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# Palladium-Mediated Ring Closure Reactions. Facile Syntheses of Enantiopure Bicyclic and Tricyclic Alkenones

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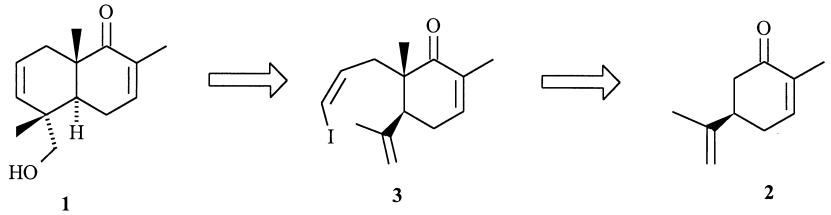
**Abstract**—(*R*)-Carvone was used as a chiral building block. Regio- and stereoselective alkylations at C6 and C2 of (*R*)-carvone and (*R*)-5-isopropyl-2-methyl-2-cyclohexenone [derived from the hydrogenation of (*R*)-carvone] followed by palladium-mediated ring closures afforded various enantiopure bicyclic and tricyclic alkenones. Hence, cyclization of (5*S*,6*S*)-2,6-dimethyl-6-(*cis*-3-iodo-2-propenyl)-5-isopropenyl-2-cyclohexenone (**3**) gave (4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-hexahydro-5-(methoxycarbonylmethyl)-2,5,8a-trimethylnaphthalen-1-one (**7**) as the major product, cyclization of (5*S*,6*S*)-2,6-dimethyl-6-(*cis*-3-iodo-2-propenyl)-5-isopropyl-2-cyclohexenone (**22**) produced (1*S*,5*R*,6*S*)-1,5-dimethyl-6-isopropyltricyclo[3.3.1.0$^{2,8}$]-3-nonen-9-one (**23**), and cyclization of (2*R*,5*S*,6*S*)-2,6-dimethyl-2-(*cis*-3-iodo-2-propenyl)-5-isopropenyl-3-cyclohexen-1-one (**25**) afforded (3a*R*,6*S*,7a*R*)-6,7a-dimethyl-5-isopropenyl-3a,6,7,7a-tetrahydro-1*H*-inden-7-one (**26**). A 1,2-rearrangement reaction of bromide **16** gave hexahydro-1*H*-benzocycloheptene **17**. 

## Introduction

In the studies of chiral syntheses of biologically active natural products, pyripyropenes[1] (acyl-CoA: cholesterol *O*-acyltransferase inhibitors),[2] arisugacin (acetylcholinesterase inhibitor),[3] and chloropuupehenone and its derivatives[4] (cholesteryl ester transfer protein inhibitors); various enantiopure and substituted *trans*-bicyclo[4.4.0]-decanes were needed for the syntheses. Herein, we report the regio- and stereoselective propenylation of 6-methylcarvones followed by a modified intramolecular Heck reaction[5] in facile syntheses of enantiopure substituted *trans*-bicyclo-[4.4.0]decanones, bicyclo[5.4.0]undecenones, *cis*-hydroindans, and tricyclic alkenones starting from (*R*)-carvone (**2**). These methods, not previously reported, allow a rapid construction of various useful enantiopure bicyclic and tricyclic intermediates for natural-product synthesis.

## Results and Discussion

From our initial retrosynthetic analysis of pyripyropene A and other diterpenes, the A–B ring fragment, such as functionalized *trans*-bicyclo[4.4.0]decane **1**, can be synthesized from (*R*)-(−)-carvone (**2**) via intermediate **3** (Scheme 1). Hence, intermediate **3** was prepared from selective α-monomethylation[6] followed by α-propenylation of (*R*)-carvone. Treatment of (*R*)-carvone (**2**) with LDA in THF followed by methyl iodide gave a 79% yield of a mixture (3:1) of **4** and **5** (Scheme 2). Epimers **4** and **5**, although separable by silica




**Scheme 1.**

*Keywords*: bicyclic aliphatic compounds; cyclization; palladium and compounds; stereocontrol.

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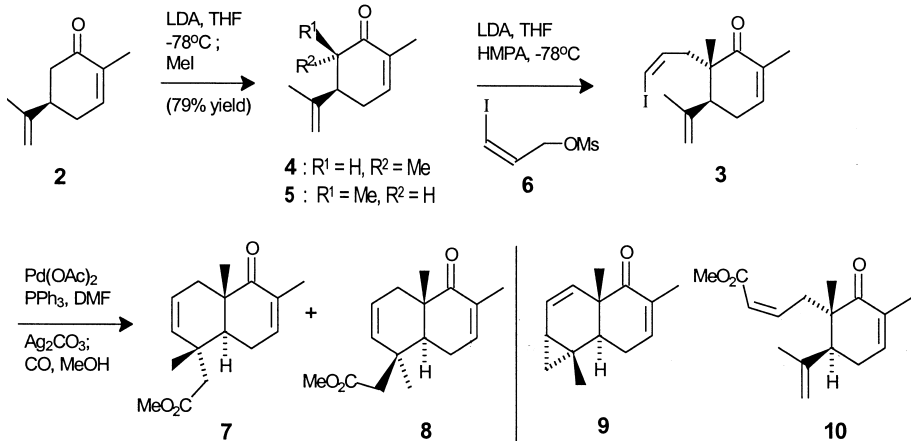



**Scheme 2.**

gel flash column chromatography, were treated together with 2 equiv. of LDA in THF at −78°C, followed by 1 equiv. of HMPA at 0°C and then *cis*-3-iodo-2-propenyl methanesulfonate (**6**)[7] to give a 78% yield of pure iodide **3** after column chromatography (along with 14% of recovered **4** and **5**) as a single stereoisomer. When 1 equiv. of LDA was used, only 51% yield of **3** was obtained. No NOE was observed between C6–Me and C5–H in the 2D NOESY spectrum of **3**. First, when iodide **3** was treated with catalytic amounts of $Pd(OAc)_2$ (0.1 equiv.) and $Ph_3P$ (0.2 equiv.), 1 equiv. of $Ag_2CO_3$, in DMF and MeOH under 1 atm of CO at 60°C, only a 6% yield of **7** and **8** was obtained along with 46% yield of unsaturated ester **10**. The results indicate that reaction of the intermediate vinylpalladium complex with CO and MeOH is faster than the intramolecular cyclization. Hence, a stoichiometric amount of palladium acetate was used to effect complete cyclization. Various reaction conditions were examined for the palladium-mediated cyclization of **3**; the results are summarized in Table 1. It was found that when CO and MeOH were added (after 30 min reaction time) prior to the addition of silver carbonate (after 1.5 h reaction time), the hexahydro-1*H*-cyclopropa[*a*]naphthalene **9** was obtained as the predominant product (64% yield; Entry 1). This implies that the relative rate of intramolecular cyclopropanation (leading to **9**) increases at higher temperature (60°C) from the same vinylic palladium intermediate (**12A**; vide infra). When silver carbonate was added at the beginning of the reaction (Entries 2–4) and CO was added after 0.7–1.5 h, although the percent yield of **8** remains similar, the percent yield of desired product **7** increases and that of **9** decreases. At lower temperatures (50 and 35°C; Entries 5 and 6) and when silver carbonate, MeOH, and CO were added after 0.5 h, **7** was formed as the major product and **9** was not detected (at 35°C); although the amount of **8** remains the same.

Based on the literature[5] and our own results, a proposed mechanism is depicted in Scheme 3. Presumably, Pd(0),[8a] derived from palladium acetate and triphenylphosphine, undergoes insertion into the vinylic iodide of **3** to give the σ-Pd complex **11** which can cyclize via the '*exo*-type' mode[8b] to provide **12A** (major) and the '*endo*-type' mode[8b] to afford **12B** (minor), as illustrated. At 35°C, the formation of **9** from **12A** is slow, and the addition of silver carbonate generates **13A** and **13B** which react with CO and MeOH to give **7** and **8**.

