Tetrahedron 66 (2010) 8722–8728

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iodine(III)-mediated ring expansion: an efficient and green pathway in the synthesis of a key precursor for the design of aminopeptidase (APN or CD13) inhibitors

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ARTICLE INFO

Article history:
Received 30 June 2010
Received in revised form 27 August 2010
Accepted 3 September 2010
Available online 15 September 2010

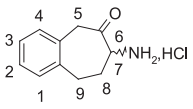
Keywords:
Aminopeptidase
Hypervalent iodine chemistry
Ring expansion
APN or CD13 inhibitors

ABSTRACT

Iodine(III)-mediated ring expansion of a methylidenebenzocyclohexane derivative into the corresponding benzosuberone was used as a key reaction for the obtention of an important precursor for the design of aminopeptidase (APN or CD13) inhibitors. It represents the first application of this environmentally friendly rearrangement to medicinal chemistry.

1. Introduction

Aminopeptidase N (APN)/CD13 (EC 3.4.11.2) is an ectopeptidase that belongs to the class of metalloenzymes from the M1 family with a zinc ion essential for catalysis.[1] The expression of this ubiquitous proteolytic enzyme has been shown to be dysregulated in many diseases and is known to play an important role in tumor angiogenesis and metastasis.[1b,2] Although many inhibitors of aminopeptidases are available, most of them are poorly selective.[3] The development of highly specific and potent inhibitors remains a challenge since most aminopeptidases are zinc-dependent enzymes that share a broad substrate specificity.[1] Specific inhibitors would be undoubtely crucial biological tools since little is known about the precise role and mechanism of action of APN in the physiological and pathological processes, in particular in angiogenesis-dependent pathologies.[2] Structural requirements for APN inhibition were previously determined[4,5] and led to the discovery of (±)-7-amino-6-benzosuberone scaffold **1** as a lead structure, showing a remarkable inhibitory potency and selectivity toward APN, with a Ki value of 1 μM.[5] In view of its minimal size, this compound displayed an excellent ligand efficiency of 0.63 according to the definition by Hopkins et al.[6]



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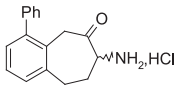

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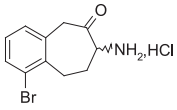

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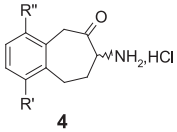

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This scaffold therefore appeared as an excellent candidate for further chemical elaboration and derivatization and we already pointed out the outstanding inhibitory activity and selectivity toward APN of the racemic 4-phenyl and 1-bromo derivatives **2** and **3**, paving thus the way to the elaboration of (±)-1,4-difunctionalized derivatives **4**. Our synthesis of **2** and **3** started from *ortho*-xylenic precursors and relied on a non-regioselective step of modest yield.[5] We present here a straightforward synthesis of the (±)-1,4-disubstituted aminobenzosuberone **5**, which potentially represents an ideal precursor to compounds of the series **4**.[7] As indicated Fig. 1, our synthesis started from natural L-tryptophane **10**

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doi:10.1016/j.tet.2010.09.005

and was based on the transformation in two steps of the 1-tetralone derivative **8** into the corresponding β-benzosuberone **6**. This overall transformation, which is based in a first step on the conversion of a six-membered ring ketone into the corresponding exomethylene derivative followed by a step of oxidative rearrangement, has been originally reported from 1-tetralone and some of its methyl or methoxy derivatives, using thallium nitrate in methanol for the ring expansion.[8] More recently, after a first report that implied non-cyclic ketones,[9a] Justik and Koser published, again from simple 1-tetralones, an analogous sequence in which [hydroxy(tosyloxy)iodo]benzene (HTIB) was employed as an excellent green alternative to the very toxic thallium salt in the rearrangement step.[9b] As reported here, this latter procedure proved very convenient for the preparation of the functionalized benzosuberone **6** from its exomethylenic precursor **7**. To the best of our knowledge, this represents the first application of Koser's procedure to medicinal chemistry.[10]

saponification and protection of the primary amine function as a trifluoroacetamide.

The preparation of 1-oxo-tetrahydronaphthalenic compound **8** required at first the tricky reduction of the carbonyl function in trifluoroacetaniline **9**. As shown in Scheme 2, this could be achieved by prolonged hydrogenation in acetic acid at 110 °C. Under these conditions, both the *N*-trifluoroacetyl and the *N*-ethoxycarbonyl protecting groups were preserved.[11] The acid chloride derivative of **15** was then submitted to a $AlCl_3$-mediated Friedel–Crafts reaction[12] yielding **8** and the lactam derivative **16** arising from prior $AlCl_3$-induced partial deprotection of the $NHCOCF_3$ moiety.

Access to the precursor **7** of the rearranged compound implied the methylenation of the oxo derivative **8**. This step required extensive trials as a Wittig reaction[13] or the use of a Tebbe reagent[14] proved quite unsatisfactory. Finally, a two-steps procedure implying the addition of methylmagnesium bromide followed by the dehydratation of the tertiary alcohol appeared much

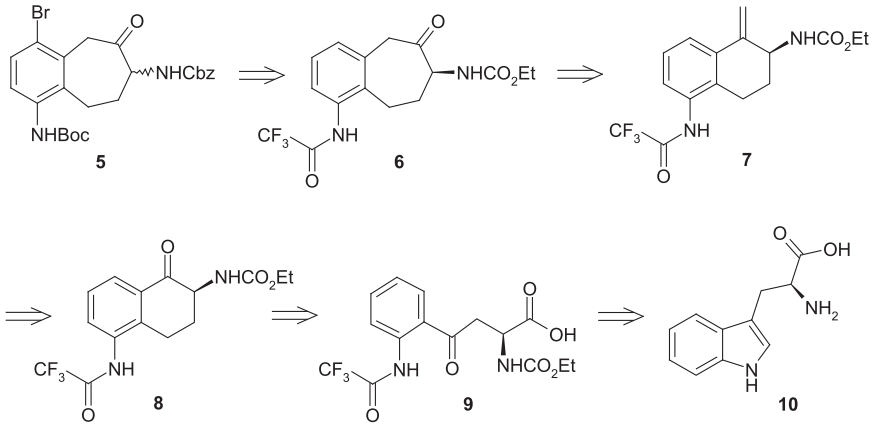


Fig. 1. Retrosynthesis of 4-bromo-1-*tert*-butylbenzyloxycarbonylamino benzosuberone derivative **5**.

