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Simple synthetic protocol for the preparation of enantiomeric 3-oxabicyclo[3.3.0]oct-6-en-2-ones

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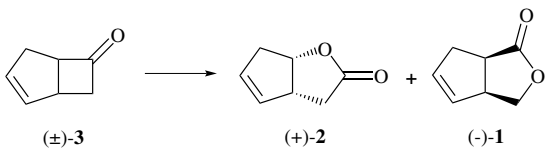
Abstract—Diastereomeric amides produced via the decomposition of easily available (±)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one by treatment with (+)- or (−)-α-methylbenzylamines were transformed into bicyclic lactam-aminals, which can easily be separated using the column chromatography on SiO_2. The latter products lead to enantiomeric 3-oxabicyclo[3.3.0]oct-6-en-2-ones after the removal of the chiral auxiliary.

1. Introduction

Functionalized chiral cyclopentenes are widely used as key starting compounds for the synthesis of cyclopentenone antibiotics,[1] prostaglandins,[2] carbanucleosides,[3] amongst others.[4,5] Enantiomers of lactone **1** are the isomers of lactone **2**; these compounds are used in the classic syntheses of prostaglandins, according to Tömösközi[6] via the Corey lactone.[7] Elaboration of **1** as a possible building block seemed to be an interesting synthetic undertaking.

The synthesis and use of racemic lactone **1** was described by Hudlicky[8] and Wang.[9] Later, Furstoss worked out a more convenient synthesis of racemic lactone **1**,[10,11] as well as its (−)-enantiomer, applying a microbial Bayer–Villiger oxidation of bicyclo [3.2.0]hept-6-en-2-one **3** (Scheme 1).[10] Chiral lactones (−)-(1*R*,5*S*)-**1** and (+)-(1*S*,5*R*)-**2** were obtained in 37% and 40% yields, respectively, by this approach. It should be noted that, in contrast to lactone **2**, chiral (−)-**1** was used only in the synthesis of Marine Brown Algae (Multifidenes, Viridiene, Caudoxirene) pheromones.[11] Compound (+)-**1** had not been described earlier, probably, owing to the very strict stereoselectivity of Bayer–Villiger microbiologic oxidation of bicyclic ketone **3**, which leads only to (−)-**1**.



(±)-**3** (+)-**2** (-)-**1**

Scheme 1.

Herein, we report a simple and practical synthetic protocol for the preparation of both enantiomers of lactone **1**, using easily available [2+2]-adduct of dichloroketene and cyclopentadiene **4** and (+)- or (−)-α-methylbenzylamines as the starting material.

2. Results and discussion

Adduct **4** and related compounds (Scheme 2) is attractive because its strained dichlorocyclobutane cycle may be the cleavage by treatment with a host of different nucleophiles.[12,13] As expected, both enantiomers of α-methylbenzylamines cleaved **4** to give diastereomeric amides **5a** and **5b** and **6a** and **6b** in high yields, according to Scheme 2. The crystallization of the diastereomeric mixtures of **5** and **6** from benzene gave one of the individual isomers in 10–15% yield in each case. However, the given method of the separation was not effective and was abandoned.

The next important problem was the hydrolysis of *gem*-dichloromethyl group in amides **5** and **6**. Treatment of these compounds with $AgNO_3$ in boiling H_2O–CH_3CN solution led to the slow transformation of **5** and **6** to bicyclic lactam-aminals **7a** and **7b** and **8a** and **8b** (Scheme 3). It

