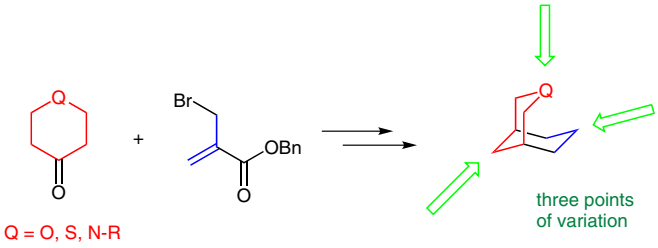
Synthesis A. Yu. Ishchenko et al. Paper

An Expedient and Practical Approach to Functionalized 3-Aza-, 3-Oxa-, and 3-Thiabicyclo[3.3.1]nonane Systems

Aleksandr Yu. Ishchenko[a,b]
Stanislav Yanik[c,†]
Eduard B. Rusanov[d]
Igor V. Komarov[*a]
Anthony J. Kirby[e]

[a] Institute of High Technologies, Taras Shevchenko National University of Kyiv, Volodymyrska 60, 01601 Kyiv, Ukraine
ik214@yahoo.com
[b] Enamine Ltd., Aleksandra Matrosova 23, 01103 Kyiv, Ukraine
[c] Chemistry Department, Taras Shevchenko National University of Kyiv, Volodymyrska 64, 01601 Kyiv, Ukraine
[d] Institute of Organic Chemistry of NAS of Ukraine, Murmanska 5, 02094 Kyiv, Ukraine
[e] University Chemical Laboratory, Cambridge CB2 1EW, UK



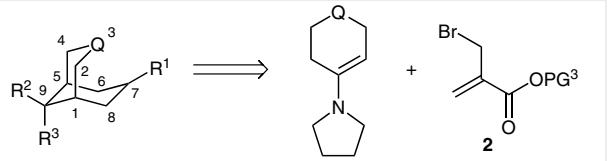
Received: 02.08.2014
Accepted after revision: 22.10.2014
Published online: 14.11.2014
DOI: 10.1055/s-0034-1379456; Art ID: ss-2014-n0487-op

Abstract The synthesis of a number of heterobicyclo[3.3.1]nonane derivatives possessing carbonyl, amino, or carboxyl groups is reported. The synthetic scheme is concise and practical, based on optimized reaction conditions for each step and an orthogonal protection group strategy. Procedures for the key synthetic steps (double annulation of α-bromomethyl acrylates to enamines and a Caglioti reaction) were improved significantly. This makes the compounds attractive for medicinal chemistry as potential chemically diverse 3D-scaffolds applicable in drug design.

Key words bicyclic compounds, annulation, Caglioti reaction, diversity-oriented synthesis, medicinal chemistry

Saturated carbo- and heterobicyclic systems are used frequently in contemporary drug design. These systems represent the so-called 3D-scaffolds;[1] when functionalized at appropriate positions they can interact efficiently with biological targets. In principle, bicyclic scaffolds allow for wide variations of the functional group disposition in space, enhancing the chances of finding derivatives with optimal pharmacological characteristics. In order to exploit this potential to the full, chemists have developed flexible and practical synthetic approaches to bicyclic scaffolds functionalized at different positions.[2] We report here on the synthesis of a library of bicyclo[3.3.1]nonane-derived compounds possessing heteroatoms N, O, and S in the bicyclic skeleton (target compounds **1**). Structural and chemical diversity of the synthesized library could be of great value for finding derivatives with improved pharmacokinetic properties, and enhanced efficiency and selectivity of interaction with biological targets. Such diversity has been the focus of the drug discovery process over the past decade.[3] The concept of diversity-oriented synthesis (DOS) was introduced, designating preparation of collections of structurally complex and diverse compounds from simple starting materials.[4] The bicyclic compounds described in this paper could be introduced into DOS by linear or branching functionalization methodology.[5] We explore this potential, aiming at improvements of known synthetic procedures and designing new ones.

Construction of the [3.3.1]bicyclic system was performed by a well-documented strategy, based on the double annulation of α-bromomethyl acrylates **2** to enamines **3** (Scheme 1). The strategy was elaborated almost a half a century ago for synthesis of carbo-bicyclic derivatives,[6] and has already proved its efficiency in preparations of 3-azabicyclo[3.3.1]nonanes,[7] 3-oxabicyclo[3.3.1]nonanes,[8] and 3-phenyl-3-phosphabicyclo[3.3.1]nonane-3-oxide.[9] A formal [3+3] cycloaddition annulation was also reported recently for rapid direct construction of the bicyclo[3.3.1] skeleton.[10] The synthesis of 3-thiabicyclo[3.3.1]nonanes and the corresponding sulfones has not so far been described in the open literature, but has been the subject of a patent application,[11] showcasing the importance of the compounds for drug design.



1, Q = N-PG[1], O, SO_2
R^1 = CO_2H, NH-PG[2]
R^2, R^3 = H, NH_2
R^2+R^3 = O
$PG^{1,2,3}$ = different protecting groups

Scheme 1 Retrosynthetic disconnection of the target compounds

The strategy outlined in Scheme 1 is particularly attractive to our purpose, because the key intermediate compounds have vast potential for functionalization, using the very rich chemistry of the carbonyl and carboxyl groups. Specific control of the stereochemistry at positions 7 and 9 is also possible, as demonstrated earlier in the literature.[12] This opens the way to chemically and structurally diverse arrays of the derivatives of **1**. The protection group strategy in our synthesis aimed at regioselectivity of further functionalization of the scaffolds, needed for the search of new drug candidates by systematic variation of the functional group type and position.

Our synthetic route to compounds **1** is shown in Scheme 2. Like previous syntheses of analogous [3.3.1]bicyclic derivatives, it is based on the double annulation reaction of **2** and **3** as the key synthetic step, but differs in several details, which make it more attractive and more practical for the needs of medicinal chemistry.

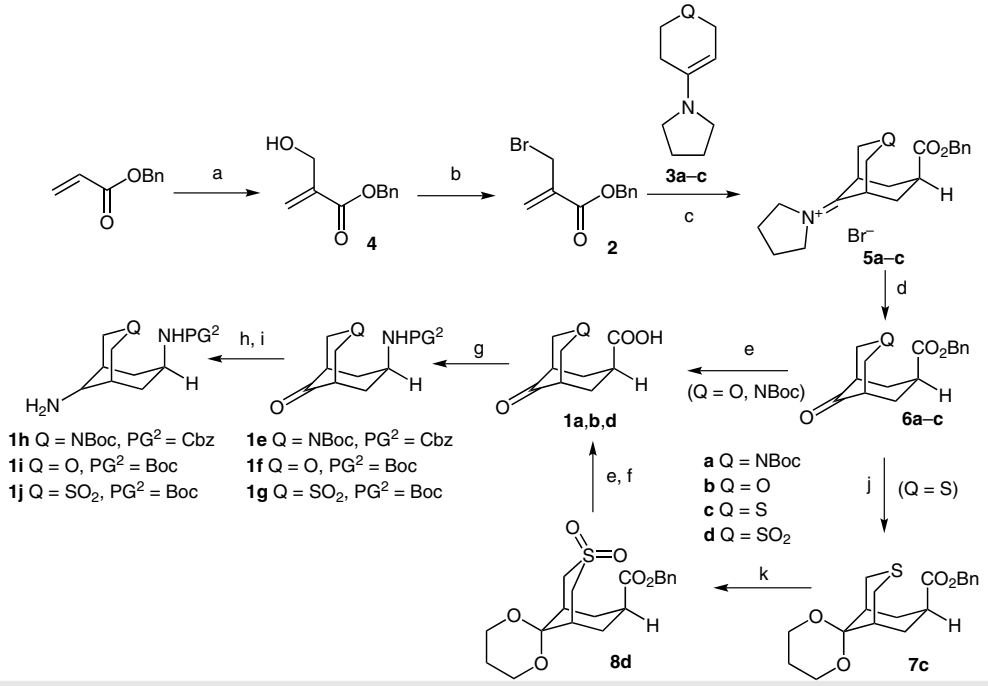
First, the α-bromomethyl acrylate **2** (PG^3 = Bn) was synthesized by a different route, from the corresponding hydroxymethyl acrylate **4**, in turn obtained by a Morita–Baylis–Hillman (MBH) reaction between formaldehyde and benzyl acrylate. The MBH reaction was chosen because it has already demonstrated high yields and scalability in similar syntheses.[13,14] Benzyl is a protecting group for CO_2H, which is easily cleaved without epimerization at position 7 during the final transformations.

Second, the annulation reaction was carried out under conditions allowing the isolation of the iminium salts **5a–c** before their smooth and clean transformation into the key intermediate compounds. The salts, formed in good yields and sufficiently pure, were transformed cleanly into **6a–c**; no purification steps were needed at this step of the synthesis.