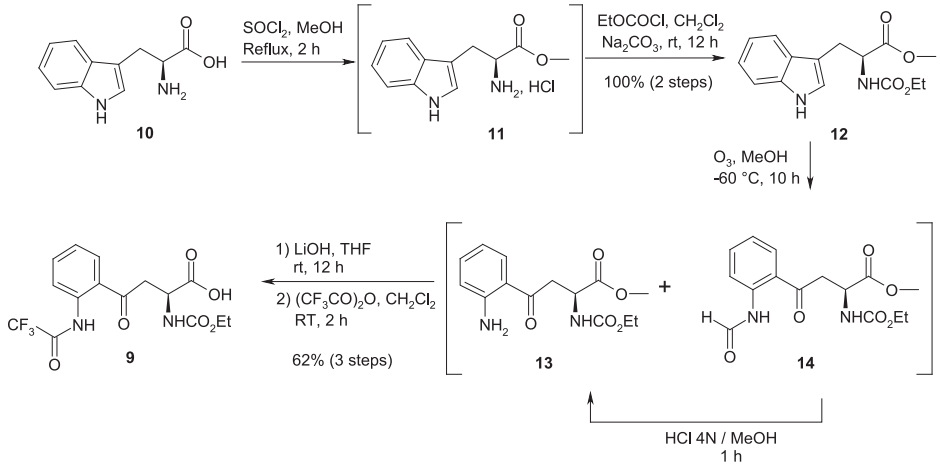
2. Results and discussion

Our synthesis started with the preparation of the 4-phenylbutanoic acid derivative **9**. This compound was readily obtained with an overall yield of 62% from natural L-tryptophane as indicated Scheme 1. After protection as a methyl ester and as a *N*-ethoxycarbonyl derivative, intermediate **12** was submitted to ozonolysis leading to an equimolar mixture of the expected *N*-formyl compound **14** and its deprotected partner **13**. A full access to **13** was possible by the treatment of **14** with methanolic HCl. The aniline derivative **13** was finally converted into **9** after more suitable and allowed us to obtain the desired intermediate in 55% overall yield.

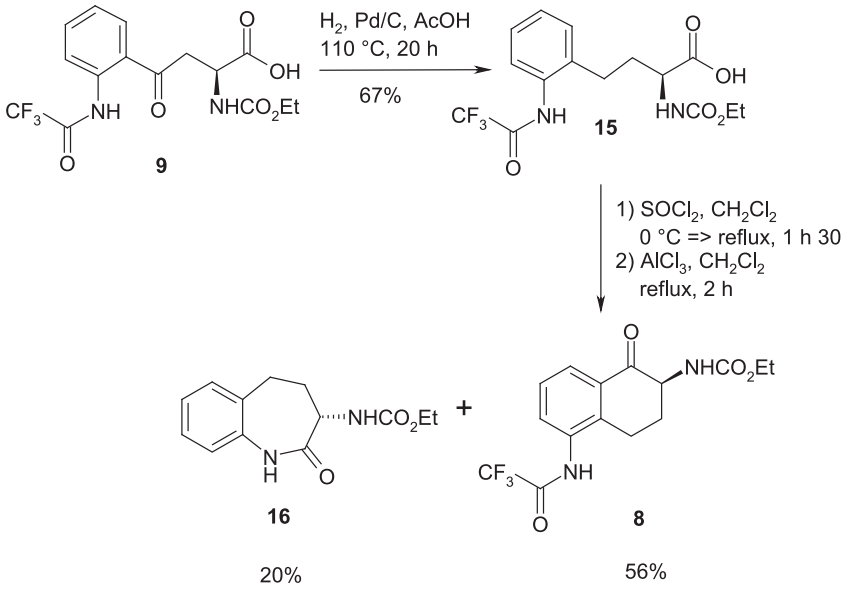
Methylenic derivative **7** was then submitted to HTIB in methanol at rt according to Koser and Justik.[9] Under these conditions, we were pleased to isolate after 1 h the desired β-benzocycloalkanone **6** in a good yield as shown in Scheme 3.

Our key-precursor **5** carrying bromo- and NHBoc subtituents for further chemical derivatization on the aromatic ring was finally prepared from **6** according to Scheme 4.

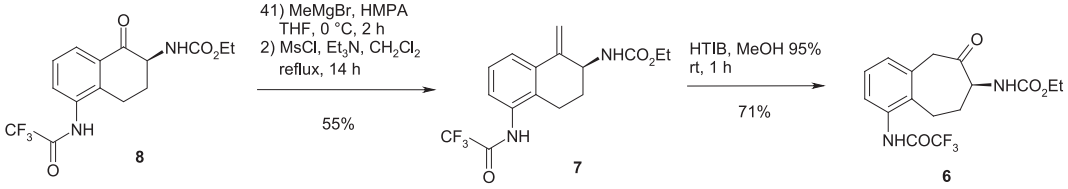
Switching the trifluoroacetyl protection of **6** to a *tert*-butyloxycarbonyl was easily accomplished using mild basic conditions to



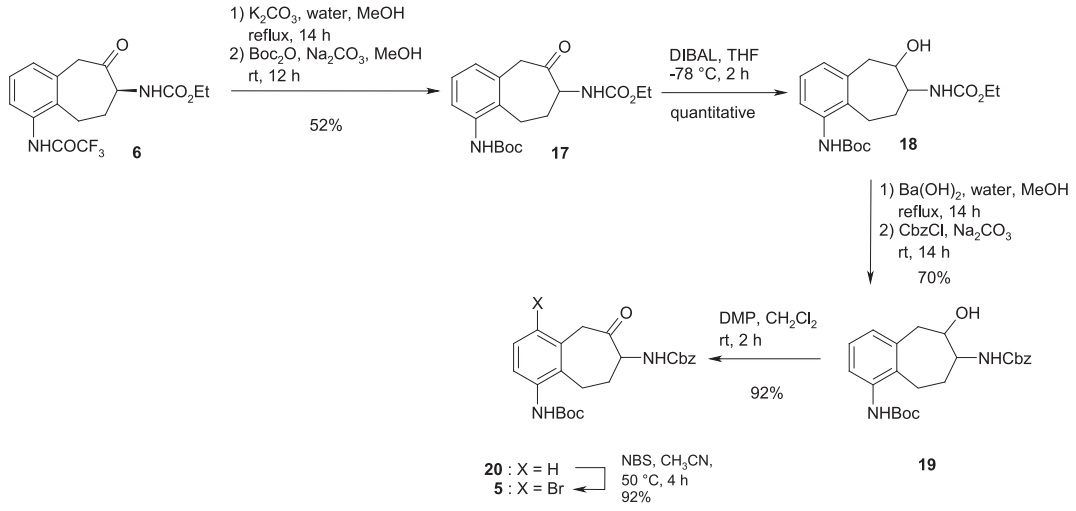
Scheme 1. Synthesis of 2-ethoxycarbonylamino-4-oxo-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid **9**.



