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Stereoselective synthesis of (±)-β-elemene by a doubly diastereodifferentiating internal alkylation: a remarkable difference in the rate of enolization between *syn* and *anti* esters

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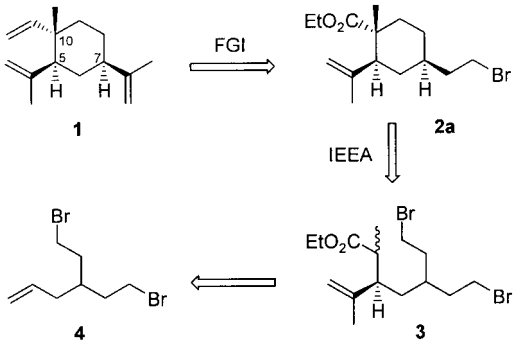
Abstract—A total synthesis of the sesquiterpene (±)-β-elemene (**1**) has been achieved starting from a simple acyclic precursor **4**. Key transformations include a 'doubly diastereodifferentiating folding and allylic strain-controlled' intramolecular ester enolate alkylation. In the course of the synthesis, we encountered remarkably different reactivity between *syn* and *anti* diastereomeric esters in the enolization step.

The sesquiterpene β-elemene (**1**), isolated from sweetflag, juniper oils and *Libanotis transcaucasica*,[1] is a constituent of many essential oils.[2] Recently, Yuan et al. reported that elemene induces apoptosis and regulates expression of bcl-2 protein in human leukemia K562 cells.[3] Elemenum emulsion is in clinical trials[4a] due to its potent antitumor activity.[4] Reported herein is a stereoselective synthesis of (±)-β-elemene (**1**)[5] using our 'doubly diastereodifferentiating folding and allylic strain-controlled'[6] intramolecular ester enolate alkylation (IEEA) as a key step. During the course of our investigation, we also observed a remarkable difference in the rate of enolization between *syn* and *anti* diastereomeric esters during the intramolecular ester enolate alkylation step (vide infra).

In our retrosynthetic analysis for (±)-β-elemene (**1**), as summarized in Scheme 1, we envisioned that key cyclohexanecarboxylate **2a** could be stereoselectively synthesized from internal alkylation substrate **3** based upon our IEEA strategy by which the two homomorphic diastereotopic bromoethyl groups in **3** could be distinguished, thus establishing the relative stereochemistry of three of the stereogenic centers of (±)-β-elemene (**1**) in a single step. Further analysis indicated dibromide **4** should be an ideal synthetic precursor for acyclic substrate **3**.

The starting dibromide **4** was prepared from the known diol **5**[7] in a straightforward five-step sequence. Thus, tosylation of diol **5**, followed by reaction of the resulting ditosylate **6** with NaCN, yielded dinitrile **7** in 77% overall yield in two steps. Methanolysis of dinitrile **7** and reduction of the corresponding diester **8** with LAH produced diol **9** in 58% yield for the two steps. Finally, conversion of diol **9** to the desired dibromide **4** was accomplished by treatment with Ph_3P and CBr_4 at 0°C in 92% yield. Ozonolysis of dibromide **4** in CH_2Cl_2 followed by in situ Wittig reaction with (carbethoxyethylidene)triphenylphosphorane furnished unsaturated ester **10** (*E:Z*=10:1, 92% total yield). Treatment of α,β-unsaturated ester **10** with DIBALH led to the formation of allylic alcohol **11** (99%), which was subjected to Johnson orthoester Claisen rearrangement conditions[8] (triethyl orthopropionate, propionic acid, 125°C) to yield a readily separable 80:20 mixture of two diastereomeric γ,δ-unsaturated esters **3a** and **3b** in 57% total yield. The relative stereochemistries of Claisen products **3a** and **3b** were assigned by comparison with an analogous system prepared



Scheme 1.

Keywords: rate of enolization; doubly diastereodifferentiating internal alkylation; (±)-β-elemene.

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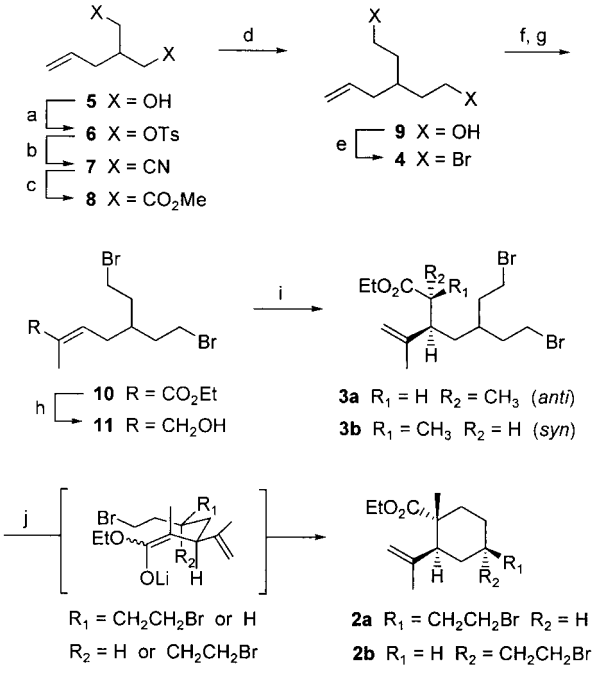
under the identical reaction conditions in the recent systematic study by Daub on the acyclic diastereoselection of the orthoester Claisen rearrangement.[8b] The moderate chemical yield of **3a**/**3b** could be improved to 87% by the use of phenol instead of propionic acid as an acid catalyst (phenol, triethyl orthopropionate, toluene, 110°C, **3a**:**3b**=63:37).

