REACTIONS OF CAGE-ANNULATED 2-METHYL-5-(TRIFLUOROMETHANESULFONYLOXY)FURANS WITH LITHIUM DIISOPROPYLAMIDE. EVIDENCE FOR NUCLEOPHILIC REACTIVITY OF LDA†

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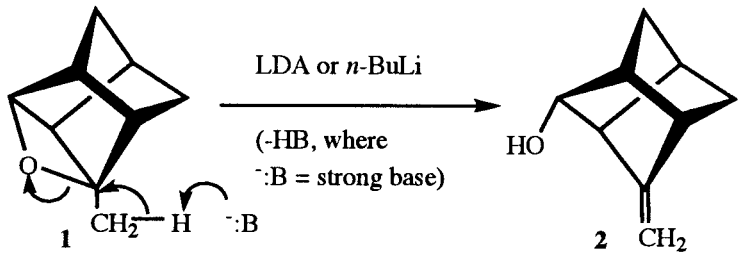
Abstract- Reaction of 3-trifluoromethanesulfonyloxy-5-methyl-4-oxahexacyclo-[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (**6a**) with lithium diisopropylamide (LDA, 6 equivalents) in dry THF affords 11-methylenepentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (**3a**) in low yield (11%). This reaction is shown to proceed *via* formation of an intermediate cage-annulated hemiaminal (**7a**), which in turn may have resulted *via* a highly unusual nucleophilic attack by (i-Pr)$_2$N:$^-$ upon *exo*-11-diisopropylamino-*endo*-11-methylpentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (**8a**). The corresponding reaction of 3-trifluoromethanesulfonyloxy-5,9,10-trimethyl-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (**6b**) with LDA (6 equivalents) in dry THF produced 1,7-dimethyl-11-methylenepentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecan-8-one (**3b**) in 10% isolated yield.

INTRODUCTION

A key step in a popular synthesis of homoallylic alcohols involves base promoted fragmentation of substituted oxetanes. This reaction is illustrated in Scheme 1, where it was employed to prepare functionalized tricyclo[3.3.0.$0^{3,7}$]octanes ("stellanes").[1-3] As part of a long-standing research program that is concerned with the synthesis and chemistry of substituted pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanes (PCUs),[4] we have had occasion to synthesize 11-methylene-PCU-8-one (**3a**) *via* Peterson olefination of PCU-8,11-dione (**4a**, Scheme 2).[5] We now report the results of a recent attempt to prepare **3a** *via* base promoted fragmentation of cage-annulated *tetrahydrofurans*.

