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Lewis Acid-Catalyzed Tandem Diels−Alder Reaction/Retro-Claisen Rearrangement as an Equivalent of the Inverse Electron Demand Hetero Diels−Alder Reaction

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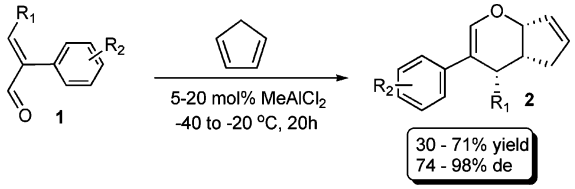

A highly stereoselective formal inverse electron demand hetero Diels−Alder reaction (HDA) occurs on reaction of 2-aryl-α,β-unsaturated aldehydes with cyclopentadiene. The major pathway for this transformation is shown to be a Lewis acid-catalyzed tandem Diels−Alder reaction/retro-Claisen rearrangement.

Introduction

The inverse electron demand hetero Diels−Alder (HDA) reaction of enones with electron-rich olefins is a simple approach for the formation of dihydro- and tetrahydropyran derivatives,[1] which are prevalent structural subunits in a variety of biologically important natural compounds, including carbohydrates, pheromones, iridoids, and polyether antibiotics.[2] Although several successful examples of enantioselective inverse electron demand HDA reactions have been achieved,[3] most of the reported methods are limited to enone derivatives bearing electron-withdrawing groups such as ester,[3a,e−f] phosphonate,[3b] or sulfone groups.[3g,h] The reaction usually occurs by a direct HDA reaction. In the reaction with cyclopentadiene, however, some examples are known of HDA products that are derived from a Diels−Alder reaction followed by a retro-Claisen rearrangement.[4] HDA reactions involving simple α,β-unsaturated aldehyde as substrates are less common.[3i] Herein, we describe that 2-aryl-α,β-unsaturated aldehydes are effective substrates for stereoselective HDA cycloadditions with cyclopentadiene. Furthermore, the mechanism of the cycloaddition is shown to be a Lewis acid-catalyzed tandem Diels−Alder cycloaddition/retro-Claisen rearrangement.[4,5]

Results and Discussions

Recently, we reported a formal [4 + 3] cycloaddition between cyclopentadiene and α,β-unsaturated aldehydes

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(4) (a) Hanessian, S.; Compain, P. *Tetrahedron* **2002**, *58*, 6521. (b) Arimori, S.; Kouno, R.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2002**, *67*, 7303. (c) Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359. (d) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098.

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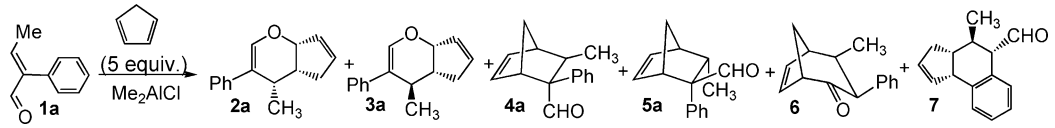
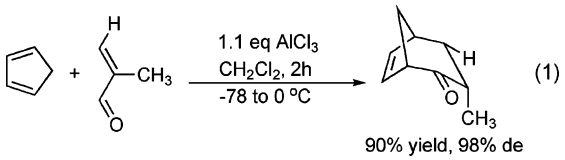
TABLE 1. [4 + 2] Reactions between 1,2-Phenyl-2-butenal (1b) and Cyclopentadiene



	reaction condition			product ratio[a]							
entry	Me_2AlCl (equiv)	*T*/°C	*t*/h	**2a**	**3a**	**4a**	**5a**	**6**	**7**	conv (%)	yield (%)[b]
1	1.1	−20	6	19	4	42	7	15	13	86	–
2	0.5	−20	6	39	3	39	7	5	7	93	**2a**(26) **4a** (27)
3	0.1	−20	6	59	2	29	7	1	2	100	**2a** (46) **4a**+**5a** (26)
4	0.02	−20	6	68	4	19	5	4	0	91	–
5	0.1	0	6	53	4	24	8	6	5	100	–
6	1.0	25	0.7	0	0	0	0	43	57	86	**6** (26) **7** (31)
7	0.1	−40	6	60	1.5	35	3.5	0	0	100	**2a** (55) **4a**+**5a** (30)
8	0.05	−40	20	89	2	7	2	0	0	100	**2a** (71) **4a**+**5a** (4)

[a] The ratio was determined from a 500 MHz ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after chromatographic purification.