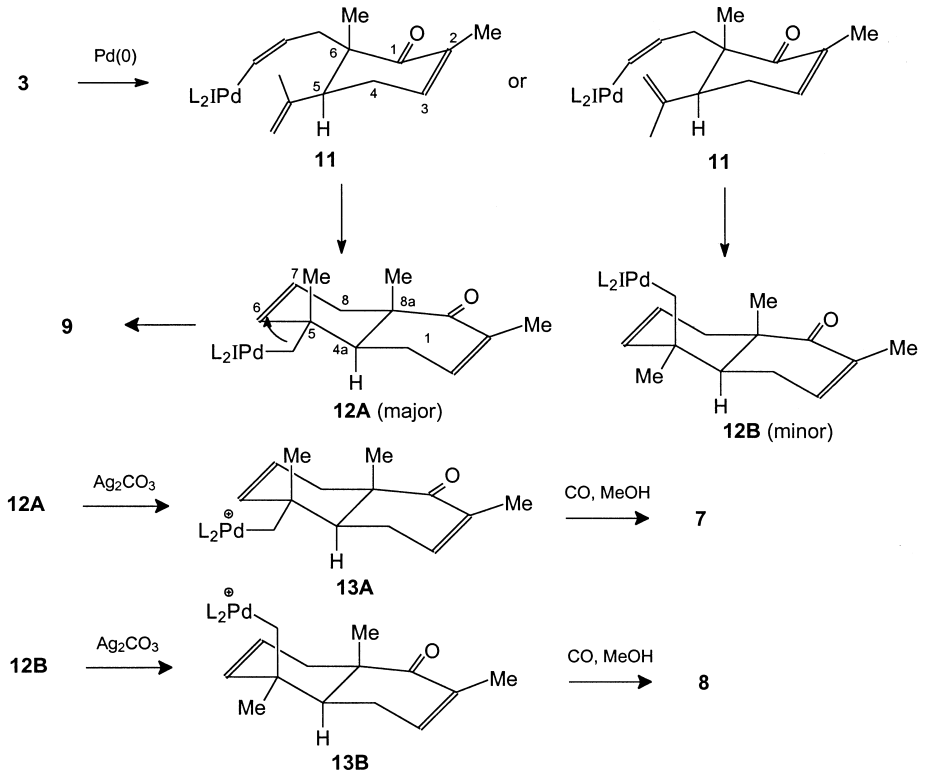
Apparently, intermediate **12B** does not undergo cyclopropanation (leading to the stereoisomer of **9**), which may be explained as follows: in the transition state, the *syn*-addition of the palladium moiety of **13B** onto C6,7-double bond (palladium is resulted at the C-7 axial position) undergoes a 1,3-diaxial interaction with C-8a axial methyl and, therefore, the activation energy would be expected to be higher than that from **12A** to **9** as well as that of the conversion to **8**. Fortunately, these different products are separable by silica gel column chromatography.

The stereochemistry is elucidated by 2D NOESY spectroscopy. The 2D spectra (NOESY) revealed NOE between C10–Me and C13–Me for **7**, C11–$CH_2$ and C13–Me (axial), C10–Me and C4a–H (axial) for **8**, and C10–Me and C1a–H, and C7a–H and C1α–H for **9**, but no NOE between C10– and C13–Me with C4a–H for **7** (Fig. 1).

**Table 1.** Cyclization of iodide **3** under various conditions. In all cases, 1 equiv. of $Pd(OAc)_2$ and 2 equiv. of $PPh_3$ were used prior to the addition of silver carbonate (1 equiv.) and CO and methanol

| Entry | Solvent | Temp. (°C) | $Ag_2CO_3$[a] (h) | MeOH[a] (h) | CO[a] (h) | Reaction time (h) | **7** (% yield) | **8** (% yield) | **9** (% yield) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | DMF | 60 | 0.5 | 0.5 | 0.5 | 30 | 0 | 18 | 64 |
| 2 | DMF | 50 | 0 | 0 | 0.7 | 10 | 36 | 18 | 7 |
| 3 | DMF | 40 | 0 | 0 | 1.5 | 5 | 17 | 17 | 17 |
| 4 | $CH_3CN$ | 50 | 0 | 0 | 1.5 | 4.5 | 15 | 15 | 15 |
| 5 | DMF | 50 | 0.5 | 0.5 | 0.5 | 4 | 40 | 20 | 5 |
| 6 | DMF | 35 | 0.5 | 0.5 | 0.5 | 3.5 | 50 | 23 | 0 |

[a] The addition time from initial reaction.




**Scheme 3.**

The conversion of ester **7** to alcohol **1** was carried out following Barton's decarboxylation–hydroxylation procedure.[9a] Treatment of carboxylic acid **14**, derived from basic hydrolysis of **7**, with NaH and oxalyl chloride in benzene followed by *N*-hydroxy-2-thiopyridinone, NaH, *t*-BuSH, oxygen, and then trimethyl phosphite, gave a 45% yield of alcohol **1** (Scheme 4). Similarly, isomer **8** was converted into the β-hydroxymethyl isomer **15** under these conditions.

During the studies of the conversion of **7** into **1**, the displacement of bromomethyl derivative **16** with hydroxyl nucleophile was also investigated (Scheme 5). Hence, bromide **16** was obtained from basic hydrolysis of **7** with KOH in MeOH–$H_2O$ at 25°C (96% yield) followed by free-radical decarboxylation–bromination[9b] with NaH–oxalyl chloride and then $CBrCl_3$-DMAP and 3-hydroxy-4-methyl-2(3*H*)-thiazolethione at 25°C (68% yield). An interesting 1,2-rearrangement was found when **16** was treated with

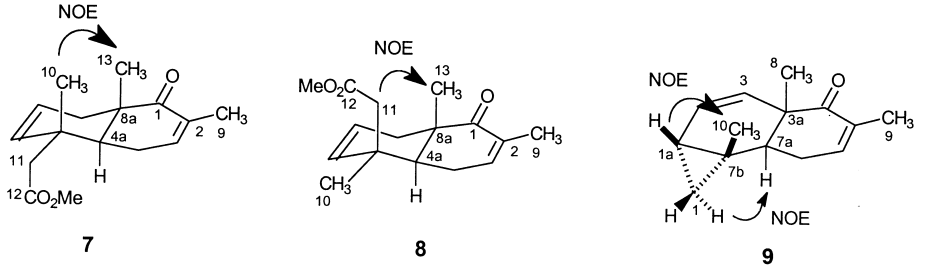
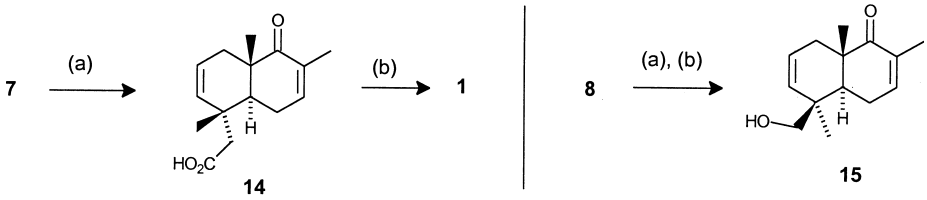
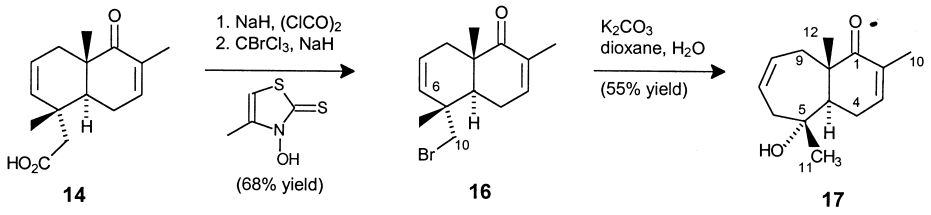


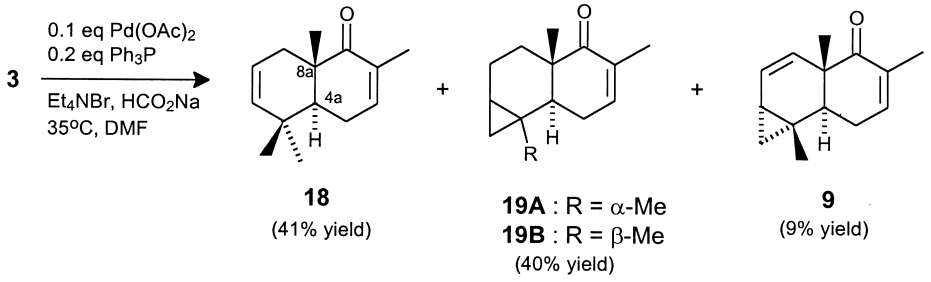

**Figure 1.**




**Scheme 4.** (a) KOH, MeOH, $H_2O$. (b) (i) NaH, $(COCl)_2$; (ii) *N*-hydroxy-2-thiopyridinone, NaH, *t*-BuSH, $O_2$; (iii) $P(OMe)_3$.



