Synthesis and Transformations of di-endo-3-Aminobicyclo-[2.2.2]oct-5-ene-2-carboxylic Acid Derivatives

Márta Palkó 1, Pál Sohár 2 and Ferenc Fülöp 1,*

1 Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös utca 6, Hungary
2 Institute of Chemistry, Eötvös Lóránd University, H-1518 Budapest, POB 32, Hungary

* Author to whom correspondence should be addressed; E-Mail: fulop@pharm.u-szeged.hu; Tel.: +36-62-545-562; Fax: +36-62-545-705.

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Abstract: all-endo-3-amino-5-hydroxybicyclo[2.2.2]octane-2-carboxylic acid (13) and all-endo-5-amino-6-(hydroxymethyl)bicyclo[2.2.2]octan-2-ol (10) were prepared via dihydro-1,3-oxazine or γ-lactone intermediates by the stereoselective functionalization of an N-protected derivative of endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2). Ring closure of β-amino ester 4 resulted in tricyclic pyrimidinones 15 and 16. The structures, stereochemistry and relative configurations of the synthesized compounds were determined by IR and NMR.

Keywords: hydroxy-β-amino acids; cyclization; heterocycles; retro Diels-Alder reaction; microwave

1. Introduction

The synthesis of non-natural α-amino acids is currently an important synthetic challenge in view of their increasing role in chemistry and biology. Among them, bicyclic amino acids exhibit biological activity; as an example, 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH) blocks the transport of nonpolar amino acids across cell membranes, acts as an insulin-releasing factor and also inhibits the flavoprotein amino acid oxidases [1]. Straub et al. determined whether protein acylation plays a part in the action of glucose on insulin-secreting β-cells. They reported that BCH, a non-metabolizable analog
of leucine that mimics the stimulatory effect of glucose on insulin secretion, increased the incorporation of $^3$H-palmitic acid into protein [2]. Maechler et al. examined the whether activation of glutamate dehydrogenase (a mitochondrial enzyme playing a key role in the control of insulin secretion) by BCH enhances glutamine oxidation and insulin secretion [3]. BCH is a model compound for the study of amino acid transporters, as it is an L-selective inhibitor that at suitable concentration can induce the suppression of cell growth and cancer cell apoptosis. [4,5] The interest in synthetic amino acids possessing a bicycle[2.2.2]octane structure is highlighted by a number of investigations relating to their biological action. Dihydroxylated derivatives of 4-aminobicyclo[2.2.2]octane-1-carboxylic acid have been used as scaffolds for antiviral agents [6,7], and 2-amino-bicyclo[2.2.2]octane-2-carboxylic acid selectively disturbs levels of neutral amino acids in the cerebral cortex [8,9]. Although of less biological importance than their $\alpha$-analogs, some bicyclic $\beta$-amino acid derivatives exert biological activity [10,11], and are also present in peptides [10,12]. For example, a series of cyclic $\beta$-amino acid dipeptide derivatives have been investigated as VLA-4 antagonists in various inflammatory and autoimmune disease states [13].

During the past 20 years, a number of bicyclic $\beta$-amino acid derivatives have been synthesized, some of them with useful pharmacological effects [4], and they are widely used for the preparation of saturated 1,3-heterocycles. The synthesis and stereochemical aspects of the diexo- and diendo-fused norbornane- and norbornene-1,3-heterocycles have been thoroughly studied [14]. To date, only a few bicyclo[2.2.2]octene-fused heterocycles have been prepared [15-19]. Because of their therapeutic interest, the syntheses of cycloalkane-fused pyrimidinones have been studied [14], but syntheses of their bicyclo[2.2.2]octene-condensed derivatives have not yet been reported.

$\text{cis}$- and $\text{trans}$-3-Aminobicyclo[2.2.2]octane-2-carboxylic acid were prepared some years ago [20-22], but their partially saturated analogs and further functionalized derivatives have not yet been described. Our work was focused on the syntheses of di-endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid and its hydroxyl-substituted derivatives by stereoselective and regioselective functionalization of the double bond via 1,3-oxazine or $\gamma$-lactone intermediates. A further aim was a study of the ring-closure reactions of amino esters, and the retro-Diels-Alder reactions of the synthesized tricyclic pyrimidinones.

2. Results and Discussion

The Diels Alder reaction of 1,3-cyclohexadiene with maleic anhydride resulted in di-endo-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (1) diastereoselectively. The starting di-endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2) was prepared selectively by hypochlorite-mediated Hoffman degradation of the carboxamide obtained by ammonolysis of anhydride 1. Amino acid 2 was esterified in the presence of EtOH and SOCl$_2$, furnishing the amino ester 4. Compound 2 was also transformed into $\text{cis}$-amino acid 3 with H$_2$ in the presence of Pd/C, and it was protected with tert-butoxypyrocarbonate to give N-acylated amino acid 5 (Scheme 1).