Scheme 2. Synthesis of ethyl [1-oxo-5-(2,2,2-trifluoroacetylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamate **8**.



Scheme 3. Synthesis of 1-(2,2,2-trifluoroacetylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **6**.



Scheme 4. Synthesis of 1-(*tert*-butoxycarbonylamino)-4-bromo-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **5**.

free the aniline moiety.[15] In spite of the mildness of this transformation, the integrity of the asymmetric center next to the carbonyl function could not be preserved and yielded **17** as a racemic mixture. Removal of the ethoxycarbonyl protection could not be accomplished easily: indeed, strong acidic or basic conditions like HBr or HCl at reflux in acetic acid,[16] use of TMSI[17] or methanolic $Ba(OH)_2$ at reflux failed to give the desired compound. Nevertheless, after reduction of the carbonyl function of **17** into a secondary alcohol, this latter basic condition worked perfectly.[18] The resulting amine was purified as a benzyloxycarbonyl derivative and easily further converted with excellent yield into its *para*-bromo derivative by action of NBS in acetonitrile.

3. Conclusion

In conclusion, we have performed the synthesis of a key 2-benzosuberone precursor **5** required for the preparation of a series of APN inhibitors of type **4**. This synthesis, which starts

from natural L-tryptophane, relies on the first utilization in medicinal chemistry of a rearrangement mediated by the Koser's reagent HTIB between a methylidenebenzocyclohexane derivative and the corresponding ring expanded benzosuberone.

4. Experimental

4.1. General methods

TLC chromatography was performed with silica gel (Merck 60 F_{254}). Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh). Melting points were recorded on a Kofler hot bench and are corrected. IR spectra were measured with a Nicolet 405 FT-IR spectrometer. Optical rotations were measured on a Schmidt–Haensch Polartronic Universal or a Perkin–Elmer 341 LC polarimeter. NMR spectra were recorded on a Bruker AV 400 spectrometer. High resolution MS were measured on a Waters Micromass Q-Tof Ultima API spectrometer. MeOH was distilled over Mg/MgI_2, THF over Na and benzophenone; CH_2Cl_2 was distilled over P_2O_5 and kept over Na_2CO_3.

*4.1.1. N-(Ethoxycarbonyl)tryptophane methyl ester (**12**)[19].* To a solution of L-tryptophane **10** (50 g, 0.245 mol) in methanol (600 mL), was added dropwise thionyl chloride (19.6 mL, 0.269 mol) at 0 °C under Ar. The mixture was heated under Ar at reflux for 2 h 30. After evaporation of methanol, we obtained the crude methyl ester **11** in quantitative yield. ^{1}H NMR (CD_3OD, 400 MHz, 295 K): δ 3.36 (dd, J=15.1, 7.0 Hz, 1H, H_{3b}), 3.42 (dd, J=15.1, 5.5 Hz, 1H, H_{3a}), 3.72 (s, 3H, H_{OMe}), 4.28 (dd, J=7.0, 5.5 Hz, 1H, H_2), 7.03 (t, J=7.9 Hz, 1H, H_{5indol}), 7.10 (t, J=7.9 Hz, 1H, H_{6indol}), 7.21 (s, 1H, H_{2indol}), 7.38 (d, J=7.9 Hz, 1H, H_{7indol}), 7.51 (d, J=7.9 Hz, 1H, H_{4indol}).

The latter compound (53.43 g, 0.245 mol) was dissolved into water (300 mL) containing sodium carbonate decahydrate (210.31 g, 0.735 mol). To this solution were added dichloromethane (300 mL) and ethyl chloroformate (23.3 mL, 0.245 mol). After stirring at rt for 14 h, the aqueous and organic phases were separated. The aqueous layer was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the *N*-(ethoxycarbonyl)tryptophane methylic ester **12** in quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.27 (t, J=7.0 Hz, 3H, CH_3 ethyl), 3.31 (d, J=5.3 Hz, 2H, H_3), 3.69 (s, 3H, H_{OMe}), 4.12 (q, J=7.0 Hz, 2H, ethyl-CH_2), 4.28 (dt, J=7.8, 5.3 Hz, 1H, H_2), 7.02 (s, 1H, H_{2indol}), 7.13 (t, J=7.8 Hz, 1H, H_{5indol}), 7.21 (t, J=7.8 Hz, 1H, H_{6indol}), 7.37 (d, J=7.8 Hz, 1H, H_{7indol}), 7.56 (d, J=7.8 Hz, 1H, H_{4indol}), 8.10 (s, 1H, H_{1indol}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.52 (ethyl-CH_3), 27.94 (C_3), 52.31 (OCH_3), 54.33 (C_2), 61.11 (ethyl-CH_2), 109.93 (Cq), 111.20 (C_{7indol}), 118.58 (C_{4indol}), 119.64 (C_{5indol}), 122.21 (C_{6indol}), 122.75 (C_{2indol}), 127.52(Cq), 136.10 (Cq), 156.03 (–NH–*C*O–OEt), 172.56 (C–*C*O–OMe). IR (cm^{-1}, KBr): 3319.2, 3058, 2986, 1753.6, 1724.1, 1685.9, 1550.7, 1462, 1434.2, 1375.3, 1289.8, 1218.7, 1067.5. $[\alpha]_D^{25}$ +47.0 (*c* 1.0, $CHCl_3$). Mp=92–94 °C. HRMS (ESI) calcd for $[C_{15}H_{18}N_2O_4, Na]^+$: 313.1159; found 313.1160.

*4.1.2. 2-Ethoxycarbonylamino-4-oxo-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid (**9**).* A solution of *N*-(ethoxycarbonyl)tryptophane methyl ester **12** (71.12 g, 0.245 mol) in methanol (700 mL) was stirred under a flux of ozone at −60 °C during 10 h and gave a mixture of 4-oxo-butyrates **13** and **14** as checked in ^{1}H NMR on a sample. After concentration to 1/4, 4 N aqueous HCl (100 mL) was added. The mixture was stirred at rt for 1 h, extracted with ethyl acetate (4×200 mL) and the combined organic solvents were evaporated, dried over $MgSO_4$, and concentrated in vacuo to give the crude methyl 4-(2-amino-phenyl)-2-ethoxycarbonylamino-4-oxo-butyrate **13** in quantitative yield. ^{1}H NMR: ($CDCl_3$, 400 MHz, 295 K): δ 1.25 (t, J=7.0 Hz, 3H, ethyl-CH_3), 3.53 (dd, J=17.8, 3.8 Hz, 2H, H_{3a}), 3.76 (dd, J=17.8, 4.2 Hz, 2H, H_{3b}), 3.75 (s, 3H, H_{OMe}), 4.12 (q, J=7.0 Hz, 2H, ethyl-CH_2), 4.28 (ddd, J=8.8, 4.2, 3.8 Hz, 1H, H_2), 5.78 (d, J=8.8 Hz, 1H, NH), 6.67 (dd, J=8.3, 1.5 Hz, 1H, H_3), 6.67 (ddd, J=8.3, 7.8, 0.8 Hz, 1H, H_4), 7.28 (ddd, J=8.3, 7.8, 1.5 Hz, 1H, H_5), 7.67 (dd, J=8.3, 0.8 Hz, 1H, H_{6aro}).

