Palladium-Catalyzed Intramolecular Oxidative Heck Cyclization and Its Application toward a Synthesis of (±)-β-Cuparenone Derivatives Supported by Computational Studies

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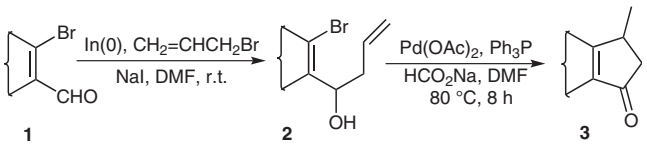
Abstract: A novel and efficient intramolecular oxidative cyclization of substituted homoallylic alcohols to form cyclic keto compounds under palladium-catalyzed conditions is described. The reaction has practical applications in the synthesis of sesquiterpenes. The mechanism of cyclization, the key step in the tandem reaction, was analyzed by using density functional theory calculations.

Key words: palladium, Heck reaction, cyclizations, terpenoids, ketones, alkenes, catalysis, oxidations, computational studies

The cyclization of unsaturated substrates by intramolecular Heck reactions promoted by organopalladium complexes is of fundamental importance for the construction of vast array of mono- and polycarbocyclic systems, and is therefore a highly attractive technique for the synthesis of cyclic natural products.[1] Palladium(II) complexes are extremely important in organopalladium chemistry. Palladium(0) complexes are fairly nucleophilic, rather labile, and easily oxidized, usually to the palladium(II) state. The most synthetically useful chemistry of palladium(0) involves the oxidative addition of aryl, vinylic, or allylic halides or triflates to palladium(0); such reactions can be very useful in the synthesis of carbocycles or heterocycles.[2] Our investigations have focused mainly on possible cycloannulations through an intramolecular Heck reaction followed by oxidation of an alcohol group, most significantly from a bromovinyl alcohol. In continuation of these studies, we have examined the corresponding reactions of homoallylic alcohol derivatives and we have inferred the mechanism of this reaction.

As part of our ongoing interest in palladium-catalyzed Heck reactions,[3] we developed a new method and we extended it to the synthesis of some precursors of sesquiterpene natural products. In the context of our general interest in the chemistry of β-bromovinyl aldehydes[4] and our exploration of the sequential indium-mediated allylation and palladium-catalyzed cyclization of such compounds, we attempted to develop a general method for the synthesis of 1-bromohexa-1,5-dien-3-ol derivatives **2** that would undergo an intramolecular Heck reaction to form the corresponding fused methyl-substituted cyclopentenone derivatives **3** (Scheme 1).



Scheme 1 Synthesis of substituted cyclopentenones

Various cyclic bromovinyl aldehydes **1.11**–**1.16** (Table 1) were subjected to an allylation protocol to assess the generality of our method. In all cases, we obtained the corresponding 1-bromohexa-1,5-dien-3-ol derivatives **2** in good-to-excellent yields.

Initially, we chose sodium formate as the base for the Heck cyclization reaction. We subsequently examined the effect on the yields of cyclopentenones of other bases, including organic bases such as triethylamine, which was not effective in promoting the reaction. Although many factors could have effects under our reaction conditions, it seemed logical to assume that the yield might be improved by using an inorganic base. We found that inorganic bases such as sodium carbonate, potassium carbonate, or sodium acetate gave the cyclized products in good-to-moderate yield. When we performed the Heck reaction of **2.16** in the presence of these inorganic bases, keeping other variables constant, we obtained the corresponding product **3.16** in 59–69% yield (Table 2).

The cyclization reaction of the allylated substrates **2.11**–**2.16** with sodium formate as the base gave the corresponding cyclized products in moderate-to-good yields (Table 3). The use of phase-transfer conditions with tetrabutylammonium chloride (TBAC) improved the yield by 12% in the case of substrate **2.16**. In this case, we believe that the greater solubility of the reagents as a result of the presence of TBAC might play a crucial role in determining the outcome of the reaction.

A fundamental goal of chemical research is to understand the mechanism of a reaction that leads to specific products. Because we could not isolate any intermediates from these reaction, there were many plausible mechanisms. We therefore performed some additional experiments to obtain some clues as to the mechanism of the reaction. By using the chiral agent (+)-(*R*)-1,1′-binaphthalene-2,2'-di-

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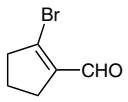
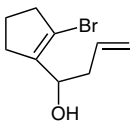
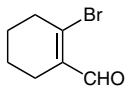
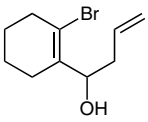
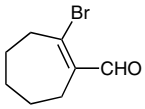
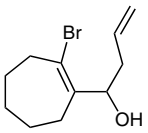
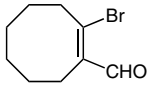
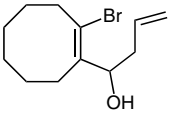
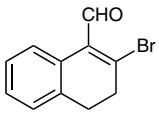
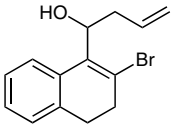
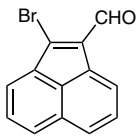
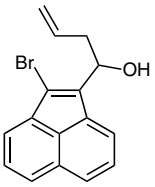
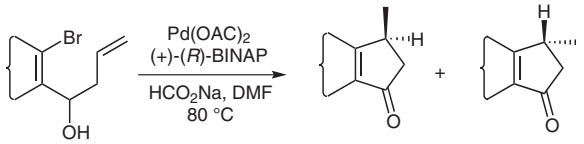
Table 1 Allylation of β-Bromovinyl Aldehydes

Entry[a]	Substrate	Product	Time (h)	Yield[b] (%)
1	 **1.11**	 **2.11**	4.0	73
2	 **1.12**	 **2.12**	3.0	61
3	 **1.13**	 **2.13**	3.5	72
4	 **1.14**	 **2.14**	4.5	76
5	 **1.15**	 **2.15**	3.5	76
6	 **1.16**	 **2.16**	4.0	81

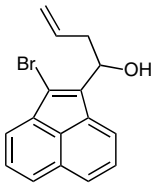
[a] Reaction conditions: β-bromovinyl aldehyde (1 mmol), In metal (1.2 mmol), CH_2=$CHCH_2Br$ (3 mmol), NaI (4 mmol), DMF, stirring, r.t., 5 h.
[b] Isolated yields after purification.

ylbis(diphenylphosphine) [(+)-(*R*)-BINAP], we attempted to induce chirality at the tertiary center formed by cyclization with the aim of determining whether a particular enantiomer would be formed in excess. However, we obtained a racemic mixture of products, implying that there no chiral induction had occurred (Scheme 2).



