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Stereoselective Syntheses of 1,2-Dialkyl-1-phenyl Cyclopentanes Involving Intramolecular Carbolithiation of Olefins

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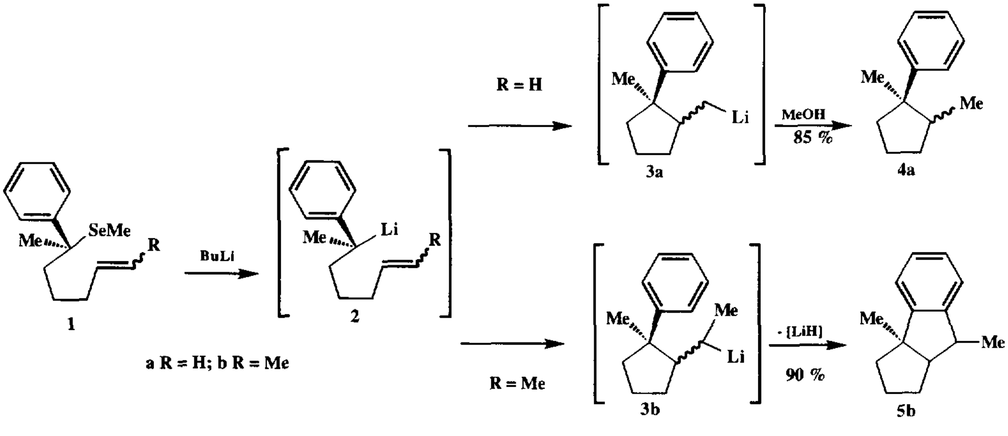
Abstract: 2-Ethyl-1-methyl-1-phenyl cyclopentane, unavailable by butyllithium-promoted carbocyclisation of the corresponding alkenyl selenide, has been efficiently produced using two different strategies involving the carbocyclisation of 6-phenyl-6-methylseleno-1-heptene as the key step. Copyright © 1996 Elsevier Science Ltd

We reported[1] that the alkenyl benzylselenide **1a** (R= H) reacts with butyllithiums and produces, *via* the corresponding alkenyl benzyllithium **2a** and 2-lithiomethyl-1-methyl-1-phenyl cyclopentane **3a**, the 1,2-dimethyl-1-phenyl cyclopentane **4a** in very high yield and with almost complete stereocontrol [*cis*-methyl groups in THF (diastereoisomeric excess (d.e. : 96%), *trans*-methyl groups in pentane (d.e. : 96%), Scheme 1]. We also described[2] that this reaction cannot be extended to the synthesis of 2-ethyl-1-methyl-1-phenyl cyclopentane **4b** (R= Me), its higher homolog, owing to the high propensity of the 2-(1'-lithioethyl)-1-methyl-1-phenyl cyclopentane **3b** to further add across the C,C double bond of the aromatic ring, to produce the cyclopent[a]indenyl derivative **5b** (90% yield, Scheme 1).[2]

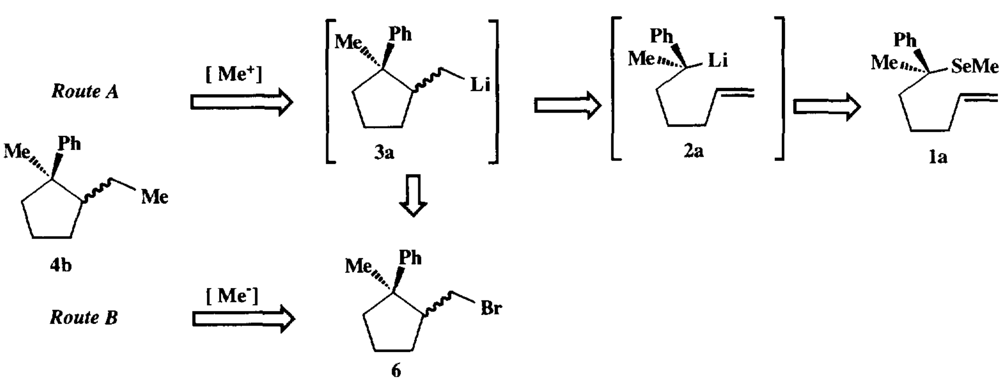
Scheme 1



We present in this paper alternative methods which use the carbocyclisation of **1a** as the key step and involve the introduction of a methyl group into the intermediate 2-lithiomethyl-1-methyl-1-phenyl cyclopentane **3a** (Scheme 2).

