Formation of Polycyclic Carbocycles through Metal–Halogen Exchange-Initiated Intramolecular Conjugate Addition Reactions

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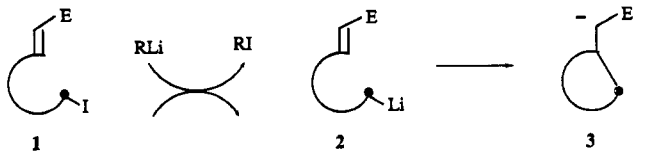
Received October 26, 1992

We have previously shown that metal–halogen exchange reactions may be used to introduce internal nucleophilic centers which may then undergo efficient intramolecular conjugate addition reactions leading to 3-, 4-, 5-, and 6-membered rings as shown in Scheme I.[1] Efficient execution of this scheme is possible with 1 (E = $COOBu^t$)[1b] only if the rate of metal–halogen exchange with primary iodides is greater than competing reactions of the lithiating agent (typically *n*-BuLi) such as the addition of RLi to the activated olefin,[1] 1,2-addition to the olefin-activating group (COOR),[2] or deprotonation reactions. Furthermore, the intramolecular ring-closure reaction of **2** must also be more rapid that such competing reactions involving the newly generated carbon–lithium center in **2**. We have observed this to be the case in reactions forming 3-, 4-, 5-membered rings but problematic in some cases involving 6-membered ring formation.[1a,b] Such rapid ring-closures[3] also serve to drive the reversible lithium–iodine exchange reaction generating **2** in the desired direction insomuch as the formation of the cyclic product **3**, a relatively stable enolate, is irreversible as well as being secure from nucleophilic attack. We now wish to demonstrate that this method may be extended to the highly efficient formation of certain polycyclic carbocycles through exchange-initiated cyclization reactions of symmetrical diiodides which undergo sequential intramolecular Michael–cycloalkylation reactions that are made possible by the rapidly reversible nature of the initiating lithium–iodine exchange reaction.

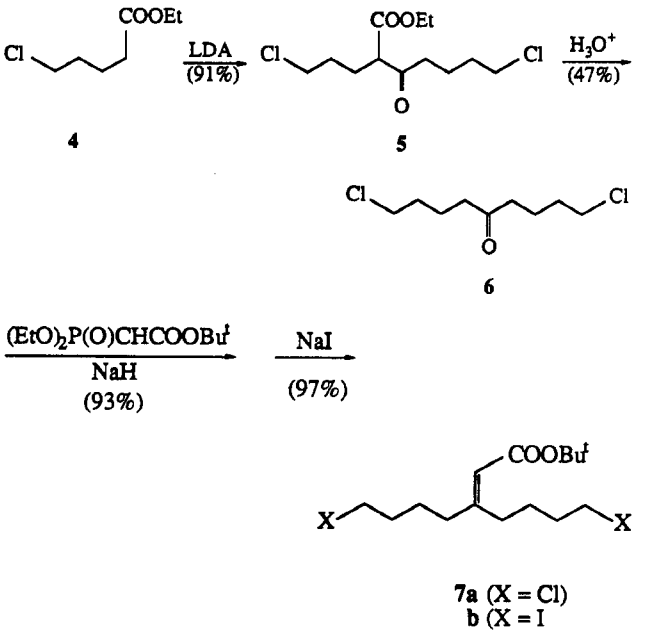
Discussion and Results

We envisioned that an unsaturated ester bearing two ω-iodoalkyl chains could, upon rapid lithium–iodine exchange at the first halocarbon center, undergo a rapid intramolecular ring-closure reaction followed by the cycloalkylation of the resulting enolate by the remaining iodoalkyl moeity. Success requires the the lithium–iodine exchange reactions be rapidly reversible insomuch as the remaining halocarbon center needed as the alkylating agent in the second step also would be expected to undergo lithium–halogen exchange, but rapid reversibility of the

