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Sequential Diels–Alder Reaction/Rearrangement Sequence: Synthesis of Functionalized Bicyclo[2.2.1]heptane Derivatives and Revision of Their Relative Configuration

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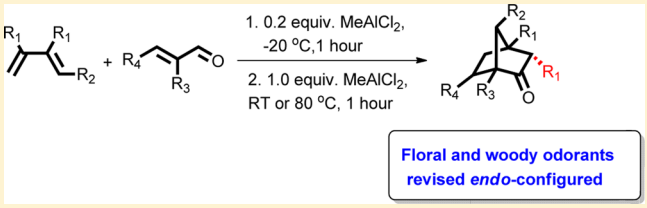
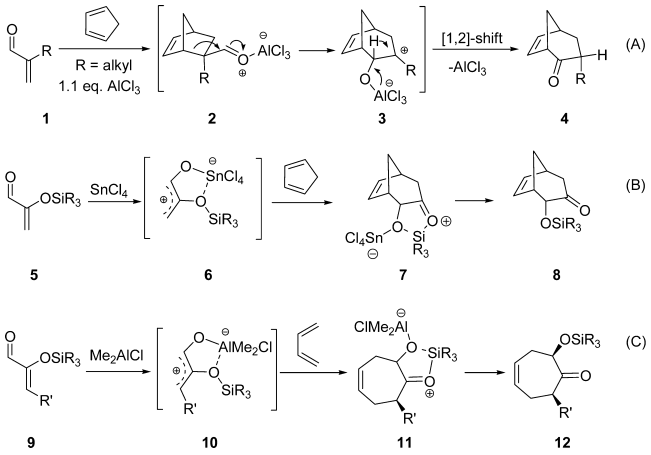
Supporting Information

ABSTRACT: A sequential Diels–Alder reaction/rearrangement sequence was developed for the synthesis of diverse functionalized bicyclo[2.2.1]heptanes as novel floral and woody odorants. The outcome of the rearrangement depended on the substitution pattern of the dienes. 2D NMR analysis has established the correct relative configuration of the bicyclo[2.2.1]heptanone, which was originally misassigned. Furthermore, when the initiating DA reaction was catalyzed by a chiral Lewis acid, the bicyclo[2.2.1]heptane derivatives including (+)-herbanone can be obtained in an enantiomeric ratio (er) up to 96.5:3.5.



The combination of Diels–Alder (DA) cycloaddition reactions with other transformations without isolating the intermediates allows a very rapid increase in the complexity of products.[1−3] For example, Lewis acid promoted rearrangements of DA products have been reported recently.[4−9] Davies and Dai showed that DA addition of alkylated acroleins with cyclopentadiene affords the formal [4 + 3] rather than the kinetic [4 + 2] cycloadducts under appropriate Lewis acid catalysis.[4,5] The reaction sequence comprises a domino DA and two consecutive 1,2-shifts, delivering bicyclo[3.2.1]oct-6-en-3-ones **4** (Scheme 1, eq A). The rearrangement proved to be stereoselective with retained enantioselectivity introduced during the DA step.[5] In contrast, α-oxy-substituted acroleins **5** and **9** were believed to undergo concerted [4 + 3] cycloadditions of allyl cations with both cyclic and acyclic dienes (Scheme 1, eqs B and C).[7−9]

Scheme 1. Formal [4 + 3] Cycloaddition Reactions



In a search for novel perfume ingredients,[10] we were interested in the development of efficient reactions to access bicyclic ketone derivatives, in particular those bearing a bicyclo[2.2.1]heptane or bicyclo[3.2.1]octane skeleton.[10,11] In this context, we present herein our results of a sequential DA reaction/rearrangement sequence which complement the preparatively useful chemistry depicted above.

The domino sequence was discovered during attempts to extend the [4 + 3] cycloaddition strategy (Scheme 1, eq A)[4,5] to access nonbridged seven-membered-ring odorants. We observed that treatment of the 1,3-butadiene DA crude adduct **13a** with 1.1 equiv of $MeAlCl_2$ at 80 °C in toluene generated a strong jasminic floral product which was initially assumed to be the ring-expansion compound **14a**. Surprisingly, NMR analysis did not fully match with **14a** but instead suggested the structure of bicyclo[2.2.1]heptanone **15a** (Scheme 2, eq D). In 1979, Baldwin and Lusch[12] had first reported a similar in situ rearrangement of Diels–Alder adducts with 2,3-disubstituted dienes **16a**, giving rise to bicyclo[2.2.1]heptanones **15b** (Scheme 2, eq E). The rearrangement was proposed to proceed via *endo*-configured intermediates **20** and **21** followed by a suprafacial 1,2-H shift to give (*endo*)-**15b**. The isomer (*endo*)-**15b** was then suggested to isomerize in situ to the thermodynamically more stable *exo* isomer.[12] In 2010, Frontier and Eisenberg suggested that the formation of (*exo*)-**15b**, obtained from a cationic Ir(III)-promoted reaction, was derived from an intermediate analogous to (*exo*)-**19**.[13] As there is no

