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Diastereoselective Synthesis of Enantioenriched, Annulated Tetrahydrofurans by Simultaneous Formation of the O-1–C-5 and the C-5–C-4 Bonds

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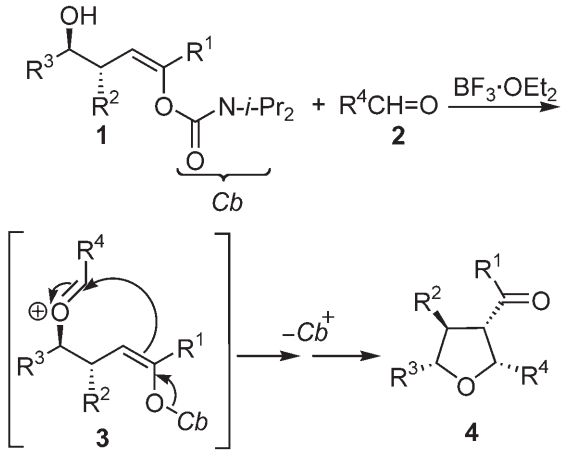
Abstract: Enantiomerically enriched 1-[2-(1-hydroxyalkyl)cycloalkylidene]methyl *N*,*N*-diisopropylcarbamates, which are easily available by an asymmetric homoaldol reaction, condense with aldehydes under the influence of boron trifluoride etherate to form cyclohexano- or cyclopentano-annulated tetrahydrofuran-3-carboxaldehydes, bearing two quaternary carbon atoms and four adjacent stereogenic centers, with complete diastereoselectivity.

Keywords: diastereoselective synthesis; enantioenriched tetrahydrofurans; α,β-enediolate synthons; enol carbamates; Mukaiyama reaction; oxabicyclic compounds

Introduction

Tetrahydrofurans are substructures of numerous natural products,[1] and a great variety of methods for their synthesis exists.[2] In 1989 we published a highly efficient and surprisingly simple general method for the synthesis of monocyclic stereohomogeneous, 2,3,4,5-tetrasubstituted tetrahydrofurans **4** (Scheme 1),[3] from homoaldol products[1,4] **1** and aldehydes **2**. The assumed decisive intermediate is the (*E*)-oxonium ion **3**, which is formed under the influence of the strong Lewis acid BF_3; it undergoes an intramolecular Mukaiyama-type[5] addition of the enolic moiety onto the former carbonyl carbon atom from the least hindered conformation. Subsequently, the carbamoyl group is extruded. The reaction is also applicable to ketals[1] and for intramolecular condensations.[3b] Some mechanistically related syntheses were published later.[6]



Scheme 1. Synthesis of tetrasubstituted tetrahydrofurans.

By applying these methods we expected to realise a synthesis of tetrahydrofurans **10** by formal combination of the dianion **C** with two different aldehydes **A** and **B** (Figure 1).

We now report the realization of the above-mentioned pathway to provide a synthesis of highly substituted bicyclic tetrahydrofurans.

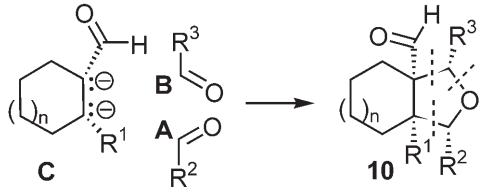
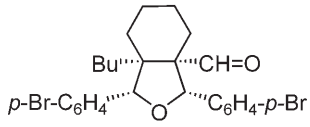
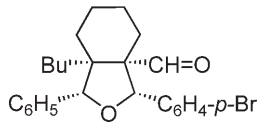
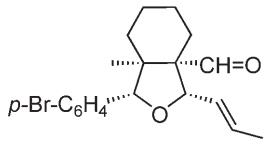
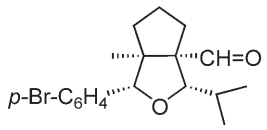


Figure 1. Formation of the bicycles **10** in a highly regio- and stereoselective manner.

Table 1. Diastereomerically pure bicyclic tetrahydrofurans **10**.

