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Synthesis of bicyclo[3.2.2]nonadienones via enantioselective cyclopropanation of racemic cyclohexen-3-yl diazoacetate

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Abstract—Optically active (1*S*,5*R*)-(+)-3-azabicyclo[3.2.2]non-6-en-2-one (+)-**7** was synthesized via enantioselective intramolecular cyclopropanation of racemic cyclohexen-3-yl diazoacetate **10** in the presence of $[Rh_2(\{(2S)\text{-meox}\}_4]$ catalyst. The cyclopropanation product (−)-**9** was converted to the azide **8**, which underwent successive Curtius and 3-aza-Cope rearrangements to afford **18**, which was reduced to the bicyclic azepinone (+)-**7**. An analogous sequence based on Cope rearrangement of the SEM-protected enol ether **20** afforded (1*S*,5*R*)-bicyclo[3.2.2]nona-3,6-dien-2-one **22**.

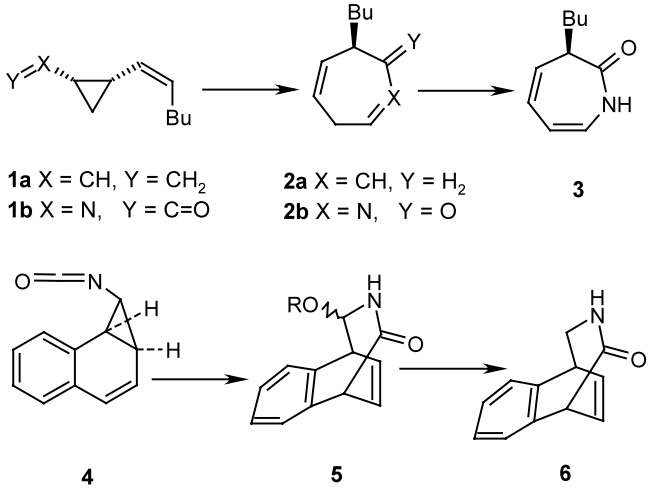
1. Introduction

The Cope rearrangement[1] and the related Claisen rearrangement[2] are both concerted suprafacial [3,3]-sigmatropic processes.[3] Owing to their high degree of stereospecificity,[4] both reactions have found numerous synthetic applications.[5] A few examples of Cope rearrangements containing nitrogen atoms in the rearranging framework are also known, mostly using isocyanates;[6] however, this 'aza-Cope' rearrangement is mechanistically much less established, and its synthetic potential has not been widely exploited.

Recently, we reported the asymmetric synthesis of (+)-dictyopterene C′ **2a**[7] via Cope rearrangement of an appropriately substituted divinylcyclopropane **1a** which, in turn, was accessible by intermolecular enantioselective cyclopropenation of diethoxypropyne.[8] The analogous aza-Cope rearrangement of the enantioenriched isocyanate **1b** was expected to afford the azepinone **2b** and, subsequently, its tautomer **3**. However, contrary to the rearrangement of **1a** which was fully stereospecific, that of **1b** was accompanied by ca. 30% racemization (Scheme 1).[9]

The cause for this partial racemization could not be established; however, it was found that the benzannulated isocyanate **4**, in which the vinyl group is locked in the conformation required for Cope rearrangement, could be converted thermally to **5** and, ultimately to **6** in a fully stereospecific manner.[10] On the grounds of these results an approach towards chiral non-racemic bicyclic azepinones was envisaged. Thus, the azepinone **7** should be available from azide **8** via sequential Curtius- and aza-Cope rearrangement followed by reduction. The azide **8**, in turn, was expected to be accessible by eliminative opening followed by azidation (Scheme 2).

The key step of the sequence is the known enantioselective cyclopropanation of racemic cyclohexen-3-yl diazoacetate **10**.[11] The intramolecular nature of the cyclopropanation ensures the *endo*-orientation of the



Scheme 1.

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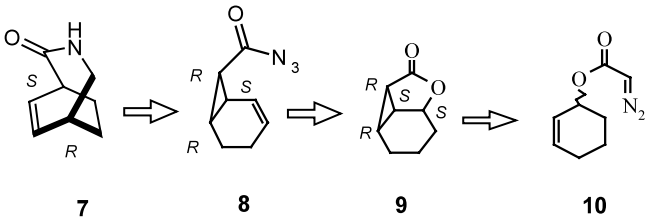
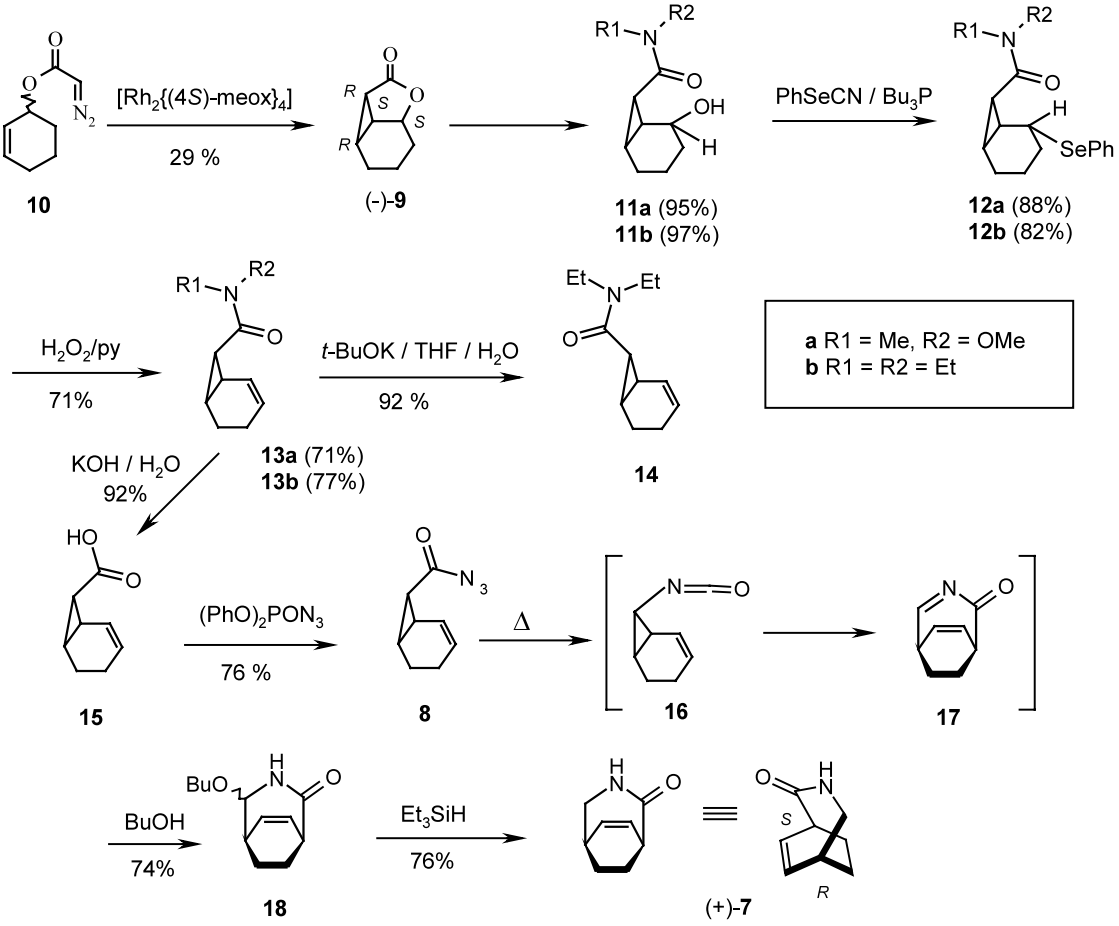


Scheme 2.