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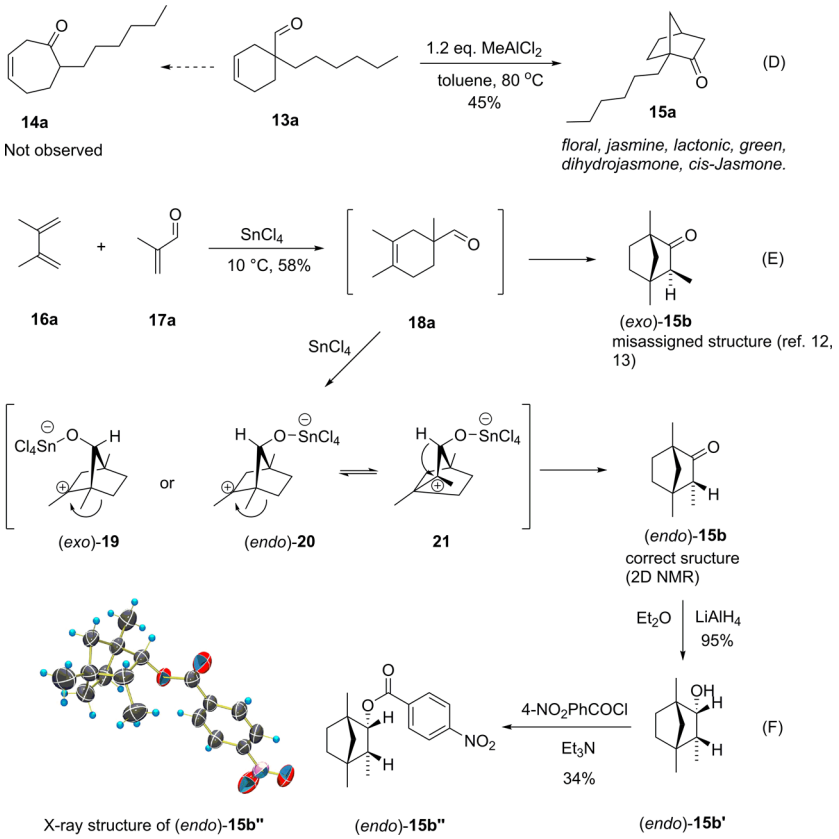
Scheme 2. Rearrangement of Diels–Alder Adduct to Bicyclo[2.2.1]heptanones and Revision of the Misassigned Configuration



analytical or chemical proof of the *exo* configuration of the product **15b**, we reproduced the reaction using the conditions reported by Baldwin and Lusch. The NMR data of the product **15b** were identical with those reported,[12,13] but further NOE data obtained from ^{1}H NMR (600 MHz) analysis indicated the *endo* configuration of the product. Compound **15b** was further reduced to alcohol **15b′** and then derived into ester **15b″**, whose X-ray structure analysis unequivocally confirmed the *endo* configuration of the methyl group (Scheme 2, eq F).

Endowed with these interesting insights, we became curious about the scope of this selective rearrangement and the structure–odor correlation of its higher functionalized bicyclo[2.2.1]heptane products (Table 1). In agreement with Baldwin's findings,[12] the reaction rates are higher with 2,3-disubstituted 1,3-butadiene, which resulted in better yields, and the rearrangement even proceeded at room temperature (Table 1, entries 1–4). The configuration of R^1 in **15c** (Table 1, entry 2) was also proved by 2D NMR analysis to be *endo*. R^1 of the diene can be Me (Table 1, entries 1 and 2) or a cyclic hydrocarbon (Table 1, entry 3), and the respective biclycoheptanones were obtained in excellent yields. In contrast to the previous study,[12] the reaction was extendable to less substituted 1,3-butadienes (Table 1, entries 5–7), although less efficient stabilization of the intervening carbenium ions resulted in lower yields of bicyclo[2.2.1]heptanones **15e–g**. In none of these cases was ring expansion to seven-membered ketone analogous to compound **14** observed. However, in the case of 1,3-pentadiene **16d**, formation of the desired product **15g** (Table 1, entry 8) was accompanied by the 1,2-pentyl shift side product 1-(2-methylcyclohex-3-en-1-yl)hexan-1-one (**22**), thus affording a low yield of **15g**. Compounds **15** with R^3 being C5–C7 linear hydrocarbon chains (**15a,c,e,g**) possess floral, jasminic odors (Table 1), although the scent of **15g** was most appreciated due to its Hedione-like character. When R^3 is a methyl group (**15b,d,f**), the compounds expectedly have borneol-like odors.

The olfactorily important methyl substitution R^2 at the bridge position in odorant **15g** suggested that introducing an acetate group at this location would result in bridged methyl dihydrojasmonate **24**. Methyl dihydrojasmonate (**25**, Hedione) with its transparent, light floral, jasminic odor, is one of the most important ingredients in modern perfumery.[10] Toward this goal, methyl hexa-3,5-dienoate **16e**[15] was applied to react with methacrolein **17a** and 2-pentylacrolein **17b**. Interestingly, the reaction did not lead to the desired compound **24** but to lactones **28** in excellent yields. This outcome is revealing with respect to the assumed *endo* configuration of intermediate **27**, characterized by the geometry of the oxy substituent at the bridged position as well as with regard to the interception of the carbenium ion by the carboxyl group as good evidence for the postulated mechanism. X-ray structural analysis of **28a** confirmed the formation and geometry of these functionalized bicycloheptanes (Scheme 3).