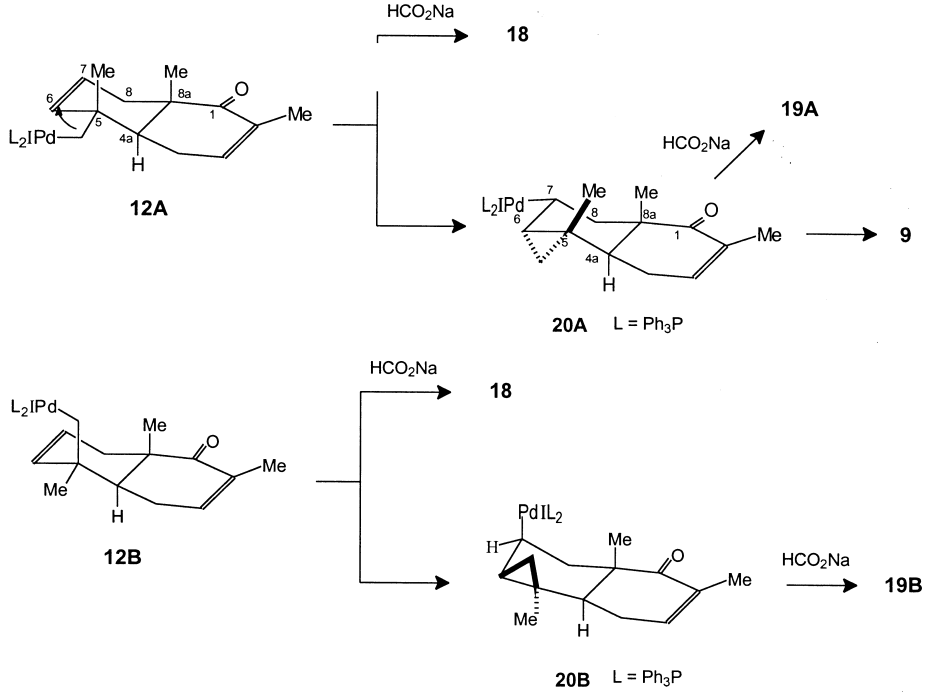

**Scheme 5.**



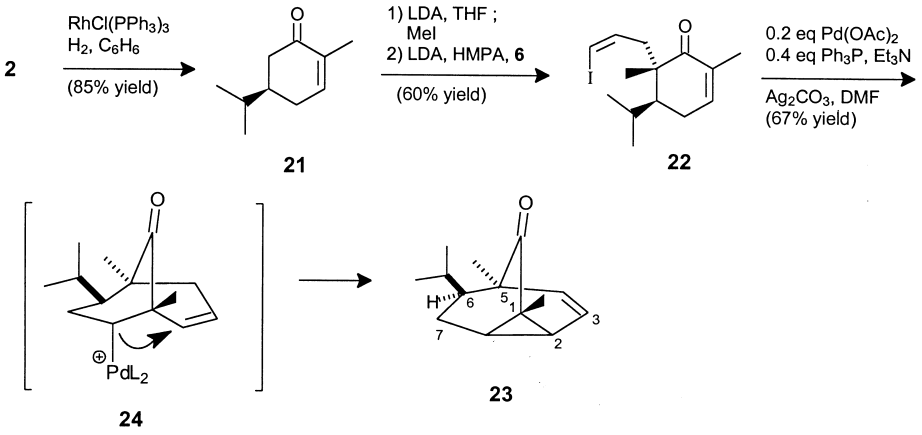

**Scheme 6.**

$K_2CO_3$–$H_2O$–dioxane under reflux for 10 h; hexahydrobenzocycloheptenone **17** (55% yield) was isolated as a single stereoisomer (Scheme 5). The stereochemistry was established by 2D NOESY in which C11 and C12 methyls exhibit an NOE, while C4a–H shows no NOE with either the C11- or C12-methyl. Presumably, the C6 vinylic carbon of **16** undergoes a 1,2-migration from C5 to C10, thereby displacing the bromide. Water or hydroxide ion attacks the resulting tertiary carbocation from the α face (opposite the C12–Me) to give **17**.

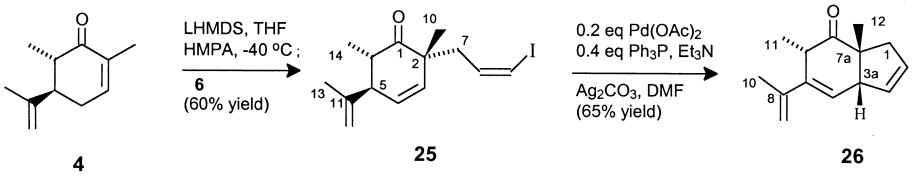
Next, we investigated the trapping of the σ-palladium complexes **12** with hydride donor[10] to effect the construction of the A-B ring fragment of chloropuupehenone via a catalytic process. It was predicted that the rate of the reaction of σ-palladium complexes **12** with a hydride donor such as sodium formate is slow compared with that of ring closure (i.e. **3** to **12**). Moreover, reaction of hydride with either **12A** or **12B** provides the same product, **18**. Hence, cyclization of **3** with 0.1 equiv. of $Pd(OAc)_2$–0.2 equiv. of $Ph_3P$–2 equiv. of $HCO_2Na$[11]–1 equiv. of $Et_4NBr$ in DMF at 35°C for 5 days gave **18** (41% yield), **19A** and **19B** (40% yield; inseparable; 2:1), and **9** (9% yield) (Scheme 6). The 2D NOESY spectrum of **18** shows no NOE between the C8a angular methyl and C4a–H. Scheme 7 proposes the formation of these products. Likely, the relative rates for the reactions of **12**




**Scheme 7.**




**Scheme 8.**




**Scheme 9.**

with sodium formate and intramolecular ring closure are similar. Product **18** and intermediates **20A** and **20B** (from the addition of σ-Pd complex with C-6,7 double bond), respectively, are formed from Pd complexes **12A** and **12B** by either reacting with hydride from sodium formate or undergoing *syn*-addition with the C-6,7 double bond. Pd complex **20A** either reacts with sodium formate to give by-product **19A** or undergoes elimination to give cycloalkene **9**. The fact that the stereoisomer of **9** did not form implies that the relative rate of the elimination of **20B** is slow compared with that of the reaction with sodium formate.

Based on these results, other catalytic cyclizations within the carvone skeleton were investigated to fully explore the use of (*R*)-carvone as a chiral building block. Hence, we envisioned ring formation between C2 and C6, and C2 and C3, of the carvone skeleton. To examine these possibilities, selective hydrogenation of the isopropenyl side chain followed by alkylations to provide vinylic iodide **22**, and selective alkylation at C2 of carvone to give iodide **25** should be studied (Schemes 8 and 9).

The reported selective hydrogenation procedure by Ireland[12] was followed. Treatment of (*R*)-carvone (**2**) with $H_2$–$(Ph_3P)_3RhCl$ in benzene gave cyclohexenone **21** (85% yield). Methylation of **21** with LDA–MeI in THF followed by propenylation with LDA–HMPA–**6** in THF gave iodide **22** (60% yield; 2 steps). Cyclization of **22** with 0.2 equiv. of $Pd(OAc)_2$, 0.4 equiv. of $Ph_3P$, 1 equiv. of $Et_3N$ and silver carbonate in DMF at 70°C for 20 h afforded a 67% yield of **23**. It is interesting to note that the intermediate σ-Pd complex **24** does not undergo *syn*-elimination but, instead, undergoes cyclopropanation followed by elimination to give **23**. This may be due to the steric hindrance, generated from the C6 isopropyl group of **24**, slowing down the *syn*-elimination reaction of $Pd(PPh_3)_2$ and C7–H.