Scheme 1

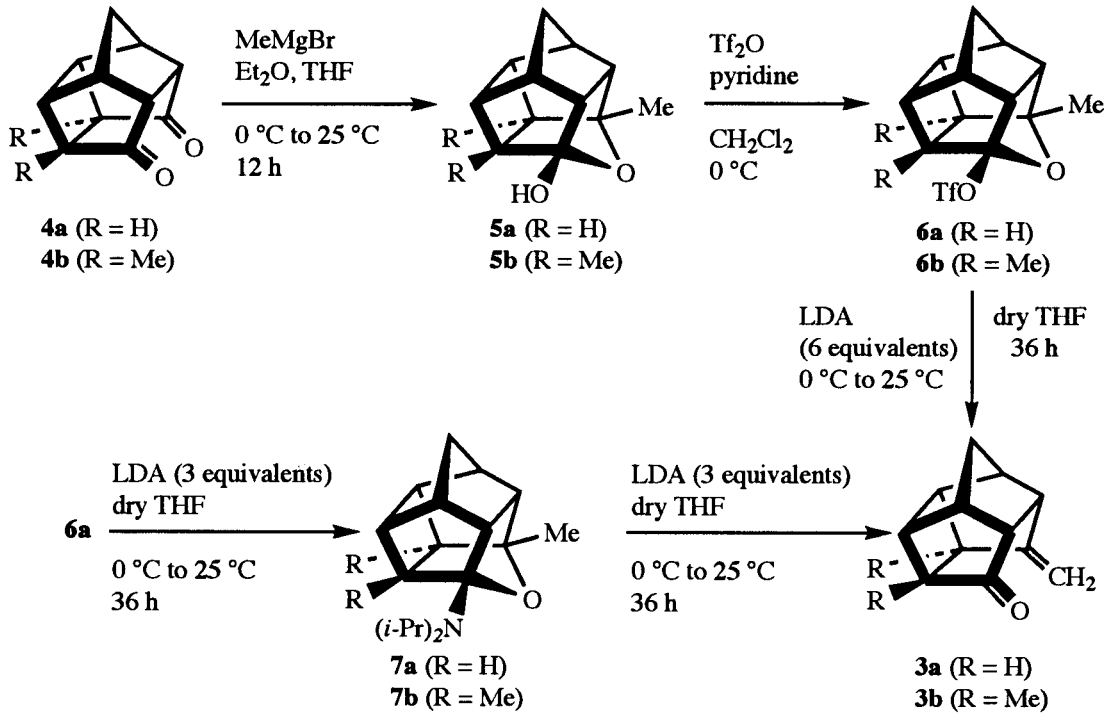


†Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

RESULTS AND DISCUSSION

The reaction of CH_3MgBr with **4a** has been reported[6] to proceed *via* addition of one equivalent of the Grignard reagent to the substrate, thereby affording **5a** (Scheme 2) in excellent yield. Having been thus synthesized, **5a** then was converted into the corresponding *O*-trifluoromethanesulfonate derivative (**6a**). Quite unexpectedly, subsequent reaction of **6a** with LDA (3 equivalents) in dry THF afforded a novel cage-annulated hemiaminal (**7a**). When **7a** thereby obtained was allowed to react with an additional 3 equivalents of LDA, it was slowly converted into the desired cage-annulated enone (**3a**), in 33% yield along with recovered **5a** (46%). In a separate experiment, the corresponding reaction of **5a**, when performed by using 6 equivalents of LDA, afforded **3a** directly in low yield along with a trace quantity of **7a**.

Scheme 2



4a (R = H)
4b (R = Me)

5a (R = H)
5b (R = Me)

6a (R = H)
6b (R = Me)

7a (R = H)
7b (R = Me)

3a (R = H)
3b (R = Me)

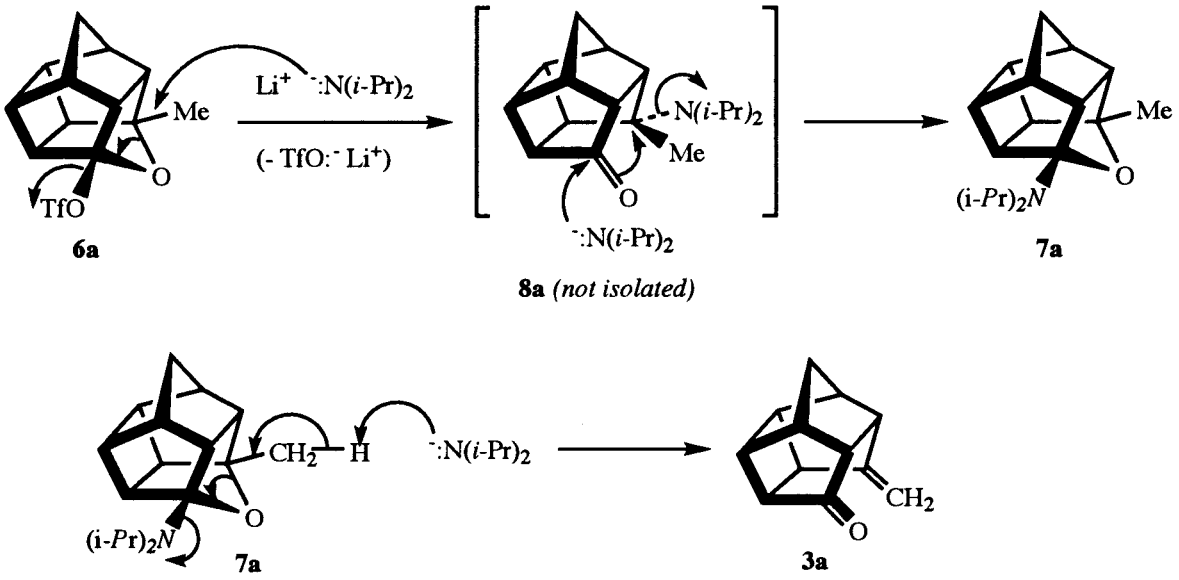
Although we considered it to be unlikely, we recognized that **3a** might be an intermediate in the formation of **7a** from **6a**. In fact, this possibility was rigorously excluded *via* the results of two separate control experiments. First, when the reaction of **6a** with LDA (3 equivalents) was quenched *via* addition of D_2O and the reaction product was isolated, we obtained only unlabeled **7a** (i.e., material in which deuterium had not become incorporated into the reaction product). Secondly, when an authentic sample of **3a** was allowed to react with LDA (3 equivalents) under the same conditions that had been employed previously for the corresponding reaction of **6a** with LDA (3 equivalents), we found no evidence for the formation of **7a**.