Initially we anticipated the relative stereochemistry of esters **3** would be inconsequential in intramolecular ester enolate alkylation since the stereochemistry would be lost during the enolization step. However, to our surprise, the two cyclization substrates **3a** and **3b** showed different reactivity as depicted in Scheme 2. Intramolecular ester enolate alkylation of *anti*-dibromo ester **3a** with excess LDA in THF at −78°C for 2 h provided the desired cyclohexanecarboxylate **2a** with 6:1 selectivity at C_7 in 89% yield. On the other hand, *syn*-dibromo ester **3b** remained mostly unchanged under the same reaction conditions and a small amount (15%) of the same 6:1 mixture of cyclohexanecarboxylates **2a** and **2b** was formed. The cyclization of *syn*-dibromo ester **3b** could be facilitated when higher temperature (rt, 10 min) was employed to yield the desired cyclohexanecarboxylate **2a** but in an inferior yield and with poor stereoselectivity (47%, 3:1 ratio at C_7) compared to *anti* isomer **3a**. The chemical yield of *syn* ester **3b** could be improved to 85% by using LHMDS instead of LDA as the base in THF at room temperature overnight.



substrate	base (in THF)	temp (°C)	time	*ds* at C_7 (**2a** : **2b**)	yield (%)
3a	LDA	-78	2 h	6 : 1	89
3b	LDA	-78	2 h	6 : 1	15 (20% conversion)
3b	LDA	rt	10 min	3 : 1	47
3b	LHMDS	rt	16 h	3 : 1	85

Scheme 2. (a) TsCl, pyridine, $CHCl_3$, 0°C, overnight, 84%. (b) NaCN, DMF, reflux, 13 h, 92%. (c) PTSA·H_2O, MeOH, reflux, 48 h, 58%. (d) LAH, THF, rt, overnight, 100%. (e) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1.5 h, 92%. (f) O_3, CH_2Cl_2, −78°C, 1 h; Ph_3P, rt, 0.5 h. (g) Ph_3P=C(Me)CO_2Et, CH_2Cl_2, rt, 14 h, 92% for two steps. (h) DIBALH, toluene, −78°C, 2 h, 99%. (i) $C_2H_5C(OEt)_3$, PhOH, toluene, reflux, 13 h, 87%; or $C_2H_5C(OEt)_3$, $CH_3CH_2CO_2H$, 125°C, 57%. (j) See table.

The above experimental observations can be rationalized by assuming that the stereoselection at C_7 is dependent upon the temperature at which the cyclization of the enolate occurs. The enolization of *anti*-isomer **3a** takes place at −78°C at a much faster rate (2 h) than the corresponding *syn*-isomer **3b** and the resulting enolate undergoes the internal alkylation at this temperature to give a good yield (89%) of the desired product **2a** with a 6:1 isomer ratio at C_7. On the other hand, the enolization of *syn*-ester **3b** with excess LDA in THF at −78°C proceeds at a much slower rate and this was confirmed by quenching the reaction mixture after 2 h with CD_3OD and showing that α-proton of the recovered *syn*-ester **3b** was not exchanged with deuterium. The enolate generated from *syn*-ester **3b** with excess LDA at room temperature undergoes the intramolecular ester enolate alkylation at a much higher temperature and this higher alkylation temperature thereby results in a lower stereoselectivity at C_7 in the case of **3b** (i.e. 3:1 vs 6:1). To our knowledge, a difference in reactivity between *syn* and *anti* diastereomeric esters in an enolization step has not been reported, and is usually not considered to be an important factor in ester enolate alkylation reactions.

Although more systematic studies are needed to elucidate the origin of the distinct differences in the rate of enolization, one possible reason may be due to imposed nonbonded interactions in Ireland's chair-like transition state model,[9] where the lithium cation is coordinated to the carbonyl oxygen and the bases as depicted in Fig. 1. Assuming that the β-hydrogen has a *gauche* conformation with the β-methyl substituent to minimize possible 1,2-interactions, the *TS* **I** of *anti*-isomer **3a** suffers from fewer nonbonded interactions than the *TS* **II** of *syn*-isomer **3b**, which has the bulky dibromo alkyl substituent near OEt group. Therefore, the deprotonation of *anti*-ester **3a** by LDA in THF proceeds at a much faster rate than the *syn*-isomer **3b**.