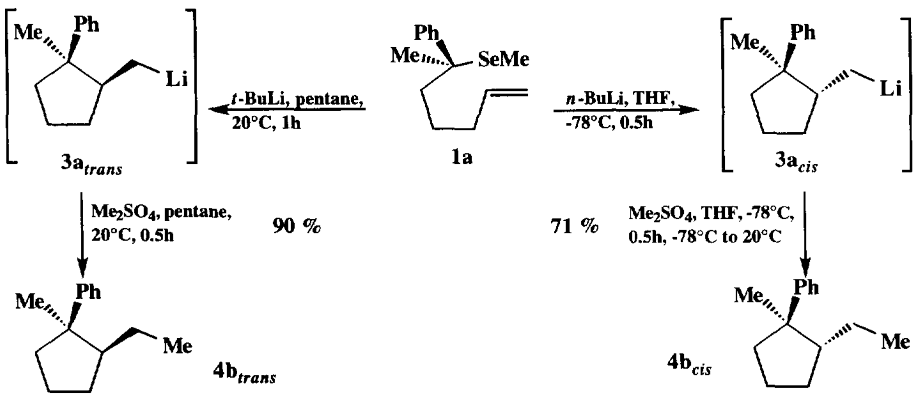
The first and most obvious route to **4b** (R= Me) was to trap 2-lithiomethyl-1-methyl-1-phenyl cyclopentane **3a** (R= H) resulting from the carbocyclisation of 6-phenyl-6-methylseleno-1-heptene with a methylating agent (Scheme 2, Route A). Alkylation of organometallics is not easy, although methylation is among the least difficult one due to the high accessibility of the electrophilic center and the absence of competing elimination reactions.[3] Most of the methylation reactions have been carried out with methyl iodide. Alkylation proved to be valuable for those alkylmetals derived from the main group metals (Mg, Li, Na, K) whose carbanionic center is stabilized by (i) an electron withdrawing group (such as an enolate)[4,5] (ii) a phenyl group[6,7] or (iii) an heterosubstituted organometallic (O,[8] B,[8] Si,[8] halogen,[8] N,[9] S,[10] Se[10]), but is often inefficient with those alkylmetals which do not possess the characteristic described above.[3,11] It is, for example, well established that halogen metal exchange often competes favorably with the alkylation reaction, especially when alkyllithiums are used.[11-14] In such cases, successful alkylation has been (i) achieved from the corresponding copper derivative[15,16] and alkyl halides (including methyl iodide) or directly on the alkyllithium using dimethyl sulfate (instead of methyl iodide) as the alkylating agent.[17,18]

Scheme 2



Sequential reaction of the benzylselenide **1a** with BuLi[1] and dimethyl sulfate affords, after hydrolysis, the expected ethyl cyclopentane derivative **4b** in high yield and with excellent stereocontrol (Scheme 3). For example, **4b**$_{cis}$ (*cis*-relationship between the methyl and the ethyl groups) is almost obtained as one stereoisomer when the cyclisation is carried out in THF [(i) 1 eq. *n*-BuLi, THF, -78°C, 0.5 h, (ii) Me_2SO_4, THF, -78°C, 0.5 h, -78°C to 20°C, 0.5 h, 71%], whereas its *trans*-stereoisomer is formed if the reaction is performed in pentane [(i) 1 eq. *t*-BuLi, pentane, 20°C, 1 h, (ii) Me_2SO_4, pentane, 20°C, 0.5 h, 90%]

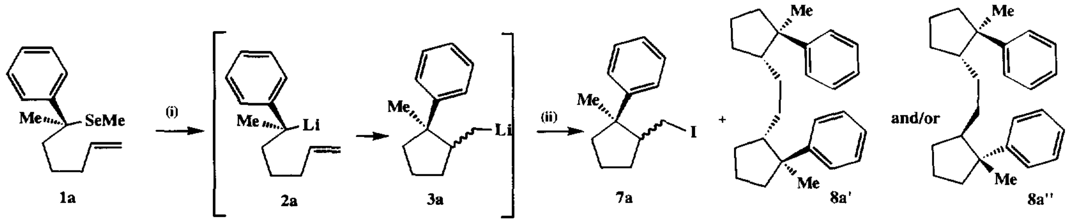
Scheme 3



The reaction takes another course if methyl iodide is used in place of dimethyl sulfate (Scheme 4). The dimer **8a** is produced when the reaction is carried out with stoichiometric amount of methyl iodide [(i) *t*-BuLi, THF, -78°C, (ii) 1 eq. MeI, -78°C, 0.5 h, 81%, Scheme 4, entry a] whereas 2-iodomethyl-1-methyl-1-phenyl cyclopentane **7a**$_{cis}$, resulting from an halogen-metal exchange reaction, is almost exclusively formed when an excess of the electrophile is instead used [(i) *t*-BuLi, THF, -78°C, (ii) 4 eq. MeI, -78°C, 0.5 h, **7a**$_{cis}$ 73%, Scheme 4, entry b). Interestingly, in diethyl ether 2-iodomethyl-1-methyl-1-phenyl cyclopentane **7a**$_{trans}$ is obtained whatever the amount of methyl iodide employed [(i) *t*-BuLi, ether, - 25°C, 0.5 h (ii) 1 or 4 eq. MeI, -25°C, 1 h, 50%, Scheme 4, entry c].

