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Alkaloids from alkaloids: total synthesis of (±)-7a-*epi*-hyacinthacine A_1 from *Z*-protected tropenone via Baeyer–Villiger oxidation

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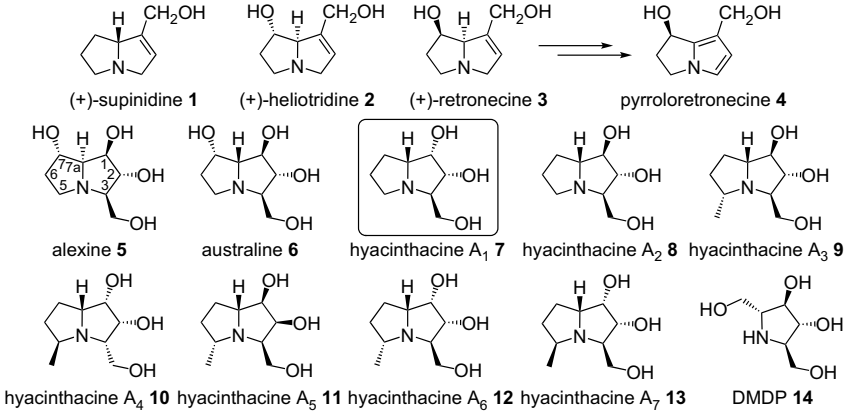
ABSTRACT

Baeyer–Villiger oxidations of several tropane derivatives have been investigated. Whereas tropenones **15a–c** underwent exclusive epoxidation to **21a–c**, the corresponding 6-oxotropane derivative **28** yielded the desired lactone **29**. Baeyer–Villiger oxidation was also possible for the *O*-isopropylidene-protected diols **32a**,**b**. The resulting lactones **33a**,**b** were employed in the total synthesis of (±)-7a-*epi*-hyacinthacine A_1 (7a-*epi*-**7**) via an intramolecular nucleophilic alkyllithium addition to a carbamate as the key lactamization step. The target compound was prepared from tropenone **15b** in 10 steps and 14% overall yield. Enzymatic resolution of pyrrolidine (±)-**36** provided a formal total synthesis to both enantiomers of **7**.

1. Introduction

Pyrrolizidine alkaloids are common constituents of a large number of plants, among them are medicinal plants such as butterbur, coltsfoot *Tussilago farfara*, and comfrey *Symphytum officinale*.[1] These compounds act as a constitutive plant defence mechanism, and depending on the structure and substitution pattern of the pyrrolizidine ring system several derivatives display hepatoxic and cancerogenic properties.[1,2] The toxicity is particularly high for those derivatives, which contain at least one ester moiety, usually at the hydroxymethyl group, and a C=C double bond at the C-1 position.[3] Prominent examples of pyrrolizidines with toxic properties are supinidine (**1**), heliotridine (**2**), and retronecine (**3**) (Scheme 1) and their corresponding esters. The cancerogenic



Scheme 1.

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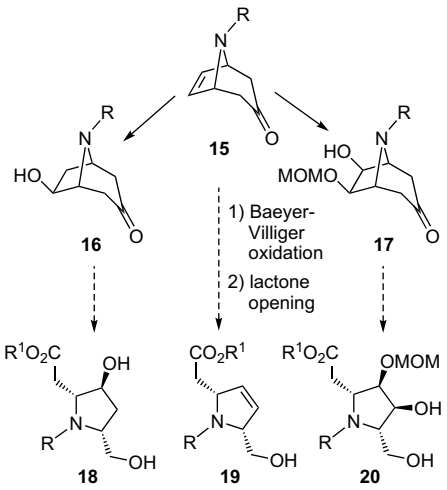
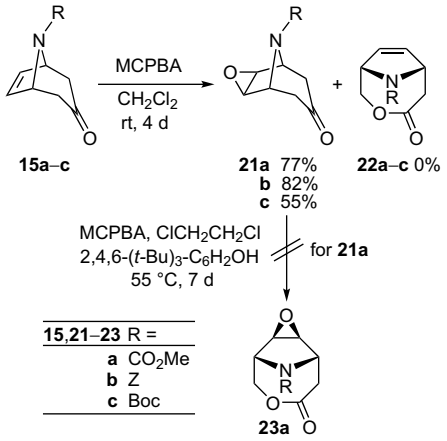


Scheme 2.