With the desired cyclohexanecarboxylate **2a** in hand, we turned our attention to its conversion to (±)-β-elemene (**1**). The inseparable mixture (6:1 at C_7) of primary bromides **2a** and **2b** was treated with potassium *t*-butoxide (THF, 0°C) to give a mixture of olefins **12a** and **12b**, which was then subjected to DIBALH reduction to yield alcohols **13a** and **13b** as an inseparable 6:1 mixture in 86% overall yield. Chemoselective Wacker[10] reaction of the terminal alkenes

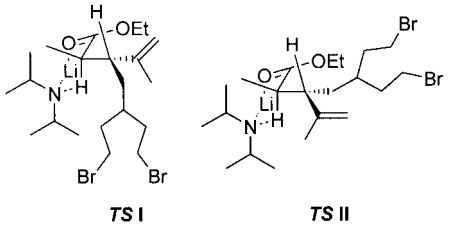
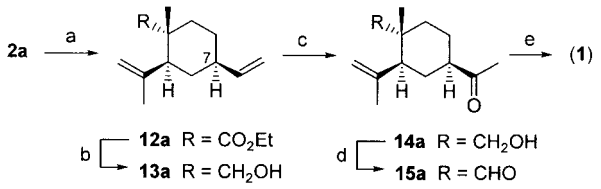


Figure 1.



Scheme 3. (a) *t*-BuOK, THF, 0°C, 8 h, 89%. (b) DIBALH, toluene, −78°C, 2 h, 92%. (c) CuCl, $PdCl_2$, O_2, DMF/H_2O, rt, 8 h, 93%. (d) i) PCC, NaOAc, CH_2Cl_2, 0°C, 2 h, 92%. ii) Separation. (e) $Ph_3P{=}CH_2$, THF, −78°C to rt, 1 h, 89%.

of **13a** and **13b**, followed by PCC oxidation, led to the formation of a readily separable mixture keto-aldehyde **15a** and its C_7 isomer **15b** (7:1, 92% total yield). Finally, double Wittig methylenation of keto-aldehyde **15a** provided the desired (±)-β-elemene (**1**) in 89% yield, whose ^{1}H and ^{13}C NMR spectral data were in good agreement with those reported by Thomas et al.[11] (Scheme 3).

In conclusion, we have accomplished a stereoselective total synthesis of (±)-β-elemene (**1**) utilizing a 'doubly diastereodifferentiating folding and allylic strain-controlled' IEEA strategy as a means of establishing the relative stereochemistry of the three stereogenic centers present in the natural product. More importantly, we encountered a remarkable difference in the rate of enolization between *syn* and *anti* diastereomeric esters during the internal alkylation, which should be considered as an important factor in applications of IEEA to natural product synthesis.[12]

1. Experimental

1.1. Data for compounds

1.1.1. Ditosylate (6). To a solution of diol **5** (5.80 g, 49.9 mmol) in $CHCl_3$ (50.0 mL) were added pyridine (12.1 mL) and TsCl (23.80 g, 124.8 mmol). The reaction mixture was stirred at 0°C overnight, diluted with EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to afford ditosylate **6** (17.80 g) in 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J=8.3 Hz, 4H), 7.35 (d, J=8.0 Hz, 4H), 5.61–5.50 (m,1H), 4.99 (d, J=11.0 Hz, 1H), 4.94 (dd, J=17.8, 1.5 Hz, 1H), 3.99 (dd, J=9.9, 4.5 Hz, 2H), 3.91 (dd, J=9.9, 5.7 Hz, 2H), 2.46 (s, 6H), 2.17–2.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.0, 133.5, 132.5, 129.9, 127.9, 118.4, 68.4, 37.7, 31.4, 21.6; IR (neat) 1362, 1174 cm^{-1}.

1.1.2. 3-Allylpentanedinitrile (7). To a solution of ditosylate **6** (767 mg, 1.81 mmol) in DMF (9.0 mL) was added NaCN (350 mg, 7.14 mmol). The reaction mixture was refluxed for 13 h, diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford dinitrile **7** (223 mg) in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70 (ddt, J=17.3, 10.0, 7.1 Hz, 1H), 5.27–5.20 (m, 2H), 2.58 (dd, J=17.1, 6.1 Hz, 2H), 2.51 (dd, J=17.0, 6.3 Hz, 2H), 2.35–2.16 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.6, 119.7, 116.9, 36.8, 32.2, 21.0; IR (neat) 2249, 1643 cm^{-1}; HRMS calcd for $C_8H_{10}N_2$ (M^+) 134.0844, found 134.0844.