The gross structure of **8a** has been established on the ground of its spectroscopical data,[19a] especially the mass spectra which clearly shows a peak (EI) of M/e 346 characteristic of its dimeric nature. Although we have not firmly established its relative stereochemistry, we suspect to be *cis* on each of its cyclopentane rings on the basis of previous work performed on the same substrate **1a** and under similar conditions (solvent, temperature and time).[1,2,19b-d] Furthermore the ^{1}H and ^{13}C NMR spectra of **8a** are both compatible with its proposed structure.

Scheme 4



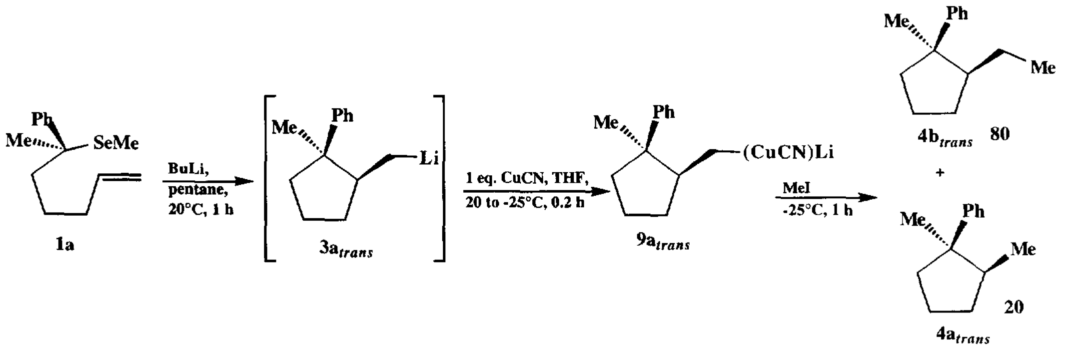
Entry	Conditions (i)	Conditions (ii)	4a % ^{a}	7a % ^{a} (%) ^{b}	8a % ^{a} (%) ^{b,19}
a	*t*-BuLi, THF, -78°C	1 eq. MeI, -78°C, 1 h	**4a**$_{cis}$ 10	-	90 (81)
b	*t*-BuLi, THF, -78°C	4 eq. MeI, -78°C, 0.5 h	**4a**$_{cis}$ 10	**7a**$_{cis}$ 81 (73)	(9)
c	*t*-BuLi, ether, - 25°C, 0.5 h	1 or 4 eq. MeI, -25°C, 1 h		**7a**$_{trans}$ (50)	

^{a} refers to the % of products obtained by GC[2], ^{b} () refers to yields of isolated analytically pure product.

These results are quite surprising, although it is well known from the work of Gilman[12] and Wittig[13] that halogen-metal exchange can favorably compete with the substitution reaction. The dimeric compound **8a** generated in THF could be produced by substitution of **7a** by **3a**, or by coupling of a (cyclopentyl)methyl radical intermediate (SET) during the iodine metal exchange.[20-22] The former process is hampered by the inertness of **3a** towards methyl iodide (even when used in excess) which should be by far more reactive than **7a** in an S$_N$2 type reaction; and also the observed inertness of **7a** towards methyllithium (10 eq., THF, 20°C, 3 days, 0% yield of **4a**). The SET mechanism is not totally consistent with the observation that an excess of methyl iodide diminishes substantially the yield of **8a**$_{cis\text{-}cis}$. Experiments are under way in order to understand these results.

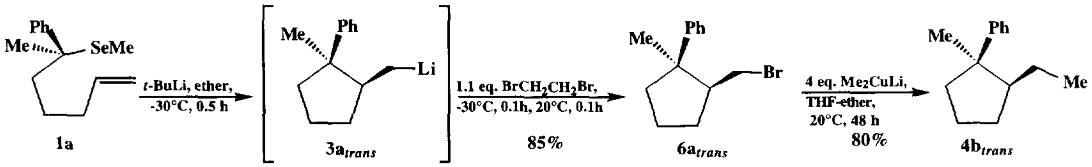
In a second approach, the methylation was performed on the cyano cuprate derived from **3a**$_{trans}$ [(i) 1 eq. CuCN, THF, -78°C to -25°C, 0.2 h (ii) 2 eq. MeI, -78°C, 1 h, (Scheme 5)].[16] Unfortunately, substantial amounts of **4a**$_{trans}$ (20%) resulting from the formal protonation of one of the organometallic species (**3a**$_{trans}$ or **9a**$_{trans}$) was obtained in addition to the desired compound **4b**$_{trans}$ (80%). We have been unable to avoid such side reaction or to separate **4a**$_{trans}$ from **4b**$_{trans}$.