Subsequently, a series of reactions similar to that shown in Scheme 2 was performed by using 1,7-dimethylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**4b**) as starting material. Thus, **4b** was converted first into **5b** and then into **6b** by following the procedure shown in Scheme 2. Subsequent reaction of **6b** with LDA (6 equivalents) in dry THF afforded **3b** in 10% isolated yield plus a small amount of an unidentified material that appears to be a mixture of at least two compounds along with recovered **5b** (50%).

SUMMARY AND CONCLUSIONS

The foregoing results suggest strongly that **7a** is an intermediate in the formation of **3a** from **6a** when this reaction is performed in the presence of a large excess of LDA (6 equivalents).[7] A mechanism that is capable of rationalizing our observations is shown in Scheme 3. Interestingly, diisopropylamide is seen to function effectively in this reaction sequence both as a strong base and as a *nucleophile*. Since LDA normally is a reagent of choice when the need arises for a non-nucleophilic base, the behavior demonstrated by $(i\text{-Pr})_2N^{:-}$ in traversing the reaction sequence **6a** → **8a** → **7a** (Scheme 3) must be regarded as being highly unusual.

Scheme 3



EXPERIMENTAL

Melting points are uncorrected. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. High-resolution MS data were obtained at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode by using methane as CI reagent gas.

5-Methyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol (5a). A solution of **4a** (1.044 g, 6.0 mmol) in dry THF (20 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring MeMgBr (4 mL of a 3 M solution in Et_2O, 12 mmol) during 20 min. After all of the Grignard reagent had been added, the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 12 h. The reaction mixture then was cooled to 0 °C *via* application of an external ice-water bath, and the reaction was quenched *via* careful, dropwise addition of saturated aqueous NH_4Cl (5 mL, excess) to the stirred reaction mixture. Water (80 mL) was added to this mixture, and the resulting aqueous suspension was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with ligroin (bp

40-60 °C) and filtered, thereby affording **5a** (1.08 g, 95%) as a colorless microcrystalline solid: mp 98-99 °C (lit., 98 °C[6a]; 99-100 °C[6b]); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.45 (*AB*, J_{AB} = 10.6 Hz, 1 H), 1.80 (A*B*, J_{AB} = 10.6 Hz, 1 H), 2.25-2.75 (m, 8 H), 5.42 (br s, disappears upon addition of a few drops of D_2O, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.9 (q), 41.7 (d), 41.9 (d), 43.3 (t), 43.9 (d), 44.6 (d), 47.8 (d), 49.4 (d), 57.7 (d), 59.7 (d), 89.2 (s), 118.4 (s).

3-Trifluoromethanesulfonyloxy-5-methyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane (6a). A solution of **5a** (285 mg, 1.5 mmol) and pyridine (237 mg, 3 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of Tf_2O (508 mg, 1.80 mmol) in CH_2Cl_2 (5 mL). After all of the Tf_2O had been added, the reaction mixture was stirred at 0 °C during an additional 3 h. Methylene chloride (50 mL) was added to the reaction mixture, and the resulting solution was washed sequentially with water (10 mL), cold 5% aqueous HCl (2 × 10 mL), and water (10 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Compound (**6a**) (414 mg, 86%) was thereby obtained as an unstable, pale yellow oil; IR (neat) 2980 (s), 2880 (w), 1420 (s), 1219 (s), 1038 (s), 862 (s), 608 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3 H), 1.57 (*AB*, J_{AB} = 10.6 Hz, 1 H), 1.90 (A*B*, J_{AB} = 10.6 Hz, 1 H), 2.45-3.15 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 18.5 (q) 41.6 (d), 41.9 (d), 43.4 (t), 43.8 (d), 44.5 (d), 47.6 (d), 49.4 (d), 57.4 (d), 59.6 (d), 90.9 (s), 125.7 (s). This material was used as obtained in the next synthetic step, without additional purification or characterization.