Scheme 3.

properties arise from hepatic metabolism of pyrrolizidines such as retronecine (**3**) to pyrrole derivatives like **4**. Pyrroles such as **4** are strong alkylating agents and induce DNA cross-linking.[1d,g,4]

On the other hand, polyhydroxylated pyrrolizidines gained attention for medicinal chemistry.[5] Alexine (**5**) and australine (**6**), which were isolated in 1988 by Nash from *Leguminosae* possess potent antiviral properties.[6,7] In 2000 Asano isolated hyacinthacines A_1–A_3 (**7**–**9**) from *Muscari armeniacum (Hyacinthaceae)*[8] and later in 2002 the hyacinthacines A_4–A_7 (**10**–**13**).[9] Due to their structural similarity with one of the most potent glycosidase inhibitors (2*R*,3*R*,4*R*,5*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP) (**14**) compounds **7**–**13** were intensively investigated with regard to their selective glycosidase inhibition. Total syntheses of hyacinthacines and their epimers mostly relied on *ex chiral pool* approaches, starting from carbohydrates,[5,10] amino acids[11] or diethyltartrate,[12] which provided the proper stereochemistry. Another route utilized a sequence of partial reduction of *N*-Boc-pyrrole and enzymatic resolution as the key steps.[13] The first auxiliary-mediated approach involved a [2+2] cycloaddition of dichloroketene to Stericol®-based enol ethers,[14] and furthermore, a chemo-enzymatic route employing aldolases has been reported.[15]

During our work on tropane derivatives we envisaged an alternative route to hyacinthacines utilizing functionalized tropenones as valuable starting materials. We recently reported that *N*-protected tropenone **15** can be easily converted to enantiomerically pure 6-hydroxytropinone **16** via enantioselective hydroboration[16] or enzymatic desymmetrization[17] and to mono-protected dihydroxytropinone **17** via enzymatic resolution (Scheme 2).[18,19]

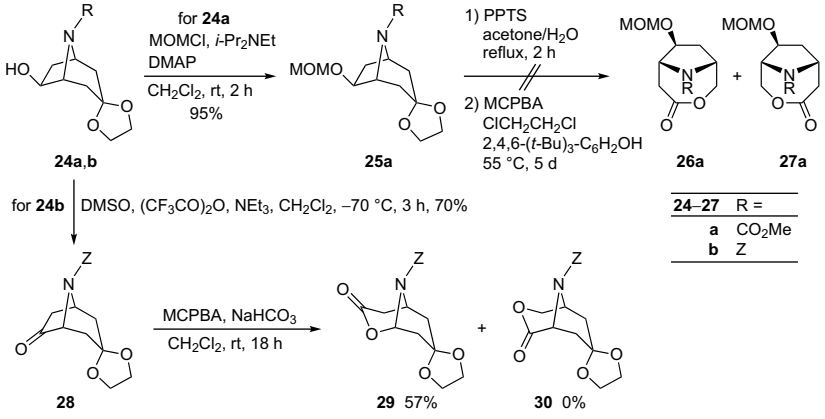
Motivated by an early report of Donnini[20] on the conversion of *O*-protected dihydroxytropenone to the pyrrolidine we anticipated that a sequence of Baeyer–Villiger oxidation followed by lactone opening should allow the transformation of tropenones **15**–**17** to the corresponding pyrrolidines **18**–**20** as precursors to hyacinthacine derivatives. The results toward this goal and the application in the total synthesis of 7a-*epi*-hyacinthacine A_1 are reported.

2. Results and discussion

Baeyer–Villiger oxidations of tropane derivatives are rarely reported.[20] For norbornenone derivatives, however, Mehta has shown that the chemoselectivity strongly depended on the reaction condition.[21] Whereas the use of MCPBA produced a (60:40) mixture of epoxide and unsaturated lactone, the use of H_2O_2/NaOH resulted in exclusive lactone formation.[21] When carbamate protected tropenone **15b** was submitted to H_2O_2/NaOH either in MeOH at 0 °C for 2 h or in Et_2O/H_2O at room temperature for 2 h the starting material **15b** could be recovered quantitatively. In contrast, MCPBA treatment of *N*-protected tropenones **15a**–**c** in CH_2Cl_2 at room temperature yielded only the epoxides **21a**–**c** in 55–82% (Scheme 3). No traces of the corresponding lactones **22** were found.

In analogy to Donnini's method, next the epoxide **21a** was treated with MCPBA in the presence of 2,4,6-tri(*tert*-butyl)phenol in dichloroethane at 55 °C (Scheme 3). However, even after 7 days, only traces of the desired lactone **23a** were detected at very low conversion.