Starting materials **7** ee [%][a]	Product **10**	Yield [%]	ee [%][b]	Alcohol **11** (yield, %)	*p*-Nitrobenzoate **12** (yield, %)
7a [76]	 **10a**	55	[78]	**11a** (70)	**12a** (79)
7b [78]	 **10b**	54	[81]	**11b** (72)	**12b** (81)
7c [86]	 **10c**	62	[91]	**11c** (73)	**12c** (84)
7d [93]	 **10d**	63	[96]	**11d** (74)	**12d** (85)

[a] Enantiomeric excess was determined by ^{1}H NMR shift experiments.[7c]
[b] Enantiomeric excess was determined by chiral HPLC.

Results and Discussion

We recently observed that the carbanionic species, obtained by (−)-sparteine-mediated deprotonation of 1-(2-alkylcycloalk-1-enyl)methyl carbamates of type **5** exhibit considerable configurational stability and, hence, can be converted efficiently to optically active homoaldol products **7** with up to 96% ee (Scheme 2).[7] The condensation of **7** with aromatic or aliphatic aldehydes[8] or 2-alkenals in the presence of 1 equivalent of boron trifluoride etherate at 0 °C or 20 °C proceeds smoothly and, after aqueous work-up, diastereomerically pure tetrahydrofurans **10** can be isolated (Table 1). Further diastereomers could not be detected by ^{1}H NMR. The enantiomeric ratios of aldehydes **10a, b**, and **d** were determined by chiral HPLC; the analysis of **10c** was carried out at the stage of ester **12c**. The ee values, as expected, correspond well with those of the starting homoaldol products **7**. For safe assignments, the racemates *rac*-**10** and *rac*-**12** were synthesised from *rac*-**7** and analysed (see Experimental Section). The high diastereoselectivity origins from the (*E*)-oxonium intermediate **8**, being highly favoured over the (*Z*) diastereomer due to allylic 1,3-strain,[9] which combines with the enolic double bond with high selectivity from the less shielded upper face and leads to a *cis*-annulation.

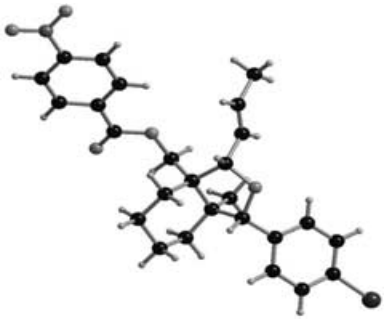
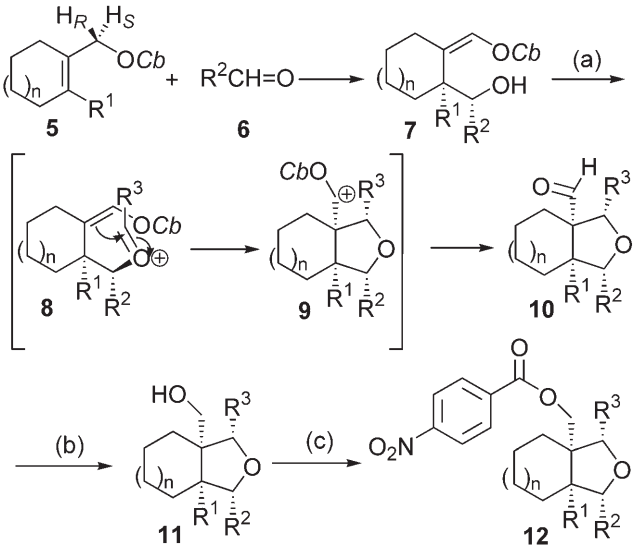


Figure 2. Solid-state structure of **12c**.[10]

For the sake of obtaining shelf-stable products, the aldehydes **10** were reduced by $LiAlH_4$ to produce the alcohols **11** (Table 1) and these converted to *p*-nitrobenzoates **12** in order to enhance the chance for crystalline compounds. Fortunately, ester **12c** gave suitable crystals for an X-ray analysis, applying anomalous dispersion; it proves the assumed relative and absolute configurations (Figure 2).[10]

Conclusion

Overall, the allyl carbamate **5** was successfully applied as a chiral 1-formylcycloalkane 2,3-dianion **C** which as-



7	n	R^1	R^2	R^3-CH=O
A	1	Bu	4-BrC_6H_4	4-BrC_6H_4CH=O
B	1	Bu	C_6H_5	4-BrC_6H_4CH=O
C	1	Me	4-BrC_6H_4	(*E*)-CH_3CH=CH-CH=O
D	0	Me	4-BrC_6H_4	$(CH_3)_2$CH-CH=O

Scheme 2. Synthesis of diastereomerically pure tetrahydrofurans **10**.

sembles two different or equal aldehydes **A** and **B** to form the bicyclic species **10** in a highly regio- and stereoselective manner (see Figure 1). The expected relative and absolute configurations of compounds were **10** established vigorously by X-ray analysis. The configuration of all four consecutive stereogenic centres in **10** arises, directly or indirectly, from the chiral induction in the (−)-sparteine-mediated deprotonation step.