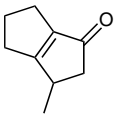
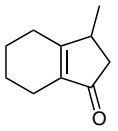
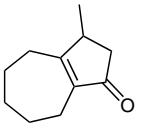
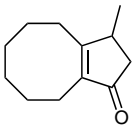
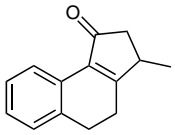
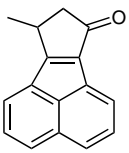
Scheme 2 Heck reaction in the presence of the (+)-(*R*)-BINAP ligand

Table 2 Heck Reaction of Substrate **2.16** in the Presence of Various Inorganic Bases

Substrate	Base[a]	Yield[b] (%)
	Na_2CO_3	68
	K_2CO_3	69
	NaOAc	59

[a] All the reactions were carried out with $Pd(OAc)_2$ (10 mol%), Ph_3P (0.25 mmol), and base (1 mmol) in DMF at 80 °C for 8 h.
[b] Isolated yield after purification

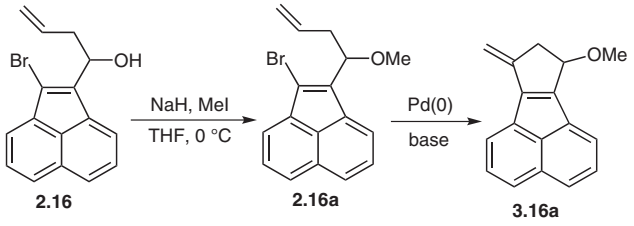
Table 3 Heck Reaction with 1-Bromohexa-1,5-dien-3-ol

Entry[a]	Substrate	Product	Yield[b] (%)
1	**2.11**		58
2	**2.12**		61
3	**2.13**		60
4	**2.14**		63
5	**2.15**		62
6	**2.16**		71

[a] All reactions were carried out with $Pd(OAc)_2$ (10 mol%), Ph_3P (0.25 mmol), and HCO_2Na (1 mmol) in DMF at 80 °C for 8 h.
[b] Isolated yield after purification.

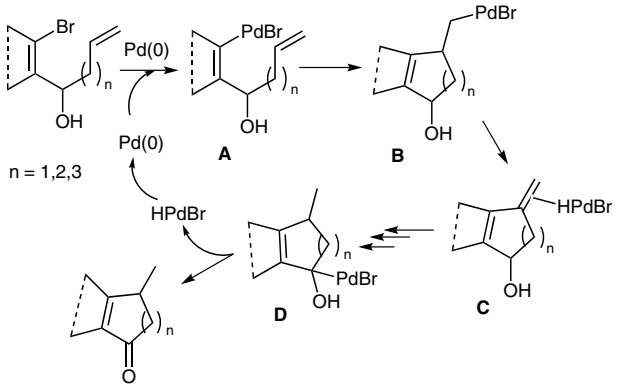
Our next experiment, however, led us to a probable mechanistic interpretation. The bromodienol *O*-methoxy derivative **2.16a** underwent Heck cyclization to afford the corresponding fused *O*-methoxycyclopentenol derivative **3.16a** containing an exocyclic double bond. Substrate **2.16a** was prepared in 67% yield by O-alkylation of 1-(2-bromoacenaphthylen-1-yl)but-3-en-1-ol (**2.16**) with iodo-

methane in the presence of sodium hydride. Heck reaction of this substrate in the presence of either sodium formate or potassium carbonate as the base gave the tetracycle **3.16a** (Scheme 3). In this case, the hydroxyl group is protected, so a keto group cannot form through isomerization. The isolation of the product with an exocyclic double bond indicates that a hypothesis based on cyclization of the homoallylic alcohol derivatives followed by β-hydride elimination is logical.



Scheme 3 Heck reaction of the *O*-methoxy derivative of 1-(2-bromoacenaphthylen-1-yl)but-3-en-1-ol **3.16a**

Our proposed oxidative cyclization mechanism involves an initial oxidative addition of palladium(0) to produce a palladium(II) complex **A**; this is followed by intramolecular ring closure to form the cyclic intermediate **B**, which undergoes β-hydride elimination followed by isomerization of the resulting intermediate **C** to give the thermodynamically stable ketone (Scheme 4).



Scheme 4 A plausible mechanism for the cyclization reaction

The existence of the cyclization step shown in Scheme 4 for the case of n = 3 was supported by a computational study (see below for details). The geometry of the intermediate after oxidative addition was modeled by using PdL (L = Ph_3P) as the catalyst. In the optimized structure **X** (Figure 1), the palladium atom adopts a square-planar geometry with coordination from carbon, bromine, and phosphorus, and the double bond. The transition state **TS** for the cyclization was located and characterized. The activation energy for this process is 102.0 kJ/mol (24.37 kcal/mol) at the BP86/def2-SVP level of theory. In the cyclized intermediate ***Y***, palladium is coordinated to the double bond and has an agostic interaction with the β-hydrogen. The reaction energy for this step is 48. 53 kJ/mol (11.60 kcal/mol). The energies were also evaluated by means of hybrid-density functional theory (DFT) B3LYP for BP86-optimized geometries. In B3LYP, the activation energy was 114.6 kJ/mol (27.39 kcal/mol) and the reaction energy was 35.02 kJ/mol (8.73 kcal/mol), in agreement with the usual energetic trends in DFT.