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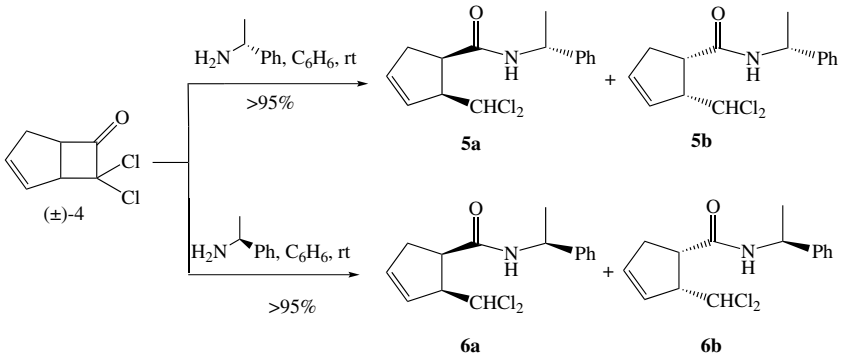
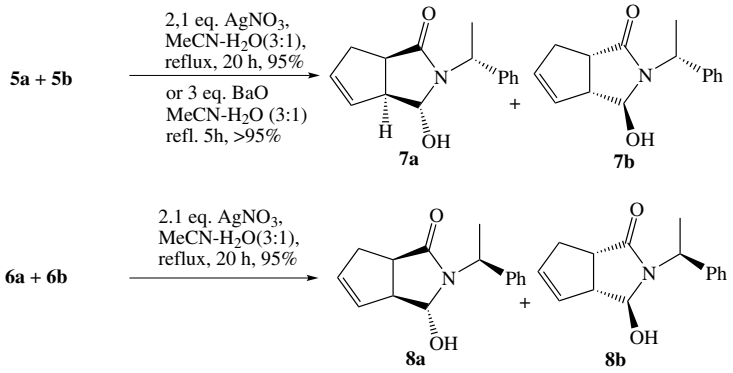


Scheme 2.



Scheme 3.

was also possible to substitute $AgNO_3$ with inexpensive BaO.

Diastereoisomers **7a/7b** or **8a/8b** could be easily separated by column chromatography on SiO_2 without practically any loss. Each of these bicyclic acetals was stereochemically pure and did not contain any C3-epimer admixture. Compounds **7a**, **7b**, **8a** and **8b** were characterized as the less hindered *exo*-epimers. Thus, in the ^1H NMR spectrum a doublet resonance of the 3-H at 5.12 ppm appeared with $J_{3,3a} = 3$ Hz, which is characteristic for **7b**. Naturally, the pairs of amides **7a** and **8a**, as well as **7b** and **8b** can be combined before the isolation of the corresponding lactones, because after removal of the chiral auxiliary compound (α-methylbenzylamine), the same lactone enantiomers would be released.

Thus, there was no need to work with both enantiomers of α-methylbenzylamine. The separation of (±)-dichloroderivatives of **5** and **6** by crystallization would require both enantiomers of the chiral auxiliary, but in the case of diastereomeric **7** or **8**, chromatography on SiO_2 was sufficient enough to bring about complete separation. From this point on, only (+)-α-methylbenzylamine was used.

The hydrolytic cleavage of amides **7** and **8** was found to be a problem. Under the standard conditions of acidic and alkali hydrolysis, the amides were highly stable. Only after the borohydride reduction of **7a** (Scheme 4) in dioxane/water at reflux was amidoalcohol **9a** produced. Its treatment with acid furnished the target structure (−)-(1*R*,5*S*)-**1**. It should be noted that during the reduction with sodium borohydride, the partial isomerization and formation of the minor *trans*-amidoalcohol **10a** (~3–5%) was observed. However, at the stage of the acidic hydrolysis, **10a** was re-epimerized to (−)-(1*R*,5*S*)-**1** while the formation of the expected *trans*-acid **11** from **10a** was not observed.[14] Analogous transformations from **7b** led to (+)-(1*R*,5*S*)-**1**.

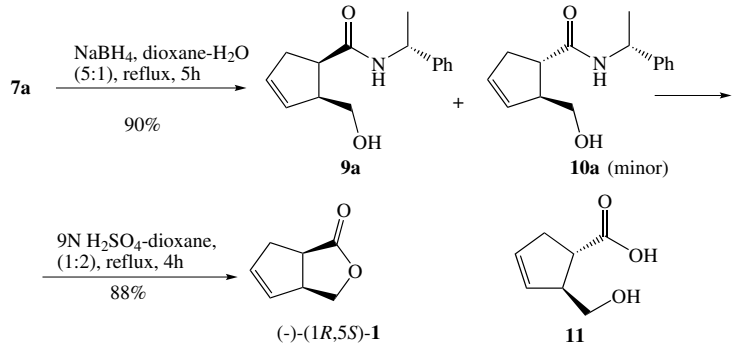
3. Conclusion

The easily available [2+2]-adducts of cyclopentadiene and dichloroketene as well as the commercially available and inexpensive (+)- and (−)-α-methylbenzylamines were used to develop a practical and scalable method for the preparation of both enantiomers of lactone **1**.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use. Reagents were generally of the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. Dichloroacetyl chloride was prepared as described in the literature (bp 107–108 °C).[15] Cyclopentadiene was obtained by the thermal cracking of