(eq 1).[6] The reaction was shown to proceed by a [4 + 2] cycloaddition followed by a Lewis acid-catalyzed ring expansion. A requirement for this transformation was the presence of an electron-donating substituent on the α,β-unsaturated aldehyde.



To expand the range of this reaction, various other substrates were examined. When 2-phenyl-2-butenal (**1a**) was used, the reaction gave a complex mixture of five products in addition to the expected [4 + 3] cycloadduct **6** (Table 1). Two diastereomeric dihydropyrans **2a** and **3a**, two diastereomeric Diels–Alder cycloadducts **4a** and **5a**, the [4 + 3] cycloadduct **6**, and the tricyclic product **7** were formed. Because the dihydropyrans are the products of a formal HDA reaction where the cyclopentadiene behaves as the dienophile,[3b,c,4,7] further studies were conducted to optimize the reaction toward the formation of **2a**. Decreasing the amount of Lewis acid in reactions conducted at −20 °C resulted in a steady improvement in the yield of the dihydropyran **2a** (entries 1–4). In contrast, when the reaction temperature was increased, the amount of the [4 + 3] cycloadduct **6** and the tricycle **7** increased (entries 5 and 6). Indeed, when a full equivalent of Lewis acid is used at 25 °C, **6** and **7** become the major products (26 and 31% isolated yields, respectively). Because **6** and **7** are presumably derived from Lewis acid-catalyzed rearrangements of the Diels–Alder cycloadducts (1,2-shift from **4a** or **5a** for **6**, Cope rearrangement from **5a** for **7**), their preferential formation under forcing conditions is a reasonable expectation. On lowering the reaction temperature to −40 °C, the dihydropyrans and Diels–Alder cycloadducts are cleanly formed (entries 7 and 8), and the optimum conditions for the formation of **2a** is 0.05 equiv of Lewis acid and extended reaction time of 20 h. Under these conditions, **2a** was obtained in 71% isolated yield (entry 8). Reducing the reaction temperature to −78 °C resulted in very low conversion.

With optimized reaction conditions in hand, the scope of this reaction was then determined. The hetero [4 + 2] cycloaddition is effective for various 2-aryl-α,β-unsaturated aldehydes with excellent diastereoselectivity and moderate to good yields of **2** (Table 2). The major competing reaction is the formation of the Diels–Alder cycloadducts **4** and **5**. Specifically, both 2-substituted acroleins (**1b** to **1d**)[8] and 2,3-disubstituted acroleins (**1a**, **1e**–**j**)[9] afford the desired products. The most interesting substrate for this reaction was cyclic substrate **1j**.[10] The steroid-type product **2j** was generated in one step, although the yield is relatively low. The indole derivative **1k** did not form the hetero [4 + 2] adduct, and the reaction was not complete even after 20 h. Ketone **1l** only generated the Diels–Alder cycloadduct **4l**, which indicates that an aldehyde functionality is necessary for the retro-Claisen rearrangement.[11]

During the preliminary experimental studies it became clear that this reaction is greatly influenced by the nature of the Lewis acid. For example, if $AlCl_3$ or $AlMe_3$ was used as the Lewis acid, very low conversions were observed and the starting aldehyde was recovered. Furthermore, the reaction is also influenced by the temperature and the amount of Lewis acid (Table 1). Even though catalytic amounts of the Lewis acid and long reaction time at low temperature favor the formation of dihydropyran **2**, complete conversion of the Diels–Alder cycloadduct **4** did

(5) For reviews of the Claisen rearrangement and tandem cycloadditions, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. (c) Neuschutz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227.

(6) (a) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692. (b) Niess, B.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 26.

(7) Examples of cyclopentadiene behaving as dienophile: (a) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129. (b) Ismail, Z. M.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 859. (c) Dvorák, D.; Arnold, Z. *Tetrahedron Lett.* **1982**, *23*, 4401. (d) Nenajdenko, V. G.; Statsuk, A. V.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 6549.