We earlier reported several methods for the synthesis of $\beta$-amino acids with hydroxy-substituted cyclopentane, cyclohexane, cyclooctane and norbornane skeletons. The hydroxy group could be introduced stereoselectively on the ring by starting from $\text{cis}$-, $\text{trans}$- or di-endo-alicyclic aminocarboxylic acids by iodolactonization or via the corresponding oxazine or oxazoline derivatives
Another method of hydroxylation of 2-aminocyclohexene-carboxylic acid is feasible by functionalization of the olefinic bond through epoxidation [30].

**Scheme 1.** Synthesis of bicyclic amino acid derivatives 2-5.

Our present aim was the functionalization of the olefinic bond of aminocarboxylic acid derivatives 4 and 5, and the synthesis and structural analysis of new hydroxy-substituted 3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid derivatives. The first step in these syntheses was the stereoselective iodolactonization of N-Boc-endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (5) under two-phase conditions, furnishing iodolactone 6, which was reduced with Bu3SnH to give N-Boc lactone 7. When 7 was reacted with TFA or HCl, only the protecting group was eliminated, resulting in lactones 8a or 8b, instead of the all-endo-3-amino-6-hydroxybicyclo[2.2.2]octane-2-carboxylic acid. The similar lactone opening of 7 was also attempted with NaN3 [31-33], BF3.OEt2 [34] or LiOH [26], but not even traces of the desired product were observed in the reaction mixture. Reductive opening of the lactone ring of 7 with LiAlH4 in THF resulted in the protected amino alcohol 9, and subsequent deprotection of the amino group by acidic hydrolysis afforded all-endo-5-amino-6-(hydroxymethyl)bicyclo[2.2.2]octan-2-ol (10) (Scheme 2).

**Scheme 2.** Synthesis of amino alcohol 10 via tricyclic γ-lactone intermediates.
When N-acetyl derivative 11 was reacted with N-iodosuccinimide (NIS), a tricyclic dihydro-iodooxazine derivative was obtained regio- and stereoselectively. Not even traces of other regio- or diastereomers were observed in the crude product. Selective reduction of the halogen group with this dihydro-iodooxazine Bu₂SnH under an argon atmosphere led to the dihydrooxazine. Hydrolysis of this derivative with dilute HCl at room temperature gave N-acetylhydroxy amino acid 12. When 12 was boiled in acidic solution, all-endo-3-amino-5-hydroxybicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (13) was produced in medium yield (Scheme 3).

Scheme 3. Synthesis of amino acid 13 via tricyclic 1,3-oxazine intermediates.

Amino ester base 4 reacted with PhNCS to give thiourea ester 14. This was cyclized by acid catalysis to 5,8-ethano-3-phenyl-2-thioxo-2,3,4,5,6,7,8,9-octahydroquinazolin-4(1H)-one (15). In a similar manner as for the related tricyclic 3-substituted 2-thioxo-5,8-methanoquinazolin-4-ones investigated earlier, these compounds readily underwent decomposition when heated to their melting points; cyclopentadiene was split off, and monocyclic 2,3-dihydro-2-thioxopyrimidin-4(1H)-ones were formed [35].

The importance of this retro Diels-Alder procedure (cycloreversion) lies in the fact that 3-substituted 2-thiouracly derivative of type 17 can be synthesized in this way [36,37]. When 15 was boiled in chlorobenzene, or heated at the melting point, or heated under MW-irradiation, the reaction mixture turned deep-brown, but the formation of 17 was not observed, the starting thioxopyrimidinone derivative 15 was not undergone any transformation.

When boiled in toluene with ethyl 4-chlorobenzimidate, amino ester base 4 furnished 2-(4-chlorophenyl)-5,8-ethano-r-4a,t-5,r-5,t-8,c-8a-tetrahydroquinazolin-4(3H)-one (16) in good yield. Cyclohexadiene could be split off 16 under mild conditions to give the known pyrimidin-4-(3H)-one 18 [37,38]. When the retro Diels-Alder reaction was carried out without any solvent, by using microwave heating, the product 18 was cleaner, the yield was higher and the reaction was faster than when 16 was boiled in chlorobenzene or heated at the melting point (Scheme 4).
Scheme 4. Synthesis of ethanoquinazolin-4-ones 15 and 16, and retro Diels-Alder reaction of 16.

2.1. IR and NMR Results

The presumed structures of the new compounds (2, 4–7, 8a,b and 9–16) follow straightforwardly from the spectral data [Tables 1 and 2; to facilitate comparison of the analogs’ spectroscopic data, the IUPAC numbering for 13 (Scheme 3) is used in this section and in Tables 1 and 2]. The following additional remarks are necessary:

The zwitterionic structures of 2 and 3 and the ammonium salt structures of 4, 8, 10 and 13 are supported by the very diffuse \( \nu_{\text{NH}_3^+} \) band in the 3500–2000 cm\(^{-1} \) IR interval [39a]. The characteristic high \( \nu_{\text{C}=\text{O}} \) frequency of 6–8 at 1762–1808 cm\(^{-1} \) is evidence of the presence of a carbonyl group in the compound the \( \gamma \)-lactone moiety [39b].