Moreover, we wanted to prove that the rearrangement is stereoselective and does not proceed with any loss of optical information under the relatively harsh reaction conditions. Good enantioselectivity of compound **18a** was obtained using Corey's Lewis acid assisted oxazaborolidine catalysts.[16–18] The best ee value in the DA reaction was obtained using $EtAlCl_2$ as assisting catalyst (97% ee), but the reaction stopped at the DA stage and the one-pot sequence could not be established. However, Yamamoto et al. had noted earlier that an excess of Lewis acid does not significantly destroy the optical induction and that the LLA is much more reactive than the Lewis acid

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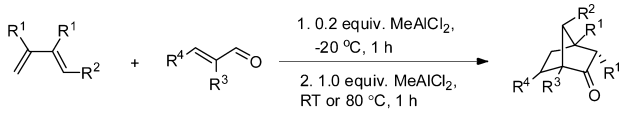
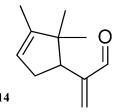
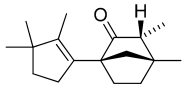
Table 1. Scope of the Tandem Diels–Alder/Rearrangement Reactions and Odor Descriptions of Bicycloheptanones 15[a]

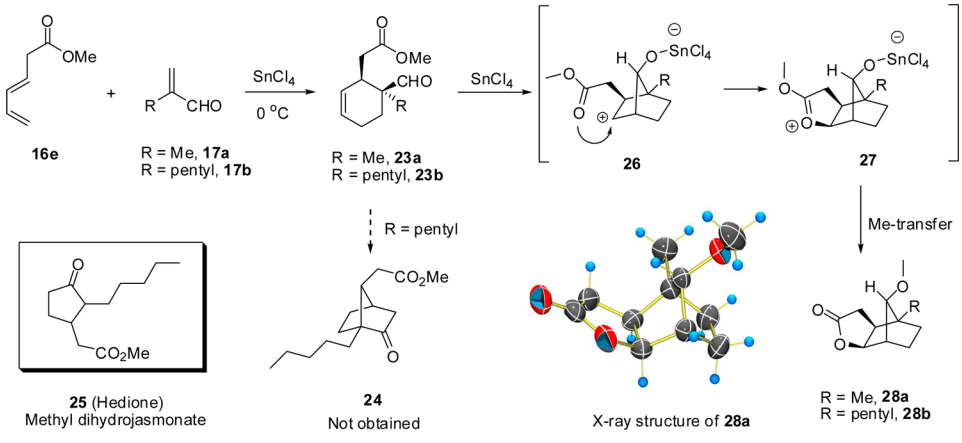


16 17 15

entry	diene	acroleine	product	yield (%)[b]	odor description
1	**16a** R^1=CH_3, R^2= H	**17a** R^3=CH_3, R^4=H	**15b**	85	Camphor, borneol, minty
2	**16a** R^1=CH_3, R^2= H	**17b** R^3=*n*-Pent, R^4=H	**15c**	90	floral, tuberose-like, leather with a bit earthy and rubber notes
3	**16b** R^1=-$(CH_2)_4$-, R^2=H	**17a** R^3=CH_3, R^4=H	**15d**	85	Herbal, camphor, slightly woody
4	**16c** R^1=R^2=H	**17c** R^3= *n*-Hex, R^4=H	**15a**	45	Floral, jasmine, lactonic, green, dihydrojasmone, *cis*-jasmone.
5	**16c** R^1=R^2=H	**17d** R^3=*n*-Hept, R^4=H	**15e**	50	Very weak, floral, jasmine, lactonic, agrestic
6	**16c** R^1=R^2=H	**17e** R^3=Me, R^4=Et	**15f**	45	Woody, camphor, dry
7	**16d** R^1=H, R^2=CH_3	**17b** R^3=*n*-Pent, R^4=H	**15g** + **22**	37	**15g**: Fresh floral, jasmin (hedion-like) with a bit rose note. **22**: Floral (jasmine-like), fruity, fresh, agrestic
8	**16a** R^1=CH_3, R^2= H	 **17f**[14]	**15h** 	75[c]	Odorless

[a]Conditions: acrolein **17** (10 mmol, 0.5 M in toluene), diene **16** (20 mmol), $MeAlCl_2$ (0.2 equiv, 1.0 M solution in hexane), −20 °C, 1 h, then $MeAlCl_2$ (1.0 equiv, 1.0 M solution in hexane), room temperature or 80 °C, 1 h. [b]Yield of isolated product. [c]The reaction proceeded using 20 mol % $SnCl_4$ in CH_2Cl_2 over 4 h.

