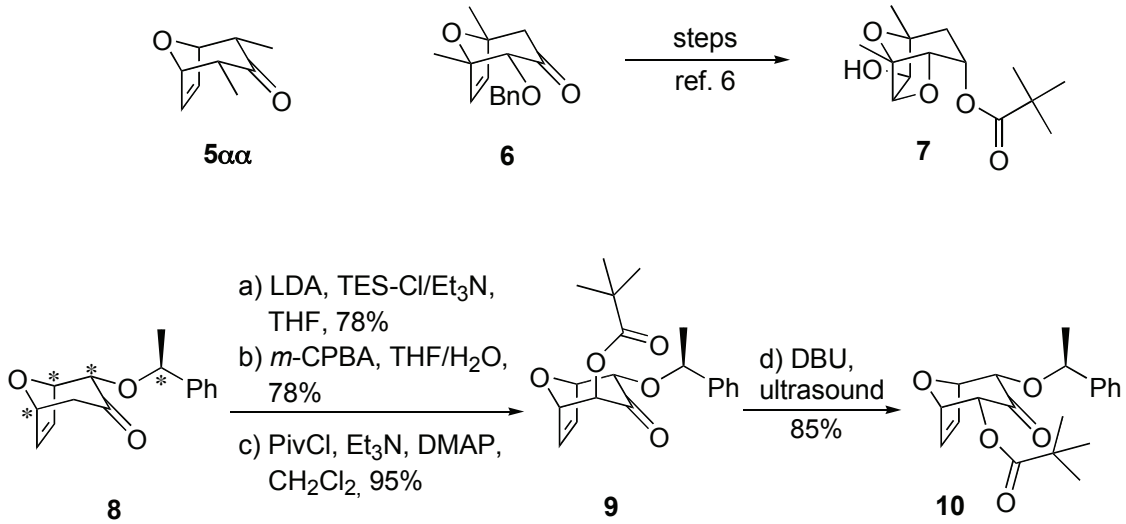
In view of the wide synthetic interest of [4+3] cycloadducts of oxyallyl cations and dienes, a variety of methods have been developed for

the generation and capture of appropriate oxyallyl cations. The classical routes to generate these reactive intermediates start from halogenated precursors:[2] α,α′-Dihalo ketones or α-monohalo ketones. For example, 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (5α,α) has been prepared from both a dihalo-[3a] and a monohaloketone[3b] and has served as a *meso*-configured workhorse for exploring desymmetrization of the seven-carbon backbone with its three pro-stereogenic sp^2 centers. Allylic halides and silver salts have been used also.[2a, 4] Further, the use of trialkylsilyloxyallyl cations from 1,1-dimethoxyacetone in [4+3] cycloadditions with furans has been reported.[5]

In the procedure described here, a triethylsilyloxyallylic cation with a π-donating benzyloxy substituent at the allylic terminus is generated via treatment of triethylsilyl enol ether **3** with TMSOTf in catalytic amount and, in presence of the 4π-component, the [4+3] cycloaddition proceeds smoothly giving 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-ones. If furan is replaced by 2,5-dimethylfuran, then cycloaddition yields are higher (leading to **6**). Increasing the equivalents of diene does not alter the yield appreciably. The availability of oxabicycle **6** opens a short route to the dioxatricyclic core of the marine metabolite dictyoxetane (**6** → **7**)[6a] and to functionalized scopolines.[6b] An asymmetric variant of the [4+3] cycloaddition involving chiral allyl cations has also been accomplished affording **8** with high *ee*.[7]