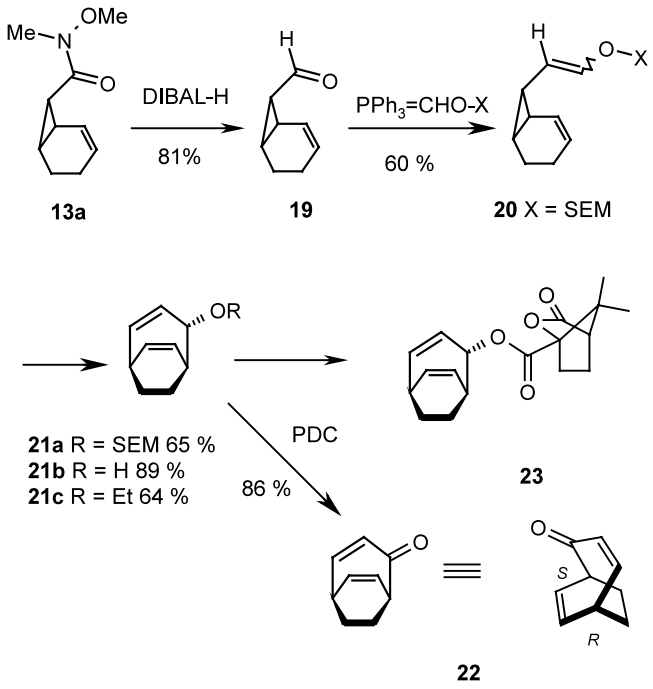
carboxylate group, which is required for the Cope-rearrangement.

2. Results and discussion

In our hands, the intramolecular cyclopropanation of racemic **10** in the presence of $[Rh_2\{(2S)\text{-meox}\}_4]$[12] afforded the lactone (–)-**9** in 29% yield and with enantiomeric excess of 94%, in good agreement with the results reported in the literature.[11] Our original plan envisaged a one-pot conversion of the lactone **9** to the unsaturated acid **15**. However, this reaction could not be realized, although a large number of systems were tried, so that an indirect route had to be devised. The lactone resisted hydrolysis under acidic and basic conditions. It did react with aqueous base; however, the resulting hydroxyacid could not be isolated owing to its spontaneous recyclization to **9** upon work-up. However, ring opening occurred smoothly with methoxymethylamine (MeMeONH·HCl) in the presence of $AlMe_3$[13] and $Et_2NH/AlCl_3$[14] to afford the hydroxy amides **11a** and **11b** in 95 and 97% yield, respectively. Their dehydration to **13a**,**b** was effected in an overall yield of ca. 75% by reaction with phenylselenocyanate/Bu_3P[15] to initially form **12a**,**b**, followed by oxidation of the resulting selenides with H_2O_2 in pyridine. The *N*-methoxyamide **13a** was hydrolyzed with aqueous KOH to afford the acid **15**. In contrast, the diethylamide **12b** was unreactive under these conditions, while more vigorous conditions ((*t*-BuOK/THF/H_2O or KOH/DMSO)[13] resulted in epimerization to the *exo*-isomer **14**. The *endo*-acid **15** was transformed to the azide **8** with $(PhO)_2PON_3$,[16] and the azide was converted in refluxing toluene to the isocyanate **16**. The isocyanate was not isolated, but rearranged to the bicyclic imine **17**, which was trapped in situ with *n*-BuOH and isolated as a 60:40 mixture of diastereomeric *N*,*O*-acetals **18**. Reduction of **18** with Et_3SiH afforded the bicyclic lactam **7** in 76% yield. Recrystallization from hexane produced (+)-**7** having 97% e.e. The absolute configuration of (+)-**7** is (1*S*,5*R*)-3-azabicyclo[3.2.2]non-6-en-4-one, attributed on the grounds of the known absolute configuration of (–)-**9** and the known stereochemical course of the reactions, which in turn, have been established for the synthesis of **6** (Scheme 3).[9]



Scheme 3.



Scheme 4.

The availability of **13a** also allowed access to the hitherto unknown optically active bicyclo[3.2.2]nona-2,6-diene-2-one (Scheme 4). The methoxyamide **13a** was reduced with DIBAL-H to the aldehyde **19**. Wittig reaction of the aldehyde **19** with SEM-triphenylphosphonium ylide[17] afforded the diene **20** as an inseparable *Z*/*E* mixture. Heating of the *Z*/*E*-mixture to 100°C in CCl_4 led to rearrangement of *Z*-**20** to **21**, which could be separated from *E*-**20**. Rearrangement of *E*-**20**, in turn, required heating to 190°C, and was accompanied by partial decomposition of the starting material. Both stereoisomers of **20** afforded the same rearrangement product **21a**, in an overall yield of 65%, indicating *E*/*Z*-interconversion under the reaction conditions. The deprotection of the SEM ethers **21a** was initially effected with $Bu_4N^+F^-$ in HMPA at 100°C in the presence of molecular sieves. Under these conditions, the desired alcohol **21b** was isolated in poor yield. The major product was the ether **21c**. However, cleavage to **21b** occurred in satisfactory yield with CsF in HMPA at 140°C.[18] Oxidation of **21b** with PDC afforded the so far unknown optically active bicyclic ketone **22** with an e.e. of 94%. Racemic **22** has been used as intermediate for the synthesis of isosesquicarene[19] and a formal synthesis of sirenin.[20]

Since the conversion of (−)-**9** to (−)-**20** and the Cope rearrangement of **20** are stereospecific, the absolute configuration of **22** is expected to be (1*S*,5*R*). This was verified by X-ray crystallography of the ester **23**, obtained by the reaction of **21b** with (−)-camphanic acid chloride. This establishes unambiguously the (1*S*,5*R*)- configuration of **21a**,**b** and also that of **22** (Fig. 1).

3. Experimental

3.1. General

See Ref. 21. All reactions were carried out under a nitrogen atmosphere.

3.2. Synthesis of (1*S*,5*R*)-(+)-3-aza-bicyclo[3.2.2]non-6-en-2-one (+)-7

3.2.1. Intramolecular cyclopropanation of racemic cyclohexen-3-yl diazoacetate 10: (1*S*,2*R*,6*S*,9*R*)-(−)-7-oxatricyclo[4.3.0.0^{2,9}]nonan-8-one 9. A solution of cyclohexen-3-yl diazoacetate **8**[10] (2.50 g, 15.0 mmol) in CH_2Cl_2 (60 mL) was added at rt over 15 h to [Rh_2{4*S*}-meox}$_4$] (107 mg, 0.14 mmol) in CH_2Cl_2 (200 mL). After the addition, the solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, pentane/AcOEt 3:2) to afford (−)-**9** (593 mg, 29%) as colorless crystals, mp 35–37°C (lit.[10] 36–37°C). $[\alpha]_D^{21} = -1.8$ (*c* = 2.50, MeOH), for 93% e.e. (Lipodex E, 120°C, $T_1 = 10.3$ min, $T_2 = 11.3$ min (major enantiomer). IR ($CHCl_3$): 2955w, 1758s, 1343w, 1206s, 971m. ^{1}H NMR (500 MHz, $CDCl_3$): 1.60–1.81 (m, 3H); 1.84–1.92 (m, 3H); 1.95–2.22 (m, 1H); 2.05–2.14 (m, 1H); 2.26 (s, 2H); 3.44 (s, 2H); 5.30–5.34 (m, 1H); 5.69–5.74 (m, 1H); 5.96–6.00 (m, 1H). ^{13}C NMR: (125 MHz, $CDCl_3$): 18.7 (t); 24.8 (t); 28.1 (t); 30.1 (q); 50.4 (t); 69.2 (d); 125.6 (d); 133.3(d); 166.8 (s); 200.7 (s).