The presence of the 5-iodo substituent in 6 causes downfield shifts of the C–4 and C–6 lines lines in the \( ^{13}\text{C} \) NMR spectrum (by 7.1 and 7.9 ppm, respectively) and an opposite change in the shift of the C–5 signal (by 4.2 ppm) as compared with 7 (\( \beta \)-effect), in accord with the literature [40a,41,42]. Further proof was supplied by the elemental analysis and the mass spectroscopic measurements.

The endo position of the 2,3-substituents is proved by the doublet split (9.5 ± 0.4 Hz) of the H–1\( ^1 \) NMR signal for 2–5, 11, 12 and 14. The bulkier carbonyl substituent (relative to 3-NH) forces the flexible bicyclooctane skeleton into a conformation in which the dihedral angle H–1,H–2 is close to 90\(^{\circ} \), and due to the Karplus relation [42,43], the corresponding vicinal coupling is small. The mutual intensity enhancements of one of H-7end\( o \) and H-2 saturating the other of them (in case of compounds 4 and 5) are unambiguous proofs of the endo position of the C-2 substituent. Consequently, only the \( ^3\text{J}(\text{H–2},\text{H–3}) \) interaction leads to a well-identifiable split of the H–2 signal.
Table 1. $^1$H NMR chemical shifts$^a$ of compounds 2–7, 8a,b and 9–16$^b$.

| Compound | H–1$^c$ ~s / br | H–2$^d$ m (1H) | H–3$^e$ m (1H) | H–4$^c$ ~s / br | H–5 1/2 signal (1/2H)$^f$ | H–6 1/2 signal (1/2H)$^f$ | NH/NH$_3^+$ br (1/3H)$^g$ | OH br (1H) |
|----------|----------------|----------------|----------------|----------------|-------------------|-------------------|----------------|-----------|
| 2        | 2.65           | 2.33           | 3.38           | 2.96           | 6.08              | 6.33              | ~8.7           | –         |
| 3$^b$    | 1.94           | 2.39           | 3.31           | 1.67           | ~1.5 m (3H),$^i$ 1.73 t (1H) | 6.33              | ~8.9           | –         |
| 4        | 2.80           | 3.2            | 3.56           | 2.96           | 6.16              | 6.33              | 7.95           | –         |
| 5        | 2.55           | 2.88           | 4.04           | 2.65           | 6.11              | 6.37              | 5.32           | 12.07$^i$ |
| 6        | ~2.2$^j$       | 2.90           | 4.12           | 2.60           | 4.43 ~s (1H)      | 4.96$^k,l$        | 4.96$^l$       | –         |
| 7        | 2.62           | 2.88           | 3.85           | 1.94$^j$       | 1.65,$^l_1$ 1.95$^j$ | 4.60              | 4.88           | –         |
| 8a       | 2.69           | 2.96           | 3.50           | 1.89           | 1.80,~2.11$^k$    | 4.75              | ~8.3           | –         |
| 8b       | 2.64           | 2.84           | 3.42           | 2.04           | ~1.75,~2.14$^k$   | 4.71              | ~8.55          | –         |
| 9$^a$    | ~1.6$^j$       | 1.88           | 3.75$^l$       | ~1.6$^j$       | 1.35,~1.65$^l$    | 3.75$^l$          | 5.37           | 4.63$^a$   |
| 10       | 1.68           | 1.95$^j$       | 3.39           | 1.95$^j$       | 1.53,$^k$ 1.70$^m$ | 3.78$^l$          | 7.88           | ~5.1$^p$   |
| 11       | 2.73           | 2.97           | 4.52           | 2.65           | 6.16              | 6.48              | 5.85           | –         |
| 12       | 2.02           | 3.05           | 4.20           | 1.88           | 5.06$^q$          | 1.76,$^m_1$ 12.85$^r$ | ~3.5         | –         |
| 13       | 2.05           | 2.65           | 3.57           | 2.03           | 3.92$^k$          | 1.58$^k_1$ 1.89$^k$ | ~8.0$^s$      | ~5.9$^s$   |
| 14       | 2.73$^s$       | 3.05           | 5.06           | 2.94$^s$       | 6.05              | 6.37              | 6.81$^l$       | –         |
| 15       | 3.32           | 3.15           | 3.91           | 2.88           | 6.44 narrow m (2H)$^u$ | 7.75              | –             | –         |
| 16       | 3.23$^r$       | 2.81           | 4.25           | 3.15$^v$       | 6.25 narrow m (2H)$^u$ | 8.90              | –             | –         |

Further signals, CH$_3$(Et), $t$ (J: 7.1): 1.18 (4$^j$, 11$^j$ and 14$^j$); CH$_3$(Ac): 1.82 (11), 2.36 (12); CH$_2$ (Pos. 7, 8), 1–4 $m$’s (4H): 1.0–1.9 ppm. In overlap with the H–1, H–5 or CH$_3$ signal (4$^j$, 6$^j$, 7$^b$, 8$^b$, 9$^j$, 11$^j$ and 14$^j$); OCH$_2$, 1 or 2m (2H): 3.94 (4$^j$), ~3.52 (9), 3.50 and 3.78$^l$ (10), 4.01 (11), 3.95 (14); CH$_3$(Boc), $s$ (9H): 1.35 (5 and 9$^j$), 1.42 (6 and 7); Phenyl (14–16): H$_{\text{ortho}}$ (2H): 7.11, 7.05 br and 7.15 br, 7.69, H$_{\text{meta}}$ (2H): 7.38, ~7.4, 7.40, H$_{\text{para}}$ (1H): 7.25, ~7.4$^j$.