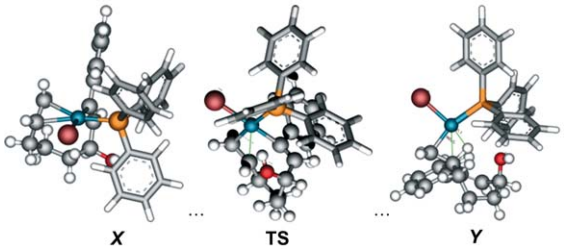
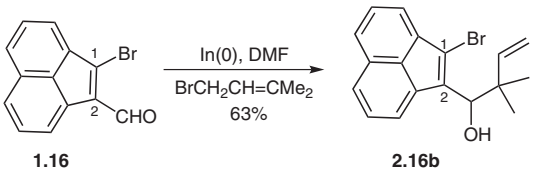


Figure 1 Optimized geometries (BP86/def2-SVP) of the species involved in the migratory insertion step

To examine whether the C1=C2 double bond plays any role in the reaction, we synthesized the novel substrate **2.16b** by indium-mediated allylation of bromovinyl aldehyde **1.16** with 1-bromo-3-methylbut-2-ene (Scheme 5).

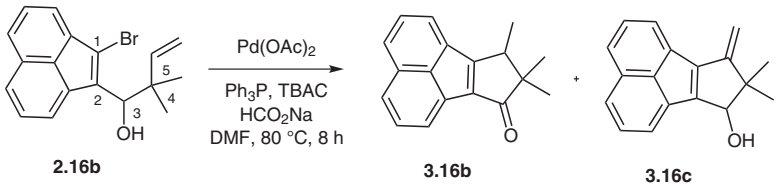


Scheme 5 Indium-mediated allylation of bromo aldehyde **1.16**

Application of Heck reaction conditions with sodium formate to substrate **2.16b** gave a mixture of products **3.16b** and **3.16c** in a 3:1 ratio (Scheme 6). It is possible that the indenol compound containing an exocyclic double bond **3.16c** was initially formed and that this readily isomerized by a route involving C1–C2 to give the thermodynamically stable ketone **3.16b**. Isomerization by the path involving C4–C5 is not possible because there are no available hydrogen atoms at C4, which is substituted by two methyl groups (Scheme 6).

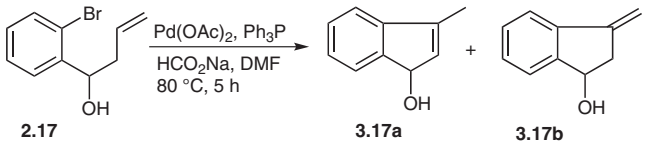
This observation was confirmed when we performed the Heck reaction with the allylated bromo aldehyde derivative **2.17** (Scheme 7).[5] In this case, inseparable mixtures of products **3.17b** and **3.17a**, containing an exocyclic and an endocyclic double bond, respectively, were obtained in proportions that depended on the reaction conditions and no keto product was isolated.

From these results, we can relate the reaction mechanism for β-bromoallyl alcohol derivatives to that of their aromatic analogues. It is possible that in the case of β-bromoallyl alcohol derivatives of vinylic bromo aldehydes, cyclization and β-elimination reactions of intermediate **A** give intermediate **C**, which undergoes two consecutive 1,5-hydrogen shifts to form the product (Scheme 8). In the case of the aromatic system, the exocyclic double bond formed after cyclization cannot participate in isomeriza-



2.16b 3.16b 3.16c

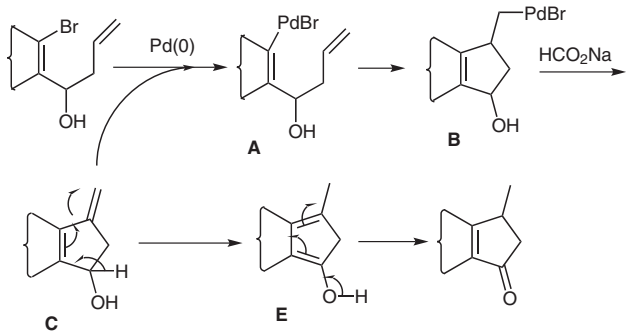
Scheme 6 Cyclization of substrate **2.16b** under Heck reaction conditions



2.17 3.17a 3.17b

Scheme 7 Heck reaction of substrate **2.17**

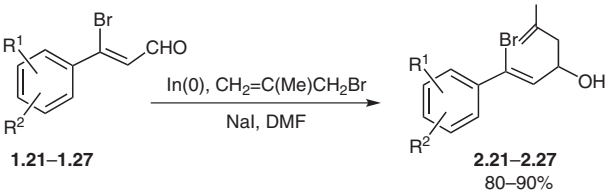
tion with the double bond of the aromatic ring system, and therefore no keto compound is obtained. We therefore speculate that the β-bromoallyl alcohol derivatives react by the pathway shown in Scheme 8.



Scheme 8

To examine the practical utility of our methodology, we developed a new and efficient method related to the previous one, and we extended it to the synthesis of sesquiterpene natural products. Many multistep methods have previously been developed for the synthesis of compounds such as (±)-α- and (±)-β-cuparenone or (±)-herbertene, but these methods are lengthy, involve hazardous materials, or give low yields.[6–8] Our need to develop a practical method involving fewer step and giving higher yields prompted us to investigate an unusual palladium-catalyzed tandem Heck cyclization. We therefore examined the formation of *gem*-dimethyl cyclopentenone moieties from 1-bromo-5-methyl-1-arylhexa-1,5-dien-3-ols under palladium-catalyzed Heck reaction conditions (Scheme 9).[9]

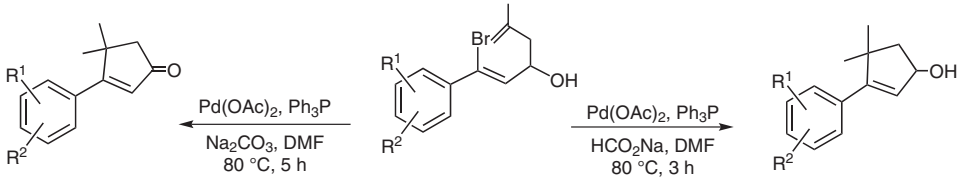
Aware of the possibilities offered by this reaction, we applied the method to obtain two different products from a common starting material by varying the reaction conditions (Scheme 9). In this scheme lies the beauty of our methodology. By applying our methodology, we aimed to synthesize various sesquiterpene natural products by changing the substituents in the aryl moiety. This convergent approach involved the preparation of the cyclization precursors **2.21**–**2.27**, which were efficiently assembled by indium-mediated methallylation of the corresponding bromo aldehydes **1.21**–**1.27** with 3-bromo-2-methylprop-1-ene in 80–90% yield (Scheme 10).