If the 3-iodo-2-propenylation of **4** could be effected at C2, then subsequent cyclization would provide hydroindene **26**. Fortunately, propenylation of **4** with lithium hexamethyldisilazide, HMPA, and mesylate **6** in THF afforded iodide **25** (60% yield) (Scheme 9). The stereochemistry of **25** was supported by 2D NOESY spectroscopy in which C6 hydrogen shows NOE with C2 methyl and the methyl group of the isopropenyl group at C5. Cyclization of **25** with 0.2 equiv. of $Pd(OAc)_2$–0.4 equiv. of $Ph_3P$–1 equiv. of $Ag_2CO_3$–2 equiv. of $Et_3N$ in DMF at 60°C for 20 h gave **26** (65% yield). NOESY spectrum of **26** shows NOE between C3a–H and C7a–Me. Table 2

**Table 2.** NOE correlations of compounds **7**, **8**, **9**, **17**, **18**, **25**, and **26**

| Compound | Proton | NOE correlations |
|---|---|---|
| Compound **7** | H-10 (Me) | H-13 (Me) |
| Compound **8** | H-11 | H-13 (Me) |
| | H-4a | H-10 (Me) |
| Compound **9** | H-1a | H-10 (Me) |
| | H-7a | H-1α |
| Compound **17** | H-4β | H-11 (Me) |
| | H-4α | H-4a |
| | H-11 (Me) | H-12 (Me) |
| Compound **18** | H-4a | H-10 (α-Me) |
| | H-4α | H-4a |
| Compound **25** | H-5 | H-12 (*cis* to C5) |
| | H-6 | H-13 (Me), H-10 (Me) |
| | H-13 (Me) | H-12 (*trans* to C5) |
| Compound **26** | H-3a | H-12 (Me) |

summarizes the NOE correlations of compounds **7**, **8**, **9**, **17**, **18**, **25**, and **26** from 2D NOESY.

## Conclusion

Three types of Pd-catalyzed cyclization reactions are illustrated starting from (*R*)-carvone which produced useful enantiopure bicyclic and tricyclic alkenones. The cyclic intermediates can be used in the synthesis of natural and other products, and will be reported in due course. An unexpected stereoselective 1,2-rearrangement of bromide **16** led to benzocycloheptenone **17** was observed.

## Experimental

### General methods

All non-aqueous reactions were carried out under argon atmosphere unless specified otherwise. Nuclear magnetic resonance spectra were obtained at 400 MHz for $^1$H and 100 MHz for $^{13}$C in deuteriochloroform. $^1$H NMR spectra are reported in ppm ($\delta$ units) downfield of internal reference tetramethylsilane (TMS), $^{13}$C NMR spectra are reported in ppm ($\delta$ units) using chloroform ($CHCl_3$) as the standard (77 ppm). Infrared spectra are reported in wavenumbers ($cm^{-1}$). Mass spectra were obtained from a Hewlett Packard GC/HPLC 5989A mass spectrometer using either EI, CI or FAB (*m*-nitrobenzyl alcohol was used as the matrix). Rotations of optically active compounds were determined with a Perkin–Elmer 241 polarimeter. Davisil silica gel, grade 643 (200–425 mesh), was used for the flash chromatographic separations. E. Merck precoated TLC plates silica gel 60F-254 were used in preparative TLC plates. Solvents such as THF and diethyl ether for organometallic reactions were distilled over sodium and benzophenone under argon, and diisopropylamine and hexamethyldisilazane were freshly distilled from $CaH_2$. (*R*)-Carvone, 2-propynol, palladium acetate, silver carbonate, triphenylphosphine, *N*-hydroxy-2-thiopyridinone, and 3-hydroxy-4-methyl-2(3*H*)-thiazolethione were purchased from Aldrich. All new compounds displayed satisfactory $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR, UV, IR, mass spectra (FAB or CI), and elemental analysis or high resolution mass spectra. The stereochemistry was determined by 2D COSY and NOESY spectroscopy as noted in the experiments.

**(6*S*,5*R*)-2,6-Dimethyl-5-(1-methylethenyl)-2-cyclohexen-1-one (4) and (6*R*,5*R*)-2,6-dimethyl-5-(1-methylethenyl)-2-cyclohexen-1-one (5).**[6] To a cold (−78°C) solution of 10 mL (71.4 mmol) of diisopropylamine in 200 mL of THF under argon was added dropwise 46 mL (73.6 mmol) of *n*-BuLi (1.6 M in hexane). After being stirred at 0°C for 1 h, the solution was cooled to −78°C, and 10 mL (63.8 mmol) of (*R*)-(−)-carvone was added dropwise via syringe. The solution was stirred at 0°C for 1 h, cooled to −40°C, and 5.2 mL (82.9 mmol) of methyl iodide was added. The resulting solution was stirred at −40°C for 3 h and 25°C for 4 h, poured onto aqueous $NH_4Cl$, and extracted three times with diethyl ether (200 mL each). The ether extracts were combined and washed with aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and ether (10:1) as eluant to give 6.23 g (59% yield) **4** and 2.08 g (20% yield) of **5**. *Compound **4**:* $[\alpha]_D^{22}$=+19.7° (*c*=1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.70 (m, 1H, C3H), 4.80 (m, 2H, =$CH_2$), 2.22–2.53 (m, 4H), 1.78 (d, *J*=1.2 Hz, 3H, C2 Me), 1.70 (dd, *J*=1.6, 0.8 Hz, 3H, =CMe), 1.04 (d, *J*=7.0 Hz, 3H, C6Me); $^{13}$C NMR 201.8 (s, C=O), 145.6 (s, C2), 143.3 (d, C3), 134.7 (s, C=), 113.2 (t, =$CH_2$), 50.5, 44.2, 31.1, 18.1, 16.1, 12.5. *Compound **5**:* $[\alpha]_D^{22}$=+36.2° (*c*=1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.72 (m, 1H, C3H), 4.93 (s, 1H, =CH), 4.74 (s, 1H, =CH), 2.70 (m, 2H), 2.50 (m, 1H), 2.30 (m, 1H), 1.79 (s, 3H, C2Me), 1.71 (s, 3H, Me), 0.93 (d, *J*=7.0 Hz, 3H, C6Me); $^{13}$C NMR 202.8 (s, C=O), 144.9 (s, C2), 144.0 (d, C3), 133.6 (s, C=), 111.4 (t, =$CH_2$), 44.7, 42.9, 26.2, 21.9, 16.0, 10.4.

**(5*S*,6*S*)-2,6-Dimethyl-6-(*cis*-3-iodo-2-propenyl)-5-isopropenyl-2-cyclohexenone (3).** To a cold (−40°C) solution of 21 mmol of LDA (prepared as described above) in THF (30 mL) and hexane (13 mL) under argon, a solution of 1.69 g (10.3 mmol) of **4** and **5** in 30 mL of ether was added slowly via cannula. The solution was stirred for 45 min at 0°C, 1.8 mL (10 mmol) of HMPA was added, the resulting solution was stirred for 4 h at 0°C, and 5.68 g (22 mmol) of *cis*-3-iodo-2-propenyl methanesulfonate (**6**)[7] was added. The reaction was stirred at 0–25°C for 12 h, poured into aqueous $NaHCO_3$, and extracted three times with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture (3:2) of hexane and methylene chloride as eluant to give 2.48 g (73% yield) of **3** and 0.24 g (14% recovery) of **4** and **5**. *Compound **3**:* $[\alpha]_D^{22}$=−31.9° (*c*=1.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.62 (m, 1H, C3H) 6.31 (dt, *J*=7.6, 1.6 Hz, 1H, =CHI), 6.13 (dt, *J*=7.6, 6.8 Hz, 1H, CH=CI), 4.83 (m, 1H, =CH), 4.74 (s, 1H, =CH), 2.72–2.62 (m, 2H), 2.46 (ddd *J*=15.2, 6.4, 1.6 Hz, 1H), 2.42–2.32 (m, 2H), 1.80 (m, 3H, C2Me), 1.65 (s, 3H, C6Me). $^{13}$C NMR 203.4 (s, C1), 145.8 (s, C2), 142.4 (d, C3), 137.7 (d, C=), 134.2 (s, C=), 114.8 (t, =$CH_2$), 84.9 (d, =CHI), 50.5 (d), 48.0 (s, C6), 42.8 (t), 29.2 (t), 22.5 (q), 19.3 (q), 16.6 (q). 2D COSY and NOESY spectra confirm the assigned stereochemistry. MS *m*/*z* CI 331 (M+1). Anal. Calcd for $C_{14}H_{19}IO$: C, 50.92; H, 5.80. Found: C, 50.77; H, 5.63.