Experimental Section

General Remarks

All reactions, which are sensitive to moisture or air, were carried out under Ar using septum and syringe techniques. All solvents were purified by distillation or dried (Et_2O, CH_2Cl_2) prior to use. Flash chromatography was carried out with silica gel (40–63 μm) using an Ar pressure of 1.2–1.4 bar. Chiral HPLC was carried out with a chiral column chiragrom-1 and chiragrom-2, 60 × 2 mm, purchased from Grom Analytic and HPLC GmbH, Herrenberg. The solvent systems used for the measurement were hexane:*i*-PrOH (100:1) and (200:1). ^1H and ^{13}C NMR spectra were recorded on ARX 300 and AMX 400 Bruker spectrometers. 2D NMR experiments were carried out on a Varian Unity Plus 600. $CDCl_3$ was used as solvent for normal NMR measurements, IR absorption spectra were recorded using an IFS 28 purchased from Bruker and a PE 298 purchased from Perkin-Elmer & Co GmbH, Überlingen. The melting point was measured on an SMP3 melting point apparatus purchased from Stuart Scientific, UK. The optical rotations were measured in a 10-cm cuvette on a polarimeter 241 purchased from Perkin-Elmer & Co GmbH, Überlingen. Elemental analysis were performed at the Microanalytical Section of the Organisch-Chemisches Institut, WWU Münster, on a Vario El III purchased from Elementar Analysen Systeme GmbH. Exact mass measurements were carried out on Micro Tof (Bruer Daltronics, Bremen), calibrations were done directly before the measurements of samples with sodium formate clusters.

General Procedure for Synthesis of Aldehydes 10 (GP1)

To a cooled (0 °C) solution of **7** (0.50 mmol) and aldehyde $R^3CH=O$ in CH_2Cl_2 (5 mL) under an argon atmosphere, $BF_3 \cdot OEt_2$ (0.60 mmol) was added in small portions with a syringe. After stirring the reaction mixture for a period of 1 h at 0 °C and 30 min at 20 °C, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined ether solutions were dried with $MgSO_4$ and concentrated under vacuum. The crude residue was purified by silica gel flash chromatography (petroleum ether: Et_2O = 4:1). Correct microanalyses were obtained at the stage of corresponding *p*-nitrobenzoates **12**.

(1S,6S,7R,9S)-7,9-Di(4-bromophenyl)-6-butyl-8-oxabicyclo[4.3.0]nonane-1-carboxaldehyde (**10a**): According to GP1, **10a** was obtained from allyl carbamate **7a** (240 mg, 0.50 mmol) and *p*-bromobenzaldehyde (111 mg, 0.60 mmol) as a colourless oil; yield: 143 mg (55%); R_F = 0.71 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −82.1 (*c* = 0.61, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 78% ee, major enantiomer appears at higher retention time.

rac-**10a** was obtained from allyl carbamate *rac*-**7a** (240 mg, 0.50 mmol) and *p*-bromobenzaldehyde (111 mg, 0.60 mmol) as a colourless oil; yield: 137 mg (53%); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, 3H, CH_3), 1.13–2.16 (m, 14H, CH_2), 4.57 (s, 1H, CH), 5.03 (s, 1H, CH), 7.08–7.49 (m, 8H, CH), 9.54 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 20.8 (CH_2), 21.9 (CH_2), 23.0 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 28.6 (CH_2), 30.4 (CH_2), 46.9 (C_q), 61.9 (C_q), 80.8 (CH), 84.8 (CH), 100.9/124.2/125.2/126.3/126.8/127.3/128.0/130.7 (CH and C_q of aryl carbons), 206.4 (C=O); IR (film): ν = 2958, 2951, 2853 (C_{aliph}-H), 1700 cm^{-1} (C=O).