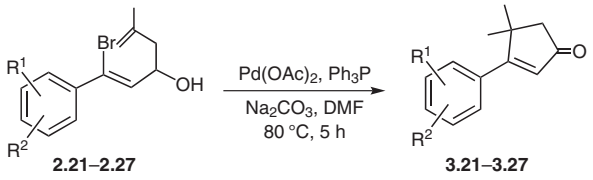
1.21–1.27 2.21–2.27 80–90%

Scheme 10

We then attempted to perform the cyclization reaction with various bases, solvents, and catalysts to optimize the reaction conditions. We found that when we carried out the reaction with 2 mol% of palladium(II) acetate, 0.5 equivalents of triphenylphosphine, and 1.5 equivalents of sodium carbonate in *N*,*N*-dimethylformamide at 80 °C for five hours, the yield of **3.21** increased to 70% (Scheme 11 and Table 4). Compound **3.21** can be converted into (±)-β-cuparenone in a single step.[10]



Scheme 9



Scheme 11

As described above, we were able to obtain the methyl-substituted fused cyclopentenone derivatives through a 1,5-hydrogen shift of the cyclized product containing an exocyclic double bond, formed by intramolecular cyclization of the allylated and propargylated derivatives of vinyl bromo aldehyde. In this case, the possibility of formation of an exocyclic double bond could be eliminated because of lack of availability of a β-hydrogen for elimination after cyclization through the 5-*exo*-trig pathway (Scheme 12).

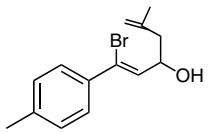
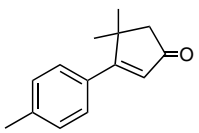
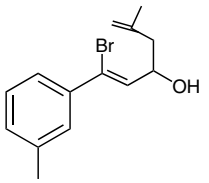
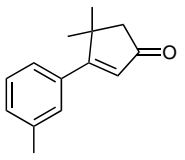
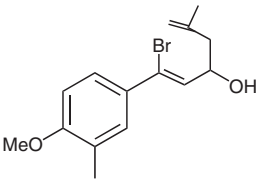
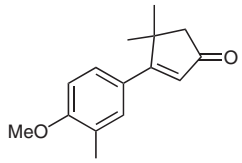
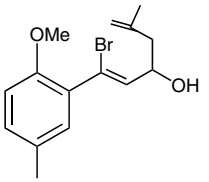
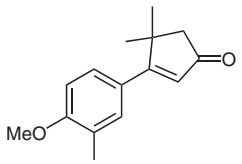
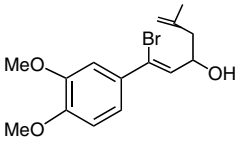
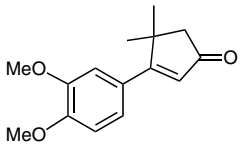
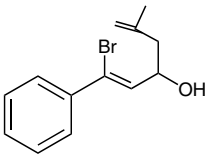
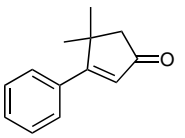
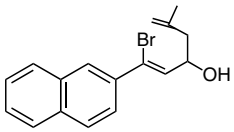
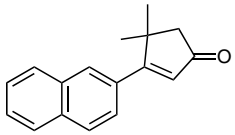
In a recent communication,[11] it was established that in the absence of a terminating agent, this type of substrate undergoes olefin insertion in the 6-*endo* mode. In our case, 5-*exo*-trig cyclization occurred, probably because of the presence of the –CHOH group in the substrate, which donates hydride for termination and is thereby converted into a carbonyl group.

By changing the reaction conditions by using sodium formate as the hydride donor in the absence of a base, we were able to isolate the cyclized hydroxy derivative as an isolable product. This may have occurred because, in the absence of a base, no hydride transfer occurred; there was therefore no proton abstraction to form the palladium hydride intermediate, and the palladium bromide intermediate cyclized directly. This reaction, in turn, terminated through capture of hydride from sodium formate to generate the nonoxidized *gem*-dimethyl cyclopentenol derivative **3.31**–**3.37** (Scheme 13 and Table 5).

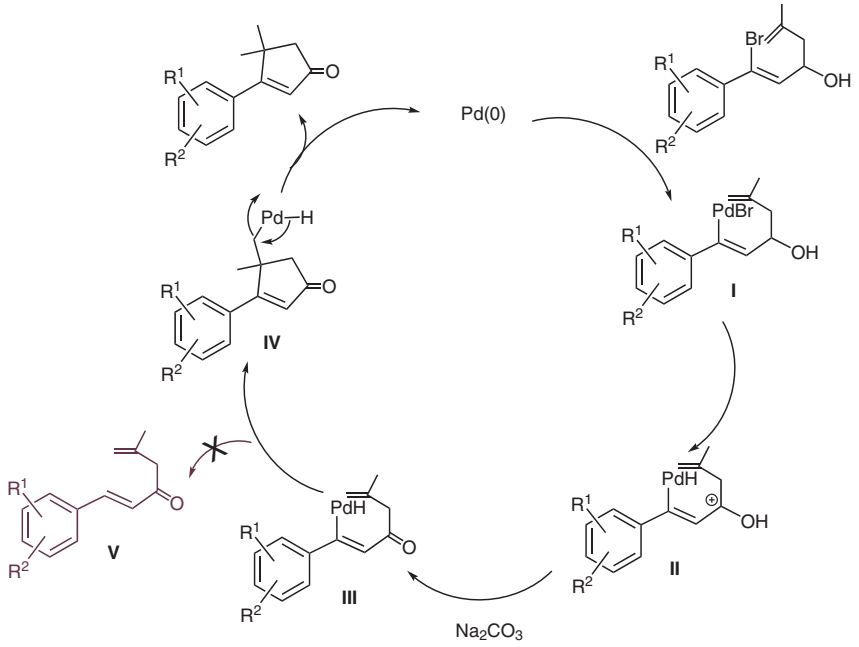
In conclusion, we have developed a new method for the synthesis of fused cyclopentenones and we have extended it to obtain *gem*-dimethyl-substituted cyclopentenones, useful in a convenient and efficient synthesis of sesquiterpene natural products. We were able to establish two different sets of reaction conditions that gave two structurally and mechanistically different products, one of which led directly to the required sesquiterpene precursors.