(8) **1b**, **1c**, **1d**, and **1l** were synthesized according to literature procedures: (a) Laitalainen, T.; Kuronen, P.; Hesso, A. *Org. Prep. Proced. Int.* **1993**, *25*, 597. (b) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Takumichi, S.; Ogasawara, K. *Chem. Lett.* **1989**, 1283. **1d** must be reacted immediately because it is very prone to dimerize.

(9) **1f**, **1h**, and **1i** were synthesized according to a literature procedure: Kim, J.-K.; Kulawiec, R. J. *J. Org. Chem.* **1996**, *61*, 7656.

(10) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126.

(11) The product **4l** was refluxed in toluene for 24 h. There was no retro-Claisen rearrangement, and the starting material was recovered.

TABLE 2. Me_2AlCl-Catalyzed Reaction of Cyclopentadiene with α,β-Unsaturated Aldehydes[a]

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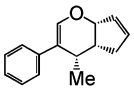
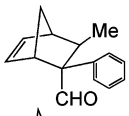
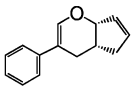
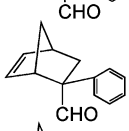
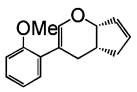
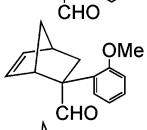
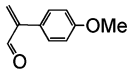
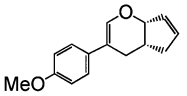
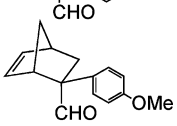
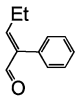
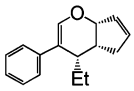
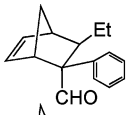
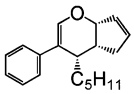
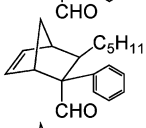
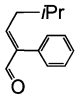
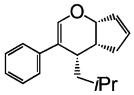
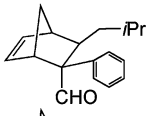
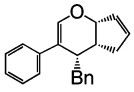
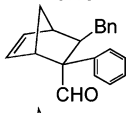
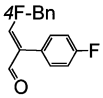
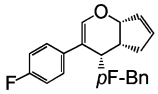
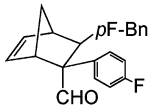
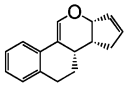
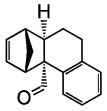
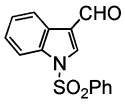
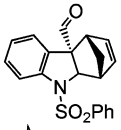
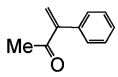
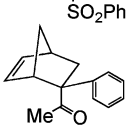
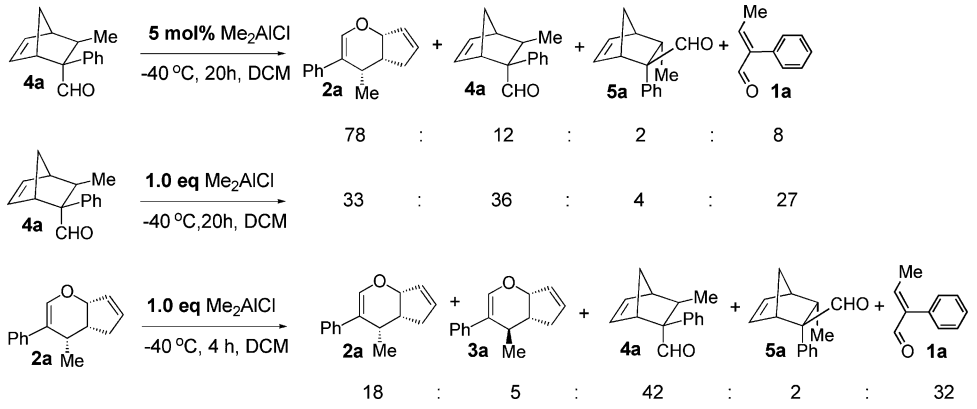
a			71 (96)		4 (7:2)
b			50 (-)		35 (3:1)
c			31 (-)		56 (3:1)
d			61 (-)		28 (7:1)
e			52 (92)		12 (3:1)
f			51(>98)		29 (4:1)
g			49 (74)		18 (4:1)
h			70 (98)		11 (4:1)
i			50(>98)		31 (4:1)
j			30(>98)		65 (7:2)
k					40 (3:4)
l					95 (>98)