$^a$In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz. Solvent: DMSO-d$_6$; for 6, 7, 11 and 14–16: CDCl$_3$; $^b$Assignments were supported by 2D-HMQC (except for 3 and 7), 2D-HMBC (except for 3, 7, 9 and 10), 2D-COSY (9 and 10) and DIFFNOE measurements (4, 5, 8b and 16); $^c$Singlet-like or broad signal (1H) with close-lying coalesced lines; $^d$ $d$ (1H), J: 9.1 (2, 4, 9.6 (3, 11, 12 and 14), 9.8 (5), 14.5 (10), 5.8 (13), $dd$ (1H), J: 9.5 and 4.8 (6, 7, 8a and 8b), 10.4 and 2.5 (15 and 16), m (1H, 9); $^e$Multiplicity and J-values are the same as for H–2 (2, 3, 13, 16), in case of 4, 5, 11, 12, 14 and 15 further split by 2.5±0.5 Hz, the $dd$ of H–2 is coalesced to a ~s (6$^i$), ~t (7$^i$) or $d$ (8a,b); $^f$ $t$ (1H), J: 7.3 (2, 4, 5, 11 and 14), 6.2 (for H–6 of 7 and 8a,b), 11.0 (for the H–6 t of 13 at 1.89); $^g$NH$_3^+$ (3H) for 2–4, 8a,b, 10 and 13. NH, d(1H), J: 10 (5, 11), broad, 1H (6, 7 and 14–16), 3.1 (9), separated signal of COOH at 12.7 ppm (13); $^h$Known [20], zwitterionic molecule; $^i$COOH; $^j$lOverlapping signals; $^k$d (1H), J: 5.1 (6), 14.5 (10), 7.7 (13, H–5), 13.5 (13, H–6), ~d with coalesced lines (8a,b); $^l$dd (1H) with coalesced lines (8a, 10 and 12); $^m$Contaminated with 10-15% 5,6-unsaturated analog; $^n$t (J: 5.3), OH (Pos. 6): 6.23 $d$(J: 8.8); $^o$~s (1H), OH (Pos. 6): 5.70 ~s; $^p$m (1H); $^q$Coalesced with the COOH signal, broad (2H); $^r$Reversed assignment is also possible; $^s$NH attached to C–3 of the bicyclic. NH(Ph): 8.01 br (1H); $^t$AB spectrum with close-lying lines; $^u$The assignment was proved by DIFFNOE measurement.
Table 2. $^{13}$C-NMR chemical shifts$^a$ of compounds 2–7, 8$^{a,b}$ and 9–16$^{a,b}$.

| Compound | C–1  | C–2  | C–3  | C–4  | C–5  | C–6  | C–7  | C–8  | C=O  |
|----------|------|------|------|------|------|------|------|------|------|
| 2        | 36.0 | 46.3 | 50.8 | 35.0 | 130.3| 137.4| 25.7 | 23.6 | 175.6|
| 3$^c$    | 29.2 | 43.5 | 48.9 | 29.1 | 25.2 | 25.9 | 19.2 | 21.9 | 176.3|
| 4        | 32.9 | 46.0 | 51.4 | 32.9 | 130.8| 135.8| 24.7 | 22.5 | 171.8|
| 5        | 36.2 | 50.2 | 52.1 | 33.2 | 130.6| 136.5| 25.3 | 22.7 | 174.6|
| 6        | 39.1 | 42.5 | 48.1 | 37.4 | 25.8 | 86.2 | 14.9 | 25.0 | 176.2|
| 7        | 37.1 | 43.9 | 48.1 | 30.3 | 30.0 | 78.3 | 15.6 | 26.4 | 177.6|
| 8$^a$    | 37.1 | 42.4 | 48.4 | 28.6 | 29.3 | 78.6 | 15.1 | 26.3 | 177.0|
| 8$^b$    | 37.2 | 42.3 | 48.4 | 28.3 | 29.3 | 78.5 | 15.2 | 26.4 | 176.9|
| 9$^f$    | 34.3 | 41.2 | 49.8 | 30.5 | 31.8 | 68.0 | 25.2 | 23.4 | –    |
| 10       | 33.8 | 40.4 | 50.1 | 28.4 | 30.6 | 67.3 | 24.1 | 22.9 | –    |
| 11       | 33.3 | 49.9 | 50.3 | 35.9 | 130.4| 136.6| 25.4 | 22.2 | 173.5|
| 12       | 25.5 | 46.7 | 45.4 | 23.0 | 76.8 | 32.3 | 24.2 | 17.5 | 172.6$^e$ |
| 13       | 33.3 | 47.8 | 49.8 | 28.9 | 67.5 | 38.0 | 19.7 | 21.5 | 174.6|
| 14       | 33.9 | 49.2 | 57.0 | 35.3 | 130.5| 136.5| 25.5 | 22.1 | 173.4|
| 15       | 35.6 | 43.5 | 54.6 | 37.5 | 133.4| 134.1| 24.2 | 22.0 | 167.7|
| 16       | 34.4 | 44.3 | 61.6 | 37.5 | 135.0| 133.4| 25.3 | 23.4 | 172.6|