The benzyl protecting groups in **6a**,**b** can then be removed by hydrogenolysis, setting the stage for the carboxylic group functionalization in the obtained compounds **1a**,**b**. Compound **6c** resisted deprotection, probably due to poisoning of the catalyst by the sulfide moiety. Therefore, the sulfur atom was oxidized in the C=O protected intermediate **7c** (protection of the carbonyl group was needed to avoid the Baeyer–Villiger reaction during the sulfur oxidation, which was observed under a variety of conditions). The obtained sulfone **8d** was smoothly deprotected to give the scaffold **1d**.

The Curtius rearrangement was used to transform compounds **1a**,**b**,**d** into the (protected) amino-substituted derivatives **1e**,**f**,**g**. The amino groups in **1e** are orthogonally protected, so they can be addressed selectively in further transformations.

The carbonyl group in compounds **1e**,**f**,**g** can be used (like the carboxylic group in **1a**,**b**,**d**) either for the synthesis of compound libraries, or for further modification of the scaffold. In order to modify the scaffold, the C=O was trans-

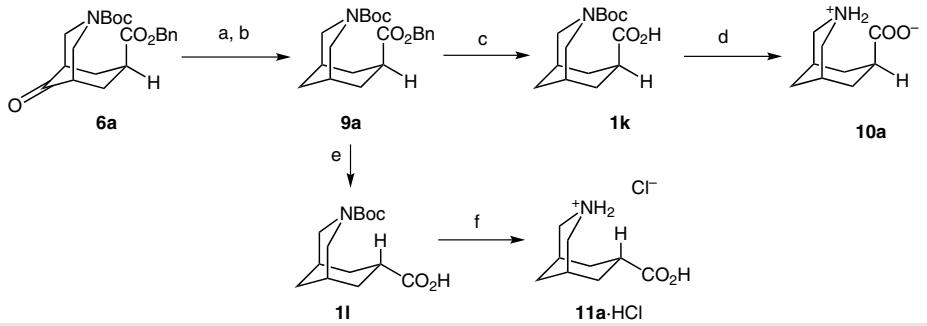


Scheme 2 Synthesis of the target compounds **1**. *Reagents and conditions*: (a) paraformaldehyde, DABCO, H_2O–1,4-dioxane, 24 h, 47%; (b) PBr_3, Et_2O, 10 °C to r.t., 1 h, 85%; (c) DIPEA, MeCN, reflux, 3 h, 47–68%; (d) H_2O/MTBE (4:1), 1 h, quant; (e) 1 atm H_2, Pd/C (10%), THF or MeOH, 8 h, 92–98%; (f) concd HCl, reflux, 2 h, 83%; (g) DPPA, DIPEA, benzene, r.t., 0.5 h, reflux, then BnOH (for **1e**) or *t*-BuOH, DPPA, Et_3N, reflux, 18 h (for **1f**,**g**), 70–43%; (h) NH_2OH, H_2O–EtOH, reflux, 3 h, quant; (i) 40 atm H_2, Raney Ni, MeOH–NH_3 (10%), 5 h, 75–89%; (j) $TMSO(CH_2)_3OTMS$, TMSOTf, CH_2Cl_2, –78 °C to r.t., 3 h, quant; (k) *m*-CPBA, CH_2Cl_2, 5 °C to r.t., 8 h, 85%.

formed into an amino group in two steps, as shown in Scheme 2. The resulting compounds **1h–j** were formed as mixtures of epimers at position 9. The isomers thus obtained are derivatives of different scaffolds possessing three points of variation.

The carbonyl group can also be reduced to give the deoxygenated scaffolds. This was demonstrated with compound **6a** (Scheme 3) through the formation of the *p*-tolylsulfonylhydrazone followed by reductive cleavage. This method (the Caglioti reaction) is well known,[15] but we developed a one-pot modification, which led to compound **9a** in quantitative yield. Thus, the *p*-tolylsulfonylhydrazone of **9a** was reduced with $NaBH_3CN$ in the presence of one equivalent of HCl in anhydrous methanol. Acetyl chloride was used as a convenient source of HCl; it can easily be quantified, and the intermediate hydrazine formed very cleanly. Thus, the hydrazine was transformed to the deoxygenated **9a** by reflux with sodium acetate in the same flask without isolation. Notably the acid-labile protecting group (Boc) tolerated the conditions of the carbonyl group removal. The NBoc and OBn groups were subsequently cleaved to obtain the deoxygenated amino acid (N-protected **1k** or fully deprotected **10a**).

The molecular structure of **10a** was established by X-ray crystallography, proving the *endo*-configuration at C(7) (Figure 1, a). Characteristic of this configuration is the vicinal coupling constant displayed by the C(7)-H signal in the ^{1}H NMR spectrum of **10a** (10.0 Hz, equatorial-equatorial coupling). Similar coupling constants were observed in the ^{1}H NMR spectra of the analogous compounds obtained (J = 7.5 Hz for **6b**; J = 6.0 Hz for **1b**) indicating that the *endo*-configuration at C(7) is the most probable for them as well. This is consistent with the formation of the bicyclic compounds with the C(7)-*endo* configuration by the double annulation reaction between **2** and **3** reported previously.[6] Notably, the mild conditions used, especially at the deprotection steps, prevented the epimerization at C(7) observed in earlier syntheses.[7b] The epimerization of **9a**, however, can be achieved almost completely in the presence of a base, as described previously for a carbocyclic analogue.[6b,c,12] The epimerized compound can also be deprotected stepwise, to give partly **1l** or fully deprotected amino acid **11a**. The molecular structure of **11a**·HCl was also confirmed by X-ray crystallography (Figure 1, b). The vicinal coupling constant for C(7)-H (axial-axial coupling) observed in the ^{1}H NMR spectrum of this compound (J = 12.5



Scheme 3 Further modifications of the scaffolds. *Reagents and conditions*: (a) $TsSO_2NHNH_2$, anhydrous EtOH, reflux, 0.5 h, quant; (b) $NaBH_3CN$, AcCl, MeOH, 0 °C, 0.5 h, then $NaOAc·3H_2O$, reflux, 3 h, quant; (c) 1 atm H_2, Pd/C (10%), THF, 8 h, 98%; (d) H_2O, reflux, 24 h, quant; (e) NaOMe in MeOH, reflux, 12 h, then H_2O, reflux, 5 h, citric acid to pH 5, 59%; (f) 10% HCl in 1,4-dioxane, r.t., 1 h, quant.

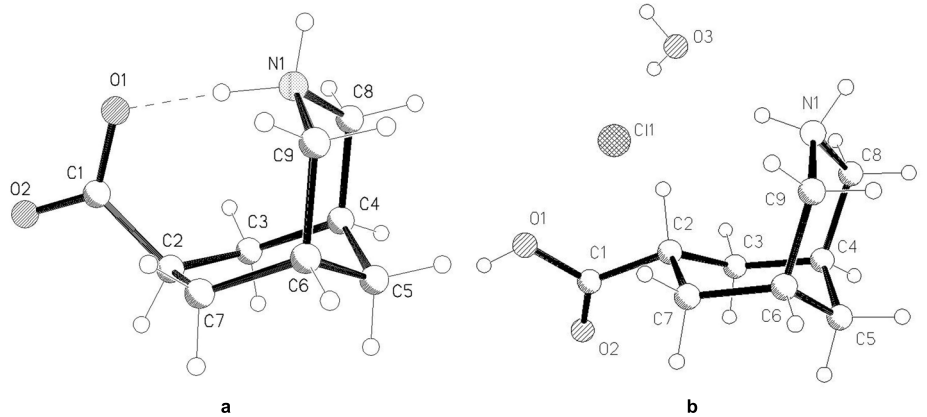


Figure 1 Molecular structures of **10a** (**a**) and **11a**·HCl (**b**) as determined by X-ray diffraction studies

Hz) as well as in **1l** (J = 13.0 Hz) is larger than the C(7)-H (equatorial-equatorial coupling) in the spectrum of **10a** (see above). Notably, the six-membered rings in **11a**·HCl adopt perfect chair conformations, while one of the six-membered rings in **10a** is considerably flattened, as can be seen from the molecular structures. The ring flattening in **10a** is clearly the result of steric interactions between the functional groups. Both non-natural amino acids **10a** and **11a** can be used for synthesis of isomeric peptidomimetics, providing the rigid scaffolds for unusual secondary structure elements.[16]

In conclusion, we have developed a practical synthetic procedure leading to functionalized 3-aza-, 3-oxa-, and 3-thiabicyclo[3.3.1]nonanes **1a**,**b**,**d**–**l**. The overall yield of the key intermediate products **6a**–**c** is 40%, and these are readily transformed further to generate chemically very diverse libraries of compounds for biological screening.

Solvents were purified according to standard procedures.[17] Melting points were measured on an automated melting point system and are uncorrected. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR, and all 2D NMR spectra were recorded at 499.9 or 400.4 MHz for ^{1}H and 124.9 or 100.4 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Mass spectra were recorded either on an Agilent 1100 LC/MSD SL instrument by chemical ionization (CI) or on a GCMS instrument with electron impact ionization (EI). CHN-analysis was done on an Elementar VarioMICRO Cube analyzer. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrophotometer.