Scheme I

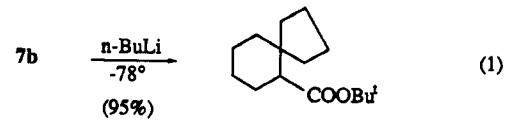


Scheme II



exchange reaction would ensure the periodic availability of the required electrophilic halocarbon center required for the final ring-closure reaction.[4]

To this end the cyclization reactions of two model substrates **7b** and **11b** have been examined (eqs 1 and 2). As shown in Scheme II, self-Claisen condensation of ethyl 5-chlorovalerate gave keto ester **5** which upon hydrolysis and decarboxylation gave dichloro ketone **6**. Horner–Emmons–Wittig phosphonate (HEW) olefination[5] of **6** provided unsaturated ester **7a** in high yield. Treatment of this ester with NaI in acetone gave the desired substrate **7b**. The slow addition of *n*-BuLi to **7b** in THF at −78 °C resulted in the formation of spiro ester **8** in 95% (89% isolated) yield (eq 1). In addition to the exceptional



(1)

efficiency of this process, it is notable that the Michael addition step involves a β,β-disubstituted acceptor.[6] Furthermore, exchange-induced intramolecular Wurtz-

(1) (a) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381. (b) Cooke, M. P., Jr. *Ibid.* **1984**, *49*, 1144. (c) Cooke, M. P., Jr. *Ibid.* **1992**, *57*, 1495. (d) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, 2199.

(2) Cooke, M. P., Jr.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 4987.

(3) This is in contract to the relatively slow cyclization reactions of corresponding unactivated alkenyllithium derivatives: (a) Drozd, V. N.; Ustynyuk, Y. A.; Tseleva, M. A.; Dmitrievi, L. B. *J. Gen. Chem. U.S.S.R.* **1969**, *39*, 1951. (b) Smith, M. J.; Wilson, S. E. *Tetrahedron Lett.* **1981**, *22*, 4615. (c) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861, 1865. (d) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. J. *Am. Chem. Soc.* **1987**, *109*, 2442. (e) Chamberlin, A. R.; Bllom, S. H.; Ceruini, L. A.; Fotach, C. H. *Ibid.* **1988**, *110*, 4788. (f) Broka, C. A.; Shen, T. *Ibid.* **1989**, *111*, 2981. (g) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044. (h) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765. (i) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742.

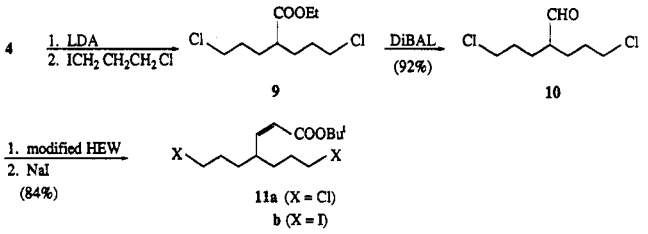
(4) This assumes that the rate of the second ring closure is slower than the rate of the iodine–lithium exchange reaction. We have generally found this to be the case in intramolecular cycloalkylation reactions of similar enolates leading to 6-membered ring formation of the type reported here.[1a,d]

(5) (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (b) Kelly, S. E. In *Comprehensive Organic Chemistry*; Trost, B., Fleming, I, Eds.; Pergamon Press: New York, 1991; p 729.

(6) β,β-Disubstitution often has a deleterous effect on intermolecular conjugate addition reactions: March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 2nd ed.; McGraw-Hill: New York, 1977; p 729.

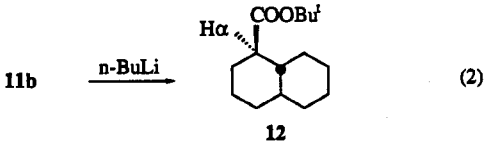
0022-3263/93/1958-2910$04.00/0

Scheme III



type coupling of the halide centers, known[7] to occur in systems containing more proximal halocarbon centers, does not occur since 9-membered ring formation is unfavorable.