All the chemicals were purchased from Sigma-Aldrich and used directly. DMF was dried, distilled and stored over molecular sieves (4 Å). THF was freshly distilled over sodium–benzophenone. Chromatographic purification was done with either 60–120 or 100–200 mesh silica gel (SRL). For reaction monitoring, precoated silica gel 60 F_{254} TLC sheets (Merck) were used. Petroleum ether refers to the fraction boiling in the range 60–80 °C. Melting points were determined on a Toshniwal electrical air heating instrument and are uncorrected. IR spectra were recorded on Perkin–Elmer 883 and Shimadzu FTIR-8300 infrared spectrophotometers. ^{1}H NMR (200 MHz) spectra were recorded on a Bruker AC 200 MHz spectrome-

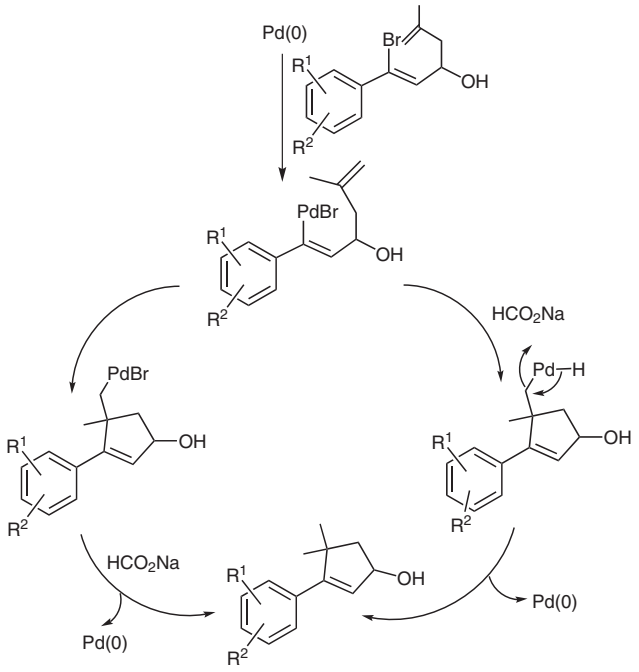
Table 4 Synthesis of *gem*-Dimethylcyclopentenone Derivatives **3.21**–**3.27** by Palladium-Catalyzed Intramolecular Cyclization of Dienols **2.21**–**2.27**

Entry[a]	Substrate	Product	Yield[b] (%)
1	 **2.21**	 **3.21**	70
2	 **2.22**	 **3.22**	75
3	 **2.23**	 **3.23**	65
4	 **2.24**	 **3.24**	60
5	 **2.25**	 **3.25**	78
6	 **2.26**	 **3.26**	75
7	 **2.27**	 **3.27**	80

[a] Reaction conditions: $Pd(OAc)_2$ (2 mol%), Ph_3P (0.5 mmol), Na_2CO_3 (1.5 mmol), DMF, 80 °C, 5 h.
[b] Isolated yield after purification.



Scheme 12



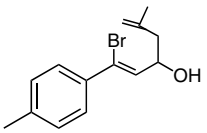
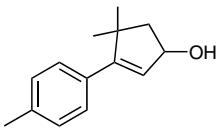
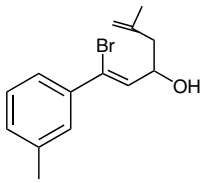
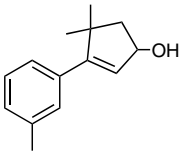
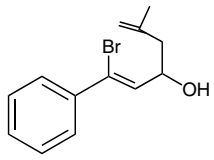
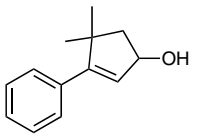
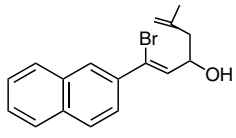
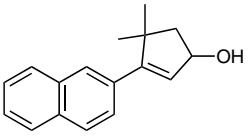
Scheme 13

ter. Chemical shifts are reported in parts per million relative to tetramethylsilane as the internal standard. ^{13}C NMR (50 MHz) spectra were recorded on the same spectrometer with complete proton decoupling. EIMS (70 eV) spectra were collected on a VG Autospec M mass spectrometer and ESI-MS spectra were collected on a Waters LCT mass spectrometer. Elemental analysis was carried out on a Vario EL ElementalAnalyzer.

Homoallylic Alcohols 2; General Procedure

A mixture of CH_2=$CHCH_2Br$ or CH_2=$C(Me)CH_2Br$ (3 mmol), In metal (1.2 mmol), and NaI (4 mmol) in DMF (3–4 mL) was stirred

Table 5 Synthesis of *gem*-Dimethyl Cyclopentenol Derivatives

Entry[a]	Substrate	Product	Yield[b] (%)
1	 **2.21**	 **3.31**	50
2	 **2.22**	 **3.32**	56
3	 **2.26**	 **3.36**	60
4	 **2.27**	 **3.37**	58

[a] Reaction conditions: $Pd(OAc)_2$ (2 mol%), Ph_3P (0.5 mmol), HCO_2Na (1.2 mmol), DMF, 80 °C, 3 h.
[b] Isolated yield.

at r.t. until the complex was completely formed. A soln of the appropriate bromo aldehyde (1 mmol) in DMF (3 mL) was then added. The reaction was monitored by TLC and after 5–6 h the reaction was quenched with a few drops of 1 M aq HCl. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the extracts were thoroughly washed with 2 M aq $Na_2S_2O_3$ (2 × 20 mL) and brine (2 × 20 mL). Evaporation of the solvent gave a residue that was purified by column chromatography [silica gel (60–120 mesh), PE–EtOAc (1:1)].

1-(2-Bromocyclopent-1-en-1-yl)but-3-en-1-ol (2.11)
Yellow liquid; yield: 182 mg (73%).

