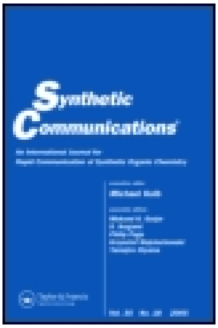


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Extended Chains of Six-Membered Rings 1. Model Studies and Key Intermediates

Robert M. Cory [a], Jeffrey R. Walker [a] & Pierre D. Zabel [a]

[a] Department of Chemistry, University of Western Ontario, London, Ontario, Canada, N6A 5B7

To cite this article: Robert M. Cory , Jeffrey R. Walker & Pierre D. Zabel (1994): Extended Chains of Six-Membered Rings 1. Model Studies and Key Intermediates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:6, 799-807

To link to this article: http://dx.doi.org/10.1080/00397919408011302

SYNTHETIC COMMUNICATIONS, 24(6), 799-807 (1994)

EXTENDED CHAINS OF SIX-MEMBERED RINGS

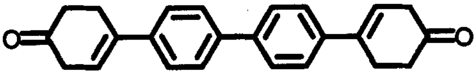
1. MODEL STUDIES AND KEY INTERMEDIATES

Robert M. Cory,* Jeffrey R. Walker and Pierre D. Zabel

Department of Chemistry, University of Western Ontario
London, Ontario, Canada N6A 5B7

ABSTRACT: McMurry coupling of 4-phenylcyclohex-3-en-1-one and double addition of 1,4-dilithiobenzene and 4,4′-dilithiobiphenyl to cyclohexanones gives linear chains of three or four six-membered carbocyclic rings, including a potential intermediate in a proposed synthesis of [0$_6$]paracyclophane.

The recent report[1] by Vögtle on the synthesis of diketone **1** prompts us to summarize our own progress in this area. Although both his group and ours are making these types of compounds with the intention of using them in syntheses of [0$_n$]paracyclophanes (cyclic oligoparaphenylenes, COPs), they are of considerable interest from many other perspectives, among which is the synthesis of liquid crystals.

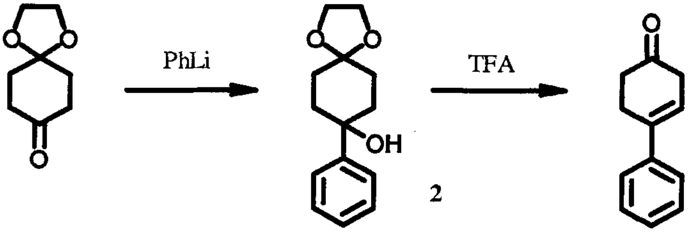


1

---

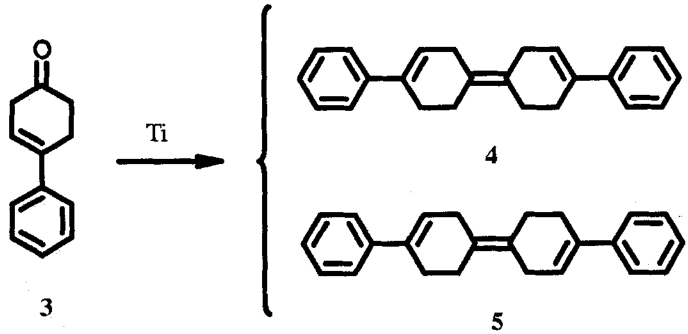
* To whom correspondence should be addressed.

Since our proposed synthesis involved, as the key step, a double McMurry coupling of diketones such as **1** to give macrocyclic cyclophanes, a model study was first carried out to test the feasibility of McMurry coupling of cyclohex-3-en-1-ones. Accordingly, phenyllithium, prepared by treatment of a solution of bromobenzene in THF at –60 °C with *tert*-butyllithium, was reacted with 1,4-cyclohexanedione *mono*-ethylene ketal to give hydroxy ketal **2** in 77% yield. Treatment of this compound with trifluoroacetic acid in methylene chloride effected concomitant dehydration and removal of the acetal protecting group, producing cyclohexenone **3** in 66% yield.