**(4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-5-(methoxycarbonylmethyl)-2,5,8a-trimethylnaphthalen-1-one (7) and (4a*S*,5*R*,8a*S*)-1,4,4a,5,8,8a-hexahydro-5-(methoxycarbonylmethyl)-2,5,8a-trimethylnaphthalen-1-one (8).** (Entry 6 in Table 1). To a dried flask, 0.387 g (1.7 mmol) of $Pd(OAc)_2$ and 0.904 g (3.4 mmol) of $Ph_3P$ were added. The compounds were dried under vacuum and maintained under argon, 20 mL of DMF was added, and the solution was stirred at 25°C for 1 h. A solution of 0.569 g (1.74 mmol) of **3** in 20 mL of DMF was added via cannula, the mixture was stirred at 32°C for 30 min, 0.476 g (1.7 mmol) of $Ag_2CO_3$ was added followed by CO gas which was introduced into the reaction mixture via a balloon, and then 10 mL of MeOH was added. After being stirred at 35°C for 15 h, the mixture was filtered, rinsed with ether, and the filtrate was diluted with 50 mL of water. The mixture was extracted three times with ether, the combined extracts were washed with water, and brine, dried ($MgSO_4$),

concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether to give 0.228 g (50% yield) of **7** and 0.104 g (23% yield) of **8**. *Compound **7**:* $[\alpha]_D^{22}=-15°$ ($c$=1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.77 (m, 1H, C3H), 5.69 (ddd, $J$=10.4, 6.4, 2.4 Hz, 1H, C7H), 5.53 (dd, $J$=10.4, 3.2 Hz, 1H, C6H), 3.62 (s, 3H, OMe), 2.42–2.07 (series of m, 7H), 1.77 (s, 3H, C2–Me), 1.12 (s, 3H, Me), 1.08 (s, 3H, Me); $^{13}C$ NMR ($CDCl_3$) $\delta$ 204.5 (s, CO), 171.7 (s, CO), 143.6 (d), 133.6 (s), 133.2 (d), 123.6 (d), 51.3 (q, CO), 46.7, 44.1, 43.4, 38.0, 32.9, 24.1, 23.7, 17.8, 16.3. MS *m*/*z* CI 263 (M+1). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.47; H, 8.21. *Compound **8**:* $[\alpha]_D^{22}=+80.6°$ ($c$=1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.78 (m, 1H, C3H), 5.68 (ddd, $J$=10.4, 6.4, 2.4 Hz, 1H, C7H), 5.56 (dd, $J$=10.4, 3.2 Hz, 1H, C6H), 3.68 (s, 3H, OMe), 2.63 (d, $J$=12.8 Hz, 1H, C11H), 2.31 (d, $J$=12.8 Hz, 1H, C11H), 2.40–2.26 (series of m, 3H, C8, C4Hs), 2.14 (d, $J$=18 Hz, 1H, C8H), 2.02 (dd, $J$=11.0, 5.0 Hz, 1H, C4aH), 1.77 (s, 3H, C2–Me), 1.21 (s, 3H, C10–Me), 1.11 (s, 3H, C13–Me); $^{13}C$ NMR ($CDCl_3$) $\delta$ 204.5 (s, CO), 172.5 (s, CO), 143.6 (d), 134.8 (s), 132.5 (d), 123.5 (d), 51.4 (q, CO), 47.8, 41.6, 38.8, 36.5, 33.5, 28.3, 23.7, 17.9, 16.3. MS *m*/*z* CI 263 (M+1). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.12; H, 8.33. The stereochemistry of **7** and **8** were determined by 2D COSY and NOESY spectroscopy.

**(1a*R*,3a*S*,7a*S*,7b*R*)-1a,3a,4,7,7a,7b-Hexahydro-3a,5,7b-trimethyl-1*H*-cyclopropa[*a*]naphthalen-4-one (9).** (Entry 1 in Table 1). A solution of 38.6 mg (0.17 mmol) of $Pd(OAc)_2$ and 90.2 mg (0.34 mmol) of $Ph_3P$ in 2 mL of DMF was stirred at 25°C under argon for 30 min. A solution of 56.8 mg (0.17 mmol) of iodide **3** in 2 mL of DMF was then added via cannula. This mixture was stirred at 60°C for 30 min, 0.476 g (1.7 mmol) of $Ag_2CO_3$ and 0.5 mL of MeOH were added, and carbon monoxide was introduced into the reaction mixture using a balloon filled with CO and maintained under CO for 30 h. The mixture was filtered, the residual solids rinsed with ether, and the filtrate with ether washings was diluted with water, and this mixture was extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture (10:1) of hexane and ether as eluant to give 22.2 mg (64% yield) of **9** and 8 mg (18% yield) of **8**. *Compound **9**:* $[\alpha]_D^{22}=-26.7°$ ($c$=1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.72 (m, 1H, C6H), 6.48 (d, $J$=10.0 Hz, 1H, C3H), 5.88 (dd, $J$=10.0, 2.8 Hz, 1H, C2H), 2.52 (m, 2H, C7H), 1.92 (dd, $J$=11.2, 6.0 Hz, 1H, C7aH), 1.76 (m, 1H, C9Me), 1.19 (s, 3H, Me), 1.18 (s, 3H, Me), 1.02 (m, 1H, C1aH), 0.72 (dd, $J$=8.8, 3.6 Hz, C1βH), 0.22 (t, $J$=4.4 Hz, 1H, C1αH); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.8 (s, CO), 146.3 (s), 143.6 (d), 134.1 (d), 127.8 (d), 47.5, 46.5, 28.5, 26.7, 23.2, 20.2, 19.2, 16.7, 16.4. MS *m*/*z* CI 203 (M+1). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.91; H, 9.16. The stereochemistry was determined from 2D COSY and NOESY spectroscopy.

**(5*S*,6*S*)-2,6-dimethyl-5-Isopropenyl-6-(3-methoxycarbonyl-2-propenyl)-2-cyclohexenone (10).** After a solution of 11.2 mg (0.05 mmol) of $Pd(OAc)_2$ and 26.2 mg (0.10 mmol) of $Ph_3P$ in 1 mL of DMF was stirred at 25°C under argon for 30 min, a solution of 54.9 mg (0.17 mmol) of iodide **3** in 1 mL of DMF and 0.7 mL of MeOH was added via cannula. This mixture was stirred at 25°C for 5 min, 46 mg (0.17 mmol) of $Ag_2CO_3$ was added, and carbon monoxide was introduced via a balloon. This mixture was maintained under CO at 60°C for 40 h, filtered, rinsed with ether, the filtrate was diluted with water, and the mixture was extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture (10:1) of hexane and ether as eluant to give 20 mg (46% yield) of **10** and 3 mg (6% yield) of a mixture (1:1.5) of **7** and **8**. *Compound **10**:* $[\alpha]_D^{22}=-48.6°$ ($c$=0.7, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.62 (m, 1H, C3H), 6.20 (ddd, $J$=11.5, 7.0, 6.9 Hz, 1H, =CH), 5.84 (dt, $J$=11.5, 2.0 Hz, 1H, =CHCO), 4.80 (s, 1H, =CH), 4.72 (s, 1H, =CH), 3.70 (s, 3H, OMe), 3.11 (ddd, $J$=16.0, 7.0, 2.0 Hz, 1H, $CH_2C$=), 2.87 (ddd, $J$=16.0, 6.7, 2.0 Hz, 1H, $CH_2C$=), 2.70 (t, $J$=6.0 Hz, 1H, CH–C=), 2.64 (m, 1H, C4H), 2.36 (m, 1H, C4H), 1.78 (s, 3H, C2Me), 1.64 (s, 3H, Me–C=), 1.18 (s, 3H, C6Me); $^{13}C$ NMR ($CDCl_3$) $\delta$ 203.6 (s, CO), 166.9 (s, CO), 146.8 (d, =CH), 145.9 (s), 142.5 (d), 134.3 (s), 120.9 (d), 114.6 (t), 51.2 (q, Me), 50.7 (d), 48.0 (s), 36.6 (t), 29.1 (t), 22.5 (q), 19.1 (q), 16.5 (q); Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.01; H, 8.72.