Scheme 4.

dicyclopentadiene. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 precoated foil plates. Column chromatography was carried out using 210–280 mesh silica gel. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer, Model 241 MC polarimeter at 20 C. IR (infrared spectra) were recorded on a Shimadzu IRPrestige-21 spectrometer as nujol mull or as neat thin films on KBr plates (film) and were reported in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^1H and 75.47 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Chemical shifts are reported in δ unit-parts per million (ppm) downfield from tetramethyl silane (TMS) as the internal reference. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet, t, triplet; q, quartet; quint., quintet. Mass spectra were recorded on Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer. Melting points were recorded on a Mel-Temp apparatus and are uncorrected.

4.2. General protocol for (±)-7-dichlorobicyclo[3.2.0]hept-2-en-6-ones 4

To a flame-dried, nitrogen-purged flask were added hexane (400 mL), cyclopentadiene (53 g, 0.8 mol) and dichloroacetyl chloride (60 g, 0.4 mol). Triethylamine (53 g, 0.8 mol) in hexane (300 mL) was added via syringe and allowed to stir for 15 h at room temperature. The triethylammonium hydrochloride salt was removed by filtration through a short pad of Celite and washed with hexane (2 × 50 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by distillation to furnish **4** (55.23 g, 78%) as a yellow oil, bp 49–50 °C/0.3 mmHg.

4.2.1. (±)-7-Dichlorobicyclo[3.2.0]hept-2-en-6-ones 4. Yield 78%; bp 49–50 °C/0.3 mmHg; IR (film) 1805, 1028, 887, 814, 797, 754, 731, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 2.48–2.88 (m, 2H, 4-H), 4.04–4.22 (m, 1H, 5-H), 4.32–4.42 (m, 1H, 1-H), 5.78–5.90 (m, 1H, 3-H), 6.03–6.17 (m, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 35.21 (C4), 58.60 (C1), 59.53 (C5), 88.18 (C7), 128.41 (C3), 136.88 (C2), 197.79 (C6). MS (APCI), *m*/*z* (%): 177 [MH^+, ^{35}Cl] (100), 149 (13.3). Anal. Calcd for $C_7H_6OCl_2$: C, 47.46; H, 3.38; Cl, 40.11. Found: C, 47.23; H, 3.09; Cl, 39.96.

4.3. General protocol for 2-(dichloromethyl)-*N*-[(1*R*)-1-phenylethyl]cyclopent-3-ene-1-carboxamides 5

To a stirred solution of **4** in benzene (40 mL) at room temperature under nitrogen was added dropwise a solution of (+)-[(1*R*)-1-phenylethyl]amine (1.09 g, 9 mmol) in benzene (10 mL). The reaction was monitored by TLC (3:7 ethyl acetate–petroleum ether) and after stirring 3–3.5 h at rt, the solution was filtered to remove **5b** (300 mg, 11.9%) as a white solid, and the residue on the filter was washed with two 10-mL portions of hexane. The filtrate was concentrated under reduced pressure, and the residue was diluted with CH_2Cl_2 (50 mL) and washed with water, 5% aqueous solution HCl, water and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded an unseparable 4/3 mixture of carboxamides **5a** and **5b** (2.1 g, 83.1%) as a yellow solid, mp 114–122 °C; $[\alpha]_D^{20} = +108$ (*c* 0.75, CH_3OH).