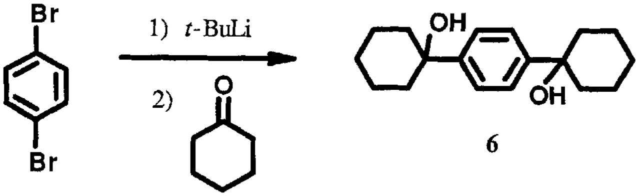


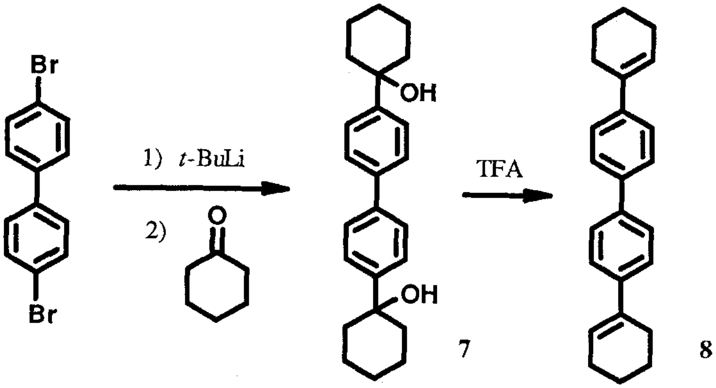
Reductive self-coupling of enone **3** was carried out employing McMurry's $TiCl_3$/DME/Zn-Cu system, in which the low-valent titanium reagent is generated by the reduction of $TiCl_3(DME)_{1.5}$ by zinc-copper couple in refluxing dimethoxyethane (DME).[2] Cyclohexenone **3** was allowed to react with this reagent at reflux for 12 hours, giving a mixture of trienes **4** and **5** in 31% yield. An ^1H NMR spectrum of this mixture indicated that the two isomers were present in a 43:57 ratio, although which isomer was the major product was not determined.

In order to test the efficacy of formation of 1,4-dilithiobenzene by the method described above for phenyllithium, 1,4-dibromobenzene was treated with *tert*-butyllithium under the same conditions and reacted with cyclohexanone to

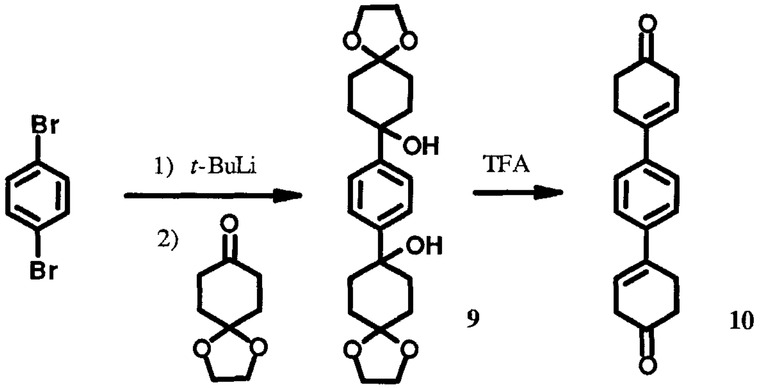


give a 57% yield of diol **6**. Similarly, 4,4′-dibromobiphenyl gave diol **7**, which could be dehydrated as for **2** above to produce diene **8** in 67% overall yield.





Finally, this method was applied with success to the synthesis of diketone **10** via diol **9**. An investigation of the double McMurry self-coupling of **10** is now in progress.



Experimental

All reactions were run in flame-dried or oven-dried glassware under a positive pressure of argon. THF (tetrahydrofuran) and DME (1,2-dimethoxyethane) were dried by distillation from sodium benzophenone ketyl. Dry column flash chromatography was performed using Merck 60 grade, 230–400 mesh (60 Å) silica gel, and TLC was performed using 250 µm layer, pre-coated silica gel on PET polyester plates, with a fluorescent indicator. ^{1}H NMR spectra were recorded at 200 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. All NMR spectra were run in deuterated chloroform. Mass spectra were determined by electron impact employing an ionizing voltage of 70 eV.

4-Hydroxy-4-phenylcyclohexanone ethylene ketal (2)

To 1.49 g (9.5 mmol) of bromobenzene in 20 mL of THF at –60 °C was added 11.2 mL (1.7 *M*; 19 mmol) of *tert*-butyllithium dropwise, with stirring, via syringe. The reaction mixture was stirred at –60 °C for 3 h. 1,4-Cyclohexanedione *mono*-ethylene ketal (1.50 g, 9.5 mmol) in 10 mL of THF was added via syringe.

The reaction mixture was warmed to room temperature by evaporation of the dry ice from the cooling bath and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated aq. NaCl (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 1.7 g of **2** as a white crystalline solid (77%): mp 94–96 °C; ^{1}H NMR δ 7.2–7.6 (m, 5H), 4.01 (s, 4 H), 2.40 (bs, 1 H), 2.0–2.3 (m, 4 H), 1.6–1.9 (m, 4 H); ^{13}C NMR δ 148.7 (C), 128.4 (CH), 127.0 (CH), 124.6 (CH), 108.5 (O_2C), 72.3 (COH), 64.3 (CH_2), 36.4 (CH_2), 30.6 (CH_2); MS *m/z* (relative intensity) 234 (M^+, 0.1), 217 (0.2), 99 (100), 87 (72); HRMS *m/z* for $C_{14}H_{18}O_3$ calcd. 234.1256, found 234.1258.