2-Hydroxymethylacrylic Acid Benzyl Ester (4)

A 1 L round-bottomed flask was charged with paraformaldehyde (15.42 g, 0.51 mol), DABCO (57.2 g, 0.51 mol), and H_2O (250 mL). The contents of the flask were stirred for a few minutes until the DABCO had dissolved, then 1,4-dioxane (250 mL) and benzyl acrylate (249.9 g, 1.54 mol)[18] were added. The mixture was stirred at r.t. for 24 h. The organic layer was separated on a separatory funnel and the aqueous layer was extracted with MTBE (4 × 100 mL). The combined extracts and organic layer were evaporated on a rotary evaporator. The residue was dissolved in MTBE (500 mL) and washed with aq 10% citric acid (150 mL), and sat. aq $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and evaporated. Pure **4** was obtained by vacuum distillation; yield: 46 g (47%); bp 136–142 °C/0.5 mmHg. Analytical and spectral data for the obtained compound were identical to those described in the literature.[19]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 5 H), 6.31 (d, J = 1 Hz, 1 H), 5.87 (d, J = 1 Hz, 1 H), 5.22 (s, 2 H), 4.35 (d, J = 5.2 Hz, 2 H), 2.75 (t, J = 5.2 Hz, 1 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 166.0, 139.5, 135.7, 128.5, 128.2, 128.0, 125.7, 66.5, 61.8.

2-Bromomethylacrylic Acid Benzyl Ester (2)

Ester **4** (65 g, 0.34 mol) was dissolved in anhydrous Et_2O (500 mL) under argon, and the solution was cooled to –10 °C (ice/MeOH bath). PBr_3 (45.77 g, 16 mL, 0.17 mol) was added dropwise to the solution under stirring, keeping the temperature of the reaction mixture at 10 ± 2 °C. After the addition, the cooling bath was removed, and the mixture was stirred for ~1 h. After completion of the reaction (TLC, eluent: hexane–EtOAc, 2:1), H_2O (50 mL) was carefully added, the mixture was stirred for 10 min, and then diluted with hexane (100 mL). The organic layer was separated and washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated on a rotary evaporator. The residue was dissolved in MTBE (100 mL) and filtered through a silica gel pad (230–400 mesh, ~300 g on a glass sinter filter), and the pad was washed with MTBE (50 mL). The filtrate was evaporated and kept under vacuum (0.5 mmHg, 23 °C, 3 h). The product **2** was used in the next step without further purification; yield: 73.7 g (85%). Analytical and spectral data for the obtained compound were identical to those described in the literature.[19]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.33 (m, 5 H), 6.39 (s, 1 H), 5.98 (s, 1 H), 5.27 (s, 2 H), 4.21 (s, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 164.7, 137.4, 135.6, 129.5, 128.7, 128.4, 128.2, 67.1, 29.3.

Iminium Salts 5a–c; General Procedure

The freshly prepared enamine **3a**, **3b**, or **3c** (prepared analogously to the procedure described[7b] for the corresponding *N*-Bz derivative, 1 equiv) and DIPEA (i-Pr_2NEt; 0.1 equiv) were dissolved in MeCN (freshly distilled over P_2O_5) and the solution was heated to 60 °C under an argon atmosphere. 2-Bromomethylacrylic acid benzyl ester (**2**; 1 equiv) was added dropwise to the warm stirred mixture at the rate to maintain gentle reflux of the mixture (the reaction was exothermic). The mixture was refluxed for 3 h after the addition, then left for 8 h at r.t. The crystalline product **5a**, **5b**, or **5c** was filtered, washed on the filter (with anhydrous MeCN in the case of **5a** and anhydrous MTBE in the case of **5b**,**c**) and dried at 90 °C in vacuum. The obtained products were used in the next step without further purification. The salts are highly sensitive to moisture, therefore, their NMR spectra were measured in carefully dried $(CD_3)_2SO$ (distilled over pyromellitic anhydride). Despite the precautions, traces of the hydrolyzed products were still observed in the ^{1}H and ^{13}C NMR spectra of **5b**,**c** (below, only the assigned iminium salt signals are listed). Elemental analysis and IR spectra measurements should also be carried out with careful protection from moisture.

7-*endo*-1-(7-Benzyloxycarbonyl-3-*tert*-butoxycarbonyl-3-azabicyclo[3.3.1]non-9-ylidene)pyrrolidinium Bromide (5a)

Prepared from **2** (73.7 g, 0.29 mol), **3a** (0.29 mol, prepared from 57.58 g of *N*-Boc-4-piperidone), and DIPEA (3.73 g, 5.0 mL, 0.029 mol) in MeCN (400 mL); yield: 101.5 g (68%); white crystals; mp >235 °C (dec.).

IR (KBr): 2978, 2941, 2867 (CH), 1731 (C=O), 1688 (C=N$^+$), 1400, 1277, 1186, 1175 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.37 (m, 5 H_{arom}), 5.08 (s, PhCH_2, 2 H), 4.12, 4.04 [2 m, N$^+$$(CH_2)_2$ + 2(4)-H, 6 H], 3.39 and 3.27 [2 m, 1,5-H + 2(4)-H, 4 H], 2.65 (m, 7-H, 1 H), 2.44 (m, 2 H), 2.15 (m, 2 H), 2.08 [m, $(CH_2)_2$, 4 H], 1.41 (s, t-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 190.5, 186.4, 172.5, 154.8, 136.0, 128.6, 128.2, 128.1, 80.2, 66.0, 54.1, 49.8 (br), 38.1, 35.9, 31.9, 28.0, 24.0.

Anal. Calcd for $C_{25}H_{35}BrN_2O_4$: C, 59.17; H, 6.95; N, 5.52. Found: C, 59.30; H, 7.02; N, 5.43.

7-*endo*-1-(7-Benzyloxycarbonyl-3-oxabicyclo[3.3.1]non-9-ylidene)pyrrolidinium Bromide (5b)

Prepared from **2** (71.1 g, 0.28 mol), **3b** (0.28 mol, prepared from 27.9 g of 4-pyranone), and DIPEA (3.6 g, 4.8 mL, 0.028 mol) in MeCN (400 mL); yield: 52.0 g (47%); yellowish powder; mp 185–186 °C.

IR (KBr): 2929, 2752 (CH), 1729 (C=O), 1692 (C=N$^+$),1448, 1234, 1190 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.39–7.34 (m, 5 H$_{arom}$), 5.09 (s, PhCH_2, 2 H), 4.04 [m, N$^+$(CH_2)$_2$, 4 H], 3.96 (d, J = 11 Hz, 2,4-H, 2 H), 3.86 (d, J = 11 Hz, 2,4-H, 2 H), 3.11 (s, 1,5-H, 2 H), 2.75 (m, 6,8-H + 7-H, 3 H), 2.39 (m, 6,8-H, 2 H), 2.07 [m, (CH_2)$_2$, 4 H].

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 189.1, 171.9, 136.3, 128.6, 128.1, 128.0, 71.9, 65.9, 53.6, 36.2, 32.1, 23.9.

Anal. Calcd for $C_{20}H_{26}BrNO_3$: C, 58.83; H, 6.42; N, 3.43. Found: C, 58.76; H, 6.33; N, 3.16.

7-*endo*-1-(7-Benzyloxycarbonyl-3-thiabicyclo[3.3.1]non-9-ylidene)pyrrolidinium Bromide (5c)

Prepared from **2** (36.68 g, 0.144 mol), **3c** (0.144 mol, prepared from 16.7 g of 4-thiapyranone), and DIPEA (1.86 g, 2.5 mL, 0.014 mol) in MeCN (180 mL); yield: 39.0 g (64%); white flakes; mp 191–194 °C.

IR (KBr): 2980, 2755 (CH), 1714 (C=O), 1688 (C=N$^+$), 1432, 1319, 1168 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.37 (m, 5 H$_{arom}$), 5.12 (s, PhCH_2, 2 H), 4.20 and 3.91 [2 m, N$^+$(CH_2)$_2$, 2 H and 2 H], 3.68 (m, 1,5-H, 2 H), 3.36 (d, J = 13.0 Hz, 2,4-H, 2 H), 2.79 (d, J = 13.0 Hz, 2,4-H, 2 H), 2.61 (m, 7-H, 1 H), 2.40 (m, 6,8-H, 2 H), 2.24 (m, 6,8-H, 2 H), 2.04 [m, (CH_2)$_2$, 4 H].

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 192.6, 173.2, 136.1, 128.6, 128.1, 127.9, 65.9, 54.4, 127.9, 38.3, 38.0, 36.6, 31.1, 24.0.

Anal. Calcd for $C_{20}H_{26}BrNO_2S$: C, 56.60; H, 6.18; N, 3.30; S, 7.56. Found: C, 56.25; H, 6.01; N, 2.98; S, 7.18.