Scheme 5



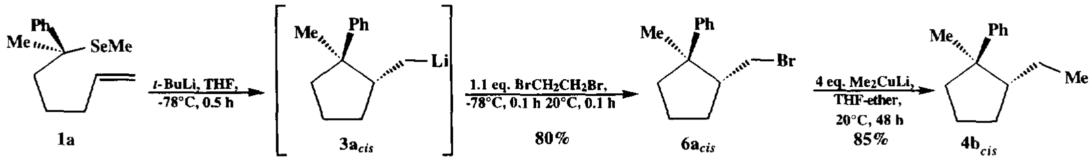
Finally, $\mathbf{4b}_{trans}$ has been synthesized from **1a** in 68% isolated yield by a three step, two-pot sequence (Scheme 6). It involves sequential reaction of **1a** with *t*-butyllithium in ether, followed by addition of dibromoethane,[12] which produced 2-bromomethyl-1-methyl-1-phenyl cyclopentane $\mathbf{6a}_{trans}$ [(i) *t*-BuLi, ether, -30°C, 0.5 h (ii) 1.1 eq. $(CH_2Br)_2$, -30°C, 0.1 h, 20°C, 0.1 h, 85% yield, d.e. : 80%] and further reaction of the latter with lithium dimethyl cuprate [23] (THF-ether, 20°C, 48 h, 80% yield, d.e. : 80%).

Scheme 6



A similar reaction, performed in THF instead of ether, leads to the formation of 2-ethyl-1-methyl-1-phenyl cyclopentane $\mathbf{4b}_{cis}$ in reasonably good yield [(i) *t*-BuLi, THF, -78°C, 0.5 h (ii) 1.1 eq. $(CH_2Br)_2$, -78°C, 0.1 h, 20°C, 0.1 h, 85% yield in $\mathbf{6a}_{cis}$ d.e. : 92% (iii) 4 eq. Me_2CuLi, THF-ether, 20°C, 48 h, 85% yield in $\mathbf{4b}_{cis}$, d.e. : 92%, Scheme 7].

Scheme 7



In conclusion, 6-methylseleno-6-phenyl-1-methyl-1-heptene **1a** is a valuable precursor of 1,2-dimethyl-1-phenyl cyclopentane **4a** and of 2-ethyl-1-methyl-1-phenyl cyclopentane **4b**. The reaction takes place by sequential reaction with butyllithium and methanol or dimethyl sulfate and occurs in high yield and with almost complete stereocontrol [*cis*-methyl groups in THF (d.e. : 96%), *trans*-methyl groups in pentane (d.e. : 96%)]. Alternative methods using cuprates require more steps and are less efficient, but they open valuable routes to higher homologs.

Experimental Section

General : ^{1}H-NMR spectra were performed on JEOL JNM EX 400 (400 MHz for ^{1}H or 100.4 MHz for ^{13}C), PMX 60 SI (60 MHz) and FX 90 Q (90 MHz or 22.5 MHz for ^{13}C) spectrometers. The spectra were measured in CCl_4 or $CDCl_3$ with TMS as an internal standard (δ : 0.00 ppm). IR data reported in cm^{-1} were obtained using a Perkin-Elmer model 337 spectrophotometer. The spectra were recorded for neat liquids. Mass spectra were obtained on an HP 5995 A GC/MS spectrometer. In the discussion $M^{\bullet}$ refers to $M^{+\bullet}$ and only a few characteristics are reported. Microanalyses were performed in the Microanalysis Laboratory of the Paris VI University (Paris, France). Layer chromatography : Analytical thin-layer chromatographies (TLC) were performed on pre-made, glass-backed plates SiO_2, $60PF_{254}$, 250 μ (Merck 5719). Compounds were visualised by UV illumination and by heating to 150°C after spraying phosphomolybdic acid in ethanol. Preparative layer chromatography (PLC) was performed on SiO_2 plates prepared as previously described.[24] Preparative HPLC have been performed on Prochrom LC50 stainless steel column [Diam.: 50 mm, Length : 350 mm filled with 400 g of SiO_2 (Merck 15.111 (15-40 μm)] using a flow rate of 100 ml/min. and the detection was performed using UV detector (λ= 254 nm). All the reactions were performed in two necked round bottomed flasks equipped with a septum stopper and an argon filled balloon or in sealed tubes *(vide infra)*. All glassware was warmed prior to use and degassed at 0.1 mmHg. All transfers of reagents were performed *via* syringes. Reactions performed at -78°C have been carried out in a flask immersed in a Dewar filled with a dry-ice acetone mixture.