Further signals, CH$_3$ (ethyl group): 14.8 (4), 14.5 (11, 14); CH$_3$(Ac): 23.8 (11); OCH$_3$: 61.4 (4), 62.7 (9), 60.8 (11, 14); CH$_3$(BOC): 29.0 (5 and 9), 28.7 (6 and 7); C$_{quat}$(Boc): 78.9 (5), 80.8 (6), 80.3 (7), 78.5 (9); C=O (Boc): 155.3 (5), 155.8 (6 and 7), 156.1 (9); C=O (amide): 169.3 (11), 172.5$^e$ (12); phenyl, C$_{substit}$(14–16): 136.3, 139.1, 132.8, C$_{ortho}$: 125.1, (? broad), 128.1, C$_{meta}$: 130.3, 128.9, 129.3, C$_{para}$: 127.4, 129.3, 137.3; C=S: 180.6 (15); C=N: 146.6 (16).

$^a$ In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz. Solvent: DMSO-d$_6$; for 6, 7, and 8a–16, CDCl$_3$; $^b$ Assignment were supported by 2D-HMQC (except for 3 and 7), 2D-HMBC (except for 3, 7, 9 and 10), and DEPT (except for 7 and 8a); $^c$ Known compound [20]; $^d,e$ Interchangeable assignments; $^f$ Contaminated with 10–15% 5,6-unsaturated analog.

In 6–8, the condensed $\gamma$-lactone ring forces the molecules into a stereo structure in which the dihedral angle H–1, H–2 is smaller, while the angle H–2, H–3 remains practically unaltered. Thus, both interactions lead to well-observable splits and the H–2 signal appears as a doublet.

The zwitterionic and strained (condensed $\gamma$-lactone ring) structures of 2, 3, and 6–8 are manifested, as expected [40b], in low field shifts of the C=O line (175.6, 176.3, and 176.9 $\pm$ 0.7 ppm, respectively) relative to the values measured for the other compounds (171.8–174.6 ppm) (thioimide 15 is an exception for which this line is at 167.7 ppm, in accord with the literature data [40b]) in the diendo-position.

In 10, the steric interaction between the 2-hydroxymethyl and 6-hydroxy groups in the di-exo-position compensates the effort of the bulkier NH$_3^+$ group to occupy an out of plane position (relative to the plane of the methylene carbon and C-2,3), and consequently the cyclohexane ring bearing three substituents is forced into a nearly ideal boat conformation (in contrast with the other compounds discussed above), with a dihedral angle H–2, H–3 of ca. 0°. Thus, this compound exhibits the highest split (14.5 Hz) of the H–2 doublet.

As a result of steric hindrance of the substituents in 13, here in Pos. 2, 3 and 5, the dihedral angle H–2, H–3 is most distant from 0° and the corresponding split is the smallest (5.8 Hz).
In pyrimidone-condensed 15 and 16, the anisotropy of the neighbouring carbonyl [40c] results in a downfield shift of the H−1 signal (3.32 and 3.23 ppm), in contrast with the values of 1.68–2.80 ppm measured for the other compounds.

The strained skeleton in 6–8 and the steric hindrance in 9 and 10 (between the diendo substituents in Pos. 2 and 6) show up in upfield shifts (steric compression shifts or field effects [40d]) of the C−2 line (at 40.4–43.9 ppm) as compared with the values observed for 2, 4, 5 and 11–14 (46.0–50.2 ppm). In 15 and 16, a similar situation due to the condensed heteroring also leads to strain in the molecular skeleton as proved by upfield shifts of involved carbon signals.

Similarly, the C−7 line is upfield-shifted (14.9–15.6 ppm) for 6, 7 and 8a,b. In the other cases, these shifts are between 24.1 and 25.7 ppm (except for 3 and 13, where the bulky NH3+ and the 7-CH2 groups are also in steric interaction (19.2 and 19.7 ppm)).

Mention should be made of the significant downfield shift of the exo H−8 signal in 6 (at 2.22 ppm, whereas in 7 this shift is ca. 1.75 ppm), which originates from the anisotropic effect of the iodo substituent [40e] at Pos. 5.