Hydrolysis of the Iminium Salts 5a–c; General Procedure

The iminium salts **5a**–**c** were hydrolyzed in a mixture H$_2$O/MTBE (4:1, 5 L in the case of **5a** and 1:5, 180 mL in the case of **5b**,**c**) under vigorous stirring for 1 h. The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 200 mL). The combined extracts and the organic layer were dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator. The obtained compounds **6a**–**c** (quantitative yields) were used for the next step without further purification. They were crystallized for analytical purpose from cold MTBE.

7-*endo*-9-Oxo-3-azabicyclo[3.3.1]nonane-3,7-dicarboxylic Acid 7-Benzyl Ester 3-*tert*-Butyl Ester (6a)

Prepared from **5a** (101.5 g, 0.2 mol) in a mixture of H$_2$O/MTBE (4:1; 5 L); yield: 74.0 g (quant); white crystals; mp 95–97 °C.

IR (KBr): 2981, 2858 (CH), 1729 (C=O), 1688 (C=O), 1437, 1389, 1365, 1231, 1162 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.37 (m, 5 H$_{arom}$), 5.09 (s, PhCH_2, 2 H), 4.16 (br s, 2,4-H, 2 H), 3.04 (br s, 2,4-H, 2 H), 2.43 (m, 3 H), 2.34 (m, 2 H), 2.18 (m, 2 H), 1.42 (s, t-C$_4$H$_9$, 9 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 215.4, 173.3, 155.4, 136.6, 128.9, 128.5, 128.2, 80.1, 66.2, 51.4 (br), 50.2 (br), 45.0, 36.9, 32.2, 28.4.

LC-MS (CI, + scan): m/z = 274.2 (M – Boc + 1), 336.1, 374.1 (M + 1), 397.1 (M + Na), 414.1 (M + 39).

Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.06; H, 7.58; N, 3.84.

7-*endo*-9-Oxo-3-oxabicyclo[3.3.1]nonane-7-carboxylic Acid Benzyl Ester (6b)

Prepared from **5b** (52.0 g, 0.129 mol) in a mixture of H$_2$O/MTBE (1:5, 180 mL); yield: 35.4 g (quant); yellowish powder; mp 64–65 °C.

IR (KBr): 3035, 2962, 2858 (CH), 1729 (C=O), 1448, 1312, 1234, 1189 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.36 (m, 5 H$_{arom}$), 5.14 (s, PhCH_2, 2 H), 4.15 (d, J = 11.5 Hz, 2,4-H, 2 H), 3.68 (d, J = 11.5 Hz, 2,4-H, 2 H), 2.97 (d, J = 14 Hz, 6,8-H, 2 H), 2.63 (t, J = 7.5 Hz, 7-H, 1 H), 2.32 (br s, 1,5-H, 2 H), 2.20 (dt, J = 17, 7.5 Hz, 6,8-H, 2 H).

^{13}C NMR (124.9 MHz, CDCl$_3$): δ = 213.5, 172.0, 135.7, 128.1, 128.0, 127.8, 73.6, 66.3, 48.1, 36.9, 32.6.

LC-MS (CI, + scan): m/z = 275.2 (M + 1).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.44; H, 6.75.

7-*endo*-9-Oxo-3-thiabicyclo[3.3.1]nonane-7-carboxylic Acid Benzyl Ester (6c)

Prepared from **5c** (39.0 g, 0.092 mol) in a mixture of H$_2$O/MTBE (1:5; 180 mL); yield: 26.7 g (quant); yellow powder; mp 71–72.5 °C.

IR (KBr): 3033, 2940, 2909 (CH), 1714 (C=O), 1432, 1319, 1168 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.34 (m, 5 H$_{arom}$), 5.14 (s, PhCH_2, 2 H), 3.20 (d, J = 12 Hz, 6,8-H, 2 H), 2.76 (m, 1,5-H, 2 H), 2.5–2.7 (m, 6,8-H + 2,4-H, 4 H), 2.40 (m, 7-H + 2,4-H, 3 H).

^{13}C NMR (124.9 MHz, CDCl$_3$): δ = 216.7, 173.1, 135.4, 128.2, 127.9, 127.7, 66.13, 44.6, 39.3, 37.1, 30.8.

LC-MS (CI, + scan): m/z = 291.2 (M + 1), 313.2 (M + Na).

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25, S, 11.04. Found: C, 66.53; H, 6.55, S, 11.42.

OBn Deprotection of Compounds 6a,b; General Procedure

The respective keto ester **6a**,**b** was dissolved in THF under an argon atmosphere. Pd/C (10%) was added, the flask was charged with H$_2$ gas and the content was shaken under H$_2$ (1 atm) for 8 h. After no starting material was left in the mixture (TLC, eluent: hexane–EtOAc, 1:1), the catalyst was filtered off, washed with warm MeOH (50 mL), and the filtrate was evaporated on a rotary evaporator by keeping the temperature not higher that 80 °C in the bath for **1a** (the Boc protection might cleave off at higher temperatures). The products were sufficiently pure for the further transformations. They were crystallized from MeOH for analytical purpose.

7-*endo*-9-Oxo-3-azabicyclo[3.3.1]nonane-3,7-dicarboxylic Acid 3-*tert*-Butyl Ester (1a)

Prepared from **6a** (74 g, 0.2 mol) in THF (500 mL) in the presence of 10% Pd/C catalyst (27 g); yield: 55.0 g (98%); white crystals; mp 126 °C.

IR (KBr): 2992, 2833 (CH), 1708 (C=O), 1436, 1392, 1368, 1222, 1174 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 4.34 (br s, 2 H), 3.07 (d, J = 9.3 Hz, 2 H), 2.50 (s, 2 H), 2.43–2.37 (5 H), 1.48 (s, 9 H).

^{13}C NMR (124.9 MHz, CDCl$_3$): δ = 215.3, 177.5, 155.2, 80.6, 50.9 (br), 44.5, 36.4, 31.6, 27.9.

LC-MS (CI, – scan): m/z = 282.1 (M – 1).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.39; H, 7.44; N, 4.93.

7-*endo*-9-Oxo-3-oxabicyclo[3.3.1]nonane-7-carboxylic Acid (1b)

Prepared from **6b** (35.4 g, 0.129 mol) in THF (400 mL) in the presence of 10% Pd/C catalyst (15 g); yield: 21.9 g (92%); white powder; mp 191 °C.

IR (KBr): 3021, 2941, 2854 (CH), 1712 (C=O), 1443, 1313, 1135 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 11.74 (br s, CO_2H, 1 H), 4.27 (d, *J* = 10.5 Hz, 2,4-H, 2 H), 3.73 (d, *J* = 10.5 Hz, 2,4-H, 2 H), 2.95 (d, *J* = 14.0 Hz, 6,8-H, 2 H), 2.66 (t, *J* = 6.0 Hz, 7-H, 1 H), 2.36 (s, 1,5-H, 2 H), 2.22 (dd, *J* = 6.0, 14.0 Hz, 6,8-H, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 213.6 (C=O), 178.2 (CO_2H), 73.6, 48.0, 36.8, 32.4.

LC-MS (CI, – scan): *m*/*z* = 183.0 (M – 1).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.66; H, 6.60.

Benzyl 7′-*endo*-Spiro[1,3-dioxane-2,9′-[3]thiabicyclo[3.3.1]nonane]-7′-carboxylate (7c)[20]

Compound **6c** (11.13 g, 38.3 mmol) and 1,3-bis(trimethylsilyloxypropane) (10.14 g, 46 mmol) were dissolved in anhydrous CH_2Cl_2 (90 mL) under an argon atmosphere. The solution was cooled to –78 °C (acetone/dry ice bath) and then trimethylsilyl triflate (0.5 g, 2 mmol) was added under stirring. The cooling bath was not removed; no more dry ice was added to it, and the mixture was stirred until the internal temperature became around 0 °C (it took approximately 3 h). Sat. aq $NaHCO_3$ (90 mL) was added, the mixture was stirred vigorously for 1 h at r.t., then the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer and extracts were dried (Na_2SO_4), the solvent was evaporated, and the residue was kept at 100 °C under vacuum (0.2 mm Hg). The obtained compound **7c** (quant) was sufficiently pure for the next transformations; yield: 14.0 g (quant); colorless oil; crystallized on standing; mp 82 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 5 H_{arom}), 5.11 (s, PhCH_2, 2 H), 3.88 [m, O$(CH_2)_2$, 4 H], 3.24 (d, *J* = 12 Hz, 6′,8′-H, 2 H), 2.72 (m, 1 H), 2.48 (m, 2 H), 2.43 (m, 4 H), 2.25 (d, *J* = 12 Hz, 2 H), 2.19 (m, 2 H), 1.71 (m, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 174.4 (C=O), 136.0, 128.1, 127.8, 127.6 (arom), 96.3 (spiro-C), 66.1, 58.1, 57.7, 35.6, 31.5, 30.4, 26.4, 24.8.