4-Phenyl-3-cyclohexenone (3)

To 1.70 g (7.3 mmol) of diol **2** in 15 mL of CH_2Cl_2 was added 5 mL of CF_3COOH. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ (added until the acid was neutralized) and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated aq. NaCl (75 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a white solid. Trituration with hexanes yielded 0.83 g of **3**[3] as a white crystalline solid (66%): mp 72–73 °C; ^{1}H NMR δ 7.2–7.45 (m, 5 H), 6.10 (m, 1 H), 3.07 (m, 2 H), 2.92 (m, 2 H), 2.65 (t, 2 H, *J* = 7 Hz); ^{13}C NMR δ 209.8 (C=O), 140.5 (C), 137.3 (C), 128.2 (CH), 127.1 (CH), 124.9 (CH), 120.7 (CH), 39.3 (CH_2), 38.1 (CH_2), 27.2 (CH_2); MS *m/z* (relative intensity) 172 (M^+, 78), 160 (12), 130 (100), 115 (71), 105 (30), 91 (17), 77 (29); HRMS *m/z* for $C_{12}H_{12}O$ calcd. 172.0888, found 172.0883.

Bis(4-phenyl-3-cyclohexenylidene) (4 + 5)

A slurry of 5.06 g (17.4 mmol) of $TiCl_3(DME)_{1.5}$[2] and 4.81 g (68 mmol) of Zn/Cu couple[2] in 50 mL of DME was stirred at reflux for 2.5 h. A solution of enone **3** (0.65 g, 3.8 mmol) in 15 mL of DME was added via syringe. The reaction mixture was stirred at reflux for 12 h, cooled to room temperature and filtered through Florisil.® The Florisil® was washed with pentane (3 × 50 mL; 1 × 100 mL). The organic layer was concentrated *in vacuo* to give a yellow solid. Purification by dry column flash chromatography (ethyl acetate/cyclohexane) yielded 0.18 g of a mixture of geometric isomers **4** and **5** as a light-yellow solid (31% yield): mp 110–112 °C; TLC (1/9 ethyl acetate/cyclohexane) $R_f = 0.61$. *Minor isomer* (43 mole %): ^{1}H NMR δ 7.2–7.45 (m, 10 H), 6.15 (m, 2 H), 3.13 (bd, J = 3.3 Hz, 4 H), 2.62 (m, 8 H); ^{13}C NMR δ 142.1 (C), 137.0 (C), 128.3 (CH), 126.6 (CH), 125.7 (C), 125.0 (CH), 124.1 (CH), 29.6 (CH_2), 28.8 (CH_2), 26.8 (CH_2). *Major isomer* (57 mole %): ^{1}H NMR δ 7.2–7.45 (m, 10 H), 6.15 (m, 2 H), 3.06 (d, J = 2.3 Hz, 4 H), 2.57 (m, 8 H, CH_2); ^{13}C NMR δ 142.1 (C), 137.1 (C), 128.3 (CH), 126.6 (CH), 125.8 (C), 125.0 (CH), 124.0 (CH), 30.1 (CH_2), 29.2 (CH_2), 26.4 (CH_2); MS *m/z* (relative intensity) 312 (M^+, 32), 196 (15), 182 (43), 167 (14), 156 (100), 141 (20), 129 (16), 115 (21), 105 (15), 91 (35); HRMS *m/z* for $C_{24}H_{24}$ calcd 312.1878, found 312.1875.

1,4-bis(1-hydroxycyclohexyl)benzene (6)

To 2.36 g (10 mmol) of *p*-dibromobenzene in 20 mL of THF at –70 °C was added 23.5 mL (1.7 *M*, 40 mmol) of *t*-BuLi dropwise over 10 min. The reaction mixture was allowed to warm to –50 °C over 1.5 h. Cyclohexanone (2.07 mL, 1.96 g, 20 mmol) in 10 mL of THF was added dropwise over 5 min, and the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 25 mL of saturated aq. NH_4Cl. Extraction with CH_2Cl_2 (3 × 50 mL) was followed by washing the combined organic layers once with water and twice with saturated aq. NaCl. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to give 2.47 g of yellow crystals. The crude product was purified by recrystallization from cyclohexane to yield **11** (57%) as white needles: mp 139–140 °C; ^1H NMR δ 7.47 (s, 4 H), 1.78 (m, 20 H), 1.56 (s, 2 H); ^{13}C NMR δ 147.8 (C), 124.5 (CH), 73.0 (COH), 38.8 (CH_2), 26.9 (CH_2), 25.5 (CH_2), 22.2 (CH_2); IR (CCl_4) 3570, 1100 cm^{-1}; MS *m/z* (relative intensity) 274 (M^+, 96), 231 (100), 203 (46), 147 (29), 133 (79), 99 (69), 81 (39), 55 (59); HRMS *m/z* for $C_{18}H_{26}O_2$, calcd 274.1933, found 274.1933.