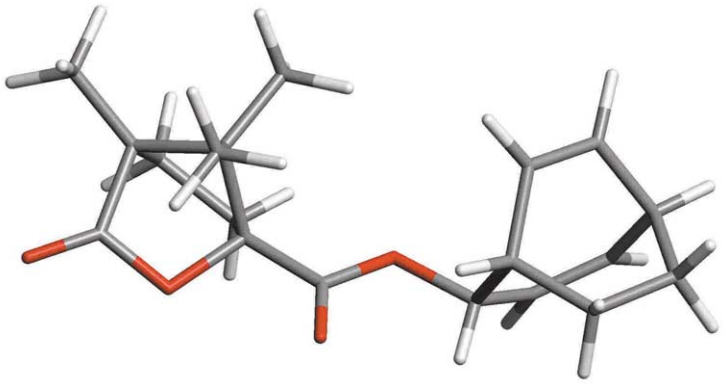


Figure 1. X-Ray structure of **23**.

3.2.2. (1*S*,2*S*,6*R*,7*R*)-2-Hydroxy-*N*-methoxy-*N*-methylbicyclo[4.1.0]heptane-7-carboxamide 11a. $AlMe_3$ (2.83 mL, 2 M in heptane, 5.67 mmol) was added at rt within 20 min to *N*,*O*-dimethylhydroxylamine (422 mg, 4.33 mmol) in CH_2Cl_2 (18 mL). After stirring for 30 min, compound **9** (200 mg, 1.45 mmol) was added to the homogeneous solution, which was then stirred overnight. After cooling to 0°C the mixture was treated with 10% HCl (15 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and the residue was purified by flash chromatography (SiO_2; pentane/AcOEt, 4:1) to give **11a** (274 mg, 95%) as a colorless oil, which solidified upon standing, mp <25°C. $[\alpha]_D^{21} = -122.8$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3460mbr, 3022s, 2940m, 1636s, 1042m. ^{1}H NMR (500 MHz, $CDCl_3$, 50°C): 0.93–1.02 (m, 1H); 1.08–1.16 (m, 2H); 1.42–1.48 (m, 1H); 1.52–1.58 (m, 1H); 1.64–1.72 (m, 1H); 1.88–2.05 (m, 3H); 3.26 (s, 3H); 3.73 (s, 3H); 4.10–4.17 (m, 1H); 4.30 (s large, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 20.0 (d); 20.2 (d); 20.3 (t); 22.5 (t); 24.6 (d); 31.9 (t); 32.9 (q); 61.1 (q); 66.6 (d); 172.9 (s). MS: 199 ($M^{+\bullet}$, 1), 182 (20), 142 (9), 140 (7), 139 (72), 121 (21), 111 (10), 97 (6), 96 (5), 95 (16), 94 (11), 93 (85), 91 (16), 84 (6), 83 (12), 82 (8), 81 (23), 79 (20), 77 (21), 73 (5), 69 (9), 68 (10), 67 (32), 66 (10), 65 (9), 62 (5), 61 (100), 60 (7), 58 (12), 57 (11), 56 (7), 55 (55), 54 (7), 53 (33), 51 (7), 46 (10), 45 (7). HRMS: 199.1230 ($C_{10}H_{17}O_3N^{+\bullet}$, calcd 199.1208).

3.2.3. (1*S*,2*S*,6*R*,7*R*)-*N*,*N*-Diethyl-2-hydroxybicyclo[4.1.0]heptane-7-carboxamide 11b. A solution of Et_2NH (660 mg, 9.06 mmol) in dichloroethane (DCE, 2.0 mL) was added slowly, at 0°C to a suspension of $AlCl_3$ (630 mg, 4.72 mmol) in DCE (2.0 mL). After stirring the mixture for 30 min the cooling was stopped, and a solution of **9** (500 mg, 3.62 mmol) in DCE (1.0 mL) was added at once to the homogeneous solution. The mixture was stirred at rt for 1.5 h, and a white precipitate separated. H_2O (5.0 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with 1 M HCl (50 mL) and H_2O, then dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (SiO_2, pentane/AcOEt, 1:1) afforded **11b** as a colorless solid (745 mg, 97%), mp 58–60°C. $[\alpha]_D^{21} = -117.3$ ($c = 1.29$, $CHCl_3$). IR ($CHCl_3$): 3352mbr, 2999m, 1610s, 1484m, 1447m, 1265m, 1148w, 725w. ^{1}H NMR (500 MHz, $CDCl_3$): 0.71–0.79 (m, 1H); 0.87–0.97 (m, 1H); 0.99–1.06 (m, 1H); 1.07 (t, $J = 7.1$, 3H); 1.14 (t, $J = 7.2$, 3H); 1.33–1.39 (m, 1H); 1.44–1.57 (m, 2H); 1.67 (dd, $J = 9.5$, 8.9, 1H); 1.81–1.90 (m, 2H); 3.08 (dq, $J = 6.9$, 6.9, 1H); 3.25 (dq, $J = 7.2$, 7.2, 1H); 3.59 (dq, $J = 7.2$, 6.9, 1H); 3.67 (dq, $J = 7.2$, 6.9, 1H); 4.00–4.08 (m, 1H); 5.27 (d, $J = 11.3$, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.2 (q); 13.8 (q); 19.0 (d); 20.0 (t); 20.1 (d); 22.6 (t); 25.1(d); 31.8 (t); 39.9 (t); 42.3 (t); 66.7 (d); 170.1(s). MS: 211 ($M^{+\bullet}$, 10), 196 (8), 194 (7), 193 (27), 192 (12), 178 (5), 168 (23), 167 (31), 155 (5), 154 (47), 152 (25), 140 (5), 139 (9), 126 (13), 124 (5), 121 (10), 115 (35), 101 (5), 100 (86), 97 (5), 95 (9), 94 (7), 93 (20), 91 (10), 86 (6), 83 (7), 82 (6), 81 (24), 80 (5), 79 (12), 77 (11), 74 (15), 73 (15), 72 (86), 71 (6), 70 (7), 69 (7), 68 (5), 67 (13), 66 (5), 65 (5), 58 (100), 57 (7), 56 (13), 55 (32), 54 (5), 53 (19). HRMS: 211.1549 ($C_{12}H_{21}O_2N^{+\bullet}$, calcd: 211.1572).