GC-MS (EI): *m*/*z* (%) = 348 (M^+, 25), 113 (100), 91 (88), 55 (30).

LC-MS (CI, + scan): *m*/*z* (%) = 371.1 (M + Na, 77), 349.2 (M + 1, 100).

Benzyl 7′-*endo*-Spiro[1,3-dioxane-2,9′-[3]thiabicyclo[3.3.1]nonane]-7′-carboxylate 3′,3′-Dioxide (8d)

Compound **7c** (11.68 g, 34 mmol) was dissolved in CH_2Cl_2 (50 mL), and the solution was cooled in an ice bath (1–5 °C internal temp). *m*-Chloroperbenzoic acid (17.3 g, 100 mmol) in CH_2Cl_2 (50 mL) was added to the solution under stirring. The cooling bath was removed and the mixture was stirred for 8 h at r.t. The reaction mixture was washed with sat. aq Na_2SO_3 (5 × 50 mL), dried (Na_2SO_4), and evaporated. The residue was recrystallized from benzene to afford **8d**; yield: 11 g (85%); white crystals; mp 134–135 °C.

^1H NMR (500 MHz $CDCl_3$): δ = 7.35 (m, 5 H_{arom}), 5.11 (s, PhCH_2, 2 H), 3.90 [m, O$(CH_2)_2$, 4 H], 3.47 (d, *J* = 12 Hz, 6′,8′-H, 2 H), 3.12 (m, 1 H), 2.91 (m, 4 H), 2.51 (t, *J* = 12 Hz, 2 H), 2.33 (m, 2 H), 1.77 (m, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 174.4 (C=O), 135.7, 128.2, 127.7, 127.6 (arom), 95.8 (spiro-C), 65.9, 59.2, 54.5, 32.7, 31.1, 25.0, 24.3.

LC-MS (CI, + scan): *m*/*z* = 273.2, 381.2 (M + 1).

Anal. Calcd for $C_{19}H_{24}O_6S$: C, 59.98; H, 6.36, S, 8.43. Found: C, 59.94; H, 6.38, S, 8.45.

7-*endo*-9-Oxo-3-thiabicyclo[3.3.1]nonane-7-carboxylic Acid 3,3-Dioxide (1d)

Compound **8d** (9.04 g, 23.8 mmol) was dissolved in MeOH (50 mL), the solution was combined with 10% Pd/C (3 g), and hydrogenated (1 atm H_2) for 8 h. The catalyst was filtered off, washed several times with warm MeOH (50 mL), and the filtrate was evaporated to obtain 7′-*endo*-spiro[1,3-dioxane-2,9′-[3]thiabicyclo[3.3.1]nonane]-7′-carboxylic acid 3′,3′-dioxide (6.9 g, quant), sufficiently pure for the next transformations (contained residual MeOH, <3 mol%).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.88 (m, OCH_2, 4 H), 3.23 (d, *J* = 13.0 Hz, 2,4-H, 2 H), 2.99 (d, *J* = 13.0 Hz, 2,4-H, 2 H), 2,92 (d, *J* = 10.0 Hz, 1,5-H, 2 H), 2.82 (tt, *J* = 8.0, 11.0 Hz, 7-H, 1 H), 2.19 (m, 6,8-H, 2 H), 2.10 (m, 6,8-H, 2 H), 1.64 (m, $CH_2CH_2CH_2$, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 176.5 (CO_2H), 96.1 (OCO), 59.2, 59.0, 54.7, 32.6, 30.8, 25.3, 24.4).

This intermediate compound was suspended in concd HCl (100 mL), and set to a gentle reflux under stirring. The starting carboxylic acid dissolved first, then the product **1d** started to precipitate. After 2 h of the reflux, the reaction mixture was cooled in an ice bath, filtered, and the product was washed thoroughly on the filter with cold H_2O (5 × 30 mL), dried at 50 °C under vacuum (0.2 mmHg) for 5 h to afford **1d**; yield: 4.5 g (83%); white crystals; mp 286–287 °C.

IR (KBr): 3028, 2944 (CH), 1705 (C=O), 1412, 1325 (S=O), 1319, 1140 cm^{-1} (S=O).

^1H NMR (400.4 MHz, DMSO-d_6): δ = 3.68 (dd, *J* = 5.2, 14.4 Hz, 2,4-H, 2 H), 3.56 (d, *J* = 14.4 Hz, 2,4-H, 2 H), 2.83 (m, 1,5-H, 2 H), 2.76 (pent, *J* = 13.2 Hz, 6,8-H, 2 H), 2.32 (m, 6,8-H + 7-H, 3 H).

^{13}C NMR (100.4 MHz, DMSO-d_6): δ = 211.4 (C=O), 175.0 (CO_2H), 56.0, 41.3, 35.3, 30.3.

LC-MS (CI, – scan): *m*/*z* = 231.2 (M – 1).

Anal. Calcd for $C_{12}H_{18}O_6S$: C, 49.64; H, 6.25, S, 11.04. Found: C, 49.66; H, 6.28, S, 11.00.

Curtius Rearrangement of Compound 1a;[21] *tert*-Butyl 7-*endo*-7-{[(Benzyloxy)carbonyl]amino}-9-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (1e)

A mixture of the keto acid **1a** (55.0 g, 0.194 mol), DPPA (64.1 g, 50.2 mL, 0.233 mol), and DIPEA (diphenyl phosphoryl azide; 30.1 g, 40.57 mL, 0.233 mol) in anhydrous benzene (500 mL) was stirred at r.t. for 0.5 h, and then refluxed for another 0.5 h. Benzyl alcohol (25.19 g, 24.1 mL, 0.233 mol) was added to the reaction mixture and the reflux continued for another 17 h. The mixture was cooled, washed with 5% aq citric acid (2 × 100 mL), sat. aq $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was crystallized from MTBE–benzene mixure (1:10) to obtain the pure product **1e**; yield: 53.0 g (70%); white crystals; mp 136 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.30 (5 H_{arom}), 5.07 (s, PhCH_2, 2 H), 4.71 (s, 1 H), 4.32 (d, *J* = 10.2 Hz, 2 H), 3.62 (s, 1 H), 3.02 (d, *J* = 12.3 Hz, 2 H), 2.5–2.4 (m, 4 H), 1.77 (t, *J* = 10.2 Hz, 2 H), 1.49 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 214.5, 155.3, 154.9, 135.9, 128.2, 127.9, 80.1, 66.5, 51.3, 44.5, 43.9, 35.3, 28.0.

LC-MS (CI, + scan): *m*/*z* = 289.0 (M – Boc + 1), 411.0 (M + Na).

Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.95; H, 7.23; N, 7.25.

Curtius Rearrangement of Compounds 1b,d;[21] General Procedure

A mixture of the keto acid **1b** or **1d** (1 equiv), DPPA (1 equiv), Et_3N (1.05 equiv), and freshly distilled *t*-BuOH (32 equiv) was refluxed for 18 h, and then evaporated. The residue was taken up in benzene (200 mL), washed with sat. aq $NaHCO_3$ (4 × 50 mL), H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. The products were crystallized from benzene to obtain the pure product **1f** or **1g** as white crystals.

7-*endo*-7-{[(*tert*-Butyloxy)carbonyl]amino}-9-oxo-3-oxabicyclo[3.3.1]nonane (1f)

Prepared from **1b** (52.7 g, 0.29 mol), DPPA (78.74 g, 61.66 mL, 0.29 mol), and Et_3N (30.4 g, 41.8 mL, 0.3 mol) in *t*-BuOH (860 mL); yield: 33 g (45%); mp 154 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.61 (d, *J* = 9 Hz, NH, 1 H), 4.19 (br d, *J* = 11.5 Hz,, 2,4-H, 2 H), 4.03 (br s, 7-H, 1 H), 3.83 (d, *J* = 9 Hz, NH, 1 H), 2.47 (m, 6,8-H, 2 H), 2.39 (s, 1,5-H, 2 H), 2.13 (d, *J* = 14.5 Hz, 6,8-H, 2 H), 1.45 (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 213.3, 155.1, 78.8, 73.4, 47.9, 40.8, 38.8, 28.1.

LC-MS (CI, + scan): *m*/*z* = 200.1 (M – *t*-Bu + 1), 278.1 (M + Na), 296.1 (M + Na + H_2O).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.55; H, 8.61; N, 5.58.

tert-Butyl 7-*endo*-(3,3-Dioxido-9-oxo-3-thiabicyclo[3.3.1]non-7-yl)carbamate (1g)

Prepared from **1d** (21.3 g, 0.092 mol), DPPA (25.24 g, 19.76 mL, 0.092 mol), and Et_3N (9.74 g, 13.4 mL, 0.096 mol) in *t*-BuOH (275 mL); yield: 12.0 g (43%); mp 213–214 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.59 (br s, NH, 1 H), 3.67 (br s, 7-H, 1 H), 3.55 (d, *J* = 14 Hz, 2,4-H, 2 H), 3.36 (d, *J* = 14 Hz, 2,4-H, 2 H), 2.95 (d, *J* = 9.5 Hz, 1,5-H, 2 H), 2.72 (pent, *J* = 12.5 Hz, 6,8-H, 2 H), 2.49 (dd, *J* = 12.5, 9.5 Hz, 6,8-H, 2 H), 1.42 (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 210.2 (C=O), 154.5 (NHCO), 79.6 [*C*$(CH_3)_3$], 57.9, 42.8, 41.2, 32.2, 28.0.