To a solution of the preceeding butyrate **13** (23.42 g, 0.11 mol) in THF (300 mL) were added water (300 mL), methanol (15 mL), and LiOH (50 g). The mixture was stirred at rt for 14 h. Aqueous 6 N HCl was then added dropwise to obtain pH=3. After separation, the aqueous layer was extracted with ethyl acetate (×5). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Trifluoroacetic anhydride (18.2 mL, 0.13 mol) was then added and the mixture was stirred at rt for 2 h. Water was added at this stage to hydrolyze excess of trifluoroacetic anhydride. After extraction with dichloromethane (×4), the organic phases were dried over $MgSO_4$ and concentrated in vacuo to give an orange oil. The residue was purified by FC (cyclohexane/AcOEt/AcOH, 70/28/2) yielding the butanoic acid derivative **9** in 78% yield. ^{1}H NMR: ($CDCl_3$, 400 MHz, 295 K): δ 1.26 (t, J=7.0 Hz, 3H, ethyl-CH_3), 3.71 (dd, J=18.4, 4.0 Hz, 2H, H_{3a}), 3.80 (dd, J=18.4, 4.0 Hz, 2H, H_{3b}), 4.13 (q, J=7.0 Hz, 2H, ethyl-CH_2), 4.82 (dt, J=8.1, 4.0 Hz, 1H, H_2), 5.76 (d, J=8.1 Hz, 1H, NH), 7.31 (t, J=7.8 Hz, 1H, H_4), 7.68 (t, J=8.1 Hz, 1H, H_5), 7.99 (d, J=7.8 Hz, 1H, H_3), 8.72 (d, J=8.1 Hz, 1H, H_{6ar}), 12.57 (s, 1H, Hacid). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.43 (–CH_2–CH_3), 41.94 (C_3), 49.59 (C_2), 61.64 (–CH_2–CH_3), 117.7 (q, J=286 Hz, –CF_3), 121.29 (C_{4ar}), 121.69 (C_{2ar}), 124.82 (C_{5ar}), 131.21 (C_{3ar}), 136.12 (C_{6ar}), 138.6 (C_{1ar}), 156.39 ($C_{carbamate}$), 158.1 (q, J=37 Hz, –C_{amide}), 177.32 (C_1), 202.18 (C_4). ^{19}F NMR: ($CDCl_3$, 376.5 MHz, 295 K): δ −76.4. IR (cm^{-1}, KBr): 3357, 3314.8, 3112, 2986, 2935, 1717.6, 1703, 1653, 1590.9, 1535.9, 1455.8, 1285.6, 1157.7. $[\alpha]_D^{25}$ +71.5 (*c* 1.0, $CHCl_3$). Mp=100–102 °C.

*4.1.3. 2-Ethoxycarbonylamino-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid (**15**).* 2-Ethoxycarbonylamino-4-oxo-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid **9** (25 g, 66.44 mmol) was dissolved in acetic acid (120 mL). This solution was added dropwise under H_2 at rt to a suspension of Pd/C (5 g) in acetic acid (300 mL). The mixture was heated at reflux (110 °C) under strirring for 30 h. This solution was filtered off on Celite and acetic acid was evaporated to give a brown oil, which was purified by FC (cyclohexane/AcOEt/AcOH, 70/28/2) to give 2-ethoxycarbonylamino-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid **15** with a yield of 67%. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.25 (t, J=7.2 Hz, 3H, ethyl-CH_3), 1.91 (m, 1H, H_{3a}), 2.10 (m, 1H, H_{3b}), 2.69 (t, J=7.7 Hz, 2H, H_4), 4.10 (q, J=7.2 Hz, 2H, ethyl-CH_2), 4.10 (m, 1H), 7.24–7.36 (m, 4H, Har). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 15.03 (–CH_2–CH_3), 28.7 (C_4), 33.49 (C_3), 54.95 (C_2), 62.18 (–CH_2–CH_3), 117.7 (q, J=286 Hz, –CF_3), 128.38 (C_{4ar}), 128.54 (C_{2ar}), 128.95 (C_{6ar}), 129.54 (C_{5ar}), 130.74 (C_{1ar}), 131.31 (C_{3ar}), 158.1 (q, J=37 Hz, C_{amide}), 159.07 ($C_{carbamate}$), 175.73 (C_1). ^{19}F NMR: (CD_3OD, 376.5 MHz, 295 K): δ −76.4 ppm. IR (cm^{-1}, KBr): 3302, 3061, 2993, 1711.5, 1689, 1541.2, 1285, 1258.1, 1202, 1164.6, 1055.7. $[\alpha]_D^{25}$ −10.2 (*c* 1.0, $CHCl_3$). Mp=112–115 °C. HRMS calcd for $[C_{15}H_{17}N_2O_5F_3, H]^+$=363.1162; found 363.1162.

*4.1.4. Ethyl [1-oxo-5-(2,2,2-trifluoroacetylamino)-1,2,3,4-tetrahydronaphthalen-2-yl]-carbamate (**8**) and ethyl [2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl]-carbamate (**16**).* To a solution of butanoic acid derivative **15** (16.15 g, 0.044 mol) in dichloromethane (100 mL) was added dropwise thionyl chloride (3.6 mL, 0.049 mol) at 0 °C under Ar. This mixture was heated at reflux for 1 h 30 min to give a solution of an acyl chloride, which was added dropwise for 2 h to a solution of $AlCl_3$ (23.79 g, 0.18 mol) in dichloromethane (200 mL) at rt. The mixture was stirred for 2 h and then quenched with ice. After separation, the aqueous layer was extracted with dichloromethane (×4). The organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a brownish

oil. The residue was purified by FC (dichloromethane/AcOEt, 95/5) to give the ethyl [1-oxo-5-(2,2,2-trifluoroacetylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamate **8** in 56% yield and the ethyl [2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]-carbamate **16** (20% yield).