3.2.4. (1*S*,2*R*,6*R*,7*R*)-*N*-Methoxy-*N*-methyl-2-phenylseleno bicyclo[4.1.0]heptane-7-carboxamide 12a. To a mixture of **11a** (166 mg, 0.83 mmol) and Bu_3P (337 mg, 1.67 mmol) in refluxing THF (3.5 mL) was added PhSeCN (303 mg, 1.67 mmol) in THF (1.0 mL) over 10 min. After heating under reflux for 14 h the volatiles were removed by evaporation in vacuo, and the residue was purified by FC (SiO_2, pentane/AcOEt, 4:1) to afford **12a** as a yellowish oil (248 mg, 88%). $[\alpha]_D^{21} = -12.9$ ($c = 2.94$, $CHCl_3$). IR ($CHCl_3$): 3015s, 2937s, 1651s, 1477m, 1437m, 1317w. ^{1}H NMR (500 MHz, $CDCl_3$, 50°C): 1.45–1.57 (m, 4H); 1.69 (dt, $J = 9$, 3, 1H); 1.81–1.88 (m, 2H); 1.89–1.99 (m, 2H); 3.19 (s, 3H); 3.66 (s, 3H); 3.87–3.89 (m, 1H); 7.22–7.26 (m, 3H); 7.56–7.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.6 (d); 18.4 (t); 20.6 (d); 20.7 (t); 23.4 (d); 29.4 (t); 32.8 (q); 35.4 (d); 61.2 (q); 127.0 (d); 128.9 (d); 130.4 (s); 134.0 (d); 171.8 (s). MS: 339 ($M^{+\bullet}$, 3), 337 ($M^{+\bullet}$, 1%), 334 (7), 183 (12), 182 (96), 178 (5), 177 (52), 160 (5), 159 (9), 158 (27), 157 (28), 156 (15), 155 (19), 154 (14), 153 (8), 152 (19), 151 (13), 150 (10), 123 (8), 122 (13), 121 (100), 117 (5), 116 (6), 95 (13), 94 (19), 93 (46), 92 (8), 91 (45), 88 (5), 81 (18), 80 (7), 79 (35), 78 (44), 77 (71), 74 (5), 73 (6), 69 (5), 68 (6), 67 (11), 66 (13), 65 (26), 62 (5), 60 (12), 59 (6), 58 (24), 57 (75), 56 (9), 55 (39), 53 (18), 52 (5), 51 (22), 50 (8). HRMS: 339.0750 and 337.0731 ($C_{16}H_{21}O_2N^{78}Se^{+\bullet}$, calcd 337.0730 and $C_{16}H_{21}O_2N^{80}Se^{+\bullet}$, calcd 339.0738).

3.2.5. (1*S*,2*R*,6*R*,7*R*-*N*,*N*-Diethyl-2-phenylseleno-bicyclo[4.1.0]heptane-7-carboxamide 12b. The procedure described for reaction of **11a** was applied to **11b** (1.60 g) and afforded **12b** as a yellow oil (2.17 g, 82%). $[\alpha]_D^{21} = -26.7$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3021m, 2400w, 1622w, 1522s, 1206s, 928w, 748s. ^{1}H NMR (500 MHz, $CDCl_3$): 1.10 (t, $J = 7.1$, 3H); 1.14 (t, $J = 7.1$, 3H); 1.20–1.29 (m, 1H); 1.36–1.42 (m, 1H); 1.43–1.59 (m, 4H); 1.71–1.81 (m, 2H); 1.83–1.91 (m, 1H); 3.29–3.45 (m, 4H); 3.95–3.99 (m, 1H); 7.25–7.28 (m, 3H); 7.58–7.61 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.2 (q); 14.0 (q); 15.1 (d); 19.5 (t); 20.4 (t); 21.4 (d); 22.2 (d); 29.1 (t); 36.3 (d); 39.2 (t); 41.5 (t); 127.0 (d); 128.9 (d); 130.3 (s); 133.9 (d); 169.2 (s). SM: 351 ($M^{+\bullet}$, 4), 349 ($M^{+\bullet}$, 2), 195 (20), 194 (100), 166 (12), 157 (5), 154 (6), 121 (15), 100 (69), 95 (5), 93 (13), 91 (11), 81 (7), 79 (15), 78 (8), 77 (19), 74 (9), 72 (56), 67 (5), 66 (5), 65 (6), 58 (7), 55 (9), 53 (6), 52 (8). HRMS: 349.1113 and 351.1086 ($C_{18}H_{25}ON^{78}Se^{+\bullet}$, calcd 349.1109 and $C_{18}H_{25}ON^{80}Se^{+\bullet}$, calcd 351.1101).

3.2.6. (1*S*,6*R*,7*R*)-*N*-Methoxy-*N*-methylbicyclo[4.1.0]-hept-2-ene-7-carboxamide 13a. To a solution of **12a** (85 mg, 0.25 mmol) and pyridine (0.040 mL) in CH_2Cl_2 (1.2 mL) was added 30% aqueous H_2O_2 (0.057 mL) and the mixture was stirred at rt for 10 min. THF (0.2 mL) was added, and stirring was continued for 30 min until all of **12a** was consumed. After addition of Et_2O (3.0 mL) the mixture was washed with 10% $Na_2S_2O_4$ (3.0 mL) followed by H_2O (2.0 mL), dried (Na_2SO_4), and evapo-

rated. The residue was purified by FC (SiO_2, pentane/AcOEt 1:1) to give **13a** as a colorless liquid (32 mg, 71%). $[\alpha]_D^{21}=+124.2$ ($c=1.20$, $CHCl_3$). IR ($CHCl_3$): 3016s, 2935w, 1650s, 1437m, 1213s. ^1H NMR (500 MHz, $CDCl_3$, 50°C): 1.59–1.69 (m, 2H); 1.83–1.90 (m, 1H); 1.97–2.06 (m, 3H); 2.17–2.23 (m, 1H); 3.18 (s, 3H); 3.71 (s, 3H); 5.70 (dt, $J=10.1$, 4.1, 1H); 5.83–5.87 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 15.8 (d); 16.5 (t); 16.9 (d); 21.9 (t); 25.9 (d); 33.1 (q); 60.9 (q); 122.1 (d); 128.2 (d); 171.2 (s). MS: 181 ($M^{+\bullet}$, 17), 150 (25), 121 (31), 120 (6), 103 (15), 94 (12), 93 (100), 92 (11), 91 (74), 89 (6), 81 (6), 79 (36), 78 (13), 77 (70), 73 (7), 67 (6), 66 (5), 65 (21), 63 (5), 61 (11), 58 (18), 55 (36), 53 (12), 52 (6), 51 (11). HRMS: 181.1098 ($C_{10}H_{15}O_2N^{+\bullet}$, calcd 181.1103).

3.2.7. (1*S*,6*R*,7*R*)-*N*,*N*-Diethyl-bicyclo[4.1.0]hept-2-ene-7-carboxamide 13b. To a solution of **12b** (115 mg, 3.28 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (15 mL) was added rapidly 30% H_2O_2 (0.75 mL) at rt after stirring the mixture for 5 min. THF (2.5 mL) was added, and stirring was continued for 30 min, when all of **12b** had reacted. Et_2O (35 mL) was added, and the solution was washed with 10% $Na_2S_2O_4$ (10 mL) and H_2O (10 mL), then dried (Na_2SO_4) and evaporated. FC of the residue (SiO_2, pentane/AcOEt, 1:1) gave **13b** as a colorless oil (49 mg, 77%). $[\alpha]_D^{21}=+48.8$ ($c=0.66$, $CHCl_3$). IR ($CHCl_3$): 3001m, 1623s, 1435m, 1263w, 1140w, 776m. ^1H NMR (500 MHz, $CDCl_3$): 1.06 (t, $J=7.1$, 3H); 1.17 (t, $J=7.1$, 3H); 1.58–1.62 (m, 2H); 1.75 (dd, $J=9.1$, 8.2, 1H); 1.78–1.97 (m, 3H); 2.17–2.24 (m, 1H); 3.24 (dq, $J=6.9$, 6.9, 1H); 3.39–3.49 (m, 2H); 3.58 (dq, $J=7.2$, 7.2, 1H); 5.63–5.68 (m, 1H); 5.90–5.95 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 12.8 (q); 13.9 (q); 15.1 (d); 17.0 (t); 17.2 (d); 21.9 (t); 27.3 (d); 39.1 (t); 41.7 (t); 123.0 (d); 127.1 (d); 169.4 (s). MS: 194 (10), 193 ($M^{+\bullet}$, 67), 192 (21), 178 (21), 164 (6), 152 (5), 126 (7), 124 (5), 121 (21), 120 (15), 119 (6), 115 (6), 101 (6), 100 (81), 94 (8), 93 (31), 92 (20), 91 (71), 87 (5), 86 (10), 84 (6), 82 (9), 81 (10), 80 (9), 79 (31), 78 (14), 77 (53), 74 (13), 73 (6), 72 (100), 70 (6), 68 (6), 67 (9), 66 (12), 65 (26), 63 (6), 58 (26), 56 (15), 55 (25), 54 (6), 53 (21), 52 (9), 51 (14). HRMS: 193.1461 ($C_{12}H_{19}ON^{+\bullet}$, calcd 193.1467).