3. Experimental

3.1. General

The chemicals were purchased from Aldrich or Fluka. Melting points were determined on a Kofler micro melting point apparatus. Elemental analyses were performed with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyser; Merck Kieselgel 60F254 plates were used for TLC: the eluent was 4:1 toluene-MeOH. Products were purified by column chromatography on Merck 0.063–0.2 mm silica gel; the elution mixtures were determined case by case. Microwave reactions were performed in a CEM Discover LabMate MW reactor. The 1H- and 13C-NMR spectra were recorded in CDCl3 or DMSO-d6 solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 (1H) and 125 (13C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT.AU to generate NOE was used. DEPT spectra were run in a standard manner, using only the Θ = 135° pulse to separate CH/CH3 and CH2 lines phased “up” and “down”, respectively. The 2D-HSC spectra were obtained by using the standard Bruker pulse program HXCO.AU.

di-endo-3-Aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2): di-endo-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (1, 6.4 g, 30 mmol) was added in portions to dilute NH4OH (50 mL, 6%) at 0 °C. The mixture was stirred for 30 min, and 2 M NaOH (60 mL) was then added dropwise at 0 °C over a period of 30 min, after which the excess of NH3 was removed under reduced pressure at 40 °C. The residue was cooled to 0 °C and 1 M NaClO solution (40 mL) was added dropwise with stirring, the temperature being maintained at 0 °C throughout. The mixture was stirred at the same temperature for 1 h, held at 70–75 °C for 10 min, then cooled to ambient temperature, adjusted with 10 M HCl to pH 7 and evaporated to dryness. The residue was extracted with three 150 mL portions of hot MeOH, and the extract was evaporated. The residue was dissolved in a small amount of water and the HCl was removed by means of a Dowex 50 ion-exchange column (acid cycle). Elution was effected with 1 M NH4OH solution. Each fraction was evaporated and the dry residue was dissolved in water, acetone
was added until turbidity appeared, and the mixture was then allowed to stand in a refrigerator. The solid crystals were filtered off. Yield 3.35 g (66%); m.p. 204–208 °C \( \text{C}_9\text{H}_{13}\text{NO}_2 \) (167.09): calcd. C 64.65, H 7.84; m.p. 204–208 °C; found C 64.77, H 7.96, N 8.43.

**cis-3-Aminobicyclo[2.2.2]octane-2-carboxylic acid (3):** A solution of amino acid 2 (350 mg, 2.1 mmol) and 10% Pd/C (100 mg) in MeOH (100 mL) was stirred under H\(_2\) (50 atm) for 3 days at room temperature. The Pd was then filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from water-acetone. Yield 0.18 g (51%); a white solid, m.p. 215–220 °C, lit. m.p. 232–235 °C (HCl salt) [20] \( \text{C}_9\text{H}_{15}\text{NO}_2 \) (169.11): calcd. C 63.88, H 8.93; N 8.28, found C 64.02, H 8.12, N 8.19.

**Ethyl di-endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate (4):** SOCl\(_2\) (2.6 mL, 35 mmol) was added dropwise with stirring to absolute EtOH (30 mL) at \(-10\) °C. **cis-3-Aminobicyclo[2.2.2]octane-2-carboxylic acid (3), 5.5 g, 33 mmol** was added in portions to the mixture, which was stirred for 30 min at 0 °C, and then for 3 h at room temperature, after which the mixture was refluxed for 1 h and next evaporated. The residue was crystallized from Et\(_2\)O and recrystallized from EtOH/ Et\(_2\)O). Yield 6.6 g (87%); a white solid, m.p. 209–213 °C, \( \text{C}_{11}\text{H}_{18}\text{ClNO}_2 \) (231.10): calcd. C 57.02, H 7.83; Cl: 15.30, N 6.04, found C 57.22, H 7.92, Cl, 15.38, N 6.19.

**di-endo-3-tert-Butoxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (5):** 1 M NaOH (20 mL) was added to a solution of 3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2, 3.34 g, 20 mmol) in a 2:1 dioxane/H\(_2\)O mixture (60 mL). The solution was cooled to 0 °C in an ice bath and di-tert-butyl dicarbonate (4.8 g, 22 mmol) was added slowly. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 4 h. The solvent was concentrated to 20 mL, the pH was then adjusted to 2.5 with 10% H\(_2\)SO\(_4\), and the resulting solution was extracted with EtOAc (3 × 50 mL). The combined extracts were dried (\( \text{Na}_2\text{SO}_4 \)) and evaporated, to give 5 as a white solid, which was recrystallized from iPr\(_2\)O. Yield 3.4 g (63%); m.p. 117–120 °C \( \text{C}_{14}\text{H}_{21}\text{NO}_4 \) (267.15): calcd. C 62.90, H 7.92, N 5.24, found C 62.78, H 7.99, N 5.11.

**\((r-1,c-2,t-3,t-6,c-7,t-10)-10\text{-tert}-\text{Butoxycarbonylamino-2-iodo-4-oxatricyclo[4.3.1.0^3,7]decan-5-one (6):}** To a solution of 5 (3.04 g, 11.4 mmol) in CH\(_2\)Cl\(_2\) (100 mL), NaHCO\(_3\) solution (0.5 M, 70 mL), KI (11.62 g, 70 mmol) and I\(_2\) (5.84 g, 23 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then poured into 10% aqueous Na\(_2\)S\(_2\)O\(_3\) solution (50 mL). The reaction mixture was extracted with 3 × 20 mL CH\(_2\)Cl\(_2\) and the combined extract was washed with brine (20 mL), dried (\( \text{Na}_2\text{SO}_4 \)) and evaporated. The residue was recrystallized from iPr\(_2\)O. Yield 2.9 g (64%); m.p. 172–174 °C. \( \text{C}_{14}\text{H}_{20}\text{INO}_4 \) (393.04): calcd. C 42.76, H 5.13, N 3.56, found C 42.91, H 5.09, N 3.61.