(1S,6S,7R,9S)-9-(4-Bromophenyl)-6-butyl-7-phenyl-8-oxabicyclo[4.3.0]nonane-1-carboxaldehyde (**10b**): According to GP1, **10b** was obtained from allyl carbamate **7b** (193 mg, 0.50 mmol) and *p*-bromobenzaldehyde (111 mg, 0.60 mmol) as a colourless oil; yield: 119 mg (54%); R_F = 0.70 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −59.3 (*c* 0.61, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, e.r. = 91.5:9.5 (81% ee), major enantiomer appears at lower retention time.

rac-**10b** was obtained from allyl carbamate *rac*-**7b** (193 mg, 0.5 mmol) and *p*-bromobenzaldehyde (111 mg, 0.6 mmol) as a colourless oil; yield: 121 mg (55%); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H, CH_3), 1.13–1.86 (m, 14H, CH_2), 4.56 (s, 1H, CH), 5.02 (s, 1H, CH), 7.11–7.46 (m, 9H, CH), 9.53 (s,

1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (CH_3), 20.4 (CH_2), 21.4 (CH_2), 23.3 (CH_2), 28.6 (CH_2), 30.0 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 46.5 (C_q), 60.9 (C_q), 79.8 (CH), 83.8 (CH), 110.9/124.2/125.2/126.3/127.2/128.0/130.7 (CH and C_q of aryl carbons), 206.1 (C=O); IR (film): ν = 2958, 2916, 2860 (C_{aliph}-H), 1721 cm^{-1} (C=O).

*(1S,6S,7R,9S)-7-(4-Bromophenyl)-6-methyl-9-[(*E*)-prop-1-enyl]-8-oxabicyclo[4.3.0]nonane-1-carboxaldehyde* (**10c**): According to GP1, **10c** was obtained from allyl carbamate **7c** (123 mg, 0.28 mmol) and (*E*)-2-butenal (28 mg, 0.40 mmol) as a colourless oil; yield: 63 mg (62%); R_F = 0.70 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −94.2 (*c* 0.50, $CHCl_3$). Chiral HPLC: chiragrom-1, hexane:*i*-PrOH = 200:1, 91% ee, major enantiomer appears at higher retention time.

rac-**10c** was obtained from allyl carbamate **7c** (123 mg, 0.28 mmol) and (*E*)-2-butenal (28 mg, 0.40 mmol) as a colourless oil; yield: 66 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 3H, CH_3), 1.33–2.16 (m, 11H, CH_2 and CH_3), 4.45 (d, 1H, CH), 4.97 (s, 1H, CH), 5.55 (m, 1H, CH), 5.81 (m, 1H, CH), 7.18 (m, 2H, CH), 7.39 (m, 2H, CH), 9.64 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (CH_3), 19.8 (CH_3), 21.2 (CH_2), 21.4 (CH_2), 26.8 (CH_2), 36.1 (CH_2), 47.7 (C_q), 61.2 (C_q), 85.2 (CH), 86.8 (CH), 121.6 (C_q), 127.3 (CH), 127.8 (CH), 131.3 (CH), 132.2 (CH), 138.4 (C_q), 203.3 (C=O); IR (film): ν = 2958, 2920, 2853 (C_{aliph}-H), 1719 cm^{-1} (C=O).

(1S,2S,4R,5S)-4-(4-Bromophenyl)-5-methyl-2-(1-methylethyl)-3-oxabicyclo[3.3.0]octane-1-carboxaldehyde (**10d**): According to GP1, **10d** was obtained from allyl carbamate **7d** (106 mg, 0.25 mmol) and 2-methylpropanal (29 mg, 0.40 mmol) as a colourless oil; yield: 55 mg (63%); R_F = 0.71 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −119.1 (*c* 0.51, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 96% ee, major enantiomer appears at lower retention time.