3.2.8. (1*S*,6*R*,7*S*)-*N*,*N*-Diethyl-bicyclo[4.1.0]hept-2-ene-7-carboxamide 14. To the diethylamide **13b** (40 mg, 0.21 mmol) in THF (2.0 mL) was added, successively H_2O (7.5 μL, 0.41 mol) and *tert*-BuOK (186 mmol, 1.66 mmol). The mixture was stirred vigorously at rt for 2 h. It was acidified to pH 2–3, and was then extracted with AcOEt (3×10 mL). The combined organic phases were washed with H_2O (10 mL) and satd NaCl (10 mL), dried (Na_2SO_4) and evaporated. Purification of the residue by FC (SiO_2, pentane/AcOEt, 1:1) yielded **14** as a colorless oil (37 mg, 92%). $[\alpha]_D^{21}=+140.1$ ($c=2.03$, $CHCl_3$). IR ($CHCl_3$): 3006m, 1633s, 1445m, 1264w, 1135w, 757m. ^1H NMR (500 MHz, $CDCl_3$): 1.11 (t, $J=7.1$, 3H); 1.21 (t, $J=7.1$, 3H); 1.61–1.69 (m, 1H); 1.71–1.80 (m, 2H); 1.88–1.97 (m, 2H); 2.00–2.05 (m, 1H); 3.30–3.45 (m, 4H); 5.51–5.57 (m, 1H); 5.99–6.03 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.3 (q); 14.9 (q); 17.6 (t); 20.0 (d); 20.9 (t); 23.0 (d); 24.1 (d); 40.8 (t); 42.1 (t); 124.5 (d); 126.7 (d); 171.1 (s). MS: 193 ($M^{+\bullet}$, 77), 192 (25), 178 (23), 164 (16), 151 (15), 124 (7), 124 (12), 121 (25), 118 (6), 115 (8), 102 (7), 100 (82), 94 (18), 93 (36), 92 (20), 91 (73), 85 (15), 84 (6), 83 (9), 82 (13), 80 (9), 79 (34), 78 (15), 77 (55), 74 (13), 72 (9), 72 (100), 68 (16), 68 (11), 66 (12), 65 (25), 58 (26), 56 (25), 55 (15), 53 (21), 52 (9), 51 (14). HRMS: 193.1461 ($C_{12}H_{19}ON^{+\bullet}$, calcd 193.1467).

3.2.9. (1*S*,6*R*,7*R*)-Bicyclo[4.1.0]hept-2-ene-7-carboxylic acid 15. The amide **13a** (20 mg, 0.11 mmol) was heated under reflux with KOH (31 mg, 0.55 mmol) in H_2O (1.0 mL) for 4 h. The mixture was cooled to rt, then extracted with CH_2Cl_2 (3.0 mL). The aqueous layer was acidified with 1 M HCl and extracted with AcOEt (5×10 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford **15** as a colorless solid (14 mg, 92%), mp 83–85°C (from MeOH). $[\alpha]_D^{21}=+359.8$ ($c=0.57$, $CHCl_3$). IR ($CHCl_3$): 2933m, 1702s, 1441m, 1228m, 1115w, 896m, 705s. ^1H NMR (500 MHz, $CDCl_3$): 1.59–1.65 (m, 1H); 1.72 (dt, $J=8.5$, 3.7, 1H); 1.79 (dd, $J=8.9$, 8.2, 1H); 1.83–1.90 (m, 1H); 1.92–2.01 (m, 3H); 5.66–5.71 (m, 1H); 5.77–5.82 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 15.7 (t); 17.4 (d); 17.9 (d); 21.6 (t); 26.6 (d); 120.5 (d); 130.2 (d); 176.5 (s). MS: 138 ($M^{+\bullet}$, 48), 123 (5), 120 (10), 110 (9), 97 (18), 95 (6), 94 (9), 93 (100), 92 (26), 91 (86), 84 (13), 79 (44), 78 (23), 77 (76), 70 (5), 69 (6), 68 (5), 67 (11), 66 (35), 65 (27), 63 (9), 60 (40), 57 (9), 55 (12), 53 (17), 52(8), 51 (19), 50 (7), 45 (10). HRMS: 138.0685 ($C_8H_{10}O_2^{+\bullet}$, calcd 138.0681). (35), 65 (27), 63 (9), 60 (40), 57 (9), 55 (12), 53 (17), 52(8), 51 (19), 50 (7), 45 (10). HRMS: 138.0685 ($C_8H_{10}O_2^{+\bullet}$, calcd 138.0681).

3.2.10. (1*S*,6*R*,7*R*)-Bicyclo[4.1.0]hept-2-ene-7-carbonyl azide 8. To **15** (96 mg, 0.70 mmol) in toluene (7 mL) was added Et_3N (0.39 mL, 2.78 mmol) and $(PhO)_2PON_3$ (0.30 mL, 1.39 mmol) at 0°C. After stirring for 30 min at rt, the mixture was cooled to 0°C, and satd $NaHCO_3$ (2.0 mL) and Et_2O (4.0 mL) were added. The aqueous layer was separated and extracted with Et_2O (3×8 mL), the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (SiO_2, pentane/AcOEt, 4:1) gave **8** (84 mg, 76%) as light-yellow oil. $[\alpha]_D^{21}=+89.6$ ($c=0.317$, $CHCl_3$). IR ($CHCl_3$): 3024w, 2150m, 1689s, 1660s, 1220s, 740m. ^1H NMR (500 MHz, $CDCl_3$): 1.79 (dq, $J=7.9$, 2.8, 1H); 1.85 (dd, $J=8.5$, 8.5, 1H); 1.91–1.99 (m, 2H); 2.01–2.06 (m, 1H); 2.07–2.12 (m, 2H); 5.69–5.73 (m, 1H); 5.91–5.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 15.4 (t); 19.5 (d); 20.5 (d); 21.5 (t); 29.5 (d); 119.7 (d); 130.9 (d); 176.8 (s). MS: 163 ($M^{+\bullet}$, 1), 135 (26), 134 (39), 121 (15), 120 (38), 118 (7), 116 (5), 108 (7), 107 (62), 106 (41), 93 (27), 92 (41), 91 (84), 90 (9); 81 (5); 80 (31); 79 (100), 78 (24); 77 (66); 67 (9); 66 (15); 65 (31); 64 (5); 63 (12); 62 (5), 56 (7); 55 (9), 54 (12); 53 (27); 52 (51); 51 (36), 50 (17). HRMS: 163.0745 ($C_8H_9O_2N_3^{+\bullet}$, calcd 163.0743).