4.3.1. (1*S*,2*R*)-(Dichloromethyl)-*N*-[(1*R*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 5b. Yield 11.9%; mp 139–140 °C; $[\alpha]_D^{20} = +69$ (*c* 0.5, CH_3OH); IR (nujol mull) 3312, 2951, 2853, 1922, 1635, 1618, 1548, 1456, 1446, 1392, 1375, 1240, 752, 709, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 1.51 (d, $J = 6.8$ Hz, 3H, CH_3), 2.53–2.73 (m, 2H, 5-H), 3.14 (q, $J = 7.7$, 8.3 Hz, 1H, 1-H), 3.61–3.75 (m, 1H, 2-H), 5.12 (quint., $J = 7.1$ Hz, 1H, CH–Ph), 5.78–5.94 (m, 2H, 4-H and N–H), 5.95–6.05 (m, 1H, 3-H), 6.31 (d, $J = 7.1$ Hz, 1H, $CHCl_2$), 7.18–7.48 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 21.29 (CH_3), 36.49 (C5), 46.65 (C1), 48.70 (CHPh), 58.95 (C2), 74.33 ($CHCl_2$), 126.13, 127.40, 128.65 (Ph), 128.89 (C4), 133.37 (C3), 142.8 (Ph), 171.07 (C=O). MS (APCI), *m*/*z* (%): 298 [MH^+, ^{35}Cl] (100), 149 (12.5). Anal. Calcd for $C_{15}H_{17}Cl_2NO$: C, 60.40; H, 5.70; N, 4.70; Cl, 23.83. Found: C, 60.32; H, 5.55; N, 4.69; Cl, 23.54.

4.4. 2-(Dichloromethyl)-*N*-[(1*S*)-1-phenylethyl]cyclopent-3-ene-1-carboxamides 6

These compounds were synthesized following a procedure similar to the one described above for the preparation of

5. To a stirred solution of **4** (1.0 g, 5.7 mmol) in benzene (27 mL) was added dropwise a solution (−)-[(1*S*)-1-phenylethyl]amine (0.72 g, 5.95 mmol) in benzene (7 mL). The reaction mixture gave **6a** (210 mg, 12.5%) as a white crystalline residue on the filter. Removal of the solvent under reduced pressure afforded an inseparable 3/4 mixture of carboxamides **6a** and **6b** (1.39 g, 82.5%) as a yellow solid, mp 114–122 °C; $[\alpha]_D^{20} = -110$ (*c* 1.0, CH_3OH).

4.4.1. (1*R*,2*S*)-(Dichloromethyl)-*N*-[(1*S*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 6a. Yield 11.9%; mp = 139–140 °C. $[\alpha]_D^{20} = -70$ (*c* 1.0, CH_3OH); IR (nujol mull) 3314, 2953, 2853, 1636, 1618, 1548, 1458, 1449, 1392, 1375, 1240, 754, 710, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 1.52 (d, $J = 6.9$ Hz, 3H, CH_3), 2.54–2.72 (m, 2H, 5-H), 3.16 (q, $J = 7.8$, 8.2 Hz, 1H, 1-H), 3.64–3.74 (m, 1H, 2-H), 5.15 (quint., $J = 7.1$ Hz, 1H, CH–Ph), 5.72–5.86 (m, 1H, N–H), 5.99–6.07 (m, 1H, 4-H), 5.99–6.07 (m, 1H, 3-H), 6.33 (d, $J = 7.1$ Hz, 1H, $CHCl_2$), 7.23–7.41 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 21.28 (CH_3), 36.49 (C5), 46.67 (C1), 48.69 (CHPh), 58.95 (C2), 74.33 ($CHCl_2$), 126.13, 127.40, 128.68 (Ph), 128.91 (C4), 133.37 (C3), 142.50 (Ph), 171.07 (C=O). MS (APCI), *m*/*z* (%): 298 [MH^+, ^{35}Cl] (100), 149 (14.7). Anal. Calcd for $C_{15}H_{17}Cl_2NO$: C, 60.40; H, 5.70; N, 4.70; Cl, 23.83. Found: C, 60.35; H, 5.52; N, 4.67; Cl, 23.64.

4.5. General protocol for (3a,6a)-3-hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[*c*]pyrrol-1(2*H*)-ones 7

Method A: To a stirred solution of 1/1 mixture of **5a** and **5b** (2.7 g, 9 mmol) in CH_3CN (40 mL) at room temperature was added a solution of $AgNO_3$ (3.21 g, 19 mol) in H_2O (14 mL). After being stirred at room temperature for 0.5 h, the reaction solution was refluxed for 20 h, monitored by TLC (1:1 ethyl acetate–petroleum ether), cooled to room temperature and concentrated under vacuum. The residue was diluted with water (15 mL) and extracted with 3 × 20 mL ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification of the products by column chromatography (3:7 ethyl acetate–petroleum ether) afforded **7a** (1.04 g, 47%) as a yellow crystalline solid and **7b** (1.06 g, 48%) as a white crystalline solid.