rac-**10d** was obtained from allyl carbamate *rac*-**7d** (106 mg, 0.25 mmol) and 2-methylpropanal (29 mg, 0.40 mmol) as a colourless oil; yield: 54 mg (61%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.02 (d, 6H, CH_3), 1.35–2.19 (m, 6H, CH_2), 2.15 (m, 1H, CH), 4.14 (d, *J* = 6.5 Hz, 1H, CH), 4.43 (s, 1H, CH), 7.14 (m, 2H, CH), 7.34 (m, 2H, CH), 9.59 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (CH_3), 19.5 (CH_3), 19.6 (CH_3), 21.2 (CH_2), 21.5 (CH_2), 23.6 (CH_2), 27.3 (CH), 47.7 (C_q), 61.5 (C_q), 75.5 (CH), 86.3 (CH), 121.4 (C_q), 131.4 (CH), 132.5 (CH), 138.9 (C_q), 203.5 (C=O); IR (film): ν = 2958, 2951, 2853 (C_{aliph}-H), 1721 cm^{-1} (C=O).

General Procedure for Synthesis of Alcohols 11 (GP2)

To a solution of aldehyde **10** (0.25 mmol) in Et_2O (5 mL), $LiAlH_4$ (1 M solution in Et_2O; 0.25 mmol) was added in small portions at 0 °C. After stirring at 0 °C for 30 min and subsequently, at room temperature for 3 h, Et_2O (20 mL) and a saturated aqueous solution of NH_4Cl (10 mL) were added. The aqueous phase was extracted (Et_2O, 2 × 20 mL), the combined solutions were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel flash column chromatography (petroleum ether:Et_2O = 4:1).

(1R,6S,7R,9S)-{7,9-Di(4-bromophenyl)-6-butyl-8-oxabicyclo[4.3.0]non-1-yl}-methanol (**11a**): According to GP2, **11a** was obtained from **10a** (130 mg, 0.25 mmol) as a colourless oil; yield: 91 mg (70%); R_F = 0.18 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −36.5 (*c* 0.65, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 78% ee, major enantiomer appears at higher retention time.

rac-**11a** was obtained from **10a** (130 mg, 0.25 mmol) as a colourless oil; yield: 94 mg (72%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.16–1.86 (m, 14H, CH_2), 3.54 (d, 1H, *J* = 11.7 Hz, CH), 3.69 (d, *J* = 11.6 Hz, 1H, CH), 4.54 (s, 1H, CH), 4.58 (s, 1H, CH), 7.12–7.40 (m, 8H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0 (CH_3), 20.4 (CH_2), 21.8 (CH_2), 23.7 (CH_2), 28.5 (CH_2), 30.3 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 46.8 (C_q), 49.4 (C_q), 63.9 (CH_2), 79.6 (CH), 83.8 (CH), 111.5/124.4/125.8/126.6/127.3/128.2/130.4/130.5 (CH and C_q of aryl carbons); IR (film): ν = 3370 (OH), 2958, 2930, 2867 cm^{-1} (C_{aliph}-H).

(1R,6S,7R,9S)-{9-(4-Bromophenyl)-6-butyl-7-phenyl-8-oxabicyclo[4.3.0]non-1-yl}methanol (**11b**): According to GP2, **11b** was obtained from **10b** (110 mg, 0.25 mmol) as a colourless oil; yield: 80 mg (72%); R_F = 0.18 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: +30.1 (*c* 0.48, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 81% ee, major enantiomer appears at higher retention time.

rac-**11b** was obtained from **10b** (110 mg, 0.25 mmol) as a colourless oil; yield: 77 mg (70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.14–1.86 (m, 14H, CH_2), 3.58 (d, 1H, *J* = 11.7 Hz, CH), 3.71 (d, *J* = 11.8 Hz, 1H, CH), 4.84 (s, 1H, CH), 4.99 (s, 1H, CH), 7.11–7.28 (m, 9H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 (CH_3), 21.2 (CH_2), 21.9 (CH_2), 23.8 (CH_2), 26.2 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 33.5 (CH_2), 45.4 (C_q), 49.9 (C_q), 64.6 (CH_2), 79.9 (CH), 83.6 (CH), 111.9/124.4/125.7/126.3/127.2/127.6/128.9/130.5 (CH and C_q of aryl carbons); IR (film): ν = 3426 (OH), 2979, 2923, 2853 cm^{-1} (C_{aliph}-H).