3.2.11. (1*S*,4*S*,5*R*)- and (1*S*,4*R*,5*R*)-4-Butoxy-3-aza-bicyclo[3.2.2]non-6-en-2-one 18. The azide **8** (80 mg, 0.49 mmol) and *n*-butanol (36 mg, 0.49 mmol) in toluene (6.0 mL) was heated under reflux for 15 min. The mixture was rapidly cooled with an ice-bath. The

solvent was evaporated in vacuo and the residue was purified by FC (SiO_2, pentane/AcOEt, 1:1) to afford **18** (71 mg, 65%) as a 60:40 mixture of diastereomers as a semi-solid, yellowish oil. IR ($CHCl_3$): 3390w, 2960m, 1675s, 1450m, 1080m, 970w. ^{1}H NMR (500 MHz, $CDCl_3$): 0.91 (t, $J=7.4$, 3H); 0.93 (t, $J=7.3$, 3H); 1.32–1.45 (m, 4H); 1.52–1.62 (m, 4H); 1.69–1.95 (m, 5H); 2.05–2.23 (m, 2H); 2.32–2.41 (m, 1H); 2.74–2.79 (m, 1H); 3.0–3.08 (m, 1H); 3.19–3.25 (m, 2H); 3.37–3.43 (m, 1H); 3.48–3.54 (m, 1H); 3.65 (dd, $J=6.6$, 6.6, 1H); 4.47–4.50 (m, 1H); 4.52–4.54 (m, 1H); 5.65 (s large, 1H); 5.83 (s large, 1H); 6.16–6.34 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.7 (q); 19.2 (t); 19.3 (t); 20.7 (t); 23.9 (t); 24.3 (t); 24.7 (t); 31.7 (t); 31.8 (t); 35.9 (d); 36.0 (d); 43.4 (d); 43.5 (d); 67.5 (t); 67.6 (t); 86.3 (d); 88.6 (d); 129.6 (d); 130.3 (d); 131.0 (d); 132.4 (d); 173.4 (s); 174.2 (s). MS: 209 ($M^{+\bullet}$, 1), 151 (5), 149 (23), 125 (6), 123 (6), 122 (5), 121 (5), 119 (8), 113 (5), 112 (5), 111 (10), 110 (9), 109 (36), 108 (8), 107 (5), 105 (13), 99 (6), 97 (14), 96 (10), 95 (23), 94 (8), 93 (7), 92 (8), 91 (21), 85 (18), 84 (12), 83 (21), 82 (11), 81 (39), 80 (100), 79 (80), 78 (11), 77 (28), 73 (7), 72 (7), 71 (37), 70 (12), 69 (26), 68 (24), 67 (18), 66 (8), 65 (9), 59 (6), 57 (51), 56 (79), 55 (46), 54 (8), 53 (18), 52 (11), 51 (17), 50 (9), 46 (8). SM-HR: 209.14150 ($C_{12}H_{19}O_2N^{+\bullet}$, calcd 209.14158).

3.2.12. (1*S*,5*R*)-3-Aza-bicyclo[3.2.2]non-6-en-2-one 7. To a solution of **18** (56 mg, 0.27 mmol and Et_3SiH (98 mg, 0.84 mmol) in CH_2Cl_2 (3.0 mL) was added CF_3COOH (0.2 mL) dropwise at rt. After the addition, the solution was stirred for 15 min, and then poured on a mixture of ice and satd $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×12 mL) and the organic phase was washed with satd NaCl (6.0 mL), dried (Na_2SO_4) and evaporated. Treatment of the residue with pentane (0.5 mL) afforded colorless crystals of **7** (28 mg, 76%), mp 127–130°C (from hexane). $[\alpha]_D^{21}=-234.5$ ($c=0.81$, $CHCl_3$) for 88% e.e. (HPLC: Chiracel OD-H; *n*-hexane: *i*-propanol = 10/1; 0.5 mL/min; T_1: 21.8 min (major enantiomer), T_2: 36.5 min GC: 85% e.e. (β-dex 120 to 130°; T_1: 60.5 min (major enantiomer), T_2: 74.9 min). IR ($CHCl_3$): 3630w, 3019w, 1651s, 1430w, 756s. ^{1}H NMR (500 MHz, $CDCl_3$): 1.68–1.77 (m, 2H); 1.84–1.90 (m, 1H); 2.15–2.21 (m, 1H); 2.56–2.62 (m, 1H); 3.03–3.07 (m, 1H); 3.24–3.27 (m, 2H); 5.40 (s large, 1H); 6.17–6.24 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 24.4 (t); 25.6 (t); 31.3 (d); 43.1 (d); 49.5 (t); 131.0 (d); 132.4 (d); 174.3 (s). MS: 137 ($M^{+\bullet}$, 16), 95 (7), 94 (22), 93 (9), 92(5), 91 (9), 81 (9), 80 (35), 79 (100), 78 (11), 77 (29), 69 (45), 66 (10), 65 (7), 57 (8), 55 (5), 54 (5), 53 (12), 52(8), 51 (40), 50 (19), 45 (58). HRMS: 137.0837 ($C_8H_{11}ON^{+\bullet}$, calcd 137.0841).

3.3. Synthesis of (1*S*,5*R*)-bicyclo[3.2.2]nona-3,6-dien-2-one 22

3.3.1. (1*S*,6*R*,7*R*)-Bicyclo[4.1.0]hept-2-ene-7-carboxaldehyde 19. DIBAL-H (1 M in THF, 3.80 mL, 3.78 mmol) was added dropwise to **13a** (343 mg, 3.78 mmol) in THF (23 mL) at −78°C. After stirring for 3 h at −78°C the solution was hydrolyzed with satd NH_4Cl. The aqueous phase was extracted with Et_2O (3×20 mL) and the organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (SiO_2, pentane/AcOEt, 4:1) to yield **19** as a colorless oil (187 mg, 81%). $[\alpha]_D^{21}=+143$ ($c=0.98$, $CHCl_3$). IR ($CHCl_3$): 2932m, 1721w, 1685s, 1129w, 702m. ^{1}H NMR (500 MHz, $CDCl_3$): 1.65–1.77 (m, 2H); 1.78–1.85 (m, 1H); 1.91–2.02 (m, 2H); 2.03–2.10 (m, 1H); 2.19–2.27 (m, 1H); 5.73–5.78 (m, 1H); 5.89–5.94 (m, 1H); 9.23 (d, $J=7.1$, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.8 (t); 19.7 (d); 22.6 (d); 22.8 (t); 34.9 (d); 122.3 (d); 127.7 (d); 203.3 (d). MS: 122 ($M^{+\bullet}$, 16), 104 (8), 103 (5), 93 (16), 92 (9), 91 (35), 80 (9), 79 (43), 78 (100), 77 (50), 66 (6), 65 (11), 53 (6), 52 (5), 51 (10). HRMS: 122.0731 ($C_8H_{10}O^{+\bullet}$, calcd 122.0732).