Scheme 3. Domino Rearrangement of DA Adduct to Bicyclo[2.2.1]heptanes



alone.[19] Indeed, when $SnCl_4$ (20 mol %) was used instead of $EtAlCl_2$, smooth rearrangement was observed at room temperature and compound **15b** was achieved in a domino fashion with an enantiomeric ratio (er) of 96.5:3.5. The DA intermediate showed the same ratio. An even faster turnover was achieved when $HClO_4$ was added to the reaction mixture after the DA reaction was completed. In order to demonstrate the preparative usefulness of the method, we performed this asymmetric DA reaction/rearrangement protocol to prepare (+)-herbanone[20] from myrcene and methacrolein in 45% yield and in an enantiomeric ratio (er) of 91:9 (Scheme 4). *rac*-Herbanone is a well-known woody odorant with a relatively high odor threshold of 18.9 ng/L air. The optical isomer (2*S*,4a*S*,8a*R*)-**31** has a very similar odor description and odor

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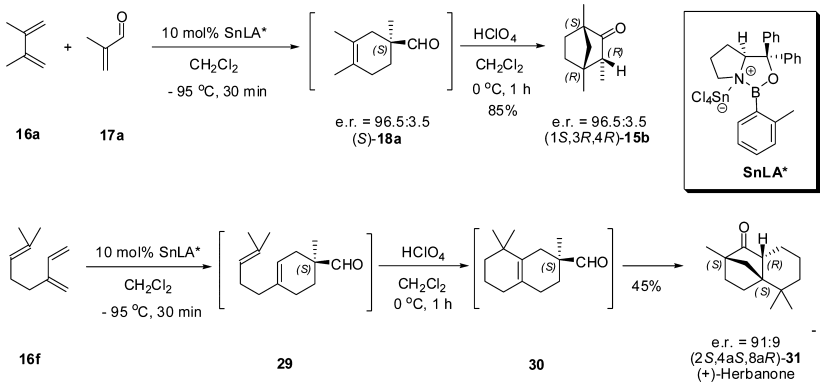
Scheme 4. Domino Enantioselective DA/Rearrangement to Bicyclo[2.2.1]heptanes



threshold of 13.7 ng/(L of air). The absolute configurations of major enantiomers of **15b** and herbanone were assigned by the model by Corey and Yamamoto.[16−19]

In summary, we have developed a preparatively useful sequential DA reaction/rearrangement reaction among a variety of 1,3-butadienes and unsaturated aldehydes. The relative configuration of the bicyclo[2.2.1]heptanone products has been revised. The chiral information in the first step was shown to be completely retained in the final rearranged product. In particular, the enantioselective construction of bicyclo[2.2.1]-heptanones including (+)-herbanone was achieved by a one-pot domino sequence using a Lewis and Brønsted acid assisted chiral Lewis acid catalysis.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and 2D NMR spectra were recorded with 300, 400, and 600 MHz spectrometers in $CDCl_3$ or C_6D_6. ^{13}C NMR spectra were recorded with 75, 100, and 150 MHz spectrometers in $CDCl_3$ or C_6D_6. Chemical shifts in $CDCl_3$ and C_6D_6 are reported in δ (ppm) relative to tetramethylsilane (TMS). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT 90 and DEPT 135 spectra and is given in parentheses. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, bs = broad singlet, sept = septet. Solvents for extraction and chromatography were technical grade and were used without further purification. Flash chromatography was performed using silica gel (200 ± 300 mesh). Unless otherwise noted, a mixture of hexane and MTBE (50/1) was used as eluent. IR spectra were recorded with a FT-IR spectrometer. High-resolution MS were obtained by an electron ionization (EI) technique with a double-focusing magnetic sector mass spectrometer, and GC/MS spectral data were obtained from an EI source. The enantiomeric ratio (er) of **15b** was determined by GC in comparison to the corresponding racemic samples using a HYDRODEX-beta-6TBDM column (25 m × 0.25 mm, program 80−230 °C, 2.5 °C/min, helium carrier pressure 14.3 psi, FID detection (250 °C)). The er of **31** was determined by GC in comparison to the corresponding racemic samples using a LIPODEX column (25 m × 0.25 mm, program 50−150 °C, 2.0 °C/min, helium carrier pressure 13.6 psi, FID detection (250 °C)). The compounds were evaluated on smelling blotters by at least two professional perfumers as 10% solutions in dipropylene glycol (DPG) and in EtOH. The blotters were dipped 4 and 8 h in advance and compared with the freshly dipped samples for top, middle, and dry down odor character and linearity of the smell as well as olfactory purity.

Materials. Dienes **16a,c,d,f** and acroleins **17a,e** were commercially available. Dienes **16b**[21] and **16e**[15] were prepared by literature procedures. Acroleins **17b-d,f** are known compounds and were synthesized by using the method reported by Pihko and co-workers.[22] DA adducts **23a,b** were synthesized by a literature procedure[23] with *endo/exo* selectivity >10/1. All solvents and other commercially available chemicals were used as received.

General Procedure for the Sequential DA Reaction/Rearrangement Sequence. To a solution of α,β-unsaturated aldehyde **17** (10.0 mmol) and diene **16** (20.0 mol) in toluene (20.0 mL) that was cooled to −20 °C was added $MeAlCl_2$ (2.0 mL, 1.0 M solution in hexane, 2.0 mL) dropwise. After completion of the addition, the reaction mixture was stirred at −20 °C for 1 h to complete the DA step (monitored by GC). Then, additional $MeAlCl_2$ (10.0 mL, 1.0 M solution in hexane, 10.0 mmol) was added. The reaction temperature was increased to room temperature, and hexane was removed under reduced pressure. During this time the rearrangement reactions for **15b−d** were complete. For **15a,e,g**, the reaction mixture was heated to 80 °C for 1 h to complete the rearrangement. The reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with MTBE (50.0 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluent hexane/MTBE 100/1), followed by bulb-to-bulb distillation, to give the desired products.