Compound **8**: ($CDCl_3$, 400 MHz, 295 K): δ 1.29 (t, J=7.0 Hz, 3H, ethyl-CH_3), 1.95 (dddd, J=4.8, 12.4, 12.9, 13.8 Hz, 1H, H_{3axial}), 2.85 (m, 1H, H_{3eq}), 2.94 (ddd, J=2.3, 4.8, 17.1 Hz, 1H, H_{4eq}), 3.07 (ddd, J=5.0, 12.4, 17.1 Hz, 1H, H_{4a}), 4.18 (q, J=7.0 Hz, 2H, ethyl-CH_2), 4.10 (ddd, J=4.8, 5.3, 13.8 Hz, 1H, H_{2axial}), 5.84 (br s, J=5.3 Hz, 1H, NH carbamate), 7.46 (t, J=7.5 Hz, 1H, H_7), 7.84 (br s, 1H, NH amide), 7.95 (d, J=7.8 Hz, 1H, H_6), 8.03 (d, J=7.3 Hz, 1H, H_8). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.55 (−CH_2−CH_3), 23.57 (C_4), 29.53 (C_3), 56.97 (C_2), 61.20 (−CH_2−CH_3), 117.7 (q, J=286 Hz, −CF_3), 126.91 (C_{4ar}), 127.69 (C_{2ar}), 129.96 (C_{6ar}), 132.34 (C_{5ar}), 132.62 (C_{1ar}), 136.47 (C_{3ar}), 155.6 (q, J=37 Hz, C_{amide}), 156.35 ($C_{carbamate}$), 194.32 (C_1). ^{19}F NMR: ($CDCl_3$, 376.5 MHz, 295 K): δ −76.4. IR (cm^{-1}, KBr): 3309.3, 3263, 3065, 2993, 1716, 1684, 1540.8, 1319.7, 1270.3, 1238.5, 1196.3, 1164.6. $[\alpha]_D^{25}$ +30.0 (c 1.0, $CDCl_3$). Mp=181−182 °C. HRMS calcd for $[C_{15}H_{15}N_2O_4F_3, H]^+$=345.1057; found 345.1066.

Compound **16**: ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.22 (t, J=7.0 Hz, 3H, ethyl-CH_3), 2.01 (ddd, J=7.5, 11.6, 12.0 Hz, 1H, H_{4b}), 2.65−2.76 (m, 2H, H_{5b-4a}), 2.96 (dd, J=8.3, 12.3 Hz, 1H, H_{5a}), 4.08 (q, J=7.0 Hz, 2H, ethyl-CH_2), 4.30 (dd, J=7.1, 12.0 Hz, 1H, H_3), 5.60 (br s, 1H, NH carbamate), 7.00 (d, J=7.5 Hz, 1H, H_6), 7.17 (t, J=7.5 Hz, 1H, H_7), 7.23 (m, 2H, H_{8-9}), 7.73 (s, 1H, NH_{amide}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.94 (−CH_2−CH_3), 28.89 (C_5), 37.09 (C_4), 51.20 (C_3), 61.39 (−CH_2−CH_3), 122.82 (C_6), 126.69 (C_q), 126.93 (C_7), 128.21 (C_{8-9}), 130.28 (C_{8-9}), 134.35 (C_q), 156.16 ($C_{carbamate}$), 173.29 (C_{amide}). IR (cm^{-1}, KBr): 3266.5, 3220, 3058, 2982, 2932, 2871, 1724.3, 1675.5, 1542.1, 1258.5, 1053.5. $[\alpha]_D^{25}$ +85.1 (c 1.0, $CHCl_3$). Mp=144 °C. HRMS calcd for $[C_{13}H_{16}N_2O_3, H]^+$=249.1239; found 249.1234.

*4.1.5. Ethyl[1-methylen-5-(2,2,2-trifluoroacetylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamate (**7**).* To a solution of carbamate **8** (2.2 g, 6.4 mmol) in THF (100 mL) were added successively HMPA (1.1 mL, 6.4 mmol, 1 equiv) and MeMgBr 3 M in diethylether (15.3 mL, 0.045 mol, 7 equiv) under Ar at 0 °C. This mixture was stirred at 0 °C for 3 h. After quenching with ice and an aqueous saturated solution of NH_4Cl, extraction with Et_2O (×3), the organic phase was dried over $MgSO_4$, and concentrated in vacuo to give a brown solid with a quantitative yield. The crude product was introduced in the next reaction without purification. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.28 (t, J=7.1 Hz, 3H, ethyl-CH_3), 1.38 (s, 3H, methyl-CH_3), 1.81 (ddd, J=10.3, 12.2, 12.8 Hz, 1H, H_{3ax}), 2.10 (m, 1H, H_{3eq}), 2.79 (m, 2H, H_4), 3.89 (ddd, J=3.3, 7.8, 12.2 Hz, 1H, H_2), 4.18 (q, J=7.1 Hz, 2H, ethyl-CH_2), 5.86 (d, J=7.8 Hz, 1H, NH carbamate), 7.28 (t, J=7.8 Hz, 1H, H_7), 7.50 (d, J=7.8 Hz, 1H, H_8), 7.59 (d, J=8.0 Hz, 1H, H_6), 8.04 (br s, 1H, NH amide). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.5 (−CH_2−CH_3), 23.5 (C_4), 25.4 (C_{methyl}), 25.8 (C_3), 56.3 (C_2), 61.6 (−CH_2−CH_3), 74.0 (C_1), 116.0 (q, J=289 Hz, −CF_3), 123.5 (C_8), 123.7 (C_q), 126.0 (C_6), 127.3 (C_q), 127.4 (C_7), 131.4 (C_q), 155.4 (q, J=37.4 Hz, −C_{amide}), 157.8 ($C_{carbamate}$). ^{19}F NMR: ($CDCl_3$, 376.5 MHz, 295 K): δ −76.4. IR (cm^{-1}, KBr): 3317.5, 2986, 1718.0, 1680, 1541.3, 1418, 1261.7, 1213. Mp=80−85 °C. HRMS calcd for $[C_{16}H_{19}N_2O_4F_3, Na]^+$=383.1189; found 383.1188. To a solution of this tertiary alcohol (2.2 g, 6.4 mmol) in dichloromethane (100 mL), were added successively mesyl chloride (2.5 mL, 0.032 mol, 5 equiv) and triethylamine (4.4 mL, 0.032 mol, 5 equiv). This mixture was heated at reflux for 14 h, and then diluted with water. After separation, the aqueous layer was extracted with dichloromethane (×3). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a brown solid. The residue was purified by FC (cyclohexane/AcOEt, 70/30) to give the ethyl [1-methylene-5-(2,2,2-trifluoroacetylamino)-1,2,3,4-tetrahydronaphthalen-2-yl]-carbamate **7** with a yield of 55%. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.26 (t, J=7.1 Hz, 3H, ethyl-CH_3), 2.01(m, 1H, H_{3a}), 2.10(m, 1H, H_{3b}), 2.78 (br t, J=12.2 Hz, 2H, H_4), 4.15 (q, J=7.1 Hz, 2H, ethyl-CH_2), 4.51 (m, 1H, H_2), 4.8 (d, J=8.1 Hz, 1H, NH carbamate), 5.27 (s, 1H, $H_{alkene\ a}$), 5.62 (s, 1H, $H_{alkene\ b}$), 7.27 (dd, J=8.0, 7.8 Hz, 1H, H_7), 7.57 (d, J=8.0 Hz, 1H, H_6), 7.66 (d, J=7.8 Hz, 1H, H_8), 7.82 (br s, 1H, NH amide). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.6 (−CH_2−CH_3), 22.22 (C_4), 28.7 (C_3), 51.1 (C_2), 61.0 (−CH_2−CH_3), 110.2 ($C_{du\ methylene}$), 116.0 (q, J=289 Hz, −CF_3), 118.9 (C_1), 122.6 (C_q), 123.6 (C_6), 124.5 (C_8), 127.1 (C_7), 128.3 (C_q), 134.8 (C_q), 142.9 ($C_{carbamate}$), 155.6 (q, J=37.4 Hz, −C_{amide}). ^{19}F NMR: ($CDCl_3$, 376.5 MHz, 295 K): δ −76.5. IR (cm^{-1}, KBr): 3314, 3266.0, 3072, 2982, 2943, 1707.3, 1685, 1540.8, 1258.9, 1188, 1158.7. Mp=168−172 °C. HRMS calcd for $[C_{16}H_{17}N_2O_3F_3, Na]^+$=365.1083; found 365.1086.