Reaction of 6a with Lithium Diisopropylamide (LDA). A solution of diisopropylamine (392 mg, 3.87 mmol) in dry THF (10 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring *n*-BuLi (1.86 mL of a 2.5 M solution in hexane, 4.64 mmol). After all of the *n*-BuLi had been added, the reaction mixture was stirred at 0 °C during an additional 0.5 h. To the resulting solution was added dropwise with stirring a solution of **6a** (414 mg, 1.29 mmol) in dry THF (2 mL). After all of the THF solution of **6a** had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 36 h. The reaction mixture then was poured into ice-water (50 mL) to quench the reaction. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure **7a** (109 mg, 31%) was thereby obtained as a colorless oil; IR (neat) 2980 (s), 2872 (w), 1458 (w), 1366 (s), 1209 (s), 1086 (m), 984 (m), 814 (m), 750 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, *J* = 7.1 Hz, 12 H), 1.44 (s, 3 H), 1.52 (*AB*, J_{AB} = 10.7 Hz, 1 H), 1.86 (A*B*, J_{AB} = 10.7 Hz, 1 H), 2.40-2.64 (m, 4 H), 2.66-2.84 (m, 2 H), 2.98-3.12 (m, 2 H), 3.81 (septet, *J* = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.7 (q), 21.3 (q), 41.7 (d), 41.8 (d), 43.2 (t), 44.2 (d), 44.6 (d), 47.4 (d), 49.2 (d), 49.4 (d), 57.2 (d), 59.5 (d), 89.7 (s), 121.3 (s). Exact MS (CI-HRMS) Calcd for $C_{18}H_{28}NO$: $[M_r + H]^+$ *m/z* 274.217090. Found: $[M_r + H]^+$ *m/z* 274.216442.

Continued elution of the chromatography column with 50% EtOAc-hexane afforded a second fraction. The eluate was concentrated *in vacuo*, thereby affording recovered **5a** (113 mg, 46%) as a colorless microcrystalline solid: mp 98-99 °C. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra of authentic **5a** (*vide supra*).

11-Methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (3a). Method A. A solution of diisopropylamine (88 mg, 0.87 mmol) in dry THF (5 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring *n*-BuLi (0.42 mL of a 2.5 M solution in hexane, 1.04 mmol). After all of the *n*-BuLi had been added, the reaction mixture was stirred at 0 °C during an additional 0.5 h. To the resulting solution was added dropwise with stirring a solution of **7a** (79 mg, 0.29 mmol) in dry THF (1 mL). After all of the THF solution of **7a** had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 36 h. The reaction mixture then was poured into ice-water (30 mL) to quench the reaction. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure **3a** (16 mg, 33%) was thereby obtained as a colorless microcrystalline solid: mp 70-71 °C (lit.,[5] mp 71-72 °C). The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra that have been reported previously for authentic **3a**.[5]

Method B. A solution of diisopropylamine (1.214 g, 12 mmol) in dry THF (20 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring *n*-BuLi (5.76 mL of a 2.5 M solution in hexane, 14.4 mmol). After all of the *n*-BuLi had been added, the reaction mixture was stirred at 0 °C during an additional 0.5 h. To the resulting solution was added dropwise with stirring a solution of **6a** (644 mg, 2.0 mmol) in dry THF (2 mL). After all of the THF solution of **6a** had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 36 h. The reaction mixture then was poured into ice-water (80 mL) to quench the reaction. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed sequentially with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by using a 0-10% EtOAc-hexane gradient elution scheme. Pure **7a** (4 mg, 1.5%) was thereby obtained as a colorless oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra obtained previously for authentic **7a** (*vide supra*).

Continued elution of the chromatography column with 10% EtOAc-hexane afforded pure **3a** (19 mg, 11%): mp 70-71 °C (lit.,[5] mp 71-72 °C). The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra that have been reported previously for authentic **3a**.[5]

5,9,10-Trimethyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol (5b). A solution of **4b**[8] (808 mg, 4.0 mmol) in dry THF (15 mL) was allowed to react with MeMgBr (2.7 mL of a 3 M solution in Et_2O, 8 mmol) by using essentially the same procedure that was described previously for the corresponding synthesis of **5a** from **4a** (*vide supra*). Workup of the reaction mixture followed by fractional recrystallization of the crude product from Et_2O-pentane afforded **5b** (534 mg, 61%) as a colorless microcrystalline solid: mp 97-98 °C; IR (KBr) 3277 (br, s), 2959 (s), 2861 (m), 1447 (m), 1341 (s), 1287 (s), 1150 (s), 1080 (s), 882 (m), 683 (s) cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 0.92 (s, 3 H), 1.20 (s, 3 H), 1.45 (*AB*, J_{AB} = 10.2 Hz, 1 H), 1.78 (*AB*, J_{AB} = 10.2 Hz, 1 H), 2.14 (m, 1 H), 2.24 (m, 1 H), 2.34