**(4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-1-oxo-2,5,8a-trimethylnaphthalen-5-acetic acid (14).** To a solution of 0.127 g (0.48 mmol) of methyl ester **7** in 2 mL of MeOH and 0.5 mL of $H_2O$ was added 90 mg (1.6 mmol) of KOH. The solution was stirred at 25°C for 22 h, acidified with 1N HCl, extracted with methylene chloride three times, and the combined organic extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexanes and ether (1:1) as eluant to give 0.116 g (96% yield) of acid **14**. $[\alpha]_D^{22}=-6.2°$ ($c$=0.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.76 (m, 1H, C3H), 5.70 (ddd, $J$=10.5, 6.4, 2.0 Hz, 1H, =CH), 5.56 (dd, $J$=10.5, 2.8 Hz, 1H, =CH), 2.40–2.08 (series of m, 7H), 1.78 (s, 3H, C2Me), 1.15 (s, 3H, Me), 1.08 (s, 3H, Me); $^{13}C$ NMR ($CDCl_3$) $\delta$ 204.8 (s, CO), 177.5 (s, CO), 143.9 (d, =C), 133.8 (s, =C), 133.0 (d, =C), 124.2 (d, =C), 46.8, 44.4, 43.6, 38.2, 33.1, 24.4, 23.9, 18.1, 16.5. MS *m*/*z* CI 249 (M+1). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 8.40.

**(4a*S*,5*R*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-1-oxo-2,5,8a-trimethylnaphthalen-5-acetic acid (14B).** To a solution of 0.12 g (0.46 mmol) of methyl ester **8** in 2 mL of MeOH and 0.5 mL of $H_2O$ was added 90 mg (1.6 mmol) of KOH. The solution was stirred at 25°C for 22 h, acidified with 1N HCl, extracted with methylene chloride three times, and the combined organic extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexanes and ether (1:1) as eluant to give 0.110 g (97% yield) of acid **14B**. $[\alpha]_D^{22}=+65°$ ($c$=0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.78 (m, 1H, C3H), 5.74–5.62 (m, 2H, =CH), 2.64 (d, $J$=13.0 Hz, 1H), 2.44–2.10 (series of m, 5H), 2.03 (dd, $J$=11.4, 5.0 Hz, 1H), 1.78 (s, 3H, Me), 1.24 (s, 3H, Me), 1.10 (s, 3H, Me); $^{13}C$ NMR ($CDCl_3$) $\delta$ 204.7 (s, CO), 178.4 (s, CO), 143.8 (d, =C), 133.9 (s, =C), 132.2 (d, =C), 123.9 (d, =C), 48.1, 44.2, 41.8, 36.7, 33.8, 28.4, 24.0, 18.1, 16.5. MS *m*/*z* CI 249 (M+1). Anal.

Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.73; H, 7.98.

**(4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-1-oxo-2,5,8a-trimethylnaphthalen-5-acetyl chloride.** To a suspension of NaH (60 mg; 50% oil, 1.25 mmol) in 10 mL of benzene under argon was added a solution of 0.25 g (1 mmol) of acid **14** in 10 mL of benzene via cannula. After stirring at 25°C for 30 min, 0.26 mL (3 mmol) of oxalyl chloride was added, and the mixture was heated to reflux for 3 h. The solvent and excess of reagent were removed under vacuum to give the crude acid chloride which was used in the next step without purification. $^1$H NMR ($CDCl_3$) $\delta$ 6.76 (m, 1H, C3H), 5.77 (dd, $J$=10.0, 2.0 Hz, 1H, =CH), 5.55 (dd, $J$=10.0, 2.4 Hz, 1H, =CH), 2.94 (ABq, $J$=16.0 Hz, 2H), 2.44–2.12 (series of m, 5H), 1.78 (s, 3H, Me), 1.16 (s, 3H, Me), 1.07 (s, 3H, Me).

**(4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-5-(hydroxymethyl)-2,5,8a-trimethylnaphthalen-1-one (1).** To a solution of the above acid chloride in 10 mL of toluene under argon was added a solution of 0.162 g (1.1 mmol) of *N*-hydroxy-2-thiopyridinone in 1 mL of *t*-butanethiol and 10 mL of toluene via cannula. The solution was stirred, and 60 mg (1.25 mmol) of sodium hydride (50% oil) was added. The argon gas inlet was removed, oxygen gas was introduced into the reaction vessel, and the mixture was kept under an oxygen atmosphere and stirred at 80°C for 1 h. After cooling to room temperature, 0.25 mL (2.1 mmol) of trimethyl phosphite was added, and the mixture was stirred for 2 h at 25°C. The mixture was diluted with ether and washed with aqueous ammonium chloride, and then brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexane–ether (1:1) as eluant to give 99 mg (45% overall yield) of alcohol **1**. $[\alpha]_D^{22}$=+3.4° ($c$=0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.75 (m, 1H, C3H), 5.93 (ddd, $J$=10.4, 6.4, 2.4 Hz, 1H, C7H), 5.30 (dd, $J$=10.4, 2.8 Hz, 1H, C6H), 3.35 (d, $J$=10.8 Hz, 1H, $CH_2O$), 3.21 (d, $J$=10.8 Hz, 1H, $CH_2O$), 2.47 (dd, $J$=11.2, 4.8 Hz, 1H), 2.42–2.25 (a series of m, 3H), 2.13 (d, $J$=17.2 Hz, 1H), 1.77 (s, 3H, C2–Me), 1.56 (bs, 1H, OH), 1.09 (s, 3H, Me), 0.98 (s, 3H, Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 205.0 (s, CO), 144.6, 132, 127.8, 119.8, 69.7 (CO), 41.1, 39.9, 36.7, 33.6, 24.4, 20.0, 17.8, 16.5. MS *m*/*z* FAB (in NBA) 221 (M+1), 219, 203, 189, 179, 167. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 8.93.

**(4a*S*,5*R*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-5-(hydroxymethyl)-2,5,8a-trimethylnaphthalen-1-one (15).** By following a similar sequence of reactions as that from **14** to **1**, stereoisomer **14B** was converted into **15** in 46% yield. $[\alpha]_D^{22}$=+1.2° ($c$=0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.77 (m, 1H, C3H), 5.76 (ddd, $J$=10.4, 6.0, 2.0 Hz, 1H, C7H), 5.49 (dd, $J$=10.4, 2.8 Hz, 1H, C6H), 3.65 (d, $J$=11.2 Hz, 1H, $CH_2O$), 3.59 (d, $J$=11.2 Hz, 1H, $CH_2O$), 2.42 (m, 2H), 2.28 (dd, $J$=18.4, 6.0 Hz, 1H), 2.16 (d, $J$=18.4 Hz, 1H), 2.05 (t, $J$=8.0 Hz, 1H), 1.77 (q, $J$=1.6 Hz, 3H, C2–Me), 1.54 (bs, 1H, OH), 1.08 (s, 6H, Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 204.0 (s, CO), 144.2, 137.6, 132.0, 121.3, 67.9 (CO), 46.9, 44.0, 39.6, 33.4, 31.6, 25.8, 18.5, 16.5. MS *m*/*z* FAB (in NBA) 221 (M+1). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 75.98; H, 9.35.

**(4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-5-(bromomethyl)-2,5,8a-trimethylnaphthalen-1-one (16).** To 1 mmol of (4a*S*,5*S*,8a*S*)-1,4,4a,5,8,8a-hexahydro-1-oxo-2,5,8a-trimethylnaphthalen-5-acetyl chloride in 20 mL of $CBrCl_3$ under argon at 25°C were added 0.163 g (1.1 mmol) of 3-hydroxy-4-methyl-2(3*H*)-thiazolethione and 0.136 g (1.1 mmol) of 4-dimethylaminopyridine. The solution was heated to reflux for 10 h, cooled to 25°C, poured into 1N HCl solution, and extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexane–ether=5:1 as eluant to give 0.195 g (68% yield) of bromide **16** as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.74 (m, 1H, C3H), 5.80 (ddd, $J$=10.0, 6.0, 2.0 Hz, 1H, C7H), 5.36 (dd, $J$=10.0, 2.8 Hz, 1H, C6H), 3.34 (ABq, $J$=10.4 Hz, 1H, $CH_2O$), 3.27 (ABq, $J$=10.4 Hz, 1H, $CH_2O$), 2.44–2.10 (a series of m, 5H), 1.78 (s, 3H, C2–Me), 1.18 (s, 3H, Me), 1.09 (s, 3H, Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 204.4 (s, CO), 143.5, 132.4, 132.0, 125.7, 45.3, 44.2, 42.3, 39.5, 33.2, 24.5, 22.3, 18.0, 16.5. MS (FAB) *m*/*z* 283, 285 (M+1), 203, 142. Anal. Calcd for $C_{14}H_{19}BrO$: C, 59.37; H, 6.76. Found: C, 59.11; H, 6.55.