Substrate **11b** was prepared as shown in Scheme III. Alkylation of the enolate derived from 4 with 1-chloro-3-iodopropane gave dichloro ester **9**. Ester reduction with diisobutylaluminum hydride (DiBAL) provided aldehyde **10** which was HEW phosphonate olefinated under conditions which promote cis-olefin formation ($KN(SiMe_3)_2$, 18-crown-6, −78 °C).[8] Using these conditions, an approximately equal mixture of **11a** and its *E*-isomer was obtained. Conversion of the mixture to the corresponding iodides with NaI in acetone enabled a facile isolation of **11b** by flash chromatography. Treatment of **11b** in THF at −78 °C with *n*-BuLi, as previously described for the cyclization of **7b**, gave only *all-trans*-**12** (eq 2) in 95%



(2)

isolated yield. The stereochemical assignment for **11** follows from previous model work and from H NMR spectroscopy. We have previously shown[1c] that ring closures of this type with substrates containing *Z*-olefin geometry give cyclopentane derivatives with extremely high trans-selectivity (>300:1 trans/cis) owing to minimization of 1,3-allylic strain in the reactive conformation. The stereochemistry at Cα also follows from stereoelectronic considerations in the alkylation of the intermediate ester enolate whose energetically favored conformer is predicted to be one in which the carbon–carbon double bond is eclipsed with the adjacent ring hydrogen.[9] A similar stereochemical outcome has been observed in other Michael-induced ring-closures leading to trans-1,2-disubstituted 6-membered rings.[10] Confirmation of the axial disposition of Hα was obtained from the 500-MHz ^{1}H NMR spectrum of **12** where Hα is seen as a doublet of doublet of doublets at δ 1.967 with J = 11.8, 10.2, and 3.5 Hz. The presence of two axial–axial coupling constants (J > 10 Hz) requires an axial disposition of Hα and hence the all-trans stereochemistry assigned in **12**.

In summary, highly efficient tandem exchange-initiated conjugate addition–cycloalkylation reactions of certain symmetrical diiodides are shown to be possible owing to the rapidity and facile reversibility of the metal–halogen exchange reactions of *n*-BuLi with primary iodides.

(7) Bailey, W. F.; Gagnier, R. P. *Tetrahedron Lett.* **1982**, *23*, 5123.
(8) Still, W. C.; Gennari, C. *Ibid.* **1983**, *24*, 4405.
(9) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(10) (a) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, 2199. (b) Fang, C.-L.; Suemune, H.; Sakai, K. *J. Org. Chem.* **1992**, *57*, 4300.

Experimental Section[11]

4-Carbethoxy-1,9-dichloro-5-nonanone (5). Diisopropylamine (14.6 mL, 104 mmol) in 150 mL of THF was cooled to −78 °C and treated with 58 mL (93 mmol) of 1.6 N *n*-BuLi in hexane. This solution was transferred by cannula over 40 min into a vigorously stirred solution containing 12.8 mL (80.5 mmol) of ethyl 5-chlorovalerate at 20 °C. The mixture was stirred for 15 min, poured into 600 mL of water, acidified with 3 N HCl, and extracted with pentane. The extracts were washed with water, dried, and concentrated. Distillation gave 10.4 (91%) of **5**: bp 143–148 °C (0.1 mm); ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3 H), 1.0–2.2 (b, 10 H), 2.4–2.7 (b, 1 H), 3.45 (t, J = 7.1 Hz, 2 H). 3.52 (t, J = 6.3 Hz, 2 H), 4.20 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.1, 21.0, 25.6, 30.3, 31.9, 40.9, 44.2, 44.4, 58.3, 61.5, 169.4, 203.9; IR (neat) 1707, 1732 cm^{-1}. Anal. Calcd for $C_{12}H_{20}Cl_2O_3$: C, 50.89; H, 7.12. Found: C, 51.20; H, 7.14.