IR ($CHCl_3$): 1646, 1439, 1023, 873 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.77–1.97 (m, 3 H), 2.00–2.49 (m, 4 H), 2.58–2.67 (m, 2 H), 4.60 (t, *J* = 7.1 Hz, 1 H), 5.01–5.26 (m, 2 H), 5.68–5.88 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 29.5, 39.4, 40.1, 68.6, 117.0, 117.5, 134.0, 141.8.

Anal. Calcd for $C_9H_{13}BrO$: C, 49.79; H, 6.04. Found: C, 49.97; H, 6.12.

1-(2-Bromocyclohex-1-en-1-yl)but-3-en-1-ol (2.12)
Yellow liquid; yield: 153 mg (61%).

IR ($CHCl_3$): 2927, 1666, 1454, 1375, 1261, 1022 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.69 (br s, 4 H), 2.02 (br s, 1 H, OH), 2.29–2.36 (m, 4 H), 2.51 (br s, 2 H), 4.80 (t, *J* = 6.8 Hz, 1 H), 5.11–5.19 (m, 2 H), 5.76–5.89 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 24.7, 25.3, 36.8, 38.9, 73.2, 117.9, 120.2, 134.3, 136.9.

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.97; H, 6.54. Found: C, 52.13; H, 6.39.

1-(2-Bromocyclohept-1-en-1-yl)but-3-en-1-ol (2.13)
Yellow liquid; yield: 180 mg (72%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.41 (m, 6 H), 1.92–2.11 (m, 3 H), 2.18–2.24 (m, 2 H), 2.53–2.41 (m, 2 H), 4.76 (br s, 1 H), 4.91–5.05 (m, 2 H), 5.79–5.89 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.3, 26.3, 27.3, 31.7, 39.0, 41.6, 74.6, 117.8, 123.3, 134.3, 142.2.

Anal. Calcd for $C_{11}H_{17}BrO$: C, 53.89; H, 6.99. Found: C, 54.12; H, 6.86.

1-(2-Bromocyclooct-1-en-1-yl)but-3-en-1-ol (2.14)
Yellow liquid; yield: 190 mg (76%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.49–1.76 (br s, 8 H), 1.90 (br s, 1 H, OH), 2.24–2.47 (m, 4 H), 2.66–2.72 (m, 2 H), 4.77–4.82 (dd, *J* = 5.5 and 5.5 Hz, 1 H), 5.09–5.18 (m, 2 H), 5.74–5.91 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.5, 26.7, 27.2, 27.5, 31.3, 37.0, 39.6, 74.4, 117.8, 122.3, 134.7, 139.5.

Anal. Calcd for $C_{12}H_{19}BrO$: C, 55.61; H, 7.39. Found: C, 55.93; H, 7.23.

1-(2-Bromo-3,4-dihydronaphthalen-1-yl)but-3-en-1-ol (2.15)
Yellow liquid; yield: 190 mg (76%).

IR ($CHCl_3$): 3407, 2932, 1663, 1452, 1053 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.83 (br s, 1 H, OH), 2.50–2.63 (m, 4 H), 2.72–2.91 (m, 2 H), 5.10–5.30 (m, 3 H), 5.77–5.98 (m, 1 H), 7.09–7.24 (m, 3 H), 7.86–7.91 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7, 36.1, 39.6, 74.0, 117.8, 124.8, 125.4, 126.2, 127.1, 127.5, 132.4, 134.6, 135.7, 135.8.

Anal. Calcd for $C_{14}H_{15}OBr$: C, 60.23; H, 5.42. Found: C, 60.48; H, 5.31.

1-(2-Bromoacenaphthylen-1-yl)but-3-en-1-ol (2.16)
Yellow liquid; yield: 202 mg (81%).

IR ($CHCl_3$): 3415, 3064, 2966, 2918, 1423, 1262, 1092, 1026, 865, 804 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.91 (br s, 1 H), 2.69–2.80 (m, 2 H), 5.14–5.26 (m, 3 H), 5.83–6.03 (m, 1 H), 7.47–7.65 (m, 3 H), 7.76–7.85 (m, 2 H), 7.97–8.00 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.9, 69.5, 117.2, 118.3, 123.0, 124.7, 127.1, 127.4, 127.5, 127.6, 127.7, 128.3, 134.2, 136.4, 137.4, 141.5.

Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 63.99; H, 4.51.

1-Bromo-2-(1-methoxybut-3-en-1-yl)acenaphthylene (2.16a)
A suspension of NaH (washed with pentane; 21 mg, 0.87 mmol) in anhyd THF (5 mL) was cooled to 0 °C. A soln of alcohol **2.16** (240 mg, 0.79 mmol) in THF (5 mL) was added dropwise then the mixture was warmed to r.t. and stirred for 20 min. MeI (123 mg, 0.87 mmol) was added, and the mixture was stirred at r.t. for 4 h. The reaction was quenched with ice-water (10 g) and the mixture was diluted with Et_2O (30 mL). The organic layer was washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography [silica gel (60–120 mesh), PE–EtOAc (4:1)] to give a yellow oil; yield: 168 mg (67%).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.57–2.71 (m, 1 H), 2.76–2.90 (m, 1 H), 3.33 (s, 3 H), 4.72 (t, *J* = 6.9 Hz, 1 H), 5.03–5.15 (m, 2 H), 5.79–5.96 (m, 1 H), 7.48–7.66 (m, 3 H), 7.72–7.92 (m, 2 H), 7.97 (d, *J* = 5.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.90, 57.32, 78.89, 117.52, 119.86, 123.15, 124.58, 127.73, 128.00, 128.17, 128.53, 129.03, 134.54, 136.60, 137.74, 140.30.

Anal. Calcd for $C_{17}H_{15}BrO$: C, 64.78; H, 4.80. Found: C, 64.91; H, 4.63.

1-(2-Bromoacenaphthylen-1-yl)-2,2-dimethylbut-3-en-1-ol (2.16b)
Yellow oil; yield: 158 mg (63%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (s, 3 H), 1.23 (s, 3 H), 1.96 (br s, 1 H), 4.98 (s, 1 H), 5.19–5.21 (m, 1 H), 5.22 (s, 1 H), 5.97–6.19 (m, 1 H), 7.56–8.05 (m, 4 H), 8.09 (d, *J* = 8.3 Hz, 1 H), 8.33 (d, *J* = 6.9 Hz, 1 H).