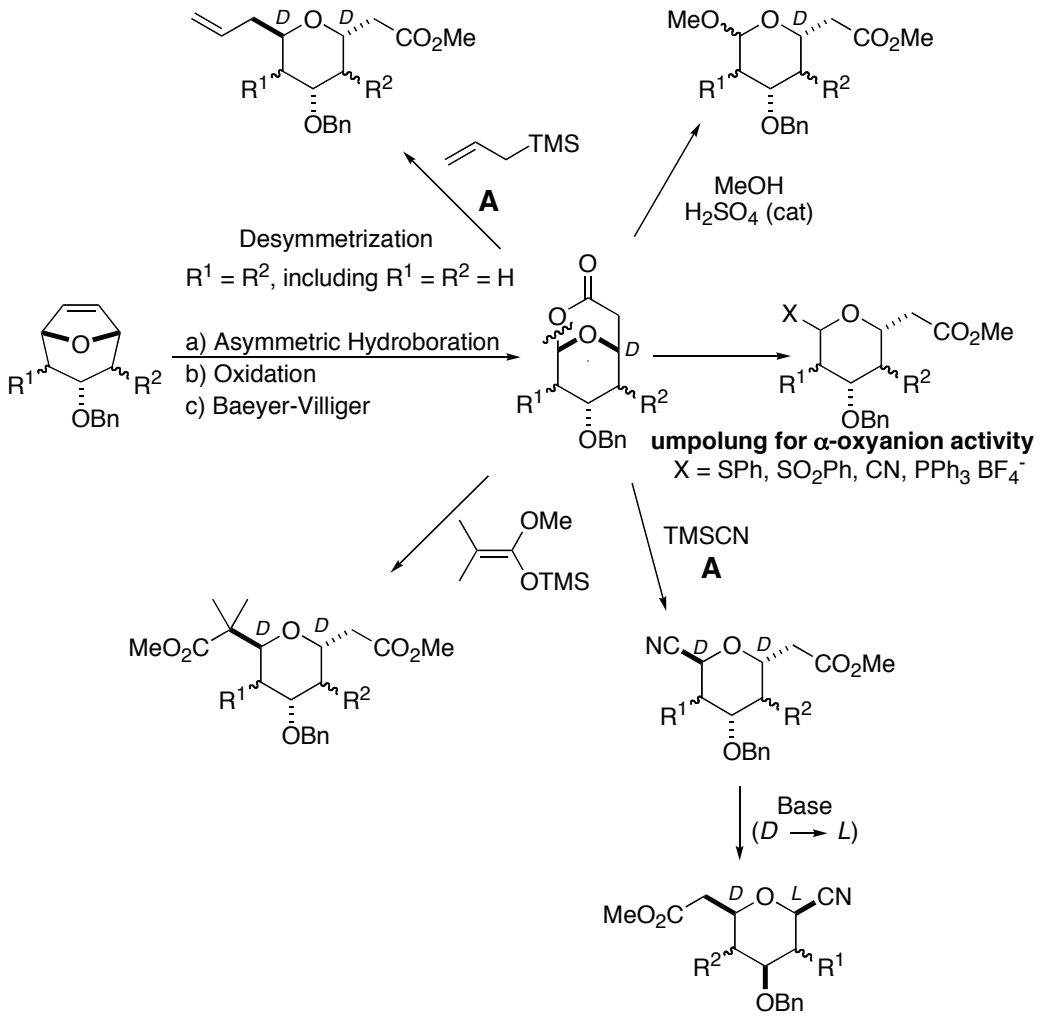
Oxabicycle **8** is a useful building block and is endowed with all the chiral information for the *de novo* construction of C-glycosides. For example, axial hydroxylation (**8** → **9**) proceeds smoothly by treatment of the derived TES enol ether with *m*-chloroperbenzoic acid provided that *wet* THF is used as solvent.[8] The use of dilute solutions of dimethyldioxirane as oxidant which is toxic and dangerous, is obviated.[9] Epimerization of **9** affords the diequatorial epimer **10**. Starting from **8** and parent 8-oxabicyclo[3.2.1]oct-6-en-3-one, a complete series of C-glycosides with fully resolved seven-carbon backbone polyol stereochemistry and with complete anomeric control has been prepared (Scheme 1).[8]

Scheme 1



8-Oxabicyclo[3.2.1]oct-6-en-3-ones have been converted into [3.3.1]lactone acetals, which are versatile synthetic intermediates and allow further stereocontrolled C–C, C–S, C–$P^{+}Ph_3X^{-}$ bond formation. C–C Bonds and extended carbon chains are formed with complete anomeric control in the presence of a Lewis acid (Me_3SiOTf) and silylated nucleophile in acetonitrile (Scheme 2).[10] 8-Oxabicyclo[3.2.1]oct-6-en-3-ones have been used as key precursors in natural product syntheses, as accomplished by the total synthesis of hinokitiol[11] and callistatin A.[1]

Intramolecular [4+3] cycloadditions have also been studied.[13] Recently, metathesis of substituted oxabicyclics combined with spiroannulation has been reported.[14] Ru-Catalyzed asymmetric ring-opening/cross-metathesis provides another efficient enantioselective route to functionalized tetrahydropyrans.[15] Vinylic nonaflates from 8-oxabicyclo [3.2.1] oct-6-en-3-ones have been used to elaborate the bicyclic scaffold.[16]



Scheme 2. Typical transformations of [3.3.1]lactone acetals illustrated for C-glycoside synthesis with generalized *D-D* type configuration. **A**: All reactions were run with TMSOTf (ca. 1 equiv) in MeCN, –40 °C to 0 °C; then addition of MeOH, r.t. followed by *in situ* esterification. Yields are uniformly about 95%.