1,9-Dichloro-5-nonanone (6). A mixture containing 3.2 g (11.3 mmol) of **5**, 15 mL of concd HCl, and 15 mL of EtOH was heated at reflux with vigorous stirring for 1 h. The mixture was diluted with water and following the addition of NaCl was extracted twice with pentane–Et_2O. The extracts were washed with water and saturated $NaHCO_3$ and dried over Na_2SO_4. Concentration gave an oil, which upon chromatography (silica gel, 20 cm, CH_2Cl_2) gave 1.11 g (47%) of pure **6**: ^{1}H NMR δ 1.74 (m, 8 H), 2.46 (t, J = 6.6 Hz, 4 H), 3.53 (t, J = 6.3 Hz, 4 H); ^{13}C NMR δ 21.1, 32.0, 41.7, 44.6, 209.5. An analytical sample was obtained by bulb-to-bulb distillation (110 °C, 0.1 mm). Anal. Calcd for $C_9H_{16}Cl_2O$: C, 51.20; H, 7.64. Found: C, 51.08; H, 7.64.

***tert*-Butyl 7-Chloro-3-(4-chlorobutyl)-2-heptenoate (7a).** NaH (80 mg (1.9 mmol), 56% in oil) was freed of oil by washing with pentane twice and then suspended in 3 mL of THF. With vigorous stirring, 338 mg (1.4 mmol) of *tert*-butyl diethylphosphonoacetate[12] was added over 2 min, and stirring was continued until the evolution of H_2 ceased and the mixture was homogeneous (5 min). Ketone **6** (220 mg (1.04 mmol)) in 0.5 mL of THF was added, and the mixture was allowed to stand for 16 h. The mixture was diluted with water and extracted with pentane. The extracts, upon concentration, gave 330 mg of crude product which upon PTLC (1:1 hexane–CH_2Cl_2) gave 298 mg (93%) of **7a**: ^{1}H NMR δ 1.47 (s, 9 H), 1.0–1.9 (b, 8 H), 2.15 (t, J = 5.9 Hz, 2 H), 3.61 (t, J = 7.3 Hz, 2 H), 3.54 (t, J = 6.3 Hz, 2 H), 3.56 (t, J = 6.3 Hz, 2 H), 5.58 (bs, 1 H); ^{13}C NMR δ 24.9, 25.7, 28.3, 30.6, 32.1, 32.5, 37.2, 44.6, 44.8, 79.7, 118.2, 160.3, 165.8. An analytical sample was obtained by bulb-to-bulb distillation (180 °C, 0.1 mm). Anal. Calcd for $C_{15}H_{26}Cl_2O_2$: C, 58.25; H, 8.47. Found: C, 58.64; H, 8.28.

***tert*-Butyl 7-Iodo-3-(4-iodobutyl)-2-heptenoate (7b).** All glassware was prewashed with $NaHCO_3$ solution and then water and dried prior to use to prevent damage to *tert*-butyl esters. A mixture of 560 mg (1.81 mmol) of **7a**, 4.5 g of NaI, and 25 mL of acetone was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the resulting residue was treated with water and extracted with pentane. The extracts were washed with water (2×), 5% $NaHSO_3$, water, and brine. Concentration of the dried extract gave 870 mg (97%) of **7b**: ^{1}H NMR δ 1.47 (s, 9 H), 1.3–2.0 (b, 8 H), 2.14 (t, J = 7.2 Hz, 2 H), 2.60 (t, J = 7.3 Hz, 2 H), 3.20 (t, J = 6.6 Hz, 2 H), 3.22 (t, J = 6.7 Hz, 2 H), 5.57 (s, 1 H); ^{13}C NMR δ 6.3, 6.7, 28.2, 28.4, 29.2, 30.2, 32.8, 33.3, 36.8, 79.6, 118.1, 160.1, 165.7. An analytical sample was obtained by bulb-to-bulb distillation (180 °C, <0.1 mm). Anal. Calcd for $C_{15}H_{26}I_2O_2$: C, 36.60; H, 5.33. Found: C, 36.43; H, 5.24.