Anal. Calcd for $C_{18}H_{17}BrO$: C, 65.67; H, 5.20. Found: C, 65.78; H, 5.31.

Palladium-Catalyzed Heck Cyclization of Methallylated Derivatives; General Procedure
A mixture of the appropriate methallylated derivative (1 mmol), $Pd(OAc)_2$ (2 mol%), Ph_3P (0.5 mmol), and Na_2CO_3 (1.5 mmol) was flashed with argon and then DMF (5 mL) was added. The mixture was degassed with argon, heated to 80 °C for 5 h, cooled, and diluted with ice-water (10 g). The resulting mixture was extracted with Et_2O (3 × 20 mL) and the extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography [silica gel (60–120 mesh), PE–EtOAc (9:1)].

Palladium-Catalyzed Heck Reaction of Homoallylic Alcohols; General Procedure
A two-necked round-bottom flask was charged with the appropriate homoallylic alcohol (1 mmol), $Pd(OAc)_2$, (10 mol%), Ph_3P (0.25 mmol), HCO_2Na (1 mmol), and DMF (6–8 mL). The mixture was then degassed with N_2 and heated to 80 °C for 8 h. The mixture was then cooled, diluted with cold H_2O (15 mL), and extracted with Et_2O (3 × 20 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a residue that was purified by column chromatography [silica gel, PE–EtOAc (8:1)].

3-Methyl-3,4,5,6-tetrahydropentalen-1(2*H*)-one (3.11)[12]
Yellow liquid; yield: 87 mg (58%).

IR ($CHCl_3$): 3391, 2927, 1679, 1633, 1438, 1263, 1170 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.9 Hz, 3 H), 1.93–2.54 (m, 4 H), 2.56–2.95 (m, 4 H), 2.98–3.01 (m, 1 H).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.58; H, 8.67.

3-Methyl-2,3,4,5,6,7-hexahydro-1*H*-inden-1-one (3.12)[13]
Yellow liquid: yield: 92 mg (61%).

IR ($CHCl_3$): 1698, 1681, 1645, 1453, 1276 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.8 Hz, 3 H), 1.63–1.76 (m, 5 H), 2.11–2.30 (m, 3 H), 2.37–2.58 (m, 2 H), 2.64–2.72 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 19.7, 21.4, 22.3, 25.7, 36.1, 43.2, 137.8, 177.5, 208.3.

MS (EI, 70 eV): *m/z* = 150 (26) [M^+], 69 (100).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found; C, 80.13; H, 9.21.

3-Methyl-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (3.13)
Yellow liquid; yield: 90 mg (60%).

IR ($CHCl_3$): 3409, 2926, 2856, 2290, 1695, 1641, 1444, 1165, 1067, 616, 521 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.0 Hz, 3 H), 1.42–1.67 (m, 6 H), 1.73–1.83 (m, 4 H), 2.26–2.58 (m, 2 H), 2.67–2.70 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9, 23.1, 26.3, 26.5, 31.1, 31.4, 37.0, 43.1, 141.7, 181.0, 208.1.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.61; H, 9.59.

3-Methyl-2,3,4,5,6,7,8,9-octahydro-1*H*-cyclopenta[8]annulen-1-one (3.14)
Faint-yellow liquid; yield: 94 mg (63%).

IR ($CHCl_3$): 3385, 1685, 1656, 1447, 1254, 1042, 814, 627 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 3 H), 1.49–1.72 (m, 8 H), 2.29–2.32 (m, 4 H), 2.48–2.69 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 21.1, 25.8, 26.0, 27.9, 28.2, 36.3, 43.3, 140.2, 178.7, 208.3.

Anal. Calcd for $C_{12}H_{18}O$; C, 80.85; H, 10.18. Found: C, 81.13; H, 9.91.

3-Methyl-2,3,4,5-tetrahydro-1*H*-cyclopenta[*a*]naphthalen-1-one (3.15)
Faint-yellow oil; yield: 93 mg (62%).

IR ($CHCl_3$): 3063, 2930, 2244, 1692, 1670, 1627, 1506, 1429, 1391, 1252, 1068, 817 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 7.1 Hz, 3 H), 2.21–2.83 (m, 4 H), 2.87–2.97 (m, 3 H), 7.17–7.68 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 24.7, 27.6, 35.3, 44.7, 124.1, 126.4, 126.9, 127.5, 127.8, 128.3, 134.0, 178.8, 205.5.

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81, H, 7.12. Found: C, 84.97; H, 7.08.

9-Methyl-8,9-dihydro-7*H*-cyclopenta[*a*]acenaphthylen-7-one (3.16)
Yellow solid; yield: 107 mg (71%); mp 148 °C.

IR ($CHCl_3$): 1679, 1628 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 7 Hz, 3 H), 2.56–2.65 (dd, J_{cis} = 2.0 Hz and J_{gem} = 18.0 Hz, 1 H), 3.23–3.32 (dd, J_{trans} = 6.2 Hz and J_{gem} = 18.0 Hz, 1 H), 3.60–3.68 (m, 1 H), 7.55–7.69 (m, 2 H), 7.82–8.02 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9, 31.5, 50.4, 124.6, 126.1, 127.6, 127.6, 128.2, 129.5, 130.6, 131.2, 133.1, 133.7, 142.8, 181.1, 200.2.

MS (EI, 70 eV): *m/z* = 220, 205, 191, 181, 152.

Anal. Calcd for $C_{16}H_{12}O$: C, 87.25, H, 5.49. Found: C, 87.54, H, 5.36.

7-Methoxy-9-methylene-8,9-dihydro-7*H*-cyclopenta[*a*]acenaphthylene (3.16a)
Yellow oil; yield 81 mg (54%).

^1H NMR (200 MHz, C_6D_6): δ = 2.99–3.16 (m, 2 H), 3.20 (s, 3 H), 4.83 (dd, *J* = 2.9, 2.9 Hz, 1 H), 5.02 (br s, 1 H), 5.49 (br s, 1 H), 7.20–7.31 (m, 2 H), 7.45–7.60 (m, 4 H).

MS (EI, 70 eV): *m/z* = 234, 219.

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.33; H, 5.88.