Method B: To a stirred solution of a 1/1 mixture of **5a** and **5b** (1.0 g, 3.33 mmol) in CH_3CN (20 mL) at room temperature was added a solution of BaO (100 mg, 0.65 mmol) in H_2O (5 mL). After being stirred at room temperature for 0.5 h, the reaction solution was refluxed for 8 h, monitored by TLC (1:1 ethyl acetate–petroleum ether), cooled to room temperature and concentrated under vacuum. The residue was diluted with water (10 mL) and extracted with 3 × 15 mL ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification of the products by column chromatography (3:7 ethyl acetate–petroleum ether) afforded **7a** (377 mg, 46%) as a white crystalline solid and **7b** (385 mg, 47%) as a yellow crystalline solid.

4.5.1. (3a*S*,6a*R*)-3*R*-Hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclo-penta[*c*]pyrrol-1(2H)-one 7a. Yield 47%; mp = 105–107 °C; $[\alpha]_D^{20} = +142.4$ (*c* 0.65, CH_3OH); IR (nujol mull) 3232, 2922, 2852, 1647, 1456, 1327, 1290, 1215, 1058, 802, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 1.68 (d, $J = 6.8$ Hz, 3H, CH_3), 2.54–2.84 (m, 2H, 6-H), 3.21–3.33 (m, 1H, 3a-H), 3.39 (t, $J = 9.08$ Hz, 1H, 6a-H), 3.73–4.03 (br s, 1H, OH), 4.63–4.73 (br s, 1H, 3-H), 5.34 (q, $J = 7.1$ Hz, 1H, CH–Ph), 5.35–5.49 (m, 1H, 5-H), 5.72–5.84 (m, 1H, 4-H), 7.13–7.35 (m, 5H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 18.66 (CH_3), 35.70 (C6), 42.83 (C6a), 49.96 (CHPh), 54.17 (C3a), 84.83 (C3), 127.316, 127.43, 128.40 (Ph), 128.61 (C5), 132.30 (C4), 139.79 (Ph), 177.27 (C=O). MS (APCI), *m*/*z* (%): 244 [MH^+] (100), 226 (43), 198 (33.3), 177 (16.7), 161 (15), 121 (11.7), 93 (16.7), 65 (8.3). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 6.99; N, 5.76. Found: C, 73.78; H, 6.76; N, 5.25.

4.5.2. (3a*R*,6a*S*)-3*S*-Hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclo-penta[*c*]pyrrol-1(2*H*)-one 7b. Yield 48%; mp = 120–121 °C; $[\alpha]_D^{20} = +37.8$ (*c* 0.8, CH_3OH). IR (nujol mull) 3244, 2922, 2852, 1651, 1616, 1456, 1336, 1303, 1273, 1222, 1058, 805, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 1.56 (d, $J = 5.7$ Hz, 3H, CH_3), 2.15–2.35 (br s, 1H, OH), 2.54–2.84 (m, 2H, 6-H), 3.13–3.22 (m, 1H, 3a-H), 3.23 (t, $J = 7.08$ Hz, 1H, 6a-H), 5.11 (d, $J = 3.0$ Hz, 1H, 3-H), 5.35 (q, $J = 7.1$ Hz, 1H, CH–Ph), 5.59–5.67 (m, 1H, 5-H), 5.75–5.85 (m, 1H, 4-H), 7.20–7.54 (m, 5H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 17.05 (CH_3), 35.64 (C6), 42.85 (C6a), 49.94 (CHPh), 53.32 (C3a), 84.38 (C3), 126.96, 127.23, 128.07 (Ph), 128.73 (C5), 132.65 (C4), 141.21 (Ph), 177.35 (C=O). MS (APCI), *m*/*z* (%): 244 [MH^+] (100), 226 (39), 198 (35.3), 177 (13.7), 161 (18.1), 121 (12.8), 93 (13.2), 65 (9.3). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 6.99; N, 5.76. Found: C, 73.97; H, 6.63; N, 5.35.