Cyclization of 7b: *tert*-Butyl Spiro[4.5]decanecarboxylate (8). Diiodide **7b** (370 mg (0.75 mmol)) was twice reconcentrated from benzene to remove any traces of protic solvents and dried at 0.05 mm for 0.5 h. This iodide was dissolved in 10 mL of THF and with vigorous stirring at −78 °C was treated with 0.55 mL (0.88 mmol) of 1.6 N *n*-BuLi added dropwise over 5 min. Stirring was continued for 1.25 h while the bath temperature was allowed to rise to −40 °C. The solvent was then removed at 20 °C under reduced pressure, and hexadecane internal GLC standard and

(11) See ref 1c for general experimental details.
(12) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, *32*, 275.

water were added followed by extraction (2×) with pentane. The yield of 8 by GLC was 95%. Concentration of the extracts and PTLC (silica gel, 1:1 hexane–CH_2Cl_2) gave 160 mg (89%) of 8: ^1H NMR δ 1.0–1.9 (b, 16 H), 1.44 (s, 9 H), 2.1–2.3 (m, 1 H); ^{13}C NMR δ 22.8, 24.3, 23.9, 25.6, 27.2, 28.2, 32.7, 38.2, 38.8, 44.6, 52.1, 79.6, 174.7. An analytical sample was obtained by bulb-to-bulb distillation (110 °C, 0.1 mm). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.78; H, 10.80.

Ethyl 5-Chloro-2-(3-chloropropyl)pentanoate) (9). Diisopropylamine (3.7 mL (26 mmol)) in 60 mL of THF was treated with stirring at −78 °C with 14 mL (24 mmol) of 1.74 N *n*-BuLi over 2 min. After 10 min, 3.18 mL (20 mmol) of 4 was added dropwise over 3 min. The mixture was stirred for 15 min and then treated with 4 mL of HMPA and 2.4 mL (22.4 mmol) of 1-chloro-3-iodopopane. The mixture was stirred for 3 h at −78 °C and then allowed to warm to 0 °C whereupon 1 mL of HOAc was added and the mixture concentrated under reduced pressure. The residue was treated with water and extracted with pentane, and the extracts were washed with water, $NaHCO_3$, dilute HCl, and water. Concentration of the dried extracts and distillation gave 3.20 g (66%) of 9: bp 122–124 °C (0.5 mm); ^1H NMR δ 1.26 (t, J = 7.1 Hz, 3 H), 1.5–1.9 (b, 8 H), 2.32 (b, 1 H), 3.53 (t, 4 H), 4.15 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.3, 29.6, 30.3, 44.2, 44.5, 60.4, 175.1. Anal. Calcd for $C_{10}H_{18}Cl_2O_2$: C, 49.80; H, 7.52. Found: C, 50.11; H, 7.57.

5-Chloro-2-(3-chloropropyl)pentanal (10). A stirred solution of 1.17 g (4.87 mmol) of 9 in 16 mL of toluene was treated at −78 °C with 5.3 mL (5.3 mmol) of 1 M DiBAL in hexanes (Aldrich) over 2 min. The mixture for stirred for 1.25 h, treated with 0.5 mL of MeOH, stirred for 15 min, treated with 1 mL of 1:1 MeOH–H_2O, and then stirred at 20 °C for 10 min. The mixture was treated with 1 mL of 4 N NaOH, stirred for 5 min, and then treated with small amount of Na_2SO_4 to coaggulate gelatinous aluminum salts from which the organic phase was decanted. The residue was washed with pentane, and concentration of the combined extracts followed by distillation gave 882 mg (92%) of 10. This material often contained approximately 5–10% of the corresponding alcohol from over-reduction but was satisfactory for use without further purification. An analytical sample was prepared by PTLC (silica gel, CH_2Cl_2) followed by bulb-to-bulb distillation (190 °C, 0.5 mm): ^1H NMR δ 1.2–2.0 (b, 8 H), 2.30 (m, 1 H), 3.55 (m, 4 H), 9.61 (d, J = 2.5 Hz, 1 H); ^{13}C NMR δ 25.6, 29.8, 44.6, 50.4, 203.8. Anal. Calcd for $C_8H_{14}Cl_2O$: C, 48.75; H, 7.16. Found: C, 48.77; H, 7.20.