*(1R,6S,7R,9S)-{7-(4-Bromophenyl)-6-methyl-9-[(*E*)-prop-1-enyl]-8-oxabicyclo[4.3.0]non-1-yl}methanol* (**11c**): According to GP2, **11c** was obtained from **10c** (61 mg, 0.17 mmol) as a colourless oil; yield: 45 mg (73%); R_F = 0.16 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −80.0 (*c* 0.25, $CHCl_3$). Chiral HPLC: chiragrom-1, hexane:*i*-PrOH = 200:1, 91% ee, major enantiomer appears at higher retention time.

rac-**11c** was obtained from **10c** (61 mg, 0.17 mmol) as a colourless oil; yield: 45 mg (74%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.40 (s, 3H, CH_3), 1.16–2.26 (m, 11H, CH_2 and CH_3), 3.56 (d, 1H, *J* = 11.7 Hz, CH), 3.73 (d, *J* = 11.7 Hz, 1H, CH), 4.06 (m, 1H, CH), 4.55 (s, 1H, CH), 5.77 (m, 2H, CH), 7.11 (m, 2H, CH), 7.38 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (CH_3), 19.8 (CH_3), 21.8 (CH_2), 21.9 (CH_2), 30.5 (CH_2), 32.1 (CH_2), 45.6 (C_q), 50.5 (C_q), 64.3 (CH_2), 83.0 (CH), 88.5 (CH), 120.8 (C_q), 128.2/128.4/129.9/130.7/131.3/131.5 (CH and C_q), 138.0 (C_q); IR (film): ν = 3372 (OH), 2956, 2932, 2869 cm^{-1} (C_{aliph}-H).

(1R,2S,4R,5S)-{4-(4-Bromophenyl)-5-methyl-2-(1-methylethyl)-3-oxabicyclo[3.3.0]oct-1-yl}methanol (**11d**): According to GP2, **11d** was obtained from **10d** (50 mg, 0.14 mmol) as a colourless oil; yield: 37 mg (74%); R_F = 0.16 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −42.7 (*c* 0.55, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 96% ee, major enantiomer appears at lower retention time.

rac-**11d** was obtained from **10d** (50 mg, 0.14 mmol) as a colourless oil; yield: 38 mg (75%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.43 (s, 3H, CH_3), 1.04 (d, 6H, CH_3), 1.33–2.16 (m, 6H, CH_2), 2.10 (m, 1H, CH), 3.53 (d, *J* = 11.7 Hz, 1H, CH), 3.75 (d, *J* = 1.7 Hz, 1H, CH), 4.13 (d, 1H, CH), 4.46 (s, 1H, CH), 7.13–7.42 (m, 4H, CH); ^{13}C NMR (75 MHz, $CDCl_3$); δ = 17.4

(CH_3), 19.8 (CH_3), 21.3 (CH_2), 21.6 (CH_2), 32.8 (CH_2), 27.7 (CH), 47.5 (C_q), 61.6 (C_q), 64.7 (CH_2), 73.1 (CH), 88.7 (CH), 128.3 (C_q), 129.6 (CH), 131.3 (CH), 138.2 (C_q); IR (film): ν = 3372 (OH), 2954, 2931, 2864 cm^{-1} (C_{aliph}-H); anal. calcd. for $C_{18}H_{25}O_2Br$ (352.29): C 61.19, H 7.13; found: C 61.44, H 7.35.

General Procedure for *p*-Nitrobenzoates 12 (GP3)

A solution of alcohol **11** (0.20 mmol), *p*-nitrobenzoyl chloride (0.30 mmol) and DMAP (0.08 mmol) in CH_2Cl_2 (5 mL) was stirred for 15 h at room temperature. Aqueous saturated solution of $NaHCO_3$ (10 mL) and Et_2O (20 mL) were added, the phases separated and the aqueous phase extracted twice with Et_2O (20 mL, each). The combined organic extracts were concentrated under vacuum and the residue purified by flash column chromatography on silica gel (petroleum ether: Et_2O = 4:1).