1.1.3. 3-Allylpentanedioic acid dimethyl ester (8). A mixture of dinitrile **7** (900 mg, 6.71 mmol) and *p*-toluenesulfonic acid monohydrate (3.83 g, 20.1 mmol) in MeOH (14.0 mL) was refluxed for 48 h. The mixture was diluted with EtOAc, and washed with saturated aqueous NH_4Cl, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 7:1) to afford dimethyl ester **8** (1.50 g) in 58% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (ddt, J=16.3, 11.0, 7.2 Hz, 1H), 5.08–5.02 (m, 2H), 3.67 (s, 6H), 2.52–2.30 (m, 5H), 2.14 (dd, J=7.1, 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 135.2, 117.5, 51.3, 38.1, 37.7, 31.6; IR (neat) 1739 cm^{-1}; HRMS calcd for $C_9H_{13}O_3$ (M^+-OCH_3) 169.0865, found 169.0865.

1.1.4. 3-Allylpentane-1,5-diol (9). To a suspension of LAH (330 mg, 8.70 mmol) in THF (5.0 mL) was added dropwise a solution of dimethyl ester **8** (435 mg, 2.17 mmol) in THF (6.0 mL) at 0°C. The mixture was stirred overnight at rt and then cooled to 0°C. To the reaction mixture were added water (0.3 mL), aqueous 3N NaOH solution (0.3 mL), and water (0.9 mL) in order. The mixture was stirred for 2 h, and filtered through a short pad of Celite. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give diol **9** (322 mg) in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85–5.71 (m, 1H), 5.08–5.00 (m, 2H), 3.77–3.48 (m, 4H), 2.10 (ddt, J=7.2, 6.2, 1.2 Hz, 2H), 2.09 (bs, 1H), 1.80 (bs, 1H), 1.78 (tt, J=12.6, 6.3 Hz, 1H), 1.66–1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5, 116.4, 60.1, 38.5, 36.0, 30.6; IR (neat) 3336 cm^{-1}; HRMS calcd for C_8H_{12} (M^+-2H_2O) 108.0939, found 108.0926.

1.1.5. 6-Bromo-4-(2-bromoethyl)hex-1-ene (4). To a solution of diol **9** (151 mg, 1.05 mmol) in CH_2Cl_2 (10.1 mL) were added Ph_3P (826 mg, 3.15 mmol) and CBr_4 (696 mg, 2.10 mmol). After 1.5 h at 0°C, the mixture was diluted with hexane, and filtered through a short silica gel column. The filtrate was concentrated at reduced pressure and the resulting residue was purified by column chromatography on silica gel (hexane) to afford dibromide **4** (260 mg) in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81–5.67 (m, 1H), 5.11–5.04 (m, 2H), 3.43 (t, J=6.6 Hz, 4H), 2.12–2.09 (m, 2H), 1.93–1.79 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 117.4, 36.7, 36.3, 35.1, 31.0; IR (neat) 1257 cm^{-1}; HRMS calcd for MH^{2+} 269.9619, found 269.9459.

1.1.6. Ethyl (*E*)-7-bromo-5-(2-bromoethyl)-2-methyl-2-heptenoate (10). To a cooled (−78°C) solution of dibromide **4** (168 mg, 0.62 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise a saturated solution of ozone in CH_2Cl_2 (−78°C) over 1 h. Excess ozone was removed by a stream of nitrogen and triphenylphosphine (160 mg, 0.61 mmol) was added, and the mixture was warmed to rt. After 30 min, (carbethoxyethylidene)triphenylphosphorane (450 mg, 1.24 mmol) was added to the reaction mixture, which was stirred overnight. The mixture was diluted with hexane and then

filtered through a short silica gel column. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 50:1) to give *E*-unsaturated ester **10** (185 mg, 83%) and *Z*-isomer (19 mg, 9%). *E*-Ester **10**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.73 (tq, J=7.4, 1.5 Hz, 1H), 4.21 (q, J=7.1 Hz, 2H), 3.46–3.39 (m, 4H), 2.22 (t, J=6.8 Hz, 2H), 2.03 (tt, J=12.9, 6.5 Hz, 1H), 1.92–1.82 (m, 7H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 138.2, 129.7, 60.4, 36.3, 35.2, 31.4, 30.7, 14.1, 12.5; IR (neat) 1711, 1254 cm^{-1}; HRMS calcd for $C_{12}H_{22}Br_2O_2$ (MH_2^{2+}) 355.9987, found 355.9813. *Z*-Ester: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (tq, J=7.5, 1.4 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.44 (t, J=7.1 Hz, 4H), 2.54–2.51 (m, 2H), 1.93 (q, J=1.4 Hz, 3H), 1.95–1.85 (m, 5H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 139.2, 129.4, 60.2, 36.6, 35.9, 32.2, 31.0, 20.8, 14.3; IR (neat) 1713, 1227 cm^{-1}