3.3.2. (*Z*/*E*)-(1*S*,6*R*,7*R*)-[2-(2-Bicyclo[4.1.0]hept-2-en-7-yl-vinyloxy)-ethyl]trimethylsilane 20a and 20b. A solution of KHMDS in toluene (5.8 mL, $c=0.5$ M, 2.89 mmol) was added dropwise to 2-(trimethylsilyl)-ethoxymethylenetriphenylphosphonium chloride (1.35 mg, 3.14 mmol) suspended in Et_2O (9.0 mL) at 0°C. The solution was stirred for 4–5 min at this temperature, after which the aldehyde **19** (187 mg, 1.53 mmol) in Et_2O (4.0 mL) was added. After stirring for 30 min at 0°C, then 1 h at rt, the mixture was hydrolyzed with satd NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3×20 mL), the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2, pentane/AcOEt, 9:1) to afford an unseparable 55:45 *Z*/*E* mixture of olefins **20** (214 mg, 60%). The pure (*Z*)-isomer **20a** was isolated by flash chromatography (see below) after partial rearrangement of the *Z*/*E* mixture at 100°C. Data: $[\alpha]_D^{21}=+78.1$ ($c=2.66$, $CHCl_3$) for 94% e.e. IR ($CHCl_3$): 2925m, 1654m, 1367m, 1075s, 862m. ^{1}H NMR (500 MHz, $CDCl_3$): 0.02 (s, 9H); 0.97–1.01 (m, 2H); 1.38–1.43 (m, 1H); 1.48–1.52 (m, 1H); 1.66–1.81 (m, 3H); 1.97–2.04 (m, 2H); 3.80–3.85 (m, 2H); 4.11 (dd, $J=9.15$, 6.3, 1H); 5.64–5.68 (m, 1H); 5.82–5.86 (m, 1H); 6.04 (dd, $J=6.3$, 0.95, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): −1.39 (q); 15.1 (d); 16.9 (t); 17.7 (d); 18.5 (t); 20.9 (d); 22.8 (t); 69.7 (t); 102.5 (d); 124.9 (d); 125.9 (d); 146.1 (d). MS: 236 ($M^{+\bullet}$, 0.5), 208 (15), 129 (5), 118 (15), 117 (18), 113 (11), 92 (7), 91 (7), 75 (12), 74 (11), 73 (100), 45 (6). HR-MS: 208.12990 ($C_{14}H_{24}OSi^{+\bullet}$–$C_2H_4$, calcd 208.12834).

Data for *E*-20: ^{1}H NMR (500 MHz, $CDCl_3$): 0.03 (s, 9H); 0.92–0.98 (m, 2H); 1.38–1.43 (m, 1H); 1.48–1.52 (m, 1H); 1.61 (q, $J=8.3$, 1H); 1.66–1.80 (m, 2H); 1.97–2.04 (m, 2H); 3.73 (dt, $J=$ 7.9, 1, 2H); 4.56 (dd, $J=12.6$, 8.15 (1H); 5.66–5.71 (m, 1H); 5.85–5.91 (m, 1H); 6.35 (d, $J=13$, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): −1.41 (q); 14.5 (d); 16.6 (t); 17.1 (d); 17.8 (t); 22.8 (t); 23.2 (d); 66.9 (t); 100.6 (d); 124.8 (d); 125.9 (d); 147.0 (d).

3.3.3.(1*S*,2*R*,5*R*)-[2-(Bicyclo[3.2.2]nona-3,6-dien-2-yloxy)-ethyl]-trimethyl-silane 21a. The *Z*/*E* mixture of **20a and 20b** (90 mg, 0.38 mmol) in anhydrous CCl_4 (2.0 mL) was heated to 100°C for 3 h. The solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, pentane/CH_2Cl_2, 9:1), then pentane (AcOEt, 9:1) to afford **21a** (36 mg, 40%). The *Z*-isomer

20a (46 mg; 51%) was recovered, characterized and transformed to **21a** upon heating to 190°C for 7 h in a sealed tube to afford **21a** in 49% yield (with respect to **20a**). Total yield with respect to **20a and 20b** 65%. Data: $[\alpha]_D^{21}=+82.9$ ($c=0.625$, $CHCl_3$). IR ($CHCl_3$): 2920w, 1630m, 1357m, 1080s, 834w. ^1H NMR (500 MHz, $CDCl_3$): 0.01 (s, 9H); 0.92–0.97 (m, 2H); 1.55–1.64 (m, 2H); 1.77–1.88 (m, 2H); 2.71–2.77 (m, 1H); 2.98–3.04 (m, 1H); 3.55 (q, $J=8.5$, 1H); 3.65 (q, $J=8.6$, 1H); 3.66–3.69 (m, 1H); 5.43 (ddd, $J=11.1$, 4, 3.5, 1H); 5.90 (dd, $J=8.1$, 7.3, 1H); 6.14 (ddd, $J=9.8$, 8.3, 1.3, 1H); 6.46 (dd, $J=8.3$, 7.8, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): −1.39 (q); 18.6 (t); 21.1 (t); 27.8 (t); 33.0 (d); 35.6 (d); 65.9 (t); 78.6 (d); 127.6 (d); 128.5 (d); 135.5 (d); 139.2 (d). MS: 236 ($M^{+\bullet}$, 1), 208 (9), 119 (7), 118 (14), 117 (16), 92 (7), 91 (14), 75 (11), 74 (9), 73 (100). HR-MS: 236.16000 ($C_{14}H_{24}OSi^{+\bullet}$, calcd 236.15964).

3.3.4. (1*S*,2*S*,5*R*)-Bicyclo[3.2.2]nona-3,6-dien-2-ol 21b and (1*S*,2*S*,5*R*)-2-ethoxybicyclo[3.2.2]nona-3,6-diene 21c. **Method A**: The silyl ether **21a** (50 mg, 0.21 mmol) and tetra-*n*-butylammonium fluoride (165 mg, 0.63 mmol) in HMPA (1.5 mL) was stirred at 100°C for 12 h in the presence of 4 Å molecular sieves. The mixture was treated with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (5×10 mL). The residue obtained after drying ($MgSO_4$) and evaporation was purified by flash chromatography (SiO_2, pentane/AcOEt, 9:1) to afford the alcohol **21b** (8.0 mg, 28%) and the ethyl ether **21c** (22 mg, 64%).

Data for 21b: colorless oil. $[\alpha]_D^{21}=+39.0$ ($c=0.96$, $CHCl_3$) for 94% e.e. IR: ($CHCl_3$): 3550wbr, 2990s, 1550w, 1221s, 990w, 790s. ^1H NMR (500 MHz, $CDCl_3$): 1.55–1.65 (m, 2H); 1.80–1.89 (m, 2H); 2.71–2.76 (m, 1H); 2.94–3.00 (m, 1H); 3.95–4.00 (m, 1H); 5.38–5.42 (m, 1H); 5.87–5.91 (m, 1H); 6.09–6.13 (m, 1H); 6.52–6.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$). 20.7 (t); 27.2 (t); 33.3 (d); 39.1 (d); 71.5 (d); 127.8 (d); 129.7 (d); 135.7 (d); 141.8 (d). MS: 136 ($M^{+\bullet}$, 7%), 117 (4), 107 (4), 100 (23), 91 (4), 79 (4). HRMS: 136.08700 ($C_9H_{12}O^{+\bullet}$, calcd 136.08882).