**\((r-1,t-3,t-6,c-7,t-10)-10\text{-tert}-\text{Butoxycarbonylamino-4-oxatricyclo[4.3.1.0^3,7]decan-5-one (7):}** Bu\(_3\)SnH (4.8 mL, 18 mmol) was added to a solution of iodolactone 6 (3.53 g, 9 mmol) in dry CH\(_2\)Cl\(_2\) (65 mL) under Ar. After stirring at 40 °C for 20 h, the solvent was evaporated off, and the residue was crystallized from \( n \)-hexane and recrystallized from iPr\(_2\)O-EtOAc. Yield 1.99 g (83%); m.p. 172–174 °C \( \text{C}_{14}\text{H}_{21}\text{NO}_4 \) (267.15): calcd. C 62.90, H 7.92, N 5.24, found C 62.81, H 8.08, N 5.31.
3.2. (r-1,t-3,t-6,c-7,t-10)-10-Amino-4-oxatricyclo[4.3.1.0^3,7]decan-5-one trifluoroacetate (8a) and hydrochloride (8b)

8a: Trifluoroacetic acid (20 mL) was added to a solution of Boc-lactone derivative 7 (0.35 g, 13 mmol) in a 9:1 THF:H₂O mixture (60 mL) and the solution was stirred at room temperature for 10 h. The solvent was next evaporated off and the residue was crystallized from Et₂O and recrystallized from H₂O-acetone. Yield 0.19 g (54%); m.p. 235–236 °C. C₁₁H₁₃F₃NO₃ (264.08): calcd. C 50.00, H 4.96, N 5.30, found C 50.11, H 5.13, N 5.41.

8b: Compound 7 (0.4 g, 2 mmol) was dissolved in aqueous HCl (20%, 20 mL) and the solution was stirred at room temperature for 10 h. The solvent was next evaporated off and the residue was recrystallized from H₂O-acetone. Yield 0.2 g (75%); m.p. 256–260 °C. C₉H₁₄ClNO₂ (203.07): calcd. C 53.08, H 6.93, Cl: 17.41, N 6.88, found C 53.21, H 6.98, Cl: 17.54, N 6.61.

all-endo-tert-Butyl-N-[5-(hydroxy-3-hydroxymethyl)bicyclo[2.2.2]octan-2-yl] carbamate (9): To a stirred suspension of LiAlH₄ (1 g, 26 mmol) in dry THF (60 mL) was added a solution of Boc-lactone 7 (0.5 g, 1.9 mmol) in dry THF (20 mL). The resulting suspension was refluxed for 4 h and then decomposed by the addition of a mixture of water (2 mL) and THF (10 mL). The inorganic material was filtered off and washed with THF (3 × 50 mL). After drying (Na₂SO₄) and filtration, the solvent was evaporated off to give a pale oil, which was purified by column chromatography (toluene-MeOH = 4:1) Yield 0.41 g (81%) C₁₄H₂₅NO₄ (271.18): calcd. C 61.97, H 9.29, N 5.16, found C 62.08, H 9.41, N 5.31.

all-endo-5-Amino-6-(hydroxymethyl)bicyclo[2.2.2]octan-2-ol hydrochloride (10): Compound 9 (0.4 g, 2 mmol) was dissolved in aqueous HCl (20%, 20 mL) and the solution was stirred at room temperature for 1 h. The solvent was next evaporated off and the residue was recrystallized from H₂O-acetone. Yield 0.3 g, (72%); m.p. 165–167 °C. C₉H₁₈ClNO₂ (207.10): calcd. C 52.05, H 8.74, Cl: 17.07, N 6.74, found C 52.24, H 8.92, Cl: 17.24, N 6.68.

Ethyl di-endo-3-acetylaminobicyclo[2.2.2]oct-5-ene-2-carboxylate (11): To a suspension of ethyl 3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate hydrochloride (4, 3 g, 13 mmol) in CHCl₃ (50 mL), Et₃N (3.8 mL, 26 mmol), and AcCl (1.1 mL, 15 mmol) were added and the reaction mixture was stirred at room temperature for 2 h, and then washed with H₂O (2 × 20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried (Na₂SO₄) and evaporated. The residue was recrystallized from n-hexane-iPr₂O. Yield 2.42 g (78%); m.p. 120–122 °C. C₁₃H₁₉NO₃ (237.14): calcd. C 65.80, H 8.07, N 5.90, found C 65.94, H 8.32, N 5.78.