*4.1.6. 1-(2,2,2-Trifluoroacetylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-one (**6**).* After dissolution of carbamate **7** (1.71 g, 5.0 mmol) into methanol (100 mL), Koser's reagent (PhI(OH)OTs) (2.94 g, 7.5 mmol, 1.5 equiv) was added. The mixture was stirred at rt for 1 h. This solution was concentrated and diluted with water and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (3×100 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a brown solid. The residue was purified by recristallisation in diisopropylether to give the 1-(2,2,2-trifluoroacetylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **6** with a yield of 70%. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.24 (t, J=7.4 Hz, 3H, ethyl-CH_3), 1.57(dddd, J=4.8, 6.8, 10.3, 12.2 Hz, 1H, H_{8a}), 2.67(br dd, J=8.5, 12.2 Hz, 1H, H_{8b}), 2.90 (m, 2H, H_{9a+b}), 3.71(d, J=15.0 Hz, 1H, H_{5a}), 3.97(d, J=15.0 Hz, 1H, H_{5b}), 4.10 (q, J=7.4 Hz, 2H, ethyl-CH_2), 4.55 (ddd, J=5.6, 8.5, 10.3 Hz, 1H, H_7), 5.56 (d, J=5.6 Hz, 1H, NH carbamate), 7.22 (d, J=7.3 Hz, 1H, H_2), 7.28 (t, J=7.3 Hz, 1H, H_3), 7.37 (d, J=7.3 Hz, 1H, H_4), 7.84 (br s, 1H, NH amide). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.5 (−CH_2−CH_3), 24.1 (C_9), 32.7 (C_8), 48.1 (C_5), 60.3 (C_7), 61.1 (−CH_2−CH_3), 116.0 (q, J=288.9 Hz, −CF_3), 125.9 (C_4), 128.0 (C_3), 129.8 (C_2), 131.6 ($C_{4'}$), 134.3 ($C_{1'}$), 135.2 (C_1), 155.6 (q, J=38.2 Hz, −C_{amide}), 155.71 ($C_{carbamate}$), 203.16 (C_6). ^{19}F NMR: ($CDCl_3$, 376.5 MHz, 295 K): −76.5. IR (cm^{-1}, KBr): 3327.6, 3274, 3076,2989, 2939, 1710.4, 1674.6, 1532.4, 1254.6, 1199, 1164.7. Mp=197−199 °C. HRMS calcd for $[C_{16}H_{17}N_2O_4F_3, Na]^+$=381.1033; found 381.1030.

*4.1.7. 1-(tert-Butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-one (**17**).* To a solution of 1-(2,2,2-trifluoroacetylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **6** (1.00 g, 2.79 mmol) in methanol (60 mL) and water (25 mL), was added K_2CO_3 (3.86 g, 27.9 mol, 10 equiv). This mixture was heated at 110 °C for 14 h, and then diluted with water and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (×5). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a brown oil. ^{1}H NMR (CD_3OD, 400 MHz, 295 K): δ 1.22 (t, J=7.1 Hz, 3H, ethyl-CH_3), 1.65(m, 1H, H_{8a}), 2.48 (m, 1H, H_{8b}), 3.04 (ddd, J=3.4, 9.4, 15.1 Hz, 1H, H_{9a}), 3.11 (ddd, J=3.3, 7.3, 15.1 Hz, 1H, H_{9b}), 3.70 (d, J=15.1 Hz, 1H, H_{5a}), 4.08(d, J=15.1 Hz, 1H, H_{5b}), 4.06 (q, J=7.1 Hz, 2H, ethyl-CH_2), 4.50 (dd, J=6.8, 11.3 Hz, 1H, H_7), 7.35 (m, 3H, H_2, H_3, H_4). To a solution of the latter compound (178 mg, 0.68 mmol) in methanol (20 mL), were added successively K_2CO_3 (722 mg, 6.81 mmol, 10 equiv) and di-*tert*-butyl dicarbonate (1.49 g, 6.81 mol, 10 equiv). This mixture was stirred at rt for 14 h, and then diluted with water and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (×5). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a brown solid. The residue was purified by FC (cyclohexane/AcOEt,