[a] Reaction was conducted at −20 to −40 °C for 20 h using 5−20 mol % Me_2AlCl and 5 equiv of diene. NOE studies support the relative configurations of all the products. See Supporting Information for specific details for each substrate. [b] Yield after chromatographic purification. [c] de was determined from a 500 MHz ^1H NMR spectrum of the crude reaction mixture. [d] Isolated yield of the mixture of endo and exo diastereomers.

not occur. Further complications with the chemistry is the possibility of generating other rearrangement products such as **6** and **7** and the retro-Diels−Alder reaction under the Lewis acid-catalyzed reaction conditions.

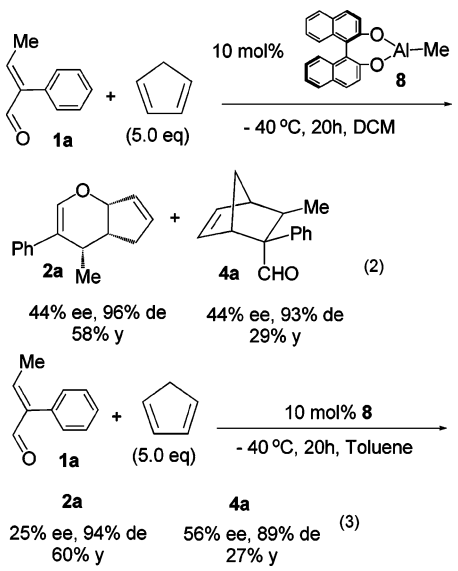
To understand the equilibrium chemistry further, control experiments were conducted with clean substrates (Scheme 1). Treatment of the [4 + 2] cycloadduct **4a** with Me_2AlCl resulted in a rearrangement product, but the ratio was dependent on the amount of Lewis acid used. When **4a** was treated with a catalytic amount of Me_2AlCl (5 mol %) at −40 °C, the dihydropyran **2a** was the major product, although some retro-Diels−Alder reaction to form the unsaturated aldehyde **1a** also occurred. When a stoichiometric amount of Me_2AlCl was used in the reaction of **4a** at −40 °C, the ratio of **2a** and **4a** was closer to 1:1 and the amount of the retro-Diels−Alder reaction was much greater. These results indicate that Me_2AlCl is not only acting as a Lewis acid catalyst but also influences the product distribution, presumably coordinating more favorably to **4a** than to **2a**. The equilibrium between **4a** and **2a** can also be reached starting from **2a**, and again the retro-Diels−Alder reac-

SCHEME 1



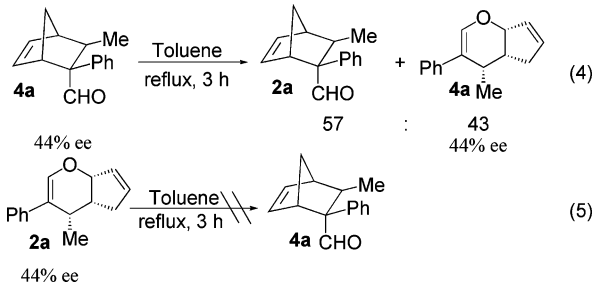
tion is a significant side reaction. As indicated in Table 1, entry 6, the formal [4 + 3] cycloadduct **6** and the tricyclic product **7** are preferentially formed under more vigorous Lewis acid-catalyzed conditions. Indeed, the formation of **6** appears to be an irreversible process because **6** did not revert back to the other products, even under forcing Lewis acid-catalyzed conditions, while **7** was unstable under such forcing conditions.