**(4a*R*,5*R*,9a*S*)-5-Hydroxy-2,5,9a-trimethyl-4,4a,5,6,9,9a-hexahydro-[1*H*]-benzocyclohepten-1-one (17).** To a solution of 27 mg (0.096 mmol) of bromide **16** in 0.5 mL of 1,4-dioxane and 0.5 mL of $H_2O$ was added 27 mg (0.2 mmol) of $K_2CO_3$ at 25°C. The solution was then stirred at 100°C for 10 h, cooled to 25°C, diluted with aqueous $NH_4Cl$, and extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexane–ether=1:1 as eluant to give 11.6 mg (55% yield) of **17**. $[\alpha]_D^{22}$=−168° ($c$=0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.73 (m, 1H, C3H), 5.88 (m, 2H, C7,8Hs), 2.88 (dd, $J$=14.4, 8.4 Hz, 1H, C6H), 2.68 (dt, $J$=20.0, 4.0 Hz, 1H, C4H), 2.55 (dd, $J$=13.0, 5.0 Hz, 1H, C9H), 2.35 (dt, $J$=20.0, 3.0 Hz, 1H, C4H), 2.28 (m, 1H, C6H), 2.20 (dd, $J$=13.0, 8.0 Hz, 1H, C9H), 2.12 (dd, $J$=12.0, 4.0 Hz, 1H, C4aH), 1.73 (m, 3H, C10Me), 1.23 (s, 3H, C11Me), 0.98 (s, 3H, C12Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 196, 144.0, 131.3, 128.9, 128.3, 71.8, 69.8, 56.6, 46.9, 43.4, 33.0, 25.0, 24.0, 16.7. MS (FAB), *m*/*z* 221 (M+1), 203, 185, 175, 161, 133. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.23; H, 9.41.

**(4a*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-2,5,5,8a-tetramethylnaphthalen-1-one (18) and (3a*S*,7a*S*)-1a,2,33a,4,7,7a,7b-octahydro-3a,5,7b-trimethyl-1*H*-cyclopropa[*a*]naphthalen-4-one (19A and 19B).** A mixture of 0.042 g (0.19 mmol) of $Pd(OAc)_2$ and 0.105 g (0.38 mmol) of $PPh_3$ in 10 mL of DMF was stirred under argon for 45 min at 25°C. To it were added a solution of 0.64 g (1.94 mmol) of iodide **3** in 10 mL of DMF via cannula, followed by 0.264 g (3.9 mmol) of $HCO_2Na$ and 0.4 g (1.94 mmol) of $Et_4NBr$. The mixture was stirred at 35°C for five days, cooled to 25°C, diluted with aqueous $NH_4Cl$, and extracted twice with ether. The combined extracts were washed with water, then brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 0.162 g (41% yield) of **18**, 0.160 (40% yield) of a mixture of **19A** and **19B** (inseparable; 2:1), and 35 mg (9% yield) of **9**. *Compound **18**:* $[\alpha]_D^{22}$=+14° ($c$=0.22, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 6.76

(m, 1H, C3H), 5.58 (ddd, *J*=10.0, 5.6, 2.0 Hz, 1H C7H), 5.38 (dd, *J*=10.0, 2.0 Hz, 1H, C6H), 2.36 (m, 2H, C4H), 2.23 (dd, *J*=18.0, 6.0 Hz, 1H, C8H), 2.12 (d, *J*=18.0 Hz, 1H, C8H), 1.96 (dd, *J*=10.8, 5.2 Hz, 1H, 4aH), 1.76 (m, 3H, =CMe), 1.07 (s, 3H, C8a–Me), 1.02 (s, 3H, C5–Me), 1.00 (s, 3H, C5–Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 203.2, 144.1, 143.1, 136.7, 121.3, 46.7, 44.2, 34.9, 33.4, 31.4, 24.5, 24.3, 17.6, 16.3. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.19; H, 9.66.

*Compounds **19A** and **19B**:* A 2:1 ratio was determined by $^1$H NMR and the relative stereochemistry was tentatively determined based on 2D NOESY spectroscopy. $^1$H NMR ($CDCl_3$) $\delta$ 6.69 (m, 1H, =CH), 2.60–2.50 (m, 1H, =C–CH, **19A**), 2.50–2.40 (m, 1H,=C–CH, **19B**), 2.18 (dt, *J*=11.0, 2.4 Hz, 1H, =C–CH, **19A**), 2.10 (m, 2H, C2H), 1.99 (dd, *J*=11.0, 3.6 Hz, 1H, C7aH), 1.90 (m, 2H, C2H), 1.76 (m, 3H, Me–C=), 1.74 (m, 3H, Me–C=), 1.65–1.53 (m, 1H, C3H), 1.26–1.15 (m, 1H, C3H), 1.06, (s, 3H, Me of **19B**), 1.03 (s, 3H, C12–Me of **19A**), 1.00 (s, 3H, Me of **19B**), 0.87 (s, 3H, C3a–Me of **19A**), 0.76–0.66 (m, 1H, C1aH of **19A** and **19B**), 0.49 (t, *J*=4.8 Hz, 1H, C1βH of **19A**; showed NOE between C3a–Me at $\delta$ 0.87), 0.45 (dd, *J*=9.6, 4.4 Hz, 1H, C1H of **19B**), 0.32 (dd, *J*=9.2, 4.8 Hz, 1H, C1αH of **19A**), 0.06 (dd, *J*=5.6, 4.4 Hz, 1H, C1H of **19B**). $^{13}$C NMR ($CDCl_3$) $\delta$ 203.0 (s, C=O), 146.0 (s, =C), 143.1 (d, =CH, **19A**), 133.5 (d, =CH, **19B**), 45.7, 44.1, 43.8, 32.0, 29.0, 27.5, 27.2, 26.9, 26.8, 24.2, 23.0, 20.8, 20.0, 19.5, 19.3, 18.6, 18.5, 18.2, 16.6, 16.4, 15.0, 14.7. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.54; H, 10.03.

**(*R*)-5-Isopropyl-2-methyl-2-cyclohexen-1-one (21).**[12] This compound was prepared by following the reported procedure[12] in 85% yield. $^1$H NMR ($CDCl_3$) $\delta$ 6.74 (m, 1H, C3H), 2.60–1.60 (a series of m, 6H), 1.76 (s, 3H, Me), 0.91 (d, *J*=7.0 Hz, 6H, Me).

**(5*R*,6*S*)-2,6-Dimethyl-5-(isopropyl)-2-cyclohexen-1-one.** To a cold (−78°C) solution of 2 mL (12.6 mmol) of diisopropylamine in 50 mL of THF under argon was added dropwise 9 mL (14.4 mmol) of *n*-BuLi (1.6 M in hexane). After being stirred at 0°C for 1 h, the solution was cooled to −78°C, and added into a cold (−78°C) solution of 1.74 g (11.4 mmol) of **21** in 20 mL was added via cannula. The solution was stirred for 30 min at −78°C and 30 min at 0°C. To it, was added 1.4 mL (22.9 mmol) of methyl iodide and the solution was stirred for 2 h at 0°C and 30 min at 25°C. The solution was poured onto aqueous $NH_4Cl$, and extracted three times with diethyl ether (100 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 1.62 g (85% yield) of (5*R*,6*S*)-2,6-dimethyl-5-(isopropyl)-2-cyclohexen-1-one. $[\alpha]_D^{22}=-37°$ (*c*=0.55, $CHCl_3$). $^1$H NMR ($CDCl_3$) $\delta$ 6.67 (m, 1H, C3H), 2.30 (m, 2H), 2.17 (m, 1H), 1.90 (m, 1H), 1.75 (s, 3H, C2 Me), 1.69 (m, 3H), 1.13 (d, *J*=6.8 Hz, 3H, Me), 0.93 (d, *J*=6.9 Hz, 3H, Me), 0.83 (d, *J*=6.9 Hz, 3H, Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 202.5 (s, C=O), 143.4 (d, C3), 134.3 (s, C2), 46.3 (d), 44.7 (d), 27.6 (d), 24.7 (t), 20.6 (q), 16.0 (q), 15.8 (q), 12.0 (q). The stereochemistry is supported by 2D COSY and 2D NOESY (no NOE was observed between C6 methyl and the CH of the isopropyl group). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.25; H, 10.67.