LC-MS (CI, + scan): *m*/*z* = 248.2 (M – *t*-Bu + 1).

Anal. Calcd for $C_{13}H_{21}NO_5S$: C, 51.47; H, 6.98; N, 4.62; S, 10.57. Found: C, 51.44; H, 6.99; N, 4.66; S, 10.55.

Reductive Amination of Compounds 1e, 1f, and 1g; General Procedure

A suspension of the carbonyl compound **1e**, **1f**, or **1g** (1 equiv) in EtOH (50 mL) was combined with a solution of NH_2OH, separately prepared by neutralization of an aqueous solution of NH_2OH·HCl (1.4 equiv) with $NaHCO_3$ (1.4 equiv). The mixture was refluxed for 3 h. Then, the mixture was evaporated to half the volume on a rotary evaporator, diluted with brine (100 mL), and the product (in the case of **1e**,**f**) was extracted with MTBE (4 × 70 mL) or filtered (in the case of **1g**). The combined organic extracts were dried (Na_2SO_4), evaporated, and the residue was kept in vacuum at 75 °C. The obtained oximes (light yellow solids; quantitative chemical yields) were used in the next step without further purification.

tert-Butyl 7-*endo*-7-(Benzyloxycarbonyl)-9-(hydroxyimino)-3-azabicyclo[3.3.1]nonane-3-carboxylate

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.24 (s, NOH, 1 H), 7.32 (m, 5 H_{arom}), 5.06 (s, OCH_2, 2 H), 4.86 (d, *J* = 8.0 Hz, NH, 1 H), 4.12 (m, 2,4-H, 2 H), 3.68 [d, *J* = 8.5 Hz, 1(5)-H, 1 H], 3.58 (br s, 7-H, 1 H), 2.86 (m, 2,4-H, 2 H), 2.64 [d, *J* = 8.5 Hz, 5(1)-H, 1 H], 2.37 (m, 6,8-H, 2 H), 1.46 (m, *t*-C_4H_9 + 6,8-H, 11 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 159.8, 155.7, 155.3, 136.0, 128.2, 127.9, 127.8, 80.12, 66.4, 51.2 (br), 49.5 (br), 44.2, 34.7, 34.6, 33.9, 28.0, 27.6.

tert-Butyl 7-*endo*-9-(Hydroxyimino)-3-oxabicyclo[3.3.1]nonan-7-ylcarbamate

^{1}H NMR (500 MHz $CDCl_3$): δ = 9.05 (s, NOH, 1 H), 6.69 (d, *J* = 10.5 Hz, NH, 1 H), 3.90–4.20 (m, 2,4-H + 7-H, 3 H), 3.71 and 3.68 (2 d, *J* = 11.5 Hz, 2,4-H, 2 H), 3.43 [s, 1(5)-H, 1 H], 2.43 [s, 5(1)-H, 1 H], 2.27 (m, 6,8-H, 2 H), 1.93 and 1.90 (2 d, *J* = 14 Hz, 6,8-H, 2 H), 1.44 (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 160.4, 155.3, 78.6, 72.8, 71.3, 41.26, 37.9, 36.8, 36.5, 30.6, 28.1.

tert-Butyl 7-*endo*-9-(Hydroxyimino)-3,3-dioxido-3-thiabicyclo[3.3.1]nonan-7-ylcarbamate

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.09 (s, NOH, 1 H), 6.97 (br s, NH, 1 H), 3.99 (m, 7-H, 1 H), 3.25 [m overlapped with H_2O residual signal, 2,4-H + 1(5)-H, 3 H], 3.11 [m, 2,4-H + 5(1)-H, 3 H], 2.17 and 2.03 (m, 3 H and 1 H, 6,8-CH_2), 1.34 (s, *t*-Bu-H, 9 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 155.0, 154.5, 77.7, 58.4, 56.6, 44.2, 33.3, 31.07, 30.0, 28.3, 25.0).

The oximes obtained as described above were hydrogenated in an autoclave at 40 atm of H_2 and r.t. in a 10% ammonia solution in MeOH in the presence of a freshly prepared Raney Ni (~10% of the weight of the substrate). The progress of the reaction was monitored by TLC (eluent: hexane–EtOAc, 1:2). After the disappearance of the starting oxime (~8 h), the mixture was filtered through a silica gel pad, and evaporated on a rotary evaporator. The residue was dissolved in MTBE (100 mL) and the solution was washed with H_2O (50 mL). The organic layer was then dried (Na_2SO_4) and evaporated on a rotary evaporator, keeping the bath temperature not higher than 50 °C. Glassy colourless solids, 88–93% yield.

tert-Butyl 7-*endo*-9-Amino-7-{[(benzyloxy)carbonyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate (1h, mixture of epimers)

The oxime was prepared from **1e** (16.0 g, 0.039 mol) in EtOH (50 mL), combined with a solution of NH_2OH·HCl (3.75 g, 0.054 mol) and $NaHCO_3$ (4.54 g, 0.054 mol) in H_2O (50 mL). The oxime obtained (16 g) was hydrogenated in a 10% ammonia solution in MeOH (100 mL) to give **1h**; yield: 13.5 g (0.035 mol, 89%); glassy solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (m, 5 H_{arom}), 5.48 (t, *J* = 12 Hz, NH, 1 H), 4.97 (s, OCH_2, 2 H), 3.99 (br s, 0.5 H), 3.90 (br s, 0.5 H), 3.81 (d, *J* = 13 Hz, 1 H), 3.51 (d, *J* = 12.5 Hz, 1 H), 3.27 (d, *J* = 12.5 Hz, 1 H), 2.93 (m, 2 H), 2.31 (m, 1 H), 2.03 (m, 1 H), 1.72 (m, 2 H), 1.65 (d, *J* = 13 Hz, 1 H), 1.38 (m, 2 H), 1.30 (s, *t*-C_4H_9, 9 H), 1.14 (br m, 2 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 156.1, 156.0, 155.4, 155.3, 136.3, 136.2, 127.92, 127.90, 127.86, 127.80, 127.77, 127.5, 127.4, 80.0, 79.7, 65.95, 65.9, 50.1, 49.1, 48.4, 42.0, 41.93, 41.92, 41.3, 41.1, 35.9, 33.1, 33.0, 28.8, 28.0, 27.8.

LC-MS (CI, + scan): *m*/*z* = 290.1 (M – Boc + 1).

Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.72; H, 8.06; N, 10.76.

7-*endo*-(9-Amino-3-oxabicyclo[3.3.1]non-7-yl)carbamic Acid *tert*-Butyl Ester (1i, mixture of epimers)

The oxime was prepared from **1f** (13.3 g, 0.052 mol) in EtOH (50 mL), combined with a solution of $NH_2OH{\cdot}HCl$ (5.06 g, 0.073 mol) and $NaHCO_3$ (6.12 g, 0.073 mol) in H_2O (50 mL). The oxime obtained (13.1 g) was hydrogenated in a 10% ammonia solution in MeOH (100 mL) to give **1i**; yield: 10.0 g (0.039 mol, 75%); glassy colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 and 6.89 (2 d, *J* = 10.0 Hz, NH, 0.5 H and 0.5 H), 4.12 and 3.95 (2 d, *J* = 11.0 Hz, 2,4-H, 1 H and 1 H), 4.02 (m, 7-H, 1 H), 3.67 and 3.62 (2 d, *J* = 11.0 Hz, 2,4-H, 1 H and 1 H), 3.08 (s, 9-H, 0.5 H), 2.94 (s, 9-H, 0.5 H), 2.34 [m, 6(8)-H, 1 H], 2.11 [m, 6(8)-H, 1 H], 1.83 [d, *J* = 14 Hz, 6(8)-H, 1 H], 1.61 [s, 1(5)-H, 1 H], 0.75–1.55 [overlapped m, 6(8)-H, 5(1)-H, NH_2, *t*-C_4H_9, 13 H].

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 155.5, 155.4, 78.1, 71.7, 64.3, 50.2, 49.8, 40.5, 40.2, 36.8, 35.0, 34.9, 28.8, 28.2.

LC-MS (CI, + scan): *m*/*z* = 157.2 (M – Boc + 1), 200.1 (M – *t*-Bu + 1), 279.1 (M + Na).

Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.95; H, 9.47; N, 10.90.