Data for 21c: colorless oil, $[\alpha]_D^{21}=+10.9$ ($c=0.4$, $CHCl_3$) for 94% e.e. IR ($CHCl_3$): 3017w, 1212m, 748m, 668w. ^1H NMR (500 MHz, $CDCl_3$): 1.18 (t, $J=6.95$, 3H); 1.55–1.61 (m, 2H); 1.75–1.86 (m, 2H); 2.69–2.74 (m, 1H); 2.98–3.04 (m, 1H); 3.49 (dq, $J=7$, 9.1, 1H); 3.60–3.68 (m, 2H); 5.38–5.42 (m, 1H); 5.88 (dd, $J=7.5$, 8.2, 1H); 6.10–6.15 (m, 1H); 6.44 (dd, $J=7.9$, 8.2, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), 15.8 (q); 21.0 (t); 27.8 (t); 33.1 (d); 35.5 (d); 64.2 (t); 78.9 (d); 127.6 (d); 128.4 (d); 135.8 (d); 139.3 (d). MS: 165 (10), 164 ($M^{+\bullet}$, 80), 139 (10), 136 (15); 135 (42), 120 (22), 118 (73), 117 (81), 110 (10), 107 (31), 103 (19), 92 (58), 91 (100), 95 (18), 80 (70), 78 (28), 67 (18), 65 (16), 57 (52), 55 (25). HR-MS: 164.12053 ($C_{11}H_{16}O^{+\bullet}$, calcd 164.12012).

Method B: A solution of the silyl ether **21a** (50 mg, 0.21 mmol) in anhydrous HMPA (1.0 mL) was added to a mixture of CsF (510 mg, 3.36 mmol) in anhydrous HMPA (0.5 mL). The mixture was stirred at 140°C for 30 h. After cooling, the mixture was poured into H_2O (3.0 mL) and extracted with Et_2O (5×10 mL). The organic layer was washed with saturated NaCl (3.0 mL), dried ($MgSO_4$, and evaporated. The residue was purified by flash chromatography (SiO_2, pentane/AcOEt, 9:1) to afford **21c** (25 mg, 89%).

3.3.5. (1S,5*R*)-Bicyclo[3.2.2]nona-3,6-dien-2-one 22. To a solution of **21b** (20 mg, 0.15 mmol) in anhydrous DMF (1.0 mL) was added PDC (138 mg, 0.37 mmol). The mixture was stirred for 1 h at rt then diluted with H_2O (5.0 mL) and extracted with Et_2O (5×10 mL). The combined organic layers were washed with satd NaCl, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (SiO_2, pentane/AcOEt, 9:1) to afford the ketone **22** as a colorless oil (17 mg, 86%). $[\alpha]_D^{21}=-99.8$ ($c=0.50$, $CHCl_3$) for 94% e.e. (HPLC, Chiracel OD-H, hexane/2-propanol, 25:1, 0.5 mL/min, T_1: 13.3 min (major enantiomer), T_2: 15.1 min). IR ($CHCl_3$): 3001w, 1660s, 1218w, 1160w, 794m, 674s. ^1H NMR (500 MHz, $CDCl_3$): 1.68–1.76 (m, 1H); 1.81–1.87 (m, 1H); 1.91–1.99 (m, 2H); 3.31–3.36 (m, 1H); 3.48–3.53 (m, 1H); 5.75 (dd, $J=11$, 2, 1H); 6.04 (dd, $J=7.9$, 7.9, 1H); 6.51 (dd, $J=7.9$, 7.9, 1H); 6.7.04 (dd, $J=11$, 8.6, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 21.2 (t); 26.9 (t); 37.0 (d); 52.3 (d); 126.6 (d); 129.9 (d); 138.6 (d); 153.4 (d); 198.6 (s). MS: 134 ($M^{+\bullet}$, 35%), 133 (17), 119 (5), 116 (9), 115 (7), 106 (11), 105 (40), 103 (9), 93 (6), 92 (62), 91 (100), 80 (14), 79 (62), 78 (90), 77 (44), 66 (7), 65 (16), 63 (5), 57 (8), 56 (5), 55 (22), 53 (14), 52 (22), 51 (21). HRMS: 134.07474 ($C_9H_{10}O^{+\bullet}$, calcd 134.07317).

3.3.6. (1*S*,2*S*,5*R*)-Bicyclo[3.2.2]nona-3,6-dien-2yl [(1*S*)-3-oxo-4,7,7-trimethyl-2-oxybicyclo[2.2.1]heptene-1]-carboxylate 23. (−)-Camphanic acid chloride (56 mg, 0.26 mmol) was added at 0°C to **21b** (27 mg, 0.20 mmol) in dry pyridine (2.0 mL). After 2 h of stirring at rt, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, pentane/AcOEt, 9:1) to afford **23** as a colorless solid (52 mg, 83%), mp 107–109°C (from hexane/CH_2Cl_2), $[\alpha]_D^{21}=+125.9$ ($c=0.49$, $CHCl_3$). IR ($CHCl_3$): 2948w, 1780s, 1730s, 1450w, 1261m, 1170w, 1112m, 1055s, 913m. ^1H NMR (500 MHz, $CDCl_3$): 0.93 (s, 3H); 1.02 (s, 3H); 1.08 (s, 3H); 1.55–1.75 (m, 3H); 1.80–1.90 (m, 3H); 1.95–2.05 (m, 1H); 2.33–2.41 (m, 1H); 2.78–2.84 (m, 1H); 2.93–2.99 (m, 1H); 5.29–5.35 (m, 2H); 5.86 (dd, $J=7.9$, 7.9, 1H); 6.24 (dd, $J=9.5$, 8.5, 1H); 6.45 (dd, $J=7.9$, 7.9, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 9.7 (q); 16.7 (q); 16.9 (q); 20.8 (t); 27.2 (t); 29.0 (t); 30.4 (t); 32.9 (d); 35.9 (d); 54.0 (s); 54.7 (s); 74.2 (d); 91.2 (s); 124.7 (d); 127.8 (d); 138.4 (d); 139.8 (d); 166.7 (s); 178.2 (s) MS: 316 ($M^{+\bullet}$, 6%), 182 (7); 180 (8); 179 (7), 171 (6); 167 (11); 165 (5); 164 (8); 155 (8); 153 (7); 149 (15); 139 (6); 137 (10); 136 (24); 135 (24); 125 (30); 124 (31); 121 (5); 119 (22); 118 (71); 117 (22); 116 (5); 111 (8); 110 (5); 109 (42); 108 (7); 107 (15); 97 (40); 96 (7); 95 (9); 93 (13); 92 (14); 91 (69); 85 (7); 84 (9); 83 (100); 82 (11); 81 (10); 79 (13); 78 (5); 77 (7), 71 (10); 70 (6); 69 (19); 68 (5); 67 (17); 65 (14); 57 (25); 56 (10); 55 (71); 53 (6); 45 (19). HRMS: 316.16971 ($C_{19}H_{24}O_4^{+\bullet}$, calcd 316.16746).

3.4. X-Ray crystal structure of 23

$C_{19}H_{24}O_4$; $M_r = 316.4$; $\mu = 0.09$ mm^{-1}, $d_x = 1.267$ g cm^{-3}, monoclinic, $P2_1$, $Z = 2$, $a = 6.7858(6)$, $b = 10.6555(10)$, $c = 11.4752(13)$ Å, $\beta = 91.865(12)°$, $V = 829.3(1)$ Å^3; cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer. Full-matrix least-squares refinement based on F using weight of $1/(\sigma^2(F_o) + 0.0002(F_o^2))$ gave final values $R = \omega R = 0.029$ and $S = 1.50(4)$ for 252 variables and 2081 contributing reflections.

Crystallographic data (excluding structure factors) for **23** have been deposited at the Cambridge Crystallographic Data Base as supplementary material, publication number CCDC 179658. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. +44 (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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