Reagents and solvents. Unless otherwise noted, the reagents and solvents used in this work have been purchased from Acros and were distilled. Anhydrous THF and ether were distilled from sodium benzophenone ketyl immediatly prior to use. Anhydrous dichloromethane was distilled from phosphorous pentoxide. *n*-BuLi (1.6 M in hexane, Aldrich) and *t*-BuLi (1.7 M in cyclopentane, Aldrich) were titrated prior to use using the procedure of Gilman.[12]

Synthesis of arylcycloalkanes by anionic cyclisation of benzylselenides : General procedure. Butyllithium (1 eq.) was added dropwise, under argon, to a stirred solution of the benzylselenide[2] in a dry solvent (0.5 M in tetrahydrofuran, ether or pentane). The resulting solution (yellow to dark red depending upon the nature of the benzyllithium) was stirred at the temperature and for the time given for each example. When the reaction mixture was quenched, the electrophile was added dropwise and the resulting mixture stirred at the temperature and for the time given for each example, then hydrolysed with water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* (20 mmHg). The residual liquid was purified by silica gel preparative thin layer chromatography. The composition of the crude mixture was determined by GC analysis using SE 30 capillary column (F.I.D. detector, $T_{det.}$= $T_{inj.}$= 250°C, He : d= 1 ml/min., 100 to 220°C, 10°C/min.) Specific details, including spectroscopic and analytical data are described below for each cited case.

Synthesis of *rel(1R,2R)*-2-ethyl-1-methyl-1-phenyl cyclopentane $4b_{cis}$ by alkylation with Me_2SO_4. Following the general procedure, 6-methylseleno-6-phenyl-1-heptene **1a** (0.7 mmol., 0.203 g) was dissolved in dry pentane and reacted with *n*-butyllithium (1.51 M, 0.50 ml, 0.7 mmol) at -78°C for 0.5 h. Dimethyl sulfate (0.5 ml) was added rapidly. The reaction mixture was stirred for an additional 0.5 h at this temperature, warmed to room temperature and quenched with NaOH (1M). The crude product was purified (eluent : pentane) to afford 0.102 g of a mixture of *rel(1R,2R)*-2-ethyl-1-methyl-1-phenyl cyclopentane $\mathbf{4b}_{cis}$

(71%) and *rel(1R,2S)*-1,2-dimethyl-1-phenyl cyclopentane **4a**$_{cis}$ (6%). The relative composition has been determined by GC^2 : retention times= 4.53 min. (**4b**$_{cis}$) and 5.49 min. (**4a**$_{cis}$).

Synthesis of *rel(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane 4b$_{trans}$ by alkylation with Me$_2$SO$_4$. Following the general procedure, 6-methylseleno-6-phenyl-1-heptene **1a** (0.7 mmol., 0.190 g) dissolved in dry pentane was reacted with *t*-butyllithium (1.57 M, 0.45 ml, 0.7 mmol) at 20°C for 1 h. Dimethyl sulfate (0.5 ml) was added rapidly and a precipitate appeared. The reaction mixture was stirred for an additional 0.5 h at this temperature, and then quenched with NaOH (1M). The crude product was purified (eluent : pentane) to afford 0.120 g of a mixture of *rel(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane **4b**$_{trans}$ (90%) and *rel(1R,2S)*-1,2-dimethyl-1-phenyl cyclopentane **4a**$_{trans}$ (6%). The relative composition has been determined by GC^2 retention times= 4.29 min. (**4b**$_{trans}$) and 5.24 min. (**4a**$_{trans}$).

Synthesis of *rel(1R,2S)*-1-iodomethyl-2-methyl-2-phenyl cyclopentane 7a$_{cis}$. Following the general procedure, benzylselenide **1a** (0.132 g, 0.5 mmol) dissolved in dry tetrahydrofuran was reacted with *t*-butyllithium (1.6 M in pentane, 0.32 ml, 0.65 mmol) at -78°C for 0.5 h. Methyl iodide (0.280 g, 2 mmol) was then added rapidly and a precipitate appeared after 0.15 h. The reaction mixture was stirred for an additional 0.75 h at this temperature, quenched with water and warmed to room temperature. The crude product was purified (eluent : pentane/toluene : 97/3 (v/v)) to afford 0.110 g (73%) of the iodide **7a**$_{cis}$; TLC : R$_f$= 0.58 (eluent : pentane/toluene : 97/3 (v/v)); IR (Film) cm^{-1} : 3088, 3055, 3025, 2957, 2871, 1653, 1598, 1494, 1443, 1377, 1185, 756, 699; ^{1}H NMR (CDCl$_3$, 90 MHz) δ (ppm) : 1.10-2.70 (m, 10H, $C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}$-; Ph-C-$C\underline{H}_3$ (1.20 ppm; s)), 2.70-3.30 (m, 2 H, -CH-$C\underline{H}_2$I), 7.2 (m, 5 H, $C_6\underline{H}_5$-); MS (m/e) : 300 [M]$^{+\bullet}$, 173 [M-I]$^+$, 157, 143, 129, 119, 102, 91; The iodide decomposes slowly at room temperature and must be conserved at -20°C.