*1-Hexylbicyclo[2.2.1]heptan-2-one (**15a**).* Colorless liquid; 0.87 g, 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (t, J = 4.2 Hz, 1H), 2.14−2.06 (m, 1H), 1.95 (dd, J = 4.5, 13.2 Hz, 1H), 1.90−1.80 (m, 1H), 1.75−1.60 (m, 3H), 1.59−1.36 (m, 4H), 1.35−1.20 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.1 (C═O, s), 57.9 (s), 46.2 (t), 41.2 (t), 34.0 (d), 31.8 (t), 30.0 (t), 29.8 (t), 28.7 (t), 28.4 (t), 25.9 (t), 22.6 (t), 14.1 (q) ppm. EI-MS (m/z, relative intensity): 194 (M^+, 24), 150 (40), 121 (13), 109 (57), 95 (22), 80 (100), 67 (42), 55 (23), 41 (27). IR (neat, ν/cm^{-1}): 2930, 2858, 1744, 1457, 1408, 1294, 1174, 1057, 957. HRMS (ESI): m/z calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1668.

*1,3-endo-4-Trimethylbicyclo[2.2.1]heptan-2-one ((endo)-**15b**).*[12,13] Colorless liquid; 1.29 g, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (q, J = 7.2 Hz, 1H), 1.70−1.50 (m, 3H), 1.48−1.25 (m, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.96 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.4 (C═O, s), 55.0 (s), 53.6 (d), 50.4 (t), 45.2 (s), 34.2 (t), 29.3 (t), 19.7 (q), 14.3 (q), 8.8 (q) ppm. EI-MS (m/z, relative intensity): 152 (M^+, 20), 137 (3), 109 (13), 95 (100), 81 (16), 69 (14), 55 (5), 41 (14). IR (neat, ν/cm^{-1}): 2957, 2870, 1745, 1455, 1378, 1322, 1182, 1029, 955, 526, 493.

*1,3-endo-4-Trimethylbicyclo[2.2.1]heptan-2-ol ((endo)-**15b′**).* An argon-flushed flask was charged with dry tetrahydrofuran (25.0 mL). Lithium aluminum hydride (3.2 g, 85 mmol) was added, and the mixture was cooled to 0 °C by an ice−water bath. A solution of (*endo*)-**15b** (8.70 g, 57.0 mmol) in tetrahydrofuran (50.0 mL) was added over 15 min via a dropping funnel. After completion of the addition, the mixture was warmed to room temperature and stirred for 15 min. Then the mixture was cooled to 0 °C again and treated successively with water (3.20 mL), 30% aqueous NaOH (3.20 mL), and then water (9.60 mL). The reaction mixture was filtered and evaporated in vacuo. The residue was purified by column chromatography (hexane/MTBE 40/1) to yield the product (8.30 g,

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95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (dd, J = 10.5, 4.0 Hz, 1H), 1.82−1.62 (m, 2H), 1.57−1.42 (m, 2H), 1.30−1.22 (m, 1H), 1.19−1.09 (m, 2H), 1.07 (s, 3H), 0.96 (s, 3H), 0.82 ppm (d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.1 (d), 50.7 (t), 48.6 (s), 46.6 (s), 43.4 (d), 30.0 (t), 28.2 (t), 20.4 (q), 19.5 (q), 8.1 (q) ppm. EI-MS (m/z, relative intensity): 154 (M^+, 1), 139 (2), 121 (5), 107 (8), 95 (100), 81 (22), 69 (7), 55 (5), 41 (7). IR (neat, ν/cm^{-1}): 3431, 2924, 2856, 1623, 1532, 1457, 1378, 1351. HRMS (ESI): m/z calcd for $C_{10}H_{18}O$ (M^+) 154.1358, found 154.1357.

*1,3-endo-4-Trimethylbicyclo[2.2.1]heptan-2-yl 4-Nitrobenzoate ((endo)-**15b**″).* An argon-flushed flask was charged with the alcohol (*endo*)-**15b**′ (8.00 g, 52.0 mmol), triethylamine (10.6 g, 104 mmol), *N*,*N*-dimethyl-4-aminopyridine (7.60 g, 62.0 mmol), and dichloromethane (100 mL) at 0 °C. 4-Nitrobenzoyl chloride (14.2 g, 78.0 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. Then water (50 mL) was added. The aqueous layer was extracted with MTBE (50.0 mL), and the combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/MTBE 100/1) to yield the product (5.40 g, 34%) as a white solid. Mp: 69.5−70.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61−7.97 (m, 4H), 5.16 (dd, J = 1.3, 10.4 Hz, 1H), 2.20−1.85 (m, 2H), 1.76−1.58 (m, 1H), 1.47−1.25 (m, 4H), 1.11 (s, 3H), 1.04 (s, 3H), 0.78 (d, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8 (C═O, s), 150.5 (s), 136.1 (s), 130.6 (d), 123.6 (d), 81.8 (d), 50.8 (t), 48.1 (s), 46.8 (s), 42.9 (d), 30.0 (t), 29.8 (t), 20.0 (q), 19.5 (q), 8.5 (q) ppm. EI-MS (m/z, relative intensity): 303 (M^+, 1), 273 (2), 260 (3), 150 (29), 136 (15), 121 (12), 107 (22), 95 (100), 81 (15), 67 (5), 55 (4), 41 (4). IR (neat, ν/cm^{-1}): 3114, 3084, 2954, 2872, 1724, 1606, 1530, 1456, 1347, 1277, 1112, 1018, 976, 870, 839, 793, 719. HRMS (EI): m/z calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1472.