(m, 1 H), 2.52 (m, 3 H), 4.40 (br s, disappears upon addition of a few drops of D_2O, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.1 (q), 12.9 (q), 15.8 (q), 42.2 (d), 42.9 (d), 43.6 (t), 46.6 (d), 46.7 (d), 51.7 (s), 53.2 (s), 58.3 (d), 60.8 (d), 88.9 (s), 116.6 (s). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.08; H, 8.42.

3-Trifluoromethanesulfonyloxy-5,9,10-trimethyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}-.0^{8,11}]dodecane (6b). A solution of **5b** (436 mg, 2.0 mmol) and pyridine (316 mg, 4.0 mmol) in CH_2Cl_2 (15 mL) was allowed to react with a solution of Tf_2O (677 mg, 2.4 mmol) in CH_2Cl_2 (5 mL) by using essentially the same procedure that was described previously for the corresponding synthesis of **6a** from **5a** (*vide supra*). Workup of the reaction mixture afforded **6b** (629 mg, 90%) as an unstable, pale yellow oil; IR (KBr) 2959 (s), 2880 (s), 1412 (s), 1211 (s), 1144 (s), 1032 (s), 864 (s), 763 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 0.98 (s, 3 H), 1.28 (s, 3 H), 1.54 (*AB*, J_{AB} = 11.2 Hz, 1 H), 1.86 (A*B*, J_{AB} = 11.2 Hz, 1 H), 2.20 (m, 1 H), 2.34 (m, 1 H), 2.43 (m, 1 H), 2.65 (m, 2 H), 3.27 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.1 (q), 12.6 (q), 15.4 (q), 42.5 (d), 42.8 (d), 43.6 (t), 45.6 (d), 46.5 (d), 53.9 (s), 54.9 (s), 56.1 (d), 60.4 (d), 90.9 (s), 125.0 (s). This material was used as obtained in the next synthetic step, without additional purifica-tion or characterization.

Reaction of 6b with Lithium Diisopropylamide (LDA). The reaction of a mixture of diisopropylamine (419 mg, 4.14 mmol) in dry THF (10 mL) and *n*-BuLi (2.0 mL of a 2.5 M solution in hexane, 0.69 mL) with **6b** (241 mg, 0.69 mmol) in dry THF (2 mL) was performed by using essentially the same procedure that was described previously for the corresponding synthesis of **7a** from **6a** (*vide supra*). Workup of the reaction mixture afforded **3b** (14 mg, 10%) as a waxy semisolid; IR (KBr) 2965 (s), 2868 (m), 1740 (s), 1667 (w), 1454 (w), 1379 (w), 1096 (m), 889 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.15 (s, 3 H), 1.62 (*AB*, J_{AB} = 10.0 Hz, 1 H), 1.88 (A*B*, J_{AB} = 10.0 Hz, 1 H), 2.10-2.75 (m, 5 H), 2.98-3.10 (m, 1 H), 4.55 (br s, 1 H), 4.72 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.1 (q), 14.8 (q), 39.5 (t), 42.3 (d), 42.7 (d), 47.2 (d), 49.0 (s), 49.2 (d), 51.3 (s), 54.0 (d), 54.8 (d), 102.4 (t), 154.0 (s), 227.8 (s); Exact MS (CI-HRMS) Calcd for $C_{14}H_{16}O$: $[M_r + H]^+$ *m/z* 201.12794. Found: $[M_r + H]^+$ *m/z* 201.12740.

Continued elution of the chromatography column with 10% EtOAc-ligroin (bp 40-60 °C) produced a small quantity (*ca.* 4 mg) of a colorless oil. Analysis of the ^1H and ^{13}C NMR spectra of this oil suggested that it may be a mixture of at least two compounds. No further attempt was made to characterize this material.

Continued elution of the chromatography column with 50% EtOAc-hexane afforded a third fraction. The eluate was concentrated *in vacuo*, thereby affording recovered **5b** (75 mg, 50%) as a colorless microcrystalline solid: mp 97-98 °C. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra of authentic **5b** (*vide supra*).

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