1.1.7. (*E*)-7-Bromo-5-(2-bromoethyl)-2-methyl-2-hepten-1-ol (11). To a cooled (−78°C) solution of *E*-unsaturated ester **10** (1.00 g, 2.81 mmol) in dry toluene (20.0 mL) was added dropwise DIBALH (8.5 mL, 1.0 M solution in toluene). After 2 h at −78°C, the reaction mixture was quenched with methanol (10.0 mL) and stirred at rt for 2 h. The precipitate was filtered off through a pad of Celite. The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give allylic alcohol **11** (875 mg, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.41 (tq, J=7.2, 1.4 Hz, 1H), 4.03 (s, 2H), 3.43 (td, J=7.0, 1.5 Hz, 4H), 2.08 (t, J=5.9 Hz, 2H), 1.90–1.84 (m, 5H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 122.2, 68.6, 36.5, 35.8, 31.2, 30.4, 13.9; IR (neat) 3350, 1011 cm^{-1}; HRMS calcd for $C_{10}H_{20}Br_2O$ (MH_2^{2+}) 313.9881, found 313.9720.

1.1.8. Ethyl (2*R,3*R**)-3-[4-bromo-2-(2-bromoethyl)-butyl]-2,4-dimethyl-4-pentenoate (3a) and ethyl (2*S**, 3*R**)-3-[4-bromo-2-(2-bromoethyl)butyl]-2,4-dimethyl-4-pentenoate (3b). Claisen rearrangement with propionic acid.** A mixture of dibromo allylic alcohol **11** (29 mg, 0.092 mmol), triethyl orthopropionate (2.0 mL) and propionic acid (1 mg) was stirred for 24 h at 125°C. Concentration in vacuo and purification of the residue on silica gel (hexane/EtOAc, 100:1) gave an easily separable 80:20 mixture of dibromo esters **3a** and **3b** (21 mg, 57%).

1.1.9. Claisen rearrangement with phenol. To a solution of dibromo allylic alcohol **11** (741 mg, 2.36 mmol) in dry toluene (6.0 mL) was added triethyl orthopropionate (1.5 mL) and phenol (7 mg). The reaction mixture was refluxed for 13 h. The solvent was removed at reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 100:1) to give dibromo esters **3a** (517 mg, 55%) and **3b** (304 mg, 32%). *anti*-Dibromo ester **3a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.86 (dq, J=1.5 Hz, 1H), 4.77–4.76 (m, 1H), 4.14–4.03 (m, 2H), 3.46–3.30 (m, 4H), 2.50–2.44 (m, 1H), 2.40 (ddd, J=11.6, 8.6, 3.3 Hz, 1H), 2.04–1.91 (m, 2H), 1.78–1.70 (m, 2H), 1.69 (dd, J=1.4, 0.7 Hz, 3H), 1.68–1.63 (m, 1H), 1.39 (ddd, J=14.0, 11.2, 3.0 Hz, 1H), 1.29 (ddd, J=13.8, 10.2, 3.6 Hz, 1H), 1.23 (t, J=7.2 Hz, 3H), 1.13 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 144.4, 114.3, 60.2, 47.5, 43.2, 37.4, 36.0, 33.3, 32.5, 30.8, 30.4, 18.9, 14.4, 14.2; IR (neat) 1731, 1179 cm^{-1}; HRMS calcd for $C_{14}H_{25}Br_2O_2$ ($MH_2^{2+}-CH_3$) 383.0221, found 383.0040. *syn*-Dibromo ester **3b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.93 (dq, J=1.6 Hz, 1H), 4.87 (d, J=1.4 Hz, 1H), 4.20–4.10 (m, 2H), 3.46–3.40 (m, 2H), 3.36–3.29 (m, 2H), 2.39 (td, J=11.0, 3.1 Hz, 1H), 2.35–2.29 (m, 1H), 2.04–1.97 (m, 1H), 1.95–1.88 (m, 1H), 1.77–1.62 (m, 3H), 1.60 (s, 3H), 1.42 (ddd, J=13.9, 11.2, 2.8 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H), 1.05 (d, J=6.7 Hz, 3H), 1.09–1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3, 143.0, 115.7, 60.3, 47.8, 43.0, 37.2, 35.8, 34.3, 33.3, 17.4, 16.4, 14.3; IR (neat) 1730, 1175 cm^{-1}; HRMS calcd for $C_{15}H_{28}Br_2O_2$ (MH_2^{2+}) 398.0456, found 398.0283.

1.1.10. Ethyl (1*R,2*S**,4*R**)-4-(2-bromoethyl)-2-isopropenyl-1-methylcyclohexane-1-carboxylate (2a) and ethyl (1*R**,2*S**,4*S**)-4-(2-bromoethyl)-2-isopropenyl-1-methylcyclohexane-1-carboxylate (2b). Cyclization of 3a with LDA.** To a cooled (−78°C) solution of *anti*-dibromo ester **3a** (134 mg, 0.34 mmol) in dry THF (41.0 mL) was added dropwise a 0.5 M solution of LDA in THF (6.7 mL). The mixture was stirred for 2 h at −78°C, quenched with saturated aqueous NH_4Cl, diluted with EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/Et_2O, 100:1) to give an inseparable mixture of cyclohexanecarboxylates **2a** and **2b** (95 mg, 89%, **2a**:**2b**=6:1 by 500 MHz ^{1}H NMR).