**(5*S*,6*S*)-2,6-Dimethyl-6-(*cis*-3-iodo-2-propenyl)-5-isopropyl-2-cyclohexenone (22).** To a cold (−40°C) solution of 0.71 mmol of LDA in 1 mL of THF under argon was added a solution of 0.06 g (0.36 mmol) of (5*R*,6*S*)-2,6-dimethyl-5-(isopropyl)-2-cyclohexen-1-one in 1 mL of THF. After being stirred the solution at 0°C for 30 min, 70 μL (0.4 mmol) of HMPA was added, stirred at the same temperature for 4 h, and a solution of 0.2 g (0.76 mmol) of **6** in 1 mL of THF. The solution was stirred at 25°C for 18 h, diluted with aqueous sodium bicarbonate, and extracted three times with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of methylene chloride and hexane (1:2) as eluant to give 91 mg (76% yield) of **22**. $[\alpha]_D^{22}=+36.1°$ (*c*=0.8, $CHCl_3$). $^1$H NMR ($CDCl_3$) $\delta$ 6.66 (m, 1H, C3H), 6.26 (ddd, *J*=7.2, 1.6, 1.2 Hz, 1H, CHI), 6.01 (dt, *J*=7.6, 5.6 Hz, 1H, =CH), 2.64 (ddd, *J*=15.0, 6.0, 2.0 Hz, 1H, $CH_2C$=), 2.45–2.37 (m, 2H), 2.34–2.25 (m, 1H, C4H), 2.03 (heptd, *J*=6.8, 2.4 Hz, 1H, $CHMe_2$), 1.86 (ddd, *J*=7.6, 5.6, 2.0 Hz, 1H, C5H), 1.75 (s, 3H, C2 Me), 1.11 (s, 3H, C6 Me), 0.91 (d, *J*=6.8 Hz, 3H, Me), 0.80 (d, *J*=6.8 Hz, 3H, Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 204.0 (s, C=O), 143.9 (d, C3), 138.1 (d), 134.0 (s, C2), 84.3 (d, =CI), 49.6 (s), 46.7, 42.5, 27.1, 23.5, 23.1, 19.4, 19.0, 16.6. The proton assignment was based on 2D COSY. Anal. Calcd for $C_{14}H_{21}IO$: C, 50.61; H, 6.37. Found: C, 50.47; H, 6.10.

**(1*S*,5*R*,6*S*)-1,5-Dimethyl-6-isopropyltricyclo[3.3.1.0$^{2,8}$]-3-nonen-9-one (23).** A solution of 3.6 mg (0.016 mmol) of palladium acetate and 8.4 mg (0.032 mmol) of triphenylphosphine in 1 mL of DMF was stirred under argon at 25°C for 1 h. To it, were added 22 mg (0.08 mmol) of silver carbonate, a solution of 26.5 mg (0.08 mmol) of iodide **22** in 1 mL of DMF, and then 45 μL (0.32 mmol) of triethylamine. The mixture was stirred at 70°C for 20 h, poured into water, and extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and ether (30:1) as eluant to give 11 mg (67% yield) of **23**: $[\alpha]_D^{22}=+5.1°$ (*c*=0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 5.76 (dd, *J*=9.0, 5.0 Hz, 1H, C3H), 5.42 (dd, *J*=9.0, 2.4 Hz, 1H, C4H), 2.05 (dd, *J*=14.0, 8.0 Hz, 1H, C7H), 1.94 (d, *J*=14.0 Hz, 1H, C7H), 1.91 (d, *J*=7.0 Hz, 1H, C2H), 1.88 (m, 1H, C6H), 1.81 (d, *J*=7.0 Hz, 1H, C8H), 1.80 (m, 1H, C12H), 1.23 (s, 3H, C10Me), 1.04 (s, 3H, C11Me), 0.82 (d, *J*=7.0 Hz, 3H, C13Me), 0.70 (d, *J*=7.0 Hz, 3H, C14Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.8, 133.8, 122.8, 59.5, 56.9, 51.4, 46.8, 45.0, 41.3, 37.5, 34.9, 32.8, 23.1, 22.1. MS (FAB) *m*/*z* 205 (M+1), 192, 165. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.11; H, 10.01. The stereochemistry was verified by 2D COSY and 2D NOESY spectroscopy.

**(2*R*,5*S*,6*S*)-2,6-Dimethyl-2-(*cis*-3-iodo-2-propenyl)-5-isopropenyl-3-cyclohexen-1-one (25).** To a cold (−78°C) solution of 0.3 mL (1.4 mmol) of hexamethyldisilazane (HMDS) in 2 mL of THF under argon was added 0.9 mL (1.4 mmol) of *n*-BuLi (1.6 M in hexane). After being stirred at 0°C for 1 h, a solution of 0.21 g (1.28 mmol) of ketone **4**

in 2 mL of THF was added via cannula at −40°C, the solution was then stirred at 25°C for 30 min, and 0.44 mL (2.8 mmol) of HMPA was added. The resulting solution was stirred at 25°C for 30 min, a solution of 0.47 g (1.8 mmol) of mesylate **6** in 2 mL of THF was added, stirred for 15 h, poured into aqueous sodium bicarbonate, and extracted three times with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and methylene chloride (3:2) as eluant to give 0.253 g (60% yield) of **25**. $^1$H NMR ($CDCl_3$) $\delta$ 6.25 (dt, $J$=7.2, 1.6 Hz, 1H, CHI) 6.01 (dt, $J$=7.6, 6.0 Hz, 1H, CH═CI), 5.60 (q, $J$=10.0 Hz, 1H, CH═), 5.59 (q, $J$=10.0 Hz, 1H, ═CH), 4.87 (m, 1H, ═CH), 4.81 (s, 1H, ═CH), 2.77 (m, 1H), 2.73 (m, 1H), 2.66 (ddd $J$=14.4, 6.4, 1.6 Hz, 1H, $CH_2C$═CI), 2.22 (ddd $J$=14.4, 7.2, 1.2 Hz, 1H, $CH_2C$═CI), 1.71 (m, 3H, ═CMe), 1.29 (s, 3H, C2Me), 0.99 (d, $J$=6.0 Hz, 3H, C6Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 214.5 (s, CO), 145.0 (s), 137.8 (d), 134.5 (d), 130.4 (d), 113.9 (t, ═$CH_2$), 84.7 (d, ═CHI), 53.8 (d), 48.9 (s), 42.8, 42.4 (t), 27.8 (q), 18.1 (q), 11.6 (q). 2D NOESY spectra supports the assigned stereochemistry. MS *m*/*z* CI 331 (M+1). Anal. Calcd for $C_{14}H_{19}IO$: C, 50.92; H, 5.80. Found: C, 50.88; H, 5.92.

**(3a*R*,6*S*,7a*R*)-6,7a-Dimethyl-5-isopropenyl-3a,6,7,7a-tetrahydro-1*H*-inden-7-one (26).** A solution of 5 mg (0.022 mmol) of palladium acetate and 12 mg (0.044 mmol) of triphenylphosphine in 1 mL of DMF was stirred under argon at 25°C for 1 h. To it, 31 mg (0.110 mmol) of silver carbonate, a solution of 37 mg (0.110 mmol) of iodide **25** in 1 mL of DMF, and 32 μL (0.22 mmol) of triethylamine were added. The resulting mixture was stirred at 60°C for 20 h, cooled to 25°C, poured into water, and extracted three times with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and ether (20:1) as eluant to give 15 mg (65% yield) of **26**: $[\alpha]_D^{22}$=+158° ($c$=0.1, $CHCl_3$); $^1$H NMR ($CDCl_4$) $\delta$ 5.99 (d, $J$=6.0 Hz, 1H, C4H), 5.66 (m, 2H, C2&3Hs), 4.98 (s, 2H, C9Hs), 3.36 (m, 1H, C3aH), 3.27 (q, $J$=7.6 Hz, 1H, C6H), 2.94 (dm, $J$=17.0 Hz, 1H, C1H, 2.30 (dq, $J$=17.0, 2.4 Hz, 1H, C1H), 1.93 (s, 3H, C10Me), 1.26 (s, 3H, C12Me), 1.24 (d, $J$=7.6 Hz, 3H, C11Me); $^{13}$C NMR ($CDCl_3$) $\delta$ 218.1, 141.3, 133.1, 128.8, 123.4, 123.3, 112.0, 55.6, 50.9, 45.7, 43.3, 24.8, 21.3, 20.0. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.86; H, 9.20.

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