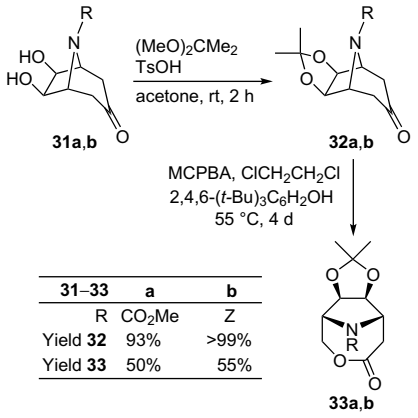
Surprisingly, also MOM-protected hydroxytropenone acetal **25a**, which was obtained from hydroxyacetal **24a**[16] by treatment with MOMCl in the presence of Hünig's base and DMAP in CH_2Cl_2 in 95% yield, gave the expected regioisomeric Baeyer–Villiger products **26a**, **27a** only in traces after cleavage of the acetal moiety with PPTS in acetone and subsequent Baeyer–Villiger oxidation (Scheme 4).



Scheme 4.

In contrast, treatment of *Z*-protected ketone **28**, which was obtained by modified Swern oxidation of alcohol **24b** in 70% yield, with MCPBA in the presence of $NaHCO_3$ in CH_2Cl_2 at room temperature gave exclusively lactone **29** in 57%. The regioisomeric lactone **30** was not detected. Presumably, the 1,2-migration of the bridgehead C–C bond is favored due to neighbor group assistance of the carbamate nitrogen. It should be noted, that Chambers[22] and Ruiz[23] reported 1,2-migration of the 'internal' C1–C2 bond rather than the bridgehead C2–C3 bond for Baeyer–Villiger oxidations of norcamphor derivatives.

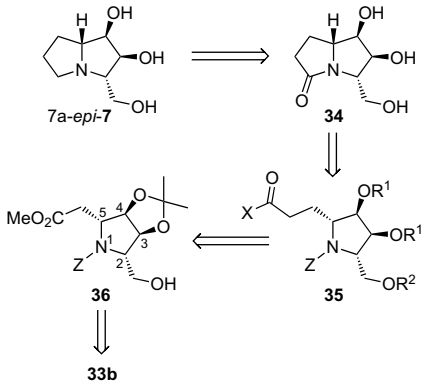
Finally, the diols **31a**,**b**[24,18] were acetalized with dimethoxypropane to give the tricyclic acetals **32a**,**b** in 93% and >99% yield, respectively (Scheme 5). Acetals **32a**,**b** were oxidized with MCPBA under Donnini's conditions[20] and the desired lactones **33a**,**b** were isolated in 50% and 55% yield, respectively. At this point it is not clear why tropane derivatives **15a–c**, **21**, and **24** behaved differently under the Baeyer–Villiger conditions as compared to **28** and **32a**,**b**.



31–33	a	b
R	CO_2Me	Z
Yield **32**	93%	>99%
Yield **33**	50%	55%

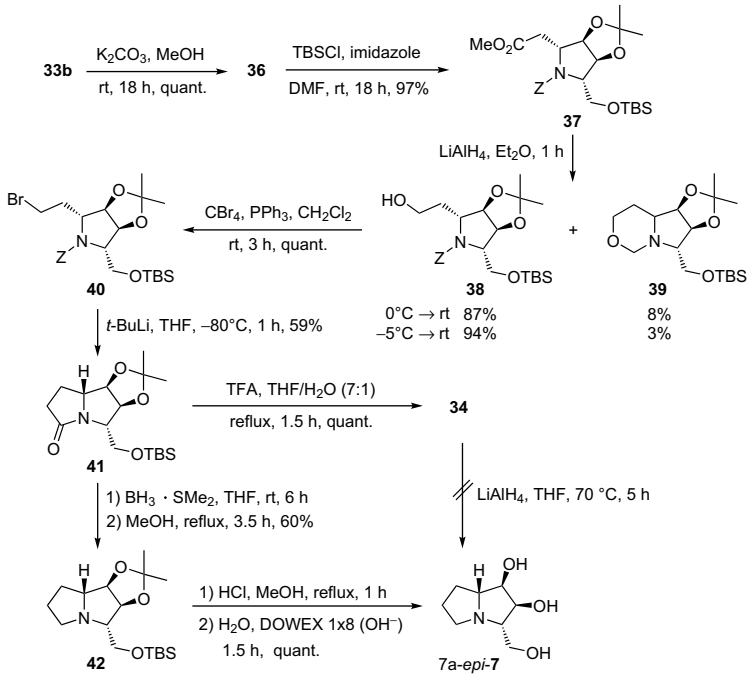
Scheme 5.