80/20) yielding 1-(*tert*-butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **17** with a yield of 52%. ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 1.24 (t, J=7.1 Hz, 3H, ethyl-CH_3), 1.52 (br s, 10H, H_{8a}, $9H_{Boc}$), 2.65(dddd, J=4.5, 7.1, 9.3, 13.1 Hz, 1H, H_{8b}), 2.94 (m, 2H, H_{9a+b}), 3.65 (d, J=15.4 Hz, 1H, H_{5a}), 3.91 (d, J=15.4 Hz, 1H, H_{5b}), 4.10 (q, J=7.1 Hz, 2H, ethyl-CH_2), 4.53 (ddd, J=7.1, 7.1, 11.1 Hz, 1H, H_7), 5.48 (d, J=7.1 Hz, 1H, NH from carbamate), 6.23 (br s, 1H, amide NH), 7.01 (d, J=7.6 Hz, 1H, H_4), 7.17 (t, J=7.8 Hz, 1H, H_3), 7.42 (d, J=7.8 Hz, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.5 ($-CH_2-CH_3$), 23.8 (C_9), 28.3 (9H from Boc), 33.3 (C_8), 48.15 (C_5), 60.52 (C_7), 60.99 ($-CH_2-CH_3$), 80.61 (C_q from Boc), 124.59 (C_2), 127.07 (C_4), 127.39 (C_3), 135.0, 133.58, 133.43 (C_q), 153.88 ($C_{carbamate}$), 155.64 ($C_{carbamate}$), 204.44 (C_6). IR (cm^{-1}, KBr): 3324.6, 2982, 2935, 2856, 1718, 1686.9, 1588, 1521.6, 1447, 1379, 1249.5, 1162.0. Mp=140–142 °C. HRMS calcd for $[C_{19}H_{26}N_2O_5, Na]^+$=385.1734; found 385.1739.

*4.1.8. 1-(tert-Butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-ol (**18**).* To a solution of 1-(*tert*-butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **17** (180 mg, 0.497 mmol) in anhydrous THF (20 mL) at −78 °C, was added dropwise DIBAL (3.5 mL, 3.48 mmol, 7 equiv). This mixture was stirred at −78 °C for 1 h, and at rt for 1 h, and then diluted with a aqueous solution 1 N of sodium tartrate and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (×5). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a white solid. 1-(*tert*-Butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-ol **18** is obtained with a quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz, 323 K): δ 1.26 (t, J=7.3 Hz, 3H, ethyl-CH_3), 1.52 (br s, 10H, H_{8b}, $9H_{Boc}$), 1.99 (ddd, J=4.0, 8.1, 13.4 Hz, 1H, H_{8a}), 2.47 (dd, J=11.3 Hz, 1H, H_{9b}), 2.98 (dd, J=8.1 Hz, 1H, H_{9a}), 3.04 (dd, J=7.1, 14.1 Hz, 1H, H_{5b}), 3.09 (d, J=14.1 Hz, 1H, H_{5a}), 3.82 (ddd, J=4.0, 7.3, 11.8 Hz, 1H, H_7), 4.08 (d, J=7.1 Hz, 1H, H_6), 4.14 (q, J=7.3 Hz, 2H, ethyl-CH_2), 5.16 (d, J=7.3 Hz, 1H, NH from carbamate), 6.23 (br s, 1H, NH from Boc), 7.02 (d, J=7.3 Hz, 1H, H_4), 7.11 (t, J=7.6 Hz, 1H, H_3), 7.33 (d, J=8.1 Hz, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 14.6 ($-CH_2-CH_3$), 24.63 (C_9), 27.63 (C_8), 28.28 (9H from Boc), 39.36 (C_5), 57.1 (C_7), 60.71 ($-CH_2-CH_3$), 69.01 (C_6), 80.46 (C_q from Boc), 125.04 (C_2), 126.48 (C_3), 129.64 (C_4), 134.3, 135.6, 137.1 (C_q), 154.34 ($C_{carbamate}$), 155.91 ($C_{carbamate}$). IR (cm^{-1}, KBr): 3494, 3364, 3316.9, 2982, 2921.3, 2853, 1697.2, 1699.9, 1521.9, 1443.1, 1367.4, 1250.7, 1166.0, 1059.9. Mp=138–140 °C. HRMS calcd for $[C_{19}H_{26}N_2O_5, H]^+$=365.2057; found 365.2060.

*4.1.9. 1-(tert-Butoxycarbonylamino)-7-benzoxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-ol (**19**).* To a solution of 1-(*tert*-butoxycarbonylamino)-7-ethoxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-ol **18** (30 mg, 0.082 mmol) in methanol (1 mL) and water (2 mL), was added $Ba(OH)_2$ (130 mg, 0.412 mmol, 5 equiv). This mixture was heated at 100 °C for 16 h, and then diluted with water and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (5×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, 323 K): δ 1.51 (s, 9H, $9H_{Boc}$), 1.78 (br s, 1H), 2.12 (br s, 3H), 2.48 (br s, 1H), 2.90 (br s, 2H), 3.11 (br s, 1H), 3.89 (br s, 1H), 6.32 (br s, 1H, NH from Boc), 7.04 (d, J=7.3 Hz, 1H, H_4), 7.11 (t, J=7.3 Hz, 1H, H_3), 7.31 (d, J=7.3 Hz, 1H, H_2). To a solution of this latter compound (0.082 mmol) in THF (5 mL), were added successively Na_2CO_3 (17.4 mg, 0.164 mmol, 2 equiv) and benzyl chloroformate (17.5 μL, 0.123 mmol, 1.5 equiv). This mixture was stirring at rt for 14 h, and then diluted with water and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate (×5). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a brown solid. The residue was purified by FC (cyclohexane/AcOEt, 80/20) to give the 1-(*tert*-butoxycarbonylamino)-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-ol **19** with a yield of 70%. ^{1}H NMR ($CDCl_3$, 400 MHz, 323 K): δ 1.52 (br s, 10H, H_{8b}, $9H_{Boc}$), 2.04 (ddd, J=4.3, 8.0, 13.3 Hz, 1H, H_{8a}), 2.48 (dd, J=11.3 Hz, 1H, H_{9b}), 2.98 (dd, J=8.0 Hz, 1H, H_{9a}), 3.04 (dd, J=7.2, 14.3 Hz, 1H, H_{5b}), 3.13(d, J=14.3 Hz, 1H, H_{5a}), 3.88 (dddd, J=2.0, 4.3, 8.0, 11.4 Hz, 1H, H_7), 4.12 (dd, J=2.0, 7.2 Hz, 1H, H_6), 5.13 (s, 2H, CH_2 from Cbz), 5.24 (d, J=8.0 Hz, 1H, NH from Cbz), 6.15 (br s, 1H, NH from Boc), 7.03 (d, J=7.8 Hz, 1H, H_4), 7.13 (t, J=7.5 Hz, 1H, H_3), 7.37 (m, 6H, H_2+5HCbz). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 24.61 (C_9), 27.74 (C_8), 28.30 (9H from Boc), 39.35 (C_5), 57.29 (C_7), 66.67 (CH_2 from Cbz), 68.93 (C_6), 80.53 (C_q from Boc), 124.97 (C_2), 125.5 (C_q from Cbz), 126.64 (C_3), 128.09 (2*C from Cbz), 128.51 (2*C from Cbz), 129.62 (C_4), 134.42, 135.18, 136.95 (C_q), 136.5 (C from Cbz), 154.34 ($C_{carbamate}$), 155.91 ($C_{carbamate}$). IR (cm^{-1}, KBr): 3433, 3323.9, 2993, 2971, 2926.1, 1698.9, 1671, 1541, 1441, 1368, 1251.3, 1166, 1046.2. Mp=174 °C. HRMS calcd for $[C_{19}H_{26}N_2O_5, H]^+$=427.2227; found 427.2228.