*3-endo-4-Dimethyl-1-pentylbicyclo[2.2.1]heptan-2-one (**15c**).* Colorless liquid; 1.87 g, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (q, J = 6.9 Hz, 1H), 1.74−1.60 (m, 2H), 1.59−1.48 (m, 2H), 1.45−1.35 (m, 2H), 1.36−1.21 (m, 8H), 1.18 (s, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.85 (t, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.3 (C═O, s), 59.3 (s), 54.2 (d), 47.4 (t), 44.9 (t), 32.7 (t), 32.5 (t), 29.0 (t), 28.8 (t), 25.6 (t), 22.5 (t), 19.7 (q), 14.0 (q), 8.7 (q) ppm. GC/MS (EI): 208 (M^+, 25), 179 (12), 151 (100), 125 (11), 109 (24), 94 (18), 81 (21). IR (neat, ν/cm^{-1}): 2928, 2870, 1742, 1458, 1372, 1323, 1301, 1249, 1181, 1135. HRMS (ESI): m/z calcd for $C_{14}H_{24}O$ (M^+) 208.1827, found 208.1828.

*(8a)-endo-2-Methyloctahydro-1H-2,4a-methanonaphthalen-1-one (**15d**).* Colorless liquid; 1.51 g, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00−1.50 (m, 9H), 1.48−1.18 (m, 6H), 1.15 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.3 (C═O, s), 57.7 (d), 55.4 (s), 50.1 (t), 45.8 (s), 34.1 (t), 33.2 (t), 27.3 (t), 26.0 (t), 22.4 (t), 21.2 (t), 14.3 (q) ppm. EI-MS (m/z, relative intensity): 178 (M^+, 56), 160 (8), 150 (15), 135 (23), 121 (11), 107 (100), 94 (68), 81 (36), 67 (19), 55 (11), 41 (18). IR (neat, ν/cm^{-1}): 2924, 2866, 1738, 1447, 1356, 1308, 1263, 1186. HRMS (ESI): m/z calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1362.

*1-Heptylbicyclo[2.2.1]heptan-2-one (**15e**).* Colorless liquid; 1.04 g, 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (t, J = 3.9 Hz, 1H), 2.15−2.05 (m, 1H), 1.92 (dd, J = 4.5, 17.7 Hz, 1H), 1.89−1.76 (m, 1H), 1.76−1.55 (m, 3H), 1.54−1.34 (m, 4H), 1.34−1.15 (m, 10H), 0.86 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.9 (C═O, s), 57.9 (s), 46.2 (t), 41.2 (t), 34.0 (d), 31.8 (t), 30.3 (t), 29.8 (t), 29.2 (t), 28.7 (t), 28.4 (t), 25.9 (t), 22.6 (t), 14.1 (q) ppm. EI-MS (m/z, relative intensity): 208 (M^+, 4), 166 (40), 164 (44), 121 (13), 109 (57), 95 (20), 80 (100), 67 (37), 55 (22), 41 (22). IR (neat, ν/cm^{-1}): 2957, 2926, 2856, 1746, 1458, 1408, 1377, 1294, 1174, 438, 414. HRMS (ESI): m/z calcd for $C_{14}H_{24}O$ (M^+) 208.1827, found 208.1813.

*6-Ethyl-1-methylbicyclo[2.2.1]heptan-2-one (**15f**).* Colorless liquid; 0.68 g, 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (d, J = 4.8 Hz, 1H), 1.90 (dd, J = 5.4, 10.5 Hz, 1H), 1.88−1.76 (m, 1H), 1.60−1.32 (m, 7H), 0.94 (s, 3H), 0.91 (dd, J = 7.8, 9.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.9 (C═O, s), 51.1 (d), 50.7 (s), 50.5 (s), 50.5 (d), 40.2 (t), 26.6 (t), 25.6 (t), 25.6 (t), 9.4 (q), 8.4 (q) ppm. EI-MS (m/z, relative intensity): 152 (M^+, 28), 123 (32), 95 (100), 81 (10), 55 (31), 41 (18). IR (neat, ν/cm^{-1}): 2964, 2878, 1746, 1461, 1381, 1314, 1181, 1031. HRMS (ESI): m/z calcd for $C_{10}H_{16}O$ (M^+) 152.1201, found 152.1194.

*7-Methyl-1-pentylbicyclo[2.2.1]heptan-2-one (**15g**).* Colorless liquid; 0.35 g, 18% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (dd, J = 2.1, 17.4 Hz, 2H), 1.98−1.77 (m, 4H), 1.52 (m, 2H), 1.45−1.20 (m, 8H), 0.91−0.81 (m, 6H, $2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.8 (C═O, s), 59.3 (s), 45.7 (d), 41.5 (t), 38.6 (d), 32.7 (t), 28.1 (t), 27.3 (t), 25.8 (t), 23.9 (t), 22.6 (t), 14.1 (q), 11.0 (q) ppm. EI-MS (m/z, relative intensity): 194 (M^+, 34), 150 (38), 109 (14), 95 (52), 81 (100), 67 (25), 55 (25), 41 (22). IR (neat, ν/cm^{-1}): 2957, 2874, 1741, 1466, 1414, 1381, 1328, 1293, 1260, 1166, 1085, 1067. HRMS (ESI): m/z calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1679.