The above experiments demonstrate that the equilibration between **2a** and **4a** can be induced by Lewis acids but do not distinguish whether the interconversion is a direct Claisen rearrangement or involves a retro-cycloaddition to **1a** and cyclopentadiene followed by a subsequent cycloaddition. To distinguish between these two possibilities, enantioenriched **2a** and **4a** were prepared and studied in the rearrangement. The enantioenriched material was prepared according to eqs 2 and 3. The reaction of **1a** with cyclopentadiene catalyzed by *R*-BINOL-modified aluminum Lewis acid **8** (10 mol %) at −40 °C in dichloromethane generated dihydropyran **2a** and normal [4 + 2] adduct **4a** both in 44% ee (eq 2). When the toluene was used as solvent, the hetero [4 + 2] product **2a** (25% ee) and normal [4 + 2] adduct **4a** (56% ee) were obtained with different enantiomeric excess (eq 3). These results indicate that **2a** in eq 2 could have been derived from a tandem Diels–Alder reaction/retro-Claisen rearrangement because **2a** and **4a** have the same



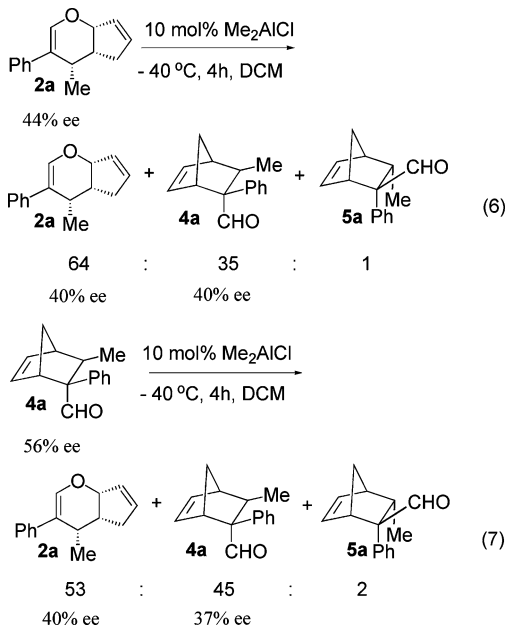
enantiomeric excess but **2a** from eq 3 must have been generated, at least partially, from a different reaction pathway.

With the enantioenriched material in hand, control experiments were conducted under thermal and the Me_2-AlCl-catalyzed reaction conditions. Heating endo [4 + 2] adduct **4a** (44% ee) under reflux in toluene for 3 h resulted in 43% conversion to **2a** while retaining the enantiomeric excess (44% ee, eq 4). In contrast, **2a** remained unchanged under these reaction conditions (eq 5). These indicate the thermal rearrangement of **4a** to **2a** is a direct retro-Claisen rearrangement.



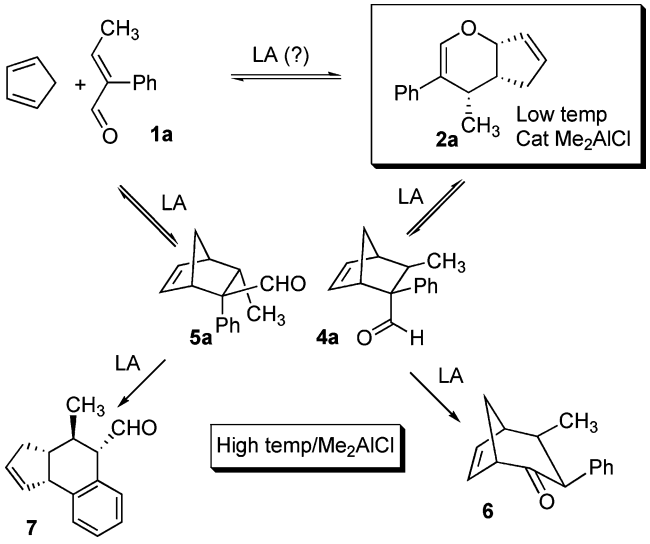
The Lewis acid-catalyzed rearrangement between **4a** and **2a** was more complex than the thermal reaction. Treatment of **2a** (44% ee) with 10 mol % Me_2AlCl at −40 °C in DCM for 4 h resulted in a mixture of **4a** (40% ee) and **2a** (40% ee) as well as small quantities of the exo isomer **5a** (eq 6). Under the same conditions, **4a** (56% ee) was converted to a mixture of **2a** (40% ee) and **4a** (37% ee) and small quantities of the exo isomer **5a**. (eq 7). The drop in enantioselectivity indicates that under the Lewis acid conditions the retro-cycloadditions are occurring in competition with the Claisen rearrangement. Furthermore, these results confirm that under the Lewis acid conditions the retro-Claisen rearrangement is reversible. It is still not clear whether the drop in enantioselectivity in the conversion of **4a** to **2a** in eq 7 is simply due to the reversible nature of the Diels–Alder reaction or whether some of **2a** was formed from a hetro-Diels–Alder reaction. The fact that some of the enantiomeric excess is retained in the conversion of **4a** to **2a** (eq 7) indicates that the retro-Claisen rearrangement between **4a** and **2a** is a viable process.