Synthesis of the coupling products 8a$_{cis\text{-}cis}$. Following the general procedure, benzylselenide **1a** (0.132 g, 0.5 mmol) dissolved in dry tetrahydrofuran was reacted with *t*-butyllithium (1.6 M, 0.32 ml, 0.65 mmol) at -78°C for 0.5 h. Methyl iodide (0.280 g, 2 mmol) was then added dropwise and a precipitate appeared after 0.15 h. The reaction mixture was stirred for an additional 0.75 h at this temperature, quenched with water and warmed to room temperature. The crude product was purified (eluent : pentane/toluene : 97/3 (v/v)) to afford 0.07 g (80%) of the coupling product **8a**$_{cis\text{-}cis}$; TLC : R$_f$= 0.50 (eluent : pentane/toluene : 97/3 (v/v)); IR (Film, cm^{-1}) 3084, 3054, 3021, 2952, 2869, 1599, 1495, 1473, 1443, 1376, 755, 699; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm) : 0.92 (m, 1 H, -CH-CH$\underline{H}$-CH$_2$-CH-), 1.08 and 1.09 (two s, 3 H, Ph-C-$C\underline{H}_3$), 1.27-1.31 (m, 3 H, -CH-$C\underline{H}$H-$C\underline{H}_2$-CH-), 1.66-1.95 (m, 12 H, two ($C\underline{H}_2$)$_3$ cyclopentane), 7.15-7.23 (m, 10 H, two $C_6\underline{H}_5$-); MS (m/e) : 266, 252, 251, 165, 118, 104, 90, 57; C$_{26}$H$_{34}$: Calc. : C, 90.11%; H, 9.89%; Found : C, 89.94%; H, 10.06%.

Synthesis of *rel(1R,2R)*-1-iodomethyl-2-methyl-2-phenyl cyclopentane 7a$_{trans}$. Following the general procedure, benzylselenide **1a** (0.267 g, 1 mmol) dissolved in dry ether was reacted with *t*-butyllithium (1.6 M, 0.65 ml, 0.65 mmol) at -30°C for 0.5 h. Methyl iodide (0.280 g, 2 mmol) was then added rapidly and a white precipitate appeared after 0.15 h. The reaction mixture was stirred for 0.75 h at this temperature, quenched with water and warmed to room temperature. The crude product was purified (eluent : pentane/toluene : 97/3 (v/v)) to afford 0.110 g (50%) of the iodide **7a**$_{trans}$; TLC : R$_f$= 0.63 (eluent pentane/toluene : 97/3 (v/v)); IR (Film) cm^{-1}: 3083, 3054, 3020, 2957, 2873, 1944, 1870, 1801, 1599, 1494, 1458, 1443, 1428, 1375, 1316, 1247, 1030, 763, 701; ^{1}H NMR (CDCl$_3$, 90 MHz) δ (ppm) : 1.20-2.6 (m, 10 H, $C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}$, Ph-C-$C\underline{H}_3$ (1.34 ppm, s)), 3.03 (m, 1 H, CH-$C\underline{H}$(H)I), 2.43 (m, 1 H, CH-CH($\underline{H}$)I), 7.25 (m, 5 H, $C_6\underline{H}_5$-); MS (m/e) : 173 $[M-I]^{+\bullet}$, 131, 129, 128, 117, 115, 105, 95, 91 (tropylium). The iodide decomposes slowly at room temperature and should be conserved at -20°C.