all-endo-3-Acetylamino-5-hydroxybicyclo[2.2.2]octane-2-carboxylic acid (12): A solution of 11 (2.42 g, 10.21 mmol) in CH₂Cl₂ (80 mL) was treated with NIS (2.3 g, 10.21 mmol) and subsequently stirred for 14 h at room temperature. When the reaction was completed, the mixture was washed with 10% NaOH solution (3 × 10 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 40 mL) and the organic phase was dried (Na₂SO₄) and evaporated. The oily dihydroiodooxazine product was sensitive to air and it was therefore used without purification in the next step.
Bu$_3$SnH (4 mL) was added to a solution of oily dihydroiodooxazine (2.5 g) in dry CH$_2$Cl$_2$ (65 mL) under Ar. After stirring for 20 h at 40 °C, the solvent was evaporated off and the residue was purified by column chromatography on silica gel (n-hexane:EtOAc 10:1) to afford the dihydrooxazine derivative as a colorless oil (1.05 g, 64%). This oily product was also sensitive to air; it was therefore used immediately. A solution of oily dihydrooxazine derivative (1.05 g) in 20% aqueous HCl (20 mL) was stirred for 2 h. The solvent was then evaporated off to afford crude 12, which was recrystallized from H$_2$O-acetone. Total yield 0.75 g (33%); m.p. 211–218 °C (with decomposition) C$_{11}$H$_{17}$NO$_4$ (227.12): calcd. C 58.14, H 7.54, N 6.16, found C 58.26, H 7.72, N 6.32.

**all-endo-3-Amino-5-hydroxybicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (13):** A solution of 0.75 g (3.3 mmol) 12 in 20% aq. HCl (30 mL) was refluxed for 30 h. The solvent was then evaporated off to afford crude 9, which was recrystallized from EtOH-Et$_2$O. Yield 0.5 g (67%); m.p. 110–112 °C. C$_{18}$H$_{22}$N$_2$O$_2$S (330.14): calcd. C 65.42, H 6.71, N 8.48, found C 65.61, H 6.59, N 8.58.

**Ethyl di-endo-3-phenylthiocarbamoylbicyclo[2.2.2]octane-2-carboxylate (14):** To a magnetically stirred toluene solution of amino ester base 4 (0.7 g, 3.6 mmol in 20 mL), one equivalent of PhNCS in toluene (0.5 g, 20 mL) was added dropwise [the free base was obtained from the hydrochloride 4 by treatment with aqueous NaOH and extraction with CHCl$_3$, followed by drying (Na$_2$SO$_4$) and evaporation]. The mixture was refluxed for 10 h, the reaction mixture was then evaporated and the oily product was crystallized from n-hexane and recrystallized from tPr$_2$O-EtOAc. Yield 0.68 g (57%); m.p. 110–112 °C. C$_{18}$H$_{22}$N$_2$O$_2$S (330.14): calcd. C 65.42, H 6.71, N 8.48, found C 65.61, H 6.59, N 8.53.

**all-2-(4-Chlorophenyl)-3H-pyrimidin-4-one (18):** Method A: (r-4a,t-5,t-8,c-8a)-2-(4-Chlorophenyl)-5,8-ethano-4a,5,8,8a-tetrahydroquinazolin-4(3H)-one (16, 0.28 g, 1 mmol) was heated in a round-bottomed flask for 30 min at 220 °C. After the mixture had cooled, the residue was recrystallized from EtOH. Yield 0.12 g (58%).
Method B: \((r\text{-}4a,t\text{-}5,t\text{-}8,c\text{-}8a)\text{-}2\text{-(4-Chlorophenyl)}\text{-}5,8\text{-ethano}\text{-}4a,5,8,8a\text{-tetrahydroquinazolin-4(3H)}\text{-}one\) (16, 0.28 g, 1 mmol) was refluxed in chlorobenzene (20 mL) for 12 h. The mixture was evaporated, and the residue was recrystallized from EtOH. Yield 0.13 g (63%).

Method C: \((r\text{-}4a,t\text{-}5,t\text{-}8,c\text{-}8a)\text{-}2\text{-(4-Chlorophenyl)}\text{-}5,8\text{-ethano}\text{-}4a,5,8,8a\text{-tetrahydroquinazolin-4(3H)}\text{-}one\) (16, 0.28 g, 1 mmol) was weighed into a 10 mL pressurized reaction vial and the crystals were heated at 250 °C for 5 min at max. 300 W microwave irradiation. The crude product was recrystallized from EtOH. Yield 0.15 g (72%) m.p. 243–245 °C, lit. m.p. 245–246 °C, [38]. \(\text{C}_{10}\text{H}_{7}\text{ClN}_{2}\text{O}\) (206.02): calcd. C 58.13, H 3.41, Cl 17.16, N 13.56, found C 58.31, H 3.59, Cl 17.34, N 13.68.

4. Conclusions

In summary, we have successfully synthetized di-endo-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid derivatives, can be used for further valuable transformations, and are good starting materials for which the syntheses of hydroxy-substituted \(\beta\)-amino acids, aminodiols and heterocycles with potential biological activity.

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Conflict of Interest

The authors declare no conflict of interest.

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**Sample Availability:** Samples of the compounds 1-18 are available from the authors.

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