***tert*-Butyl 7-Iodo-4-(3-iodopropyl)-(*Z*)-2-heptenoate (11b).** A solution containing 2.2 g (8.3 mmol) of 18-crown-6 (Aldrich) and 528 mg (2.2 mmol) of *tert*-butyl diethylphosphonoacetate[11] in 15 mL of THF was cooled to −78 °C, and with stirring, 3.8 mL (1.9 mmol) of 0.5 M $(Me_3Si)_2NK$ in toluene was added over 1 min. After 5 min, 370 mg (1.7 mmol) of 10 (90% pure) in 2 mL of THF was added over 1 min, and stirring was continued for 1.5 h. Saturated NH_4Cl solution (15 mL) was added and the mixture was twice extracted with pentane. Concentration gave crude 11a as mixture of E/Z-isomers (55:45) which was converted into the corresponding iodides by heating with excess NaI in acetone for 18 h as described above in the preparation of 7b. Flash chromatography of the isomeric iodides (silica gel, 1:1 hexane–CH_2Cl_2) gave 365 mg (45%) of the trans-isomer 11a (lower R_f) and 315 mg (39%) of the desired cis-isomer 11b. 11a: ^1H NMR δ 1.05–2.00 (m, 8 H), 1.49 (g, 9 H), 2.18 (m, 1 H), 3.16 (t, J = 6.5 Hz, 4 H), 5.70 (d, J = 15.4, Hz, 1 H), 6.60 (dd, J = 15.4, 6.3 Hz, 1 H); ^{13}C NMR δ 6.4, 28.1, 30.9, 35.2, 40.7, 80.3, 123.8, 150.1, 165.5. 11b: ^1H NMR δ 1.05–2.0 (m, 8 H), 3.18 (t, J = 6.6 Hz, 4 H), 3.48 (m, 1 H), 5.72 (m, 2 H); ^{13}C NMR δ 6.9, 28.2, 31.0, 35.5, 36.1, 80.4, 122.9, 150.8, 165.7. An analytical sample was obtained by bulb-to-bulb distillation (190 °C, <0.1 mm). Anal. Calcd for $C_{14}H_{24}I_2O_2$: C, 35.16; H, 5.06. Found: C, 35.48; H, 5.17.

Cyclization of 11b. In the manner described above for the cyclization of 7b, 225 mg (0.47 mmol) of 11b in 7 mL of THF was treated at −78 °C with 0.35 mL (0.56 mmol) of 1.6 N *n*-BuLi added dropwise over 6 min with vigorous stirring. The bath temperature was allowed to rise over 0.75 h to −60 °C, and then the bath was removed allowing the reaction mixture to come to 20 °C over 0.25 h. Concentration, treatment with water, and extraction with pentane gave, after PTLC (silica gel, 1:1 hexane–CH_2Cl_2), 100 mg (95%) of 12: ^1H NMR (500 MHz) δ 0.80–1.42 (m, ~8 H), 1.44 s, 9 H), 1.58 (m, ~2 H), 1.72–1.90 (m, ~4 H), 1.97 (ddd, J = 11.8, 10.2, 3.5 Hz, 1 H); ^{13}C NMR δ 21.5, 25.9, 28.1, 29.4, 29.6, 31.0, 31.2, 45.8, 48.2, 50.2, 79.6, 175.3. An analytical sample was obtained by bulb-to-bulb distillation (140 °C, 1.5 min). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.18; H, 10.89.

Acknowledgment. We thank the National Science Foundation for supporting a portion of this work.