8,8,9-Trimethyl-8,9-dihydro-7*H*-cyclopenta[*a*]acenaphthylen-7-one (3.16b)
Yellow solid; yield: 92 mg (61%).

IR ($CHCl_3$): 1681 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.32 (s, 3 H), 1.47 (d, *J* = 7.4 Hz, 3 H), 3.30 (q, *J* = 7.5 Hz, 1 H), 7.58–7.69 (m, 3 H), 7.84 (d, *J* = 8.3 Hz, 1 H), 7.93–8.01 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.6, 21.2, 25.6, 43.4, 54.5, 120.1, 123.8, 126.2, 127.8, 128.1, 128.4, 129.4, 131.6, 133.4, 136.0, 140.0, 178.1, 205.8.

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.30; H, 6.71.

8,8-Dimethyl-9-methylene-8,9-dihydro-7*H*-cyclopenta[*a*]acenaphthylen-7-ol (3.16c)
Yellow solid; yield: 27 mg (18%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.34 (s, 3 H), 1.71 (br s, 1 H, –OH), 4.86 (s, 1 H), 5.02 (s, 1 H), 5.50 (s, 1 H), 7.46–7.54 (m, 3 H), 7.64–7.85 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 28.6, 52.5, 79.2, 103.5, 123.2, 123.8, 127.33, 127.6, 127.9, 128.8, 133.0, 133.7, 134.3, 146.4, 149.6, 154.4.

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.33; H, 6.67.

3-Methyl-1*H*-inden-1-ol (3.17a)
White solid; yield: 118 mg (59%); mp 90 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.09 (d, *J* = 1.2 Hz, 3 H), 5.14 (br s, 1 H), 6.08 (br s, 1 H), 7.19–7.32 (m, 3 H), 7.49 (d, *J* = 6.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.9, 71.4, 117.2, 121.2, 124.1, 126.4, 130.4, 139.5, 141.9, 144.2.

Anal. Calcd for $C_{10}H_{10}O$: C, 81.77; H, 6.89. Found: C, 81.94, H, 6.65.

3-Methyleneindan-1-ol (3.17b)
Pale-yellow solid; yield: 60 mg (30%); mp 92 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.61 (d, *J* = 12.8 Hz, 1 H), 3.13 (d, *J* = 16.8 Hz, 1 H), 5.08 (s, 1 H), 5.18 (br s, 1 H), 5.52 (s, 1 H), 7.30–7.33 (m, 2 H), 7.43 (d, *J* = 4.8 Hz, 1 H), 7.51 (d, 1 H, *J* = 6.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.3, 73.1, 104.1, 120.5, 125.1, 128.6, 128.8, 140.1, 146.4, 146.9.

HRMS (ESI, 70 eV): *m/z* $[M - OH]^+$ calcd for $C_{10}H_9$: 129.0533; found: 129.1829.

Anal. Calcd for $C_{10}H_{10}O$: C, 81.77; H, 6.89. Found: C, 81.75; H, 6.90.

Other compounds **1.21**–**3.37** have been reported previously.[7a,9,14]

Computational Details

Density functional theory (DFT) calculations were performed by using the BP86[15] and B3LYP[16] functionals with empirical dispersion correction (DFT-D)[17] in conjunction with the def2-SVP[18] basis set and effective core potentials on Ni. The resolution of the identity (RI) approximation was used to speed up the BP86 calculations. TURBOMOLE V6.2[19] software was used in all the calculations.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605. (b) Oestreich, M.; Dennison, P. R.; Kondanko, J. J.; Overman, L. E. *Angew. Chem. Int. Ed.* **2001**, *40*, 1439. (c) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115. (d) Link, J. T. *Org. React. (N. Y.)* **2002**, *60*, 157. (e) Smith, A. B. III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194. (f) Alberico, D.; Paquin, J. F.; Lautens, M. *Tetrahedron* **2005**, *61*, 6283.

(2) (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 3894. (b) Cortese, N. A.; Ziegler, C. B. Jr; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (c) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 528. (d) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (e) Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035.

(3) (a) Mal, S. K.; Ray, D.; Ray, J. K. *Tetrahedron Lett.* **2004**, *45*, 277. (b) Ray, D.; Mal, S. K.; Ray, J. K. *Synlett* **2005**, 2135.

(4) Arnold, Z.; Tamura, M.; Shishido, K. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2886.

(5) Du, Z.; Wang, F.; Zhou, W.; Wang, J.-X. *J. Chem. Res.* **2010**, *34*, 475.

(6) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 9016.

(7) (a) Srikrishna, A.; Krishna, K.; Venkateswarlu, S.; Praveen Kumar, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2033. (b) Sato, T.; Hayashi, M.; Hayata, T. *Tetrahedron* **1992**, *48*, 4099. (c) Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2639.

(8) Chavan, S. P.; Ravindranathan, T.; Patil, S. S.; Dhondge, V. D.; Dantale, S. W. *Tetrahedron Lett.* **1996**, *37*, 2629.

(9) Ray, D.; Ray, J. K. *Org. Lett.* **2007**, *9*, 191.

(10) (a) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1985**, *49*, 931. (b) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329.

(11) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339.

(12) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.

(13) Andreini, B. P.; Carpita, A.; Ross, R.; Scamuzzi, B. *Tetrahedron* **1989**, *45*, 5621.

(14) Casares, A.; Maldonado, L. A. *Synth. Commun.* **1976**, *6*, 11.

(15) (a) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys* **1988**, *38*, 3098. (b) Perdew, J. P. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1986**, *33*, 8822.

(16) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(17) Grimme, S.; Antony, J.; Schwabe, T.; Mück-Lichtenfeld, C. *Org. Biomol. Chem.* **2007**, *5*, 741.

(18) (a) Eichkorn, K.; Treutler, O.; Öhm, H.; Häser, M.; Ahlrichs, R. *Chem. Phys. Lett.* **1995**, *240*, 283. (b) Eichkorn, K.; Treutler, O.; Öhm, H.; Häser, M.; Ahlrichs, R. *Chem. Phys. Lett.* **1995**, *242*, 652.

(19) *TURBOMOLE version 6.2*; TURBOMOLE GmbH: Karlsruhe, **2011**, http://www.turbomole.com.