4.6. General protocol for 2-(hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]cyclopent-3-ene-1-carboxamides 9a and 10a

To a suspension of sodium borohydride (130 mg, 3.4 mmol) in a water/dioxane mixture (1 mL/2 mL) was added a solution of **7a** in 3 mL of dioxane. The mixture was heated at reflux for 5 h and monitored by TLC (1:1 ethyl acetate–petroleum ether). The excess hydride was decomposed by the successive addition of 1 mL of water, 1.5 mL of 15% sodium hydroxide and 3 mL of water; the suspension was filtered. The filtrate was extracted with 3 × 10 mL methylene chloride. The combined methylene chloride extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification of the product by column chromatography (1:1 ethyl acetate–petroleum ether) afforded an inseparable ~95/5 mixture of epimers **9a** and **10a** (77 mg, 90%) as a white crystalline solid.

4.6.1. (1*R*,2*S*)-2-(Hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 9a. Yield 90%; mp = 115–117 °C; $[\alpha]_D^{20} = +168.5$ (*c* 0.425, CH_3OH); IR (nujol mull) 3261, 2951, 2922, 2852, 1639, 1556, 1454, 1375, 1232, 1056, 759, 748, 698 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$/TMS): δ 1.53 (d, $J = 9.0$ Hz, 3H, CH_3), 2.45–2.50 (m, 1H, 5-H), 2.70–2.80 (m, 1H, 5-H), 2.95–3.03 (m, 1H, 2-H), 3.05 (t, $J = 9.0$ Hz, 1H, 1-H), 3.41–3.61 (m, 3H, OH and CH_2–O), 5.18 (quint., $J = 7.5$, 6.0 Hz, 1H, CH–Ph), 5.55–5.61 (m, 1H, 4-H), 5.86–5.92 (m, 1H, 3-H), 6.04–6.12 (m, 1H, N–H), 7.62–7.78 (m, 5H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 21.64 (CH_3), 36.79 (C5), 47.49 (C1), 49.08 (CHPh), 51.35 (C2), 62.62 (CH_2O), 126.16, 127.45, 128.70 (Ph), 130.49 (C4), 131.21 (C3), 143.05 (Ph), 174.59 (C=O). MS (APCI), *m*/*z* (%): 246 [MH^+] (100), 228 (91.3). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.15; H, 7.67; N, 5.49.

4.6.2. (1*S*,2*S*)-2-(Hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 10a. ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 23.34 (CH_3), 35.10 (C5), 48.05 (C1), 51.02 (CHPh), 53.51 (C2), 67.52 (CH_2O), 126.01, 127.11, 128.58 (Ph), 128.97 (C4), 131.30 (C3), 144.01 (Ph), 174.23 (C=O).

4.7. General protocol for 2-(hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]cyclopent-3-ene-1-carboxamides 9b and 10b

Compound **7b** (130 mg, 0.54 mmol) was treated with sodium borohydride as described in the synthesis of **9a** and **10a**, and afforded an inseparable ~95/5 mixture of epimers **9b** and **10b** (116 mg, 89%) as a white crystalline solid.

4.7.1. (1*S*,2*R*)-2-(Hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 9b. Yield 89%; mp = 132–134 °C; $[\alpha]_D^{20} = -1.8$ (*c* 1.05, CH_3OH); IR (nujol mull) 3313, 2945, 2852, 1643, 1531, 1454, 1375, 1276, 1037, 764, 704, 547 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.55 (d, $J = 9.0$ Hz, 3H, CH_3), 2.44–2.50 (m, 1H, 5-H), 2.70–2.85 (m, 1H, 5-H), 2.98–3.10 (t, $J = 6.0$ Hz, 2H, 2-H and 1-H), 3.53–3.73 (m, 3H, OH and CH_2–O), 5.19 (quint., $J = 7.5$, 6.0 Hz, 1H, CH–Ph), 5.58–5.65 (m, 1H, 4-H), 5.85–5.92 (m, 1H, 3-H), 6.01–6.12 (m, 1H, N–H), 7.27–7.43 (m, 5H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 21.28 (CH_3), 36.64 (C5), 47.48 (C1), 49.07 (CHPh), 51.29 (C2), 62.61 (CH_2O), 126.08, 127.43, 128.53 (Ph), 130.40 (C4), 131.14 (C3), 142.77 (Ph), 174.40 (C=O). MS (APCI), *m*/*z* (%): 246 [MH^+] (100), 228 (96.5). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 72.85; H, 7.56; N, 5.49.