A general overview of the reaction of 2-phenylacrolein **1a** with cyclopentadiene is given in Scheme 2. All the steps are Lewis acid-catalyzed, including the retro-Diels–



Alder reaction, but a delicate balance exists between the Diels–Alder reaction products **4a** and **5a** and the dihydropyran **2a**. The control experiments to date are not conclusive regarding the possibility of **2a** being partially formed by direct hetero Diels–Alder reaction between cyclopentadiene and **1a**. The optimum conditions for the formation of **2a** are low temperatures and catalytic amounts of Lewis acid. An additional amount of Lewis acid drives the equilibrum more toward the Diels–Alder cycloadducts **4a** and **5a**, while high temperatures favor other irreversible rearrangements to **6** and **7**.

SCHEME 2



In conclusion, we have discovered and developed a novel formal inverse electron demand hetero Diels–Alder reaction between 2-aryl-α,β-unsaturated aldehydes and cyclopentadiene. This reaction is highly stereoselective and provides access to a variety of dihydropyran derivatives. Detailed mechanism studies demonstrated that the major pathway for the transformation is a Lewis acid-catalyzed tandem Diels–Alder reaction/retro-Claisen rearrangement.

Experimental Section

Representative Procedure for the Me_2AlCl-Catalyzed Reaction of Cyclopentadiene with α,β-Unsaturated Aldehydes. Dimethylaluminum chloride (0.14 mL, 0.14 mmol, 1.0 M in hexanes) was added dropwise to a stirred solution of 2-phenyl-2-butenal **1a** (0.42 g, 2.78 mmol) and CH_2Cl_2 (5 mL) followed by cooling for 10 min at −40 °C. After 15 min, an aliquot of freshly distilled precooled cyclopentadiene (0.92 g, 13.95 mmol) was added by syringe to the reaction mixture, giving a clear yellow solution. The resulting mixture was kept stirring at −40 °C for 20 h. The reaction was quenched by addition of 3 mL of saturated $NaHCO_3$ solution, extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using 1–2% diethyl ether/pentane as eluent to give **2a** as a colorless oil: 418 mg (71% yield); and a mixture of **4a** and **5a** as colorless oil: 23 mg (4% yield, 3.5:1 mixture).

(4*S,4*aR**,7*aR**)-4,4a,5,7a-Tetrahydro-4-methyl-3-phenylcyclopenta[*b*]pyran (2a):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 6.63 (s, 1H), 6.16 (m, 1H), 6.00 (m, 1H), 4.84 (br d, J = 6.0 Hz, 1H), 3.16 (m, 1H), 2.68 (m, 1H), 2.42–2.32 (m, 2H), 1.00 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 139.0, 137.1, 131.5, 128.1, 126.9, 125.8, 118.2, 80.6, 43.4, 33.1, 27.8, 16.6; IR (neat) 2931, 1639, 1176, 761, 701 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}O$ [M]$^+$, required m/z: 212.1196, found m/z: 212.1198.

(1*S,2*S**,3*R**,4*R**)-3-Methyl-2-phenylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4a):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, CHO, 1H), 7.38–7.18 (m, 5H), 6.39 (dd, J = 5.5, 3.0 Hz, 1H), 6.17 (dd, J = 5.5, 3.0 Hz, 1H), 3.47 (br s, 1H), 2.63 (br s, 1H), 2.60 (m, 1H), 2.00 (d, J = 8.5 Hz, 1H), 1.65 (d, J = 8.5 Hz, 1H), 0.64 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 141.6, 136.7, 133.1, 129.4, 128.4, 126.9, 67.0, 51.1, 47.2, 44.8, 37.9, 20.2; IR (neat) 2968, 1712 (C=O), 1463, 704 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}O$ [M]$^+$, required m/z: 212.1196, found m/z: 212.1196.

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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