4,4′-Bis(cyclohexen-1-yl)biphenyl (8)

To 0.56 g (1.8 mmol) of 4,4′-dibromobiphenyl in 4 mL of THF at −60 °C was added 4.3 mL (1.7 *M*; 7.3 mmol) of *tert*-butyllithium dropwise, with stirring, via syringe over 1 h. The reaction mixture was stirred at −60 °C for 2 h. This was followed by the addition of cyclohexanone (0.40 g, 4.1 mmol). The reaction mixture was warmed to room temperature by evaporation of the dry ice of the cooling bath and stirred for 20 h. The reaction was quenched with saturated aq. NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with saturated aq. NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give diol **7**: ^1H NMR δ 7.56 (s, 8 H), 1.6–1.9 (m, 10 H), 1.2–1.4 (m, 1 H); ^{13}C NMR δ 148.6 (C), 139.4 (C), 127.0 (CH), 125.2 (CH), 73.1 (COH), 38.7 (CH_2), 25.4 (CH_2), 22.0 (CH_2); MS *m/z* (relative intensity) 350 (M^+, 100), 332 (134, 314 (24), 307 (77), 289 (19), 279 (21), 221 (12), 209 (13), 191 (12), 167 (15), 152 (17); HRMS *m/z* for $C_{24}H_{30}O_2$ calcd. 350.2246, found 350.2246. The diol was taken up in 20 mL of CH_2Cl_2, and 2 mL of CF_3COOH was added. The reaction mixture was stirred at room temperature for 20 min. The reaction was quenched with saturated aq. $NaHCO_3$ (added until the acid was neutralized) and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated aq. NaCl (75 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 0.38 g of diene **8** (67%): mp 180–182 °C; ^1H NMR δ 7.25–7.5 (m, 4 H), 6.05–6.1 (m, 1 H), 2.3–2.4 (m, 2 H), 1.05–2.2 (m, 2 H), 1.5–1.8 (m, 4 H); MS *m/z* (relative intensity): 314 (M^+, 100), 286 (11), 261 (6), 234 (25), 205 (18), 191 (12), 178 (10), 165 (6); HRMS *m/z* for $C_{24}H_{26}$ calcd. 314.2034, found 314.2035.

1,4-Bis(4-oxocyclohex-1-enyl)benzene (10)

To 4.0 g (16.9 mmol) of *p*-dibromobenzene in 200 mL of THF at −78 °C was added 40 mL (1.7 *M*, 68 mmol) of *tert*-butyllithium dropwise, with stirring, via syringe over 1 h. The reaction mixture was stirred at −50°C for 6 h. This was followed by the addition of a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (5.3 g, 34 mmol) in 18 mL of THF via syringe. The reaction mixture was warmed to room temperature by evaporation of the dry ice of the cooling bath and stirred overnight (16 h). The reaction mixture was quenched with saturated aq. NH_4Cl (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with saturated aq. NaCl (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give hydroxy ketal **9** as a white solid. The crude hydroxy ketal was taken up in 50 mL of CH_2Cl_2 and 8 mL (0.10 mol) of CF_3COOH was added. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched and neutralized with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 layer was washed with saturated aq. NaCl (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a yellow solid. Recrystallization (cyclohexane/CH_2Cl_2) yielded 1.9 g of diketone **10** as a light yellow solid (42% yield): mp 126–128 °C; IR (CCl_4) 1700 cm^{-1}; TLC (1/99 ethyl acetate/CH_2Cl_2) R_f = 0.35; ^1H NMR δ 7.38 (s, 4 H), 6.11 (m, 2 H), 3.06 (m, 4 H), 2.89 (tm, J = 6.8 Hz, 4 H), 2.63 (tm, J = 6.8 Hz, 4 H); ^{13}C NMR δ 210.7 (C=O), 140.2 (C), 137.7

(C), 125.7 (CH), 121.5 (CH), 40.2 (CH_2), 38.9 (CH_2), 28.0 (CH_2); MS *m/z* (relative intensity) 266 (M^+, 100), 224 (61), 182 (48), 129 (44); HRMS *m/z* for $C_{18}H_{18}O_2$ calcd. 266.1307, found 266.1306.

Acknowledgment: Financial support of this work by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

References

(1) Friederich, R.; Nieger, M.; Vögtle, F. *Chem. Ber.* **1993**, *126*, 1723-1732.

(2) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*(15), 3748-3749.

(3) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*(17), 4777-4786.

(Received in the USA 13 September 1993)