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Appendix

Chemical Abstracts Nomenclature; (Registry number)

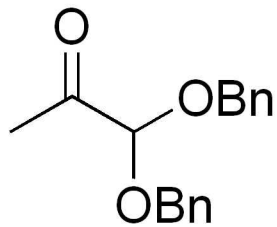
1,1-Dimethoxy-2-propanone: α,α-Dimethoxyacetone; (6342-56-9)

Chlorotriethylsilane: Silane, chlorotriethyl-; (994-30-9)

Trimethylsilyl trifluoromethanesulfonate: Trifluoromethanesulfonic acid trimethylsilyl ester; Trimethylsilyl triflate; (27607-77-8)

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4)

2,5-Dimethylfuran; (625-86-5)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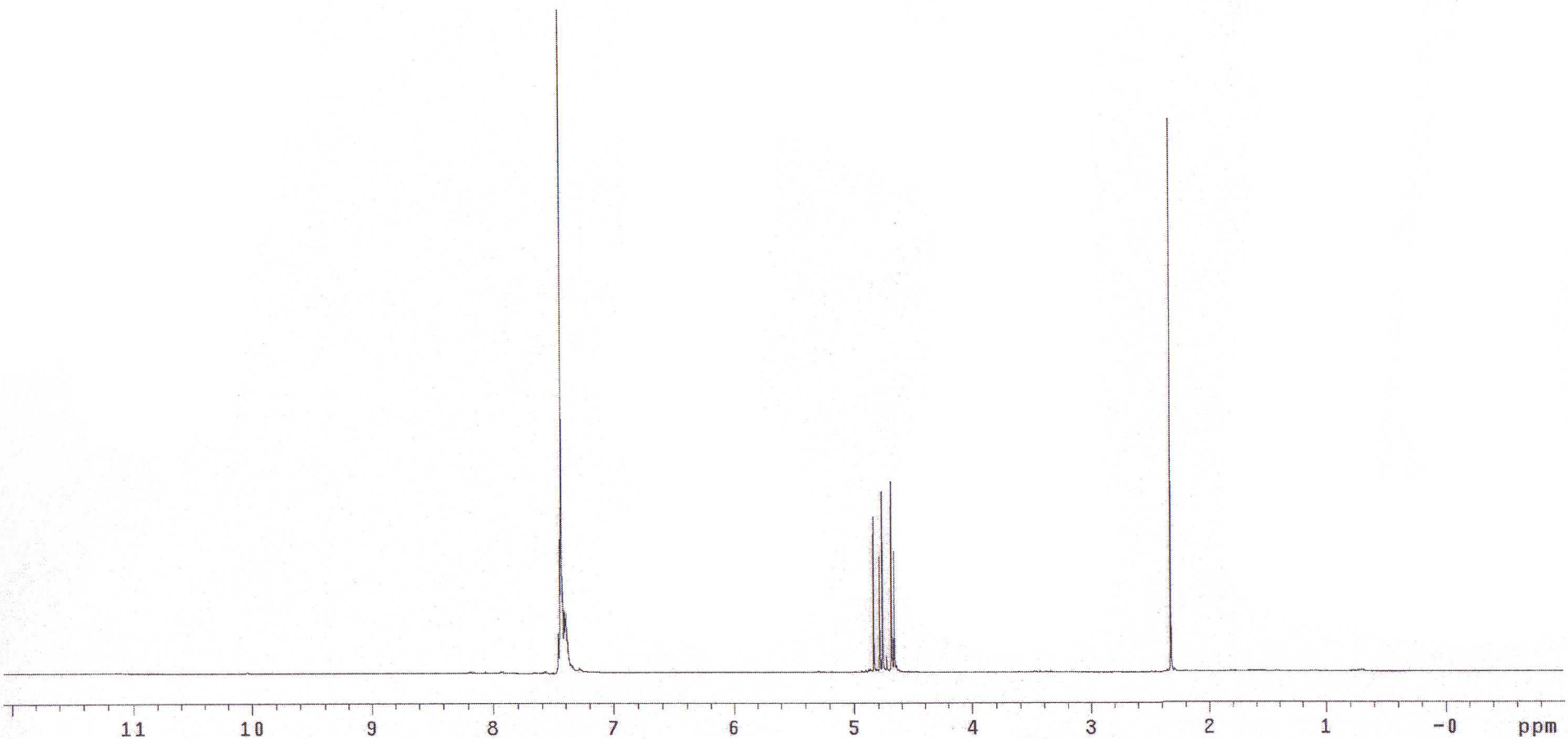
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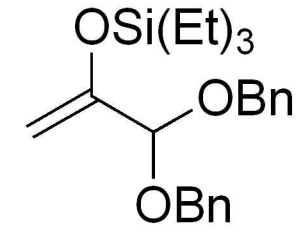
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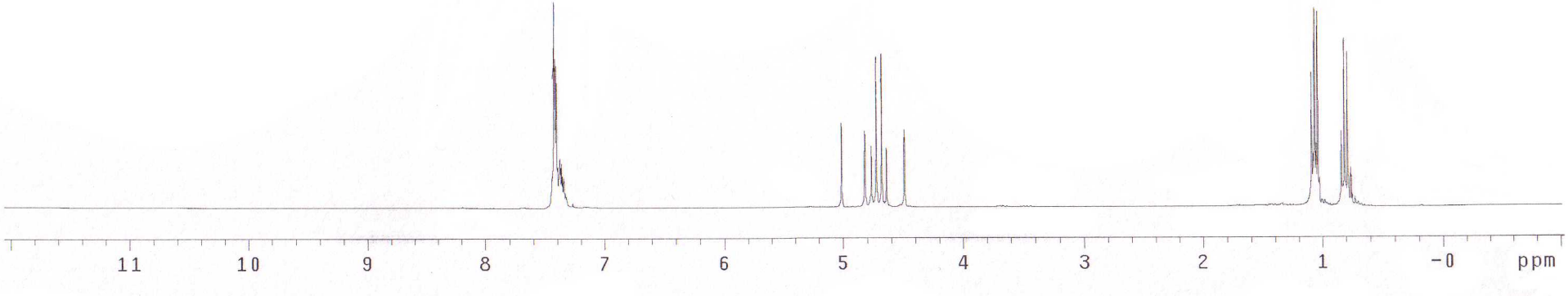
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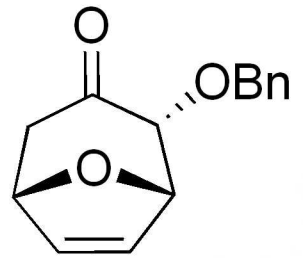
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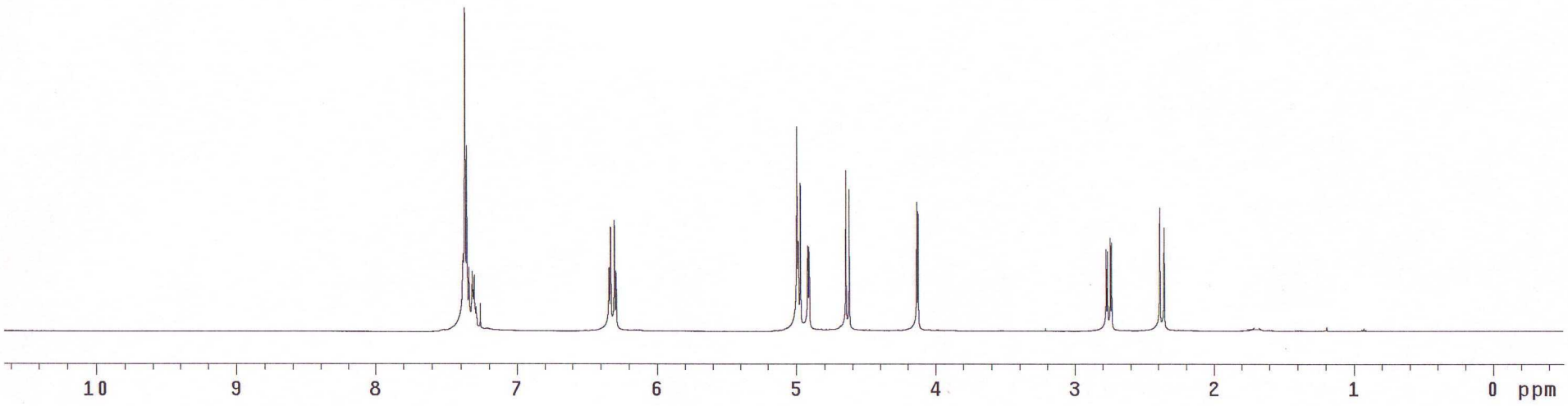
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