1.1.11. Cyclization of 3b with LDA at −78°C for 2 h and quenching with CD_3OD. To a stirred solution of *syn* dibromo ester **3b** (12.2 mg, 0.031 mmol) in dry THF (3.8 mL) was added dropwise a 0.5 M solution of LDA in THF (0.6 mL). After 2 h at −78°C, pre-cooled CD_3OD (0.5 mL) was slowly added to the mixture at −78°C. The mixture was stirred for 30 min at this temperature, diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/Et_2O, 100:1) to give a mixture of cyclohexanecarboxylates **2a** and **2b** (1.5 mg, 15%, **2a**:**2b**=6:1 by 500 MHz ^{1}H NMR), and *syn*-ester **3b** (9.8 mg, 80%).

1.1.12. Cyclization of 3b with LDA at rt. To a stirred solution of *syn* dibromo ester **3b** (16.7 mg, 0.042 mmol) in dry THF (5.0 mL) was added dropwise a 0.5 M solution of LDA in THF (0.9 mL). After 10 min at rt, the mixture was quenched with saturated aqueous NH_4Cl, diluted with EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/Et_2O, 100:1) to give a mixture of cyclohexanecarboxylates **2a** and **2b** (6.3 mg, 47%, **2a**:**2b**=3:1 by 300 MHz ^{1}H NMR).

1.1.13. Cyclization of 3b with LHMDS. To a stirred solution of *syn* dibromo ester **3b** (65 mg, 0.16 mmol) in dry THF (15.0 mL) was added dropwise a 1.0 M solution of LHMDS in THF (1.6 mL). The mixture was stirred overnight at rt, quenched with saturated aqueous NH_4Cl, diluted with

EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 100:1) to give a mixture of cyclohexanecarboxylates **2a** and **2b** (44 mg, 85%, **2a**:**2b**=3:1 by 500 MHz ^{1}H NMR). **2a** and **2b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ [4.83 (dq, J=1.6 Hz) and 4.80 (dq, J=1.6 Hz), 1H], [4.72–4.71 (m) and 4.65–4.64 (m), 1H], 4.17–4.04 (m, 2H), [3.45 (t, J=7.1 Hz) and 3.43 (t, J=7.0 Hz), 2H], [2.80 (dd, J=10.4, 4.3 Hz) and 2.67 (dd, J=13.0, 3.4 Hz), 1H], [2.05–1.99 (m) and 1.97–1.91 (m), 2H], 1.83 (q, J=7.0 Hz, 2H), [1.78–1.73 (m) and 1.67–1.56 (m), 4H], [1.70 (dd, J=1.2, 0.6 Hz) and 1.64 (dd, J=1.2, 0.7 Hz), 3H], 1.26 (t, J=7.1 Hz, 3H), [1.13 (s) and 1.12 (s), 3H]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9, 177.8, 146.6, 146.5, 113.1, 112.8, 60.3, 60.2, 48.3, 46.4, 43.1, 39.9, 37.1, 36.0, 35.8, 32.7, 32.3, 31.8, 31.3, 30.9, 30.8, 27.0, 25.3, 23.8, 22.8, 17.7, 15.2, 14.12, 14.08; IR (neat) 1725, 1235 cm^{-1}; HRMS calcd for $C_{15}H_{28}Br_2O_2$ (M^+) 316.1038, found 316.1033.

1.1.14. Ethyl (1*R,2*S**,4*R**)-2-isopropenyl-1-methyl-4-vinylcyclohexane-1-carboxylate (12a) and ethyl (1*R**,2*S**,4*S**)-2-isopropenyl-1-methyl-4-vinylcyclohexane-1-carboxylate (12b).** To a stirred solution of cyclohexanecarboxylates **2a** and **2b** (23.7 mg, 0.075 mmol, **2a**:**2b**=6:1) in dry THF (2.0 mL) was slowly added a 1.0 M solution of *t*-BuOK (1.5 mL) in THF. After 8 h at 0°C, methyl iodide was added to the mixture, which was then stirred overnight. The reaction mixture was diluted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solution in vacuo and purification of the residue on silica gel (hexane/EtOAc, 100:1) gave an inseparable 6:1 mixture of diolefins **12a** and **12b** (15.6 mg, 89%). **12a** and **12b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ [5.96 (ddd, J=17.9, 10.0, 6.1 Hz) and 5.80 (ddd, J=17.2, 10.6, 6.5 Hz), 1H], [5.07 (dt, J=6.2, 1.6 Hz), and 4.94 (dt, J=10.7, 1.5 Hz), 1H], [5.04 (d, J=1.6 Hz) and 5.01 (dt, J=17.3, 1.6 Hz), 1H], [4.82 (dq, J=1.6 Hz) and 4.80 (dq, J=1.6 Hz), 1H], [4.72–4.70 (m) and 4.66 (dt, J=1.9, 0.9 Hz), 1H], 4.05–4.17 (m, 2H), [2.86 (dd, J=10.8, 4.0 Hz) and 2.69 (dd, J=13.0, 3.4 Hz), 1H], [2.54–2.48 (m) and 2.13–2.09 (m), 1H], [1.96 (td, J=13.8, 4.3 Hz) and 1.81 (ddd, J=13.9, 10.8, 4.8 Hz), 1H], [1.69 (s) and 1.65 (t, J=1.0 Hz), 3H], [1.75–1.70 (m) and 1.67–1.59 (m), 4H], [1.39 (q, J=12.8 Hz) and 1.31–1.28 (m), 1H], [1.26 (t, J=7.2 Hz) and 1.25 (t, J=7.2 Hz), 3H], [1.16 (s) and 1.13 (s), 3H]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 177.9, 146.8, 146.6, 143.6, 142.0, 113.8, 112.8, 112.3, 60.2, 48.3, 46.4, 46.2, 43.2, 41.5, 37.1, 36.0, 32.6, 32.1, 31.4, 26.8, 25.8, 23.7, 22.8, 15.2, 14.1; IR (neat) 1729, 1227 cm^{-1}; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