*(1*R*,6*S*,7*R*,9*S*)-{7,9-Di(4-bromophenyl)-6-butyl-8-oxabicyclo[4.3.0]non-1-yl}methyl 4-Nitrobenzoate* (**12a**): According to GP3, **12a** was obtained from **11a** (90 mg, 0.17 mmol) as a colourless solid; yield: 91 mg (79%); R_F = 0.30 (petroleum ether: Et_2O = 4:1); $[\alpha]_D^{20}$: −41.1 (*c* 0.59, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 78% ee, major enantiomer appears at lower retention time.

rac-**12a** was obtained from **11a** (90 mg, 0.17 mmol) as a colourless solid; yield: 94 mg (81%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3H, CH_3), 1.16–1.64 (m, 14H, CH_2), 3.66 (d, *J* = 11.5 Hz, 1H, CH), 3.72 (d, *J* = 11.6 Hz, 1H, CH), 4.34 (s, 1H, CH), 5.19 (s, 1H, CH), 7.19–7.36 (m, 8H, CH), 8.13–8.24 (m, 4H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 21.0 (CH_2), 21.6 (CH_2), 26.2 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 30.8 (CH_2), 31.5 (CH_2), 52.3 (C_q), 56.6 (C_q), 64.8 (CH_2), 80.3 (CH), 83.2 (CH), 121.5/123.7/125.6/126.2/127.2/127.6/129.4/130.9/130.7/131.8/132.3/135.7 (CH and C_q of aryl carbons), 166.0 (C=O); IR (KBr): ν = 3021, 2958, 2853 (C_{aliph}-H), 1703 cm^{-1} (C=O); anal. calcd. for $C_{32}H_{33}Br_2NO_5$ (671.42): C 57.24, H 4.95, N 2.09; found: C 57.52, H 4.80, N 2.19.

*(1*R*,6*S*,7*R*,9*S*)-{9-(4-Bromophenyl)-6-butyl-7-phenyl-8-oxabicyclo[4.3.0]non-1-yl}methyl 4-Nitrobenzoate* (**12b**): According to GP3, **12b** was obtained from **11b** (75 mg, 0.17 mmol) as a colourless oil; yield: 81 mg (81%); R_F = 0.30 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −72.2 (*c* 0.52, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 81% ee, major enantiomer appears at higher retention time.

rac-**12b** was obtained from **11b** (75 mg, 0.17 mmol) as a colourless oil; yield: 80 mg (80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, 3H, CH_3), 1.16–1.66 (m, 14H, CH_2), 3.53 (d, *J* = 11.6 Hz, 1H, CH), 3.72 (d, *J* = 11.7 Hz, 1H, CH), 4.98 (s, 1H, CH), 5.11 (s, 1H, CH), 7.11–7.28 (m, 9H, CH), 8.12–8.27 (m, 4H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 21.0 (CH_2), 21.8 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 32.0 (CH_2), 52.1 (C_q), 56.4 (C_q), 64.8 (CH_2), 80.6 (CH), 83.8 (CH), 122.2/123.4/124.5/125.9/126.8/127.9/129.2/130.4/130.6/131.5/132.4/135.6, (CH and C_q of aryl carbons), 166.0 (C=O); IR (KBr): ν = 3014, 2951, 2853 (C_{aliph}-H), 1707 cm^{-1} (C=O); anal. calcd. for $C_{32}H_{34}NO_5Br$ (592.52): C 64.87, H 5.78, N 2.36; found: C 64.60, H 5.56, N 2.31.

*(1*R*,6*S*,7*R*,9*S*)-{7-(4-Bromophenyl)-6-methyl-9-[(*E*)-propenyl]-8-oxabicyclo[4.3.0]non-1-yl}methyl 4-Nitrobenzoate* (**12c**): According to GP3, **12c** was obtained from **11c** (40 mg, 0.11 mmol) as a colourless solid; yield: 47 mg (84%); R_F = 0.30 (petroleum ether:Et_2O = 4:1), mp 214.5 °C (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −62.2 (*c* 0.59, $CHCl_3$). Chiral HPLC: chiragrom-2, hexane:*i*-PrOH = 200:1, 91% ee, major enantiomer appears at higher retention time.