*1,2-trans-1-(2-Methylcyclohex-3-enyl)hexan-1-one (**22**).* Colorless liquid; 0.37 g, 19% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66−5.61 (m, 1H), 5.53−5.47 (m, 1H), 2.58−2.20 (m, 4H), 2.10−2.04 (m, 2H), 1.90−1.80 (m, 1H), 1.65−1.50 (m, 3H), 1.38−1.18 (m, 4H), 0.91 (d, J = 7.2 Hz, 3H, CH_3), 0.90 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.5 (C═O, s), 132.6 (d), 125.2 (d), 54.7 (d), 42.1 (t), 31.6 (d), 31.5 (t), 25.7 (t), 24.9 (t), 24.9 (t), 23.3 (t), 22.5 (t), 20.2 (q), 13.9 (q) ppm. EI-MS (m/z, relative intensity): 194 (M^+, 6), 179 (2), 123 (13), 99 (100), 71 (53), 55 (19), 43 (40). IR (neat, ν/cm^{-1}): 3020, 2927, 2872, 1737, 1652, 1457, 1408, 1374, 1207, 684, 429. HRMS (ESI): m/z calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1661.

*3,4-Dimethyl-1-(2,3,3-trimethylcyclopent-1-enyl)bicyclo[2.2.1]-heptan-2-one (**15h**).* This compound was prepared by following the procedure reported by Baldwin and Lusch.[12] The crude product was purified by column chromatography, followed by bulb-to-bulb distillation, to yield 1.84 g (75%) of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30−2.10 (m, 2H), 1.96−1.85 (m, 2H), 1.72 (s, 2H), 1.64−1.55 (m, 3H), 1.47 (s, 3H), 1.40−1.33 (m, 1H), 1.15 (s, 3H), 0.97 (d, J = 7.8 Hz, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.87−0.79 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.4 (C═O, s), 142.3 (s), 129.5 (s), 60.5 (s), 53.9 (d), 49.1 (t), 47.8 (s), 44.6 (s), 38.7 (t), 32.6 (t), 32.5 (t), 28.5 (t), 26.7 (q), 26.5 (q), 19.8 (q), 11.4 (q), 8.9 (q) ppm. EI-MS (m/z, relative intensity): 246 (M^+, 21), 231 (36), 203 (42), 189 (100), 174 (27), 135 (15), 95 (19). IR (neat, ν/cm^{-1}): 2954, 2870, 1745, 1458, 1373. HRMS (ESI): m/z calcd for $C_{17}H_{26}O$ (M^+) 246.1984, found 246.1970.

*rac-(3aR,4R,7S,7aR,8S)-8-Methoxy-4-methylhexahydro-4,7-methanobenzofuran-2(3H)-one (**28a**).* This compound was prepared by following the procedure reported by Baldwin and Lusch.[12] The crude product was purified by column chromatography to yield 1.57 g (82%) of a white solid. Mp: 69.5−70.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (d, J = 7.2 Hz, 1H), 3.33 (s, 3H), 3.24 (s, 1H), 2.65−2.32 (m, 4H), 1.86−1.66 (m, 2H), 1.31−1.16 (m, 2H), 1.13 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.5 (C═O, s), 85.1 (d), 83.6 (d), 57.6 (q), 46.5 (s), 44.7 (d), 42.5 (d), 33.6 (t), 29.8 (t), 21.8 (t), 13.9 (q) ppm. EI-MS (m/z, relative intensity): 196 (M^+, 15), 164 (86), 149 (9), 137 (26), 122 (28), 105 (77), 94 (96), 81 (100), 71 (90), 55 (39), 41 (58). IR (neat, ν/cm^{-1}): 2957, 2926, 2871, 1779, 1469, 1420, 1362, 1297, 1193, 1127, 1113, 1031, 885, 539. HRMS (ESI): m/z calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1087.

*rac-(3aR,4R,7S,7aR,8S)-8-Methoxy-4-pentylhexahydro-4,7-methanobenzofuran-2(3H)-one (**28b**).* This compound was prepared by following the procedure reported by Baldwin and Lusch.[12] The crude product was purified by column chromatography to yield 2.24 g (89%) of a white solid. Mp: 73.5−74.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 (d, J = 7.5 Hz, 1H), 3.31 (s, 3H), 3.23 (s, 1H), 2.61−2.36 (m, 4H), 1.86−1.75 (m, 1H), 1.72−1.38 (m, 3H), 1.36−1.07 (m, 8H), 0.88 (t, J = 6.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6 (C═O, s), 85.7 (d), 83.5 (d), 57.5 (q), 50.2 (s), 42.2 (d), 41.9 (d), 32.5 (t), 30.8 (t), 29.4 (t), 28.8 (t), 24.9 (t), 22.4 (t), 21.6 (t), 13.9 (q) ppm. EI-MS (m/z, relative intensity): 252 (M^+, 35), 220 (38), 181 (34), 161 (94), 149 (50), 137 (65), 121 (38), 105 (35), 93 (55), 71 (100), 55 (34), 41 (58). IR (neat, ν/cm^{-1}): 2926, 2871, 1778, 1469,

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1420, 1382, 1362, 1297, 1193, 1127, 1113, 1031, 885, 539. HRMS (ESI): m/z calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1718.