1.1.15. [(1*R,2*S**,4*R**)-2-Isopropenyl-1-methyl-4-vinylcyclohexyl]methanol (13a) and [(1*R**,2*S**,4*S**)-2-isopropenyl-1-methyl-4-vinylcyclohexyl]methanol (13b).** To a cooled (−78°C) solution of olefins **12a** and **12b** (143 mg, 0.61 mmol, **12a**:**12b**=6:1) in dry toluene (8.5 mL) was added dropwise a 1.0 M solution of DIBALH in toluene (3.6 mL). The reaction mixture was stirred for 2 h at −78°C before the addition of methanol (7.0 mL). The mixture was allowed to warm to rt and stirred for 2 h. The precipitate was filtered off through a pad of Celite. The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give an inseparable 6:1 mixture of alcohols **13a** and **13b** (108 mg, 92%). **13a** and **13b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ [5.93 (ddd, J=16.8, 11.3, 5.6 Hz) and 5.80 (ddd, J=17.2, 10.6, 6.5 Hz), 1H], [5.07 (d, J=1.9 Hz) and 4.99 (dt, J=17.3, 1.6 Hz), 1H], [5.04 (dt, J=7.6, 1.8 Hz) and 4.92 (dt, J=10.2, 1.5 Hz), 1H], 4.85–4.83 (m, 1H), 4.76–4.75 (m, 1H), 3.40–3.34 (m, 2H), [2.55–2.49 (m) and 2.05–1.96 (m), 1H], [2.34 (dd, J=12.6, 3.5 Hz) and 2.24–2.20 (m), 1H], [1.91 (ddd, J=13.6, 12.6, 5.0 Hz), 1.82–1.76 (m) and 1.66–1.10 (m), 6H], 1.75 (d, J=1.4 Hz, 3H), [0.94 (s) and 0.90 (s), 3H]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 148.7, 143.9, 142.0, 113.9, 112.80, 112.75, 112.1, 72.47, 72.43, 49.4, 44.1, 41.9, 38.9, 38.5, 36.1, 33.6, 31.6, 31.3, 27.3, 25.2, 22.7, 22.5, 16.7, 16.4; IR (neat) 3388, 1042 cm^{-1}; HRMS calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1674.

1.1.16. 1-[(1*R,3*S**,4*R**)-4-(Hydroxymethyl)-3-isopropenyl-4-methylcyclohexyl]-1-ethanone (14a) and 1-[(1*S**,3*S**,4*R**)-4-(hydroxymethyl)-3-isopropenyl-4-methylcyclohexyl]-1-ethanone (14b).** To a stirred solution of alcohols **13a** and **13b** (68 mg, 0.35 mmol, **13a**:**13b**=6:1) in DMF (7.0 mL) and water (1.0 mL) were added $PdCl_2$ (62 mg, 0.35 mmol) and CuCl (173 mg, 1.75 mmol) under an oxygen atmosphere. The reaction mixture was stirred for 8 h, diluted with a 2:1 mixture of hexane and EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to give an inseparable 8:1 mixture of ketones **14a** and **14b** (68.4mg, 93%). **14a** and **14b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.88–4.87 (m, 1H), 4.77 (dd, J=1.5, 0.6 Hz, 1H), 3.40 (d, J=10.9 Hz, 1H), 3.33 (d, J=11.0 Hz, 1H), [2.67–2.65 (m) and 2.39 (tt, J=11.9, 3.9 Hz), 1H], [2.23 (dd, J=12.6, 3.8 Hz) and 2.19 (dd, J=9.1, 4.7 Hz), 1H], 2.16 (s, 3H), 1.89–1.40 (m, 6H), 1.76 (s, 3H), [0.93 (s) and 0.89 (s), 3H]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.7, 211.2, 147.9, 147.5, 113.2, 113.0, 71.9, 71.6, 51.5, 48.3, 47.1, 45.2, 38.5, 38.4, 35.5, 32.4, 29.2, 28.1, 27.78, 27.74, 23.5, 22.9, 22.7, 21.7, 16.3; IR (neat) 3444, 1698 cm^{-1}; HRMS calcd for $C_{13}H_{22}O_2$ (M^+) 210.1620, found 210.1621.