rac-***12c*** was obtained from **11c** (40 mg, 0.11 mmol) as a colourless solid; yield: 48 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.53 (s, 3H, CH_3), 1.06–2.15 (m, 11H, CH_2 and CH_3), 3.52 (d, *J* = 11.5 Hz, 1H, CH), 3.72 (d, *J* = 11.5 Hz, 1H, CH), 4.10 (m, 1H, CH), 4.58 (s, 1H, CH), 5.78 (m, 1H, CH), 5.58 (m, 1H, CH), 7.11 (m, 2H, CH), 7.39 (m, 2H, CH), 8.13 (m, 2H, CH), 8.24 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_3), 20.2 (CH_3), 21.8 (CH_2), 22.12 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 46.1 (C_q), 49.1 (C_q), 64.6 (CH_2), 83.3 (CH), 88.2 (CH), 121.5 (C_q), 123.7 (CH), 128.4 (CH), 129.6 (CH), 130.3 (CH), 130.6 (CH), 131.0 (CH), 135.5 (C_q), 137.8 (C_q), 150.7 (C_q), 164.5 (C=O); IR (KBr): ν = 3024, 2954, 2857 (C_{aliph}-H), 1708 cm^{-1} (C=O); anal. calcd. for $C_{26}H_{28}BrNO_5$ (514.41): C 60.71, H 5.49, N 2.72; found: C 60.99, H 5.39, N 2.67.

*(1*R*,2*S*,4*R*,5*S*)-{4-(4-Bromophenyl)-5-methyl-2-(1-methylethyl)-3-oxabicyclo[3.3.0]oct-1-yl}methyl 4-Nitrobenzoate* (**12d**): According to GP3, **12d** was obtained from **11d** (35 mg, 0.10 mmol) as a colourless oil; yield: 30 mg (85%) R_F = 0.29 (petroleum ether:Et_2O = 4:1); $[\alpha]_D^{20}$: −111.1 (*c* 0.50, $CHCl_3$). Chiral HPLC: chiragrom-1, hexane:*i*-PrOH = 200:1, 96% ee, major enantiomer appears at higher retention time.

rac-**12d** was obtained from **11d** (35 mg, 0.10 mmol) as a colourless oil; yield: 29 mg (83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.56 (s, 3H, CH_3), 1.03 (d, 6H, CH_3), 1.10–2.16 (m, 6H, CH_2), 2.13 (m, 1H, CH), 3.53 (d, *J* = 11.7 Hz, 1H, CH), 3.75 (d, *J* = 11.7 Hz, 1H, CH), 4.56 (d, 1H, CH), 5.04 (s, 1H, CH), 7.17 (m, 2H, CH), 7.49 (m, 2H, CH), 8.12 (m, 2H, CH), 8.25 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (CH_3), 19.2 (CH_3), 21.1 (CH_2), 21.2 (CH_2), 23.8 (CH_2), 27.2 (CH), 47.4 (C_q), 61.3 (C_q), 64.7 (CH_2), 73.4 (CH), 88.9 (CH), 121.1 (C_q), 123.3 (C_q), 128.6 (CH), 130.3 (CH), 130.2 (CH), 131.4 (CH), 137.3 (C_q), 150.8 (C_q), 164.2 (C=O); IR (film): ν = 3023, 2962, 2852 (C_{aliph}-H), 1706 cm^{-1} (C=O); anal. calcd. for $C_{25}H_{29}BrO_5N$ (502.40): C 59.77, H 5.62, N 2.79; found: C 60.09, H 5.71, N 2.86; exact mass for $C_{25}H_{30}BrO_5N$: calcd.: 502.1236; found: 502.1230.

X-Ray Crystallographic Study[10]

X-ray crystal structure analysis HOP1432: formula $C_{26}H_{28}NO_5Br$, M = 514.40, colourless crystal 0.40 × 0.35 × 0.25 mm, a = 10.353(3), b = 12.682(2), c = 18.842(5) Å, a = 98.57(1), β = 93.55(1), γ = 102.88(1)°, V = 2373.1(10) Å^3, ϱ_{calc} = 1.440 g cm^{-3}, μ = 17.70 cm^{-1}, empirical absorption correction (0.538 ≤ T ≤ 0.666), Z = 4, triclinic, space group $P\bar{1}$ (No. 2), ? = 0.71073 Å, T = 198 K, ω and φ scans, 15773 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 E^{-1}, 7394 independent (R_{int} = 0.075) and 3613 observed reflections [$I \geq 2\,\sigma(I)$], 599 refined parameters, R = 0.068, wR^2 = 0.168, max. residual electron density 0.43 (−0.42) e Å^{-3}, contains two almost identical molecules in the asymmetric unit, hydrogen atoms calculated and refined as riding atoms.

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References and Notes

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