*(1S,3R,4R)-1,3,4-Trimethylbicyclo[2.2.1]heptan-2-one (**15b**).* The chiral ligand (*S*)-3,3-diphenyl-1-(*o*-tolyl)hexahydropyrrolo[1,2-*c*][1,3,2]oxazaborole was prepared as a clear oil from (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol and tri-*o*-tolylboroxine according to the method reported by Corey and co-workers.[16] This clear oil was used as a 0.10 M solution in dichloromethane and stored in a Schlenk flask under an argon atmosphere at −20 °C.

In a dried Schlenk flask were charged CH_2Cl_2 (100 mL) and a 0.10 M solution of the above chiral ligand in CH_2Cl_2 (10 mL, 0.10 M solution in CH_2Cl_2, 1.0 mmol) under an argon atmosphere. After this mixture was cooled to −95 °C, a 0.10 M solution of $SnCl_4$ in CH_2Cl_2 (10 mL, 0.10 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. The resulting pale yellow solution was stirred for 15 min at this temperature. To this mixture was added methacrolein (0.70 g, 10 mmol) dropwise, and after 5 min, 2,3-dimethyl-1,3-butadiene (11 mL, 0.10 M solution in CH_2Cl_2, precooled at −95 °C, 11 mmol) was added dropwise over 10 min via syringe. The reaction mixture was stirred for 4 h at −95 °C, followed by addition of $HClO_4$ (1.39 g, 72% aqueous solution, 10 mmol) at −95 °C. The reaction mixture was warmed to 0 °C slowly and then quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with MTBE (50.0 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluent hexane/MTBE 100/1), followed by bulb-to-bulb distillation to give the desired product as a colorless liquid. Yield: 1.29 g (85%). The enantiomeric excess was measured by chiral GC to be 93%. $[\alpha]_D^{24}$ = +59.4° ($CHCl_3$, *c* 0.14). NMR data are the same as those for the racemic mixtures of (*endo*)-**15b** above.

*(2S,4aS,8aR)-2,5,5-Trimethyloctahydro-1H-2,4a-methanonaphthalen-1-one (**31**).* In a dried Schlenk flask ertr charged CH_2Cl_2 (100 mL) and a 0.10 M solution of the chiral ligand (*S*)-3,3-diphenyl-1-(*o*-tolyl)hexahydropyrrolo[1,2-*c*][1,3,2]oxazaborole[16] in CH_2Cl_2 (10 mL, 0.10 M solution in CH_2Cl_2, 1.0 mmol) under an argon atmosphere. After the mixture was cooled to −95 °C, a 0.10 M solution of $SnCl_4$ in CH_2Cl_2 (10 mL, 0.10 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. The resulting pale yellow solution was stirred for 15 min at this temperature. To this mixture was added methacrolein (0.70 g, 10 mmol) dropwise, and after 5 min, myrcene (11 mL, 0.10 M solution in CH_2Cl_2, precooled at −95 °C, 11 mmol) was added dropwise over 10 min via syringe. The reaction mixture was stirred for 4 h at −95 °C, followed by addition of $HClO_4$ (1.39 g, 72% aqueous solution, 10 mmol) at −95 °C. The reaction mixture was warmed to 0 °C slowly and quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with MTBE (50.0 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluent hexane/MTBE 100/1), followed by bulb-to-bulb distillation to yield 0.93 g (45%) of a colorless liquid. The enantiomeric excess was measured by chiral GC to be 82%. $[\alpha]_D^{24}$ = +33.5° ($CHCl_3$, *c* 0.18). NMR data are the same as those for the racemic mixture reported in the literature.[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (d, *J* = 12.0 Hz, 1H), 1.90 (dd, *J* = 2.7 Hz, 13.2 Hz, 1H), 1.78 (m, 1H), 1.70−1.55 (m, 3H), 1.58−1.40 (m, 2H), 1.40−1.20 (m, 5H), 1.15 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.6 (C═O, s), 54.9 (s), 53.1 (d), 52.2 (s), 44.0 (t), 36.6 (t), 34.0 (t), 33.4 (t), 26.2 (q), 23.5 (q), 22.9 (t), 21.9 (t), 20.9 (t), 14.3 (q) ppm. EI-MS (m/z, relative intensity): 206 (M^+, 74), 191 (11), 163 (17), 149 (21), 135 (23), 121 (100), 107 (44), 93 (32), 81 (81), 67 (18), 55 (21), 41 (27). IR (neat, ν/cm^{-1}): 2930, 2868, 1741, 1455, 1386, 1177, 905, 857.

■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, and CIF files giving ^{1}H NMR and ^{13}C NMR spectra for all new compounds, X-ray structures of **15b**″ and **28a**, and chiral GC chromatograms of (1*S*,3*R*,4*R*)-**15b** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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