From these results we concluded that those pyrrolizidine alkaloids should be easily accessible via Baeyer–Villiger oxidation/lactone opening sequence, which contain a cis-diol subunit at C-1, C-2. Thus, the methodology was applied in the total synthesis of 7a-*epi*-hyacinthacine A_1 (7a-*epi*-**7**). The retrosynthesis is shown in Scheme 6. 7a-*epi*-Hyacinthacine A_1 (7a-*epi*-**7**) should be available from the pyrrolizidinone **34**, which can be traced back to the protected pyrrolidine derivative **35**. It was planned to prepare compound **35** from the pyrrolidine **36** by a sequence of protection of the primary hydroxy group, reduction, and chain extension. Compound **36** is derived from the lactone **33b** via opening and esterification.



Scheme 6.

As shown in Scheme 7, tricyclic lactone **33b** was treated with K_2CO_3 in MeOH according to the method by Ogawa[25] to give quantitatively pyrrolidine methylester **36**. The relative stereochemistry of **36** was proven by a NOESY NMR experiment, which not only displayed cross peaks for 2-H/5-H and 3-H/4-H but also cross peaks between the cis-oriented methylene groups and the hydrogen atoms, i.e., 2-CH_2/3-H, 5-CH_2/4-H, and 2-CH_2/5-CH_2. Subsequent protection of the primary hydroxy group in **36** with TBSCl in the presence of imidazole in DMF at room temperature yielded TBS ether **37** in 97%, which was then treated with $LiAlH_4$ in Et_2O. When the reaction was carried out at 0 °C and warmed to room temperature over 1 h, the desired alcohol **38** was isolated in 87% together with the tricyclic hemiaminal **39** in 8%. This byproduct is probably due to intramolecular nucleophilic attack of the primary



Scheme 7.

hydroxy group at the carbamate C=O, followed by extrusion of benzylic alcohol. The intermediate hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one is then further reduced by $LiAlH_4$ to the hemiaminal **39**. The formation of this byproduct could be minimized by lowering the reaction temperature to −5 °C and the yield of the desired product **38** was improved to 94%. Subsequent bromination of **38** under Appel conditions[26] with CBr_4 and PPh_3 in CH_2Cl_2 at room temperature yielded the bromide **40** almost quantitatively. For the conversion of the bromide **40** to the pyrrolizidinone **41** we applied a one step lactamization discovered by Dominguez.[27] Upon addition of pyrrolidine **40** to a solution of *t*-BuLi in THF at −80 °C followed by aqueous workup the desired lactam **41** could be isolated in 59% yield. Our assignment of the relative configuration in **36** was confirmed by an X-ray crystal structure analysis of **41** (Fig. 1).[28]

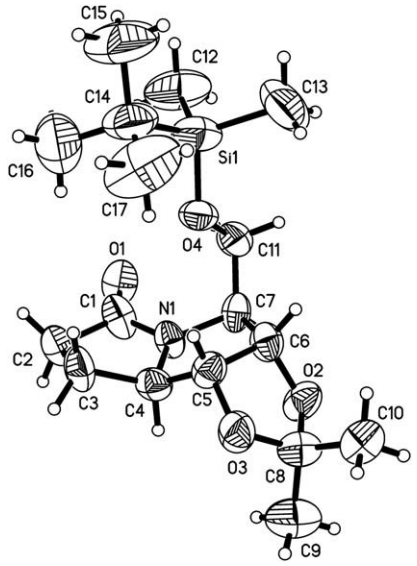


Figure 1. ORTEP presentation of lactam **41** in the solid state.

For completion of the synthesis of 7a-*epi*-**7** we first anticipated a deprotection of lactam **41** followed by reduction of the lactam moiety. Although **41** was deprotected with TFA in THF/H_2O (7:1) under reflux, all attempts failed to isolate the product from subsequent $LiAlH_4$ treatment. Therefore, protected lactam **41** was reduced with $LiAlH_4$ in THF to pyrrolizidine **42** albeit with 24% yield. The yield was improved to 60% by alternative reduction of lactam **41** with $BH_3 \cdot SMe_2$ in THF at room temperature, followed by refluxing in MeOH according to a method by Izquierdo.[29] Final deprotection was achieved by sequential treatment of **42** with HCl in MeOH under reflux and DOWEX 1×8 ion exchange resin following the method by Landais and Renaud.[30] In this way, the target compound 7a-*epi*-**7** was isolated quantitatively in analytically pure form.