4.7.2. (1*R*,2*R*)-2-(Hydroxymethyl)-*N*-[(1*R*)-1-phenylethyl]-cyclopent-3-ene-1-carboxamide 10b. ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 23.12 (CH_3), 36.64 (C5), 48.31 (C1), 48.81 (CHPh), 52.97 (C2), 66.51 (CH_2O), 125.98, 127.09, 128.70 (Ph), 128.91 (C4), 131.26 (C3), 144.11 (Ph), 174.23 (C=O).

4.8. General protocol for (−)-(1*R*,5*S*)-3-oxabicyclo[3.3.0]-oct-6-en-2-one 1

To a stirred solution of an ~95/5 mixture of **9a** and **10a** (98 mg, 0.4 mmol) in dioxane (2 mL) at room temperature was added a 9 N solution of H_2SO_4 (1 mL). The mixture was heated at reflux for 3 h and monitored by TLC (1:1 ethyl acetate–petroleum ether), cooled to room temperature and concentrated under vacuum. The residue was diluted with water (4 mL) and extracted with 3 × 7mL ether. The combined ether extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification of the products by column chromatography (1:1 ethyl acetate–petroleum ether) afforded (−)-(1*R*,5*S*)-**1** (43 mg, 88%) as a yellow oil.

4.8.1. (−)-(1*R*,5*S*)-3-Oxabicyclo[3.3.0]oct-6-en-2-one 1. Yield 88%; $[\alpha]_D^{20} = -68.0$ (*c* 0.93, CH_3Cl) (lit.[10] $[\alpha]_D^{20} = -67.9$ (*c* 2.3, CH_3Cl)); IR (film) 3058, 2920, 2858, 1762, 1446, 1377, 1173, 1142, 1053, 996, 935, 789, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 2.67–2.86 (m, 2H, 8-H), 3.10–3.18 (td, $J = 2.36$, 7.76 Hz, 1H, 1-H), 3.54–3.65 (m, 1H, 5-H), 4.24 (d, $J = 9.23$ Hz, 1H, 4-H), 4.44 (ddd, $J = 2.08$, 8.30 Hz, 1H, 4-H), 5.63–5.69 (m, 1H, 7-H), 5.85–5.90 (m, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 36.39 (C8), 41.53 (C1), 46.30 (C5), 71.98 (C4), 130.52 (C7), 132.20 (C6), 180.81 (C2). MS (APCI), *m*/*z* (%): 125 [MH^+] (100), 108 (1.8), 97 (9.1). Anal. Calcd for $C_7H_8O_2$: C, 67.74; H, 6.45. Found: C, 67.54; H, 6.10.

4.9. General protocol for (+)-(1*S*,5*R*)-3-oxabicyclo[3.3.0]-oct-6-en-2-one 1

The ~95/5 mixture of **9b** and **10b** (70 mg, 0.31 mmol), treated as described in the synthesis of **(−)-(1*R*, 5*S*)-1**, afforded (+)-(1*S*,5*R*)-**1** (31 mg, 89%) as a yellow oil.

4.9.1. (+)-(1*S*,5*R*)-3-Oxabicyclo[3.3.0]oct-6-en-2-one 1. Yield 89%; $[\alpha]_D^{20} = +67.4$ (*c* 0.92, CH_3Cl); IR (film) 3059, 2920, 2858, 1763, 1446, 1377, 1174, 1141, 1053, 995, 935, 789, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 2.67–2.86 (m, 2H, 8-H), 3.10–3.18 (td, $J = 2.36$, 7.76 Hz, 1H, 1-H), 3.54–3.65 (m, 1H, 5-H), 4.24 (d, $J = 9.23$ Hz, 1H, 4-H), 4.44 (ddd, $J = 2.08$, 8.30 Hz, 1H, 4-H), 5.63–5.69 (m, 1H, 7-H), 5.84–5.91 (m, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): δ 36.48 (C8), 41.62 (C1), 46.37 (C5), 71.98 (C4), 130.53 (C7), 132.37 (C6), 180.84 (C2). MS (APCI), *m*/*z* (%): 125 [MH^+] (100), 108 (1.5), 97 (8.7). Anal. Calcd for $C_7H_8O_2$: C, 67.74; H, 6.45. Found: C, 67.49; H, 6.19.

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