Synthesis of *rel(1R,2S)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane 6a$_{cis}$. Following the general procedure, 6-methylseleno-6-phenyl-1-heptene **1a** (1.33 g, 5 mmol) dissolved in dry tetrahydrofuran was reacted with *t*-butyllithium (1.7 M, 2.95 ml, 5 mmol) at -78°C for 0.5 h. 1,2-Dibromoethane (1.03 g, 5.5 mmol) dissolved in tetrahydrofuran was added dropwise. The reaction mixture was stirred for 0.5 h at this temperature and warmed to room temperature. The crude product was purified (eluent : pentane) to afford 0.99 g of *rel(1R,2S)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane **6a**$_{cis}$ (80%; d.e. : 92%): TLC : R_f= 0.55 (eluent : pentane); GC^2 : retention time= 10.4; **IR** (Film) cm^{-1} : 3085, 3024, 2960 ($-CH_2-$ cyclopentane), 2872, 1599 (C=C aromatic), 1495, 1443, 1378, 1321, 1228, 1135, 1030, 916, 757, 699, 650 (C-Br); ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) : 1.18 (s, 3 H, $Ph-C-C\underline{H}_3$), 1.30-2.78 (m, 7 H, $-(C\underline{H}_2)_3-C\underline{H}-$), 3.15 (dd, J= J'= 10.5 Hz, 1 H, $-CH\underline{H}Br$), 3.36 (dd, J= 10.5 Hz, J'= 4.5 Hz, 1 H, $-C\underline{H}HBr$), 7.00-7.15 (m, 5 H, $C_6\underline{H}_5-$); MS (m/e) : 254 and 252 ($[M]^{+\bullet}$, 2 and 2), 173 ($[M-Br]^{+\bullet}$, 23), 131 (23), 105 (68), 91 ($[tropylium]^+$, 100), 77 (27), 55 (17).

Synthesis of *rel(1R,2R)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane 6a$_{trans}$. Following the general procedure, 6-methylseleno-6-phenyl-1-heptene **1a** (1.33 g, 5 mmol) dissolved in dry ether reacted with *t*-butyllithium (1.7 M, 2.95 ml, 5 mmol) at -30°C for 0.5 h. 1,2-Dibromoethane (1.03 g, 5.5 mmol) dissolved in tetrahydrofuran was then added dropwise. The reaction mixture was stirred for an additional 0.5 h at this temperature and warmed to room temperature. The crude product was purified (eluent : pentane/toluene : 95/05 (v/v)) to afford 1.02 g of *rel(1R,2R)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane **6a** (85%; d.e. : 80%); TLC : R_f= 0.30 (eluent : pentane); GC^2 : retention time= 10.33 (isomer **6a**$_{trans}$: 90%) and 10.37 (isomer **6a**$_{cis}$: 10%); IR (Film) cm^{-1} : 3083, 3055, 2959 ($-CH_2-$ cyclopentane), 2875, 1944 (aromatic overtones), 1872, 1804, 1599 (C=C aromatic), 1578, 1540, 1496, 1376, 1321, 1317, 1257, 764, 701, 653 (C-Br); ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) : 1.36 (s, 3 H, $Ph-C-C\underline{H}_3$), 1.42-2.24 (m, 7 H, $-(C\underline{H}_2)_3-C\underline{H}-$), 2.60 (dd, J= 10.5 Hz and J'= 11.2 Hz, 1 H, $-C\underline{H}HBr$), 3.12 (dd, J= 10.5 Hz and J'= 2.7 Hz, 1 H, $-CH\underline{H}Br$), 7.00-7.15 (m, 5 H, $C_6\underline{H}_5-$); MS (m/e) : 254 and 252 ($[M]^{+\bullet}$, 2 and 2), 173 ($[M-Br^{\bullet}]^+$, 23), 131 (22), 105 (64), 91 ($[tropylium]^+$, 100), 77 (25), 55 (17); $C_{13}H_{17}Br$: Calc. : C, 61.67%; H, 6.76%; Found : C, 62.02%; H, 6.78%.

Synthesis of *rel(1R,2R)*-2-ethyl-1-methyl-1-phenyl cyclopentane 4b$_{cis}$ by alkylation of the bromide 6a$_{cis}$ with Me_2CuLi. In a 50 ml tube closed by a rubber septum, methyllithium (1.5 M, 5.33 ml, 8 mmol) was added under argon to a slurry of CuI (0.79 g, 4 mmol) in tetrahydrofuran (0.5 M). The mixture was cooled to -78°C. After 0.5 h, the solution was allowed to warm to room temperature and *rel(1R,2S)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane **6a**$_{cis}$ (0.25 g, 1 mmol) was added dropwise. The reaction mixture was stirred for two days and carefully hydrolysed with water. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with ammonium hydroxide solution, water, dried over $MgSO_4$, filtered and concentrated *in vacuo* (20 mmHg). The crude product was purified (eluent : pentane) to afford 0.16 g of *rel(1R,2R)*-2-ethyl-1-methyl-1-phenyl cyclopentane **4b**$_{cis}$ (85%) as a liquid; TLC : R_f= 0.85 (eluent : pentane); GC^2 : retention time= 7.60; IR (Film) cm^{-1} : 3085, 3055, 3021, 2956, ($-CH_2-$ cyclopentane), 1599 (C=C aromatic), 1579, 1495, 1457, 1376, 1313, 1236, 1156, 1033, 939, 911, 755, 699; ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) : 0.81 (t, J= 7.5 Hz, 3 H, $C\underline{H}_3-CH_2-$), 0.99 (s, 3 H, $Ph-C-C\underline{H}_3$), 1.00-2.15 (m, 9 H, $-(C\underline{H}_2)_3-C\underline{H}-C\underline{H}_2$), 7.00-7.15 (m, 5 H, $C_6\underline{H}_5-$); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ (ppm) : 13.54, 20.04, 21.94, 30.01, 43.34, 48.11, 52.01, 125.21, 126.02, 127.91, 149.86. MS (m/e) : 188 ($[M]^{+\bullet}$, 13), 145 (3), 131 (40), 118 (100), 105 (20), 91 ($[\text{tropylium}]^+$, 40), 77 (20), 55 (16); $C_{14}H_{20}$: Calc. : C, 89.36%; H, 10.63%; Found : C, 88.31%; H, 11.01%.