1.1.17. (1*R,2*S**,4*R**)-4-Acetyl-2-isopropenyl-1-methylcyclohexane-1-carbaldehyde (15a) and (1*R**,2*S**,4*S**)-4-acetyl-2-isopropenyl-1-methylcyclohexane-1-carbaldehyde (15b).** A mixture of ketones **14a** and **14b** (93 mg, 0.44 mmol, **14a**:**14b**=8:1), 4 Å molecular sieves (470 mg), sodium acetate (182 mg, 2.22 mmol) and PCC (477 mg, 2.21 mmol) in dry CH_2Cl_2 (19.0 mL) was stirred for 2 h at 0°C and then diluted with ether. The mixture was filtered through a pad of Florisil and washed repeatedly with ether. Concentration of the solution in vacuo and purification of the residue on silica gel (hexane/EtOAc, 10:1) gave the desired aldehyde **15a** (73.8 mg, 80%) and isomer **15b** (10.8 mg, 12%) in a total 92% yield. **15a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.50 (s, 1H), 4.88 (dq, J=1.5 Hz, 1H), 4.69 (dt, J=1.3, 0.7 Hz, 1H), 2.48–2.42 (m, 2H), 2.18 (s, 3H), 1.91–1.86 (m, 1H), 1.82 (dtd, J=13.5, 3.6, 1.8 Hz, 1H), 1.66 (s, 3H), 1.71–1.63 (m, 2H), 1.56–1.47 (m, 1H), 1.42 (dt, J=12.8, 3.3 Hz, 1H), 1.07 (d, J=0.4 Hz, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 210.7, 206.0, 145.0, 113.8, 50.8, 49.5, 46.6, 32.3, 28.2, 27.7, 23.2, 22.3, 12.9; IR (neat) 1711 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1463. **15b**: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.39 (s, 1H), 4.90 (dq, J=1.5 Hz, 1H), 4.71 (dt, J=1.4, 0.7 Hz, 1H), 2.71 (dq, J=4.8 Hz, 1H), 2.59 (dd, J=10.6, 4.1 Hz, 1H), 2.17 (s, 3H), 1.96–1.92 (m, 2H), 1.87–1.73 (m, 3H), 1.69 (s, 3H), 1.30–1.26 (m, 1H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.9, 205.7, 145.5, 113.6, 49.5, 46.2, 42.4, 29.0, 28.0, 26.8, 23.9, 21.4, 14.1; IR (neat) 1724 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1464.

1.1.18. (±)-β-Elemene (1). To a suspension of methyltriphenylphosphonium iodide (1.45 g, 3.59 mmol) in dry THF (5.0 mL) was slowly added a 1.6 M solution of *n*-BuLi in hexane (1.5 mL). The suspension was stirred for 10 min at −78°C and for 30 min at rt. A solution of aldehyde **15a** (50 mg, 0.24 mmol) in THF (1.7 mL) was added to the mixture at −78°C. The reaction mixture was slowly warmed to rt and stirred for 1 h. After the mixture was quenched with saturated aqueous NH_4Cl solution, the mixture was filtered through a short silica gel column. Concentration of the solution in vacuo and purification of the residue on silica gel (hexane) gave (±)-β-elemene (**1**) (43.7 mg, 89%). ^1H NMR ($CDCl_3$, 500 MHz) δ 5.82 (dd, J=17.5, 10.9 Hz, 1H), 4.91 (dd, J=8.7, 1.3 Hz, 1H), 4.88 (dd, J=2.1, 1.5 Hz, 1H), 4.82 (dq, J=1.6 Hz, 1H), 4.72–4.71 (m, 1H), 4.70 (dq, J=1.5 Hz, 1H), 4.60–4.59 (m, 1H), 2.03–2.00 (m, 1H), 1.97–1.92 (m, 1H), 1.75 (s, 3H), 1.71 (dd, J=1.4, 0.8 Hz, 3H), 1.63–1.59 (m, 1H), 1.58–1.40 (m, 5H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 150.3, 147.7, 112.1, 109.8, 108.2, 52.7, 45.7, 39.9, 39.8, 32.9, 26.8, 24.8, 21.1, 16.6; IR (neat) 1644, 887 cm^{-1}; HRMS calcd for $C_{15}H_{24}$ (M^+) 204.1878, found 204.1878.

1.2. Supporting information

Copies of the ^1H and ^{13}C NMR spectra of **10**, **3a**, **3b**, **2a** and **2b**, **15a**, **15b** and **1** as well as the IR and HRMS spectra for **1**.

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