7-*endo*-(9-Amino-3,3-dioxo-3-thiabicyclo[3.3.1]non-7-yl)carbamic Acid *tert*-Butyl Ester (1j; mixture of epimers)

The oxime was prepared from **1g** (11.69 g, 0.039 mol) in EtOH (50 mL), combined with a solution of $NH_2OH{\cdot}HCl$ (3.75 g, 0.054 mol) and $NaHCO_3$ (4.54 g, 0.054 mol) in H_2O (50 mL). The oxime obtained (11.5 g) was hydrogenated in a 10% ammonia solution in MeOH (400 mL) to give **1j**; yield: 9.0 g (0.03 mol, 76%); glassy colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.66 (m, 7-H, 0.86 H), 4.58 (d, *J* = 8.5 Hz, NH, 0.59 H), 4.52 (d, *J* = 11 Hz, NH, 0.19 H), 3.70 (d, *J* = 13 Hz, 2,4-H, 0.36 H), 3.48 (t, *J* = 3 Hz, 9-H, 0.19 H), 3.22 (d, *J* = 13 Hz and br m, 2.17 H), 3.01 (d, *J* = 13 Hz, 2,4-H, 1.54 H), 2.69 (d, *J* = 13 Hz, 2,8-H, 0.36 H), 2.49 (m, 1.78 H), 2.21–2.40 (m, 1.93 H), 1.95 (t, *J* = 13 Hz, 0.46 H), 1.75–1.82 (m, 3.22 H), 1.38 (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, $CDCl_3$): δ = 155.1, 154.9, 78.9, 78.7, 57.9, 51.5, 51.4, 42.5, 40.9, 39.6, 33.2, 29.9, 29.2, 28.0.

LC-MS (CI, + scan): *m*/*z* = 249.1 (M – *t*-Bu + 1).

Anal. Calcd for $C_{13}H_{24}N_2O_4S$: C, 51.29; H, 7.95; N, 9.20; S, 10.53. Found: C, 51.33; H, 7.94; N, 9.22; S, 10.57.

Modified Caglioti Reaction; 7-Benzyl 3-*tert*-Butyl 7-*endo*-3-Azabicyclo[3.3.1]nonane-3,7-dicarboxylate (9a)

The keto ester **6a** (27 g, 78.6 mmol) and *p*-tolylsulfonylhydrazine (16 g, 86.4 mmol) were dissolved in anhydrous EtOH (80 mL) in a 250 mL round-bottomed flask. The mixture was refluxed for 0.5 h, then left standing at r.t. for 18 h. The crystalline precipitate was filtered, washed with cold EtOH (20 mL), and dried in vacuum. The product, 7-benzyl 3-*tert*-butyl 7-*endo*-9-{[(4-methylphenyl)sulfonyl]hydrazono}-3-azabicyclo[3.3.1]nonane-3,7-dicarboxylate, proved to be sufficiently pure for the further transformations; yield: 34.1 g (80%); white crystals; mp 173 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.4 (s, NH, 1 H), 7.74 (d, *J* = 8 Hz, *o*-Ts, 2 H), 7.38 (m, 7 H_{arom}), 5.04 (s, PhCH_2, 2 H), 3.97 (br s, 2,4-H, 2 H), 3.25 (s, 1 H), 2.74 (br s, 2,4-H, 2 H), 2.42 (s, 1 H), 2.36 (s, CH_3, 3 H), 2.08 (m, 3 H), 1.88 (m, 2 H), 1.38, (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 173.5, 164.2, 155.5, 143.6, 136.8, 136.6, 129.9, 128.9, 128.5, 128.3, 127.9, 79.8, 66.1, 51.4 (br), 50.6 (br), 49.9 (br), 49.0 (br), 37.6, 37.2, 31.6, 31.4, 30.8, 28.5, 21.5.

LC-MS (CI, + scan): *m*/*z* = 542.1 (M + 1).

LC-MS (CI, – scan): *m*/*z* = 540.2 (M – 1).

The obtained *p*-tolylsulfonylhydrazone (33.7 g, 62.2 mmol) and $NaBH_3CN$ (7.82 g, 124.4 mmol) were dissolved in anhydrous MeOH (300 mL) in a 1 L round-bottomed flask under argon. The mixture was cooled to –10 °C (dry ice/acetone bath). AcCl (4.88 g, 4.42 mL, 62.2 mmol) was added to the mixture at a rate by keeping the temperature not higher than 0 °C under stirring. The stirring was continued for 1 h at 0 °C, then $NaOAc{\cdot}3H_2O$ (84 g, 622 mmol) and MeOH (300 mL) were added, and the mixture was refluxed for 3 h. The mixture was then evaporated on a rotary evaporator, H_2O (200 mL) was added to the residue, and the product **9a** was extracted with MTBE (4 × 300 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuum; yield: 22.4 g (quant); white crystals. The product **9a** was crystallized from MTBE for analytical purpose; white crystals; mp 97–100 °C.

IR (KBr): 2976, 2909, 2860 (CH), 1720 (C=O), 1689 (C=O), 1455, 1394, 1318, 1181 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.45–7.30 (m, 5 H_{arom}), 5.02 (s, PhCH_2, 2 H), 3.78 (d, *J* = 12 Hz, 2,4-H, 2 H), 2.79 (d, *J* = 12 Hz, 2,4-H, 2 H), 2.59 (m, 1 H), 2.01 (m, 2 H), 1.93 (m, 4 H), 1.63 (d, *J* = 12 Hz, 9-H, 1 H), 1.40 (m, *t*-C_4H_9 + 9-H, 10 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 174.0, 156.0, 136.9, 128.9, 128.3, 128.2, 78.9, 65.9, 49.9 (br), 49.0 (br), 36.3, 30.2, 29.7, 28.6, 26.5.

LC-MS (CI, + scan): *m*/*z* = 304.2 (M – *t*-Bu + 2).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.48; H, 8.02; N, 4.08.

7-*endo*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (1k)

This compound was obtained by the hydrogentaion of **9a** (5.0 g, 0.014 mol) in THF (50 mL) in the presence of 10% Pd/C (1.0 g) as a catalyst, as described above for **6a**,**b**; yield: 3.67 g (98%); white crystals; mp 145–146 °C.

IR (KBr): 3223 (OH), 2944, 2872 (CH), 1732 (C=O), 1647 (C=O), 1443, 1371, 1250, 1168 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.56 (br s, CO_2H, 1 H), 3.77 (br s, 2,4-H, 2 H), 2.78 and 2.65 (br s, 2,4-H, 2 H), 2.38 (br s, 1 H), 1.93 (br m, 4 H), 1.60–1.70 (m, 3 H), 1.39 (s, *t*-C_4H_9, 9 H), 1.30 (d, *J* = 13 Hz, 9-H, 1 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 176.3, 155.6, 78.7, 50.6 (br), 49.6 (br), 35.8, 29.2, 28.7, 28.6, 26.1.

LC-MS (CI, – scan): *m*/*z* = 268.0 (M – 1).

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.32; H, 8.89; N, 4.95.

7-*endo*-3-Azabicyclo[3.3.1]nonane-7-carboxylic Acid (10a)

The *N*-Boc-protected amino acid **1k** (1 g, 3.7 mmol) was refluxed in distilled H_2O (70 mL) for 24 h. At the end of this period, all the insoluble starting material was dissolved. The reaction mixture was evapo-

rated in vacuum, and the residue was kept in a dessicator over P_2O_5 for 24 h to give **10a**; yield: 0.63 g (quant); yellow powder; mp >300 °C (dec.).

IR (KBr): 3421 (NH), 2924 (CH), 1639 (C=O), 1552 (C=O), 1405, 1240 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 3.13 (d, *J* = 12.5 Hz, 2,4-H, 2 H), 3.04 (dd, *J* = 12.5, 2.5 Hz, 2,4-H, 2 H), 2.69 (tt, *J* = 10.0, 2.5 Hz, 7-H, 1 H), 2.16 (dd, *J* = 15.0, 10.0 Hz, 6,8*e*-H, 2 H), 2.11 (s, 1,5-H, 2 H), 1.70 (d, *J* = 15.0 Hz, 6,8*a*-H, 2 H), 1.62 (s, 9-CH_2, 2 H).

^{13}C NMR (124.9 MHz, D_2O): δ = 187.6 (CO_2H), 48.2, 36.3, 28.7, 27.6, 24.3.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.59; H, 8.87; N, 7.99.

X-ray Structure Determination[22]

Crystal data: $C_9H_{15}NO_2$, M = 169.22, monoclinic, space group $P2_1/c$, *a* = 9.4108(13), *b* = 7.0766(7), *c* = 12.5232(15) Å, *β* = 93.129(6)°, V = 832.76(17) Å^3, Z = 4, d_c = 1.35 g·cm^{-3}, μ = 0.095 mm^{-1}, F(000) = 368, crystal size ca. 0.42 × 0.29 × 0.25 mm. The measurements were performed on a SMART APEX II diffractometer at room temperature using Mo-Kα radiation with the omega scans technique. Intensity data of 7145 reflections were collected within range 2.17≤θ≤27.80° (1975 unique reflections R_{merg} = 0.063). Data were corrected for Lorenz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using SHELXS97 and SHELXL97 programs.[23] All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model, two NH hydrogen atoms were found in difference Fourier map and refined isotropically. Convergence was obtained at *R*1 = 0.0515 and *wR*2 = 0.1191, GOF = 1.035 for 1375 reflections with I ≥ 2σ(I) (117 parameters; observed/variable ratio 11.7). The largest and minimal peaks in the final difference map 0.26 and –0.21 e/Å^3, weighting scheme ω = 1/[ρ^2(Fo^2) + (0.0495P)^2 + 0.3067P], where P = (Fo^2 + 2Fc^2)/3.