*4.1.10. 1-(tert-Butoxycarbonylamino)-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-one (**20**).* To a solution of 1-(*tert*-butoxycarbonylamino)-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-ol (356 mg, 0.83 mmol) in dichloromethane (10 mL), was added Dess–Martin periodinane (424 mg, 1 mmol, 1.2 equiv). This mixture was stirred at rt for 2 h and then diluted with water and dichloromethane. After separation, the aqueous layer was extracted with dichloromethane (×3). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give a white solid. The residue was purified by FC (cyclohexane/AcOEt, 80/20) yielding 1-(*tert*-butoxycarbonylamino)-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **20** with a yield of 92%. ^{1}H NMR ($CDCl_3$, 400 MHz, 323 K): δ 1.50 (s, 9H, Boc), 1.54 (m, J=4.4, 7.2, 11.2, 12.8 Hz, 1H, H_{8b}), 2.66 (dddd, J=4.4, 7.6, 9.2, 12.5 Hz, 1H, H_{8a}), 2.89 (ddd, J=4.4, 7.2, 15.0 Hz, 1H, H_{9b}), 2.95 (ddd, J=4.4, 9.2, 15.0 Hz, 1H, H_{9a}), 3.64 (d, J=15.2 Hz, 1H, H_{5b}), 3.92 (d, J=15.2 Hz, 1H, H_{5a}), 4.55 (ddd, J=6.8, 7.6, 11.2 Hz, 1H, H_{7a}), 5.07 (s, 2H, CH_2 from Cbz), 5.69 (d, 1H, N*H*Cbz), 6.25 (br s, 1H, N*H*Boc), 7.02 (d, J=7.6 Hz, 1H, H_2), 7.17 (t, J=8.0 Hz, 1H, H_3), 7.30–7.36 (m, 6H, H_{Cbz}+H_2), 7.43 (d, J=8.0 Hz, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 204.2 (C_6), 155.3 (NCO_2Bn), 153.8 ($NCO_2{}^tBu$), 136.3 (C_{9a}), 135.0, 133.4 (C_{4a}, Ph), 131.8 (C_1), 128.5, 128.1, 128.0 (5C, Ph), 127.4 (C_3), 127.1 (C4), 124.5 (C_2), 80.6 (CMe_3), 66.8 (OBn), 60.6 (C_7), 48.1 (C5), 33.2 (C_8), 28.3 (3C, CMe_3), 23.8 (C_9). IR (cm^{-1}, KBr): 3353.5, 3326.7, 2971.8, 2940.5, 1720.8, 1689.2, 1519.4, 1248.1, 1241.1, 1163.3. HRMS calcd for $C_{24}H_{28}N_2O_5$ $[M+Na]^+$: 447.1890; found: 447.1886.

*4.1.11. 1-(tert-Butoxycarbonylamino)-4-bromo-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6H-benzocyclohepten-6-one (**5**).* To a solution of 1-(*tert*-butoxycarbonylamino)-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one (20 mg, 0.05 mmol) in acetonitrile (2 mL), was added *N*-bromosuccinimide (11.6 mg, 0.06 mmol, 1.3 equiv). This mixture was stirred at 50 °C for 4 h and then diluted with aqueous solution of ammonium chloride 1 N and ethyl acetate. After separation, the organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a white solid. The residue was crystallized in $^iPr_2O$ to give 1-(*tert*-butoxycarbonylamino)-4-bromo-7-benzyloxycarbonylamino-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one **5** with a yield of 92%. ^{1}H NMR ($CDCl_3$, 400 MHz, 323 K): δ 1.51 (s, 9H, Boc), 1.57 (dddd, J=4.7, 5.2, 10.6, 12.5 Hz, 1H, H_{8b}), 2.66 (dddd, J=5.2, 7.5, 11.6, 12.5 Hz, 1H, H_{8a}), 2.86 (ddd, J=4.7, 11.6, 15.5 Hz, 1H, H_{9b}), 2.96 (ddd, J=5.2, 5.2, 15.5 Hz, 1H, H_{9a}), 3.95 (d, J=17.4 Hz, 1H, H_{5b}), 4.24 (d, J=17.4 Hz, 1H, H_{5a}), 4.54 (ddd, J=6.5, 7.5, 10.6 Hz, 1H, H_{7a}), 5.07 (s, 2H, CH_2 from Cbz), 5.69 (d, 1H, NHCbz), 6.22 (br s, 1H, NHBoc), 7.36 (m, 6H, H_{Cbz}+H_2), 7.44 (d, J=8.6 Hz 1H, H_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 24.57 (C_9), 28.24

(−NHCOOC(CH_3)$_3$), 32.44 (C_8), 47.00 (C_6), 59.08 (C_7), 66.66 (CH_2 du Cbz), 81.04 (−NHCOO*C*(CH_3)$_3$), 121.03 (C_q), 125.42 (C_3), 128.05, 128.15, and 128.50 (5 CH from Cbz), 131.36 (C_3), 133.82 (C_q), 134.61 (Cq), 136.16 (Cq), 138.38 (Cq), 153.53 (−NHCOO−), 155.29 (−NHCOO−), 204.20 (C_5). IR (cm^{-1}, KBr): 3315.7, 2926.8, 1686.8, 1527.3, 1506.1, 1250.3, 1160.6, 995.0, 697.3 Mp=176 °C. HRMS calcd for $[C_{24}H_{27}BrN_2O_5, H]^+$=503.1176; found 503.1170.

Acknowledgements

The support of the Centre National de la Recherche Scientifique (FRE-3253) and the Ecole Nationale Supérieure de Chimie de Mulhouse is gratefully acknowledged. We also wish to thank the Region Alsace for a Ph.D. Grant to L.R. We thank the students Jean-Baptiste Deslandes, Yannick Bidal and Mathieu Lesieur for their participation to this work.

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