Synthesis of rel*(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane 4b$_{trans}$ by alkylation of the bromide 6a$_{trans}$ with Me_2CuLi. Methyllithium (1.5 M, 5.33 ml, 8 mmol) was added, under argon, to a slurry of CuI (0.79 g, 4 mmol) in tetrahydrofuran (0.5 M) present in a 50 ml tube sealed by a rubber septum and cooled at -78°C. After 0.5 h, the solution was allowed to warm to room temperature and *rel(1R,2S)*-2-bromomethyl-1-methyl-1-phenyl cyclopentane **6a**$_{trans}$ (0.25 g, 1 mmol; d.e. : 86%) was added dropwise. The reaction mixture was stirred for two days and carefully hydrolyzed with water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer were washed with a saturated ammonium hydroxide solution, water, dried over $MgSO_4$, filtered and concentrated *in vacuo* (20 mmHg). The crude product was purified (eluent : pentane) to afford 0.15 g of *rel(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane **4b** (80%; d.e. : 84%); TLC : Rf= 0.85 (eluent : pentane); GC^2 : retention time= 7.4 (isomer **4b**$_{cis}$: 8%) and 7.6 (isomer **4b**$_{trans}$: 92%); IR (Film) cm^{-1} : 3085, 3056, 3022, 2955 ($-CH_2-$ cyclopent.), 1599 (C=C aromatic), 1578, 1495, 1455, 1375, 1313, 1277, 1159, 1124, 1024, 1071, 1030, 942, 910, 763, 700; ^1H NMR ($CDCl_3$, 90 MHz) δ (ppm) : 0.75 (t, J= 7.5 Hz, 3 H, $C\underline{H}_3-CH_2-$), 0.96-2.30 (m, 12 H, $-(C\underline{H}_2)_3-C\underline{H}-C\underline{H}_2$; Ph-C-$C\underline{H}_3$ (1.30 ppm; s)), 7.00-7.30 (m, 5 H, $C_6\underline{H}_5-$);^{13}C NMR ($CDCl_3$, 22.5 MHz) δ (ppm) : 148.2, 127.9, 127.6, 127.2, 126.0, 125.2, 52.4, 49.3, 44.1, 37.5, 35.8, 31.9, 29.5, 28.7, 24.1, 21.7, 17.6, 13.7; MS (m/e) : 188 ($[M]^{+\bullet}$, 12), 145 (3), 131 (36), 118 (100), 105 (19), 91 ($[\text{tropylium}]^+$, 38), 77 (19), 55 (17).

Synthesis of *rel(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane 4b$_{trans}$ by alkylation of an organocuprate reagent with MeI. Following the general procedure, 6-methylseleno-6-phenyl-1-heptene **1a** (0.5 mmol, 0.134 g) dissolved in dry pentane reacted under argon with *t*-butyllithium (1.7 M, 0.35 ml, 0.5 mmol) at 20°C for 1 h. The reaction mixture was then cooled to -25°C and diluted with tetrahydrofuran (1 ml). This solution was transfered to a slurry of CuCN (45 mg, 1 eq) in 1 ml of THF and cooled to -78°C. The resulting green mixture was stirred at -25°C for 0.25 h and methyl iodide (0.14 g, 1 mmol) was added. The resulting mixture was stirred for 1 h, quenched with methanol and warmed to room temperature. The crude product was purified (eluent : pentane/toluene : 97/3 (v/v)) to afford 0.07 g of a mixture of *rel(1R,2S)*-2-ethyl-1-methyl-1-phenyl cyclopentane **4b**$_{trans}$ (80%) and *rel(1R,2S)*-1,2-dimethyl-1-phenyl cyclopentane **4a**$_{cis}$ (20%). The relative composition has been determined by GC^2.

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