7-*exo*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (11)

Na (2.4 g, 0.104 mol) was dissolved in anhydrous MeOH (100 mL) under an argon atmosphere. Compound **9a** (2 g, 5.6 mmol) was added, and the mixture was refluxed for 12 h (^{13}C NMR control). H_2O (50 mL) was carefully added, and the reflux continued for 5 h. The mixture was then evaporated to half the volume, washed with MTBE (2 × 50 mL), and acidified with concd aq citric acid till pH ~5. The precipitate formed was filtered, washed with H_2O (10 mL), and dried in air. The crude product thus obtained contained compounds **11** and **1k** in ~9:1 molar ratio; yield: 0.86 g (59%). Pure **11** was obtained from the crude product by crystallization from a CH_2Cl_2–hexane mixture (3:1) as white crystals; mp 138–140 °C.

IR (KBr): 3253 (OH), 2948, 2876 (CH), 1734 (C=O), 1646 (C=O), 1440, 1377, 1255, 1166 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.98 (br s, CO_2H, 1 H), 3.93 (br m, 2,4-H, 2 H), 3.00 and 2.88 (br s, 2,4-H, 2 H), 2.75 (tt, *J* = 13.0, 5.0 Hz, 7-H, 1 H), 1.88 (m, 4 H), 1.62 (m, 3 H), 1.53 (d, *J* = 14 Hz, 1 H), 1.39 (s, *t*-C_4H_9, 9 H).

^{13}C NMR (124.9 MHz, DMSO-d_6): δ = 177.0 (CO_2H), 154.2 (NC=O), 78.7 [$C(CH_3)_3$], 49.0 [br, 4(8)-C], 47.8 [br, 8(4)-C], 36.6, 33.1, 31.7, 28.3, 27.3.

LC-MS (CI, + scan): *m*/*z* = 214.2 (M – *t*-Bu + 1).

LC-MS (CI, – scan): *m*/*z* = 268.2 (M – 1).

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.40; H, 8.66; N, 5.22.

7-*exo*-3-Azabicyclo[3.3.1]nonane-7-carboxylic Acid Hydrochloride (11a·HCl)

Compound **11** (500 mg, 1.86 mmol) was dissolved in a 10% solution of HCl in 1,4-dioxane (20 mL). The mixture was left standing for 1 h, then cooled in an ice bath. The precipitate of **11a**·HCl was filtered, washed with anhydrous MTBE (20 mL) on the filter, and dried at 40 °C in vacuum. The yield of the crude product was quantitative (382 mg). Pure **11a**·HCl for analytical purposes was obtained by crystallization from H_2O followed by drying at 40 °C in vacuum; white crystals; mp >280 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 3.27 (d, *J* = 13.5 Hz, 2,4-H, 2 H), 3.18 (d, *J* = 13.5 Hz, 2,4-H, 2 H), 2.87, (tt, *J* = 8, 12.5 Hz, 7-H, 1 H), 2.15 (s, 1,5-H, 2 H), 1.97 (d, *J* = 11 Hz, 6,8-H, 2 H), 1.62–1.83 (m, 6,8-H + 9-H, 3 H), 1.60 (d, *J* = 12.5 Hz, 9-H, 1 H).

^{13}C NMR (124.9 MHz, D_2O): δ = 179.2 (CO_2H), 46.9, 36.4, 30.5, 28.3, 24.7.

Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.58; H, 7.88; N, 6.80.

X-ray Structure Determination[22]

Crystal data: $C_9H_{18}ClNO_3$, M=223.69, monoclinic, space group $P2_1/n$, *a* = 8.5696(4), *b* = 11.8842(4), *c* = 10.6926(3) Å, *β* = 101.297(2)°, *V* = 1067.87(7) Å^3, *Z* = 4, d_c = 1.391 g·cm^{-3}, *μ* = 0.341 mm^{-1}, *F*(000) = 480, crystal size is ca. 0.42 × 0.29 × 0.25 mm. The measurements were performed on a SMART APEX II diffractometer at room temperature using Mo-Kα radiation with the omega scans technique. Intensity data of 5223 reflections were collected within range 2.59≤*θ*≤26.37° (2175 unique reflections R_{merg} = 0.0208). Data were corrected for Lorenz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using SHELXS97 and SHELXL97 programs.[23] Hydrogen atoms were found in difference Fourier maps and refined isotropically. Convergence was obtained at *R*1 = 0.0350 and *wR*2 = 0.0857, GOF = 1.055 for 1835 reflections with *I* ≥ 2σ(*I*) (199 parameters; observed/variable ratio 9.22). The largest and minimal peaks in the final difference map 0.48 and –0.19 e/Å^3, weighting scheme ω = 1/[ρ^2(Fo^2) + (0.041P)^2 + 0.337P], where P = (Fo^2 + 2Fc^2)/3.

Acknowledgment

Financial assistance from Enamine Ltd. (www.enamine.net) is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379456.

References

(1) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.
(2) For some representative reviews, see: (a) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. *Chem. Soc. Rev.* **2011**, *40*, 3445. (b) Grygorenko, O. O.; Radchenko, D. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Komarov, I. V. *Chem. Rev.* **2011**, *111*, 5506.

(c) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524. (d) Trabocchi, A.; Scarpi, D.; Guarna, A. *Amino Acids* **2008**, *34*, 1. (e) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) Kumar, K.; Wetzel, S.; Waldmann, H. In *Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Academic/Elsevier: Amsterdam, **2008**, 187–209.

(4) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46. (b) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867.

(5) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discov. Dev.* **2006**, *9*, 700.

(6) (a) Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 2884. (b) Nelson, R. P.; McEuten, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. (c) McEuten, J. M.; Nelson, R. P.; Lawton, R. G. *J. Org. Chem.* **1970**, *35*, 690.

(7) (a) Dekkers, A. W. J. D.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1971**, 489. (b) Stetter, H.; Reinartz, W. *Chem. Ber.* **1972**, *105*, 2773. (c) Mazurov, A. A.; Kombo, D. C.; Akireddy, S.; Murthy, S.; Hauser, T. A.; Jordan, K. G.; Gatto, G. J.; Yohannes, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3927.

(8) (a) Yeh, V. S. C.; Kurukulasuriya, R.; Madar, D.; Patel, J. R.; Fung, S.; Monzon, K.; Chiou, W.; Wang, J.; Jacobson, P.; Sham, H. L.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5408. (b) Yu, J.; Liu, H.; Xia, G.; Liu, L.; Xu, Zh.; Chen, Q.; Ma, C.; Sun, X.; Xu, J.; Li, H.; Li, P.; Shi, Y.; Xiong, B.; Liu, X.; Shen, J. *ACS Med. Chem. Lett.* **2012**, *3*, 793.

(9) (a) Meeuwissen, H. J.; van der Knaap, T. A.; Bickelhaupt, F. *Phosphorus Sulfur* **1983**, *18*, 109. (b) Meeuwissen, H. J.; van der Knaap, T. A.; Bickelhaupt, F. *Tetrahedron* **1983**, *39*, 4225.

(10) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

(11) Plettenburg, O.; Lorenz, K.; Loehn, M.; Duclos, O.; Biscarrat, S. PCT Int. Appl. WO 2009/156092 A2, **2009**; *Chem. Abstr.* **2009**, *146*, 350380.

(12) (a) Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1974**, *30*, 633. (b) Renzoni, G. E.; Borden, W. T. *J. Org. Chem.* **1983**, *48*, 5231.

(13) Pautigny, C.; Jeulin, S.; Ayad, T.; Zhang, Zh.; Genêt, J.-P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008**, *350*, 2525.

(14) Grange, R. L.; Ziogas, J.; North, A. J.; Angusc, J. A.; Schiesser, C. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1241.

(15) (a) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Vol. 8; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 343–362. (b) Lane, C. F. *Synthesis* **1975**, 135.

(16) Komarov, I. V.; Grigorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785.

(17) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, **1988**, 3rd ed..

(18) Pittelkow, M.; Christensen, J. B. *Org. Lett.* **2005**, *7*, 1295.

(19) O'Leary, B. M.; Szabo, T.; Svenstrup, N.; Schalley, C. A.; Lützen, A.; Schäfer, M.; Rebek, J. Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11519.

(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(21) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(22) CCDC-1009296 and 1009297 contain the supplementary crystallographic data of compounds **11a**·HCl and **10a**, respectively, reported in this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

(23) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.