In order to allow access to enantiomerically pure compound **7** as well, the lipase-catalyzed resolution of hydroxymethyl pyrrolidine **36** was investigated (Table 1). Treatment of (±)-**36** with Novozyme 435 from *Candida antarctica* or Chirazyme L-6 from *Pseudomonas cepacia* and vinyl acetate in Et_2O or toluene[31] yielded (−)-acetate (−)-**43** and (+)-alcohol (+)-**36**. The best results were obtained with Chirazyme L-6 (entries 4, 6, and 8). In toluene (−)-acetate (−)-**43** was obtained in 42% yield with 99% ee and the remaining (+)-alcohol (+)-**36** was isolated in 48% yield albeit with 75% ee (entry 8).

When the reaction was performed in Et_2O (−)-acetate (−)-**43** was isolated with decreased optical purity (56% ee), however, the enantiomeric excess of the alcohol (+)-**36** could be raised to 99% ee (entry 6).

3. Conclusion

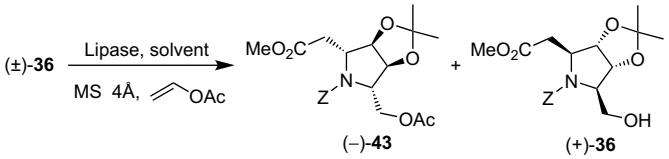
In conclusion, we have demonstrated that *N*-protected tropenones **15** could be converted into the pyrrolizidine alkaloid (±)-7a-*epi*-hyacinthacine A_1 (7a-*epi*-**7**) in 10 steps and 14% overall yield employing a Baeyer–Villiger oxidation/lactone opening sequence and a lactamization via intramolecular nucleophilic attack of an alkyllithium species to a carbamate as the key steps. This route gives also access to both enantiomeric series of **7** as was shown by the enzymatic resolution of the pyrrolidine intermediate **36**. Attempts toward the synthesis of other pyrrolizidines from tropane alkaloids are currently in progress.

4. Experimental section

4.1. General

Melting points (uncorrected) were determined on a Büchi 510 melting point apparatus. Optical rotations were determined with a Perkin–Elmer 241 LC polarimeter. IR spectra: Bruker Vektor 22 FT-IR spectrometer. Mass spectra: Finnigan MAT 95, Varian MAT 711, and Bruker Daltonics micrOTOF_Q spectrometers. NMR spectra: Bruker AC-250F, Bruker ARX 300, and Bruker ARX 500

Table 1
Enzymatic resolution of hydroxymethyl pyrrolidine (±)-**36** under various conditions[a,b]



Entry	Lipase	Solvent	Temp [°C]	Time [h]	Conversion [%]	(−)-**43** Yield [%]	[% ee]	*E*[c]	(+)-**36** Yield [%]	[% ee]	*E*
1	Novozyme 435	Et_2O	40	0.5	65	—	—	—	—	—	—
2	Chirazyme L-6	Et_2O	40	0.5	70	—	—	—	—	—	—
3	Novozyme 435	Toluene	40	2.0	45	39	45	4	50	35	3
4	Chirazyme L-6	Toluene	40	0.5	52	47	94	—	44	80	16
5	Novozyme 435	Et_2O	20	0.5	60	—	79	—	—	93	14
6	Chirazyme L-6	Et_2O	20	1.0	65	—[d]	56	—	—	99	16
7	Novozyme 435	Toluene	20	3.5	50	—	48	5	—	32	3
8	Chirazyme L-6	Toluene	20	1.5	48	42	99	>100	48	75	22

[a] The following lipases were used: Novozyme 435 from *C. antarctica*, Chirazyme L-6 from *P. cepacia*.
[b] Conversions were determined by capillary GC. Enantioselectivities were determined by chiral HPLC (see Experimental section for details). Yields refer to isolated yields.
[c] $E=\ln\{1-c[1+ee(\mathbf{43})]\}/\ln[1-c[1-ee(\mathbf{43})]\}$,[32] (whereby *c* was determined by GC).
[d] Not isolated.

spectrometers. The spectra were recorded with TMS as an internal standard. ^{13}C NMR multiplicities were determined by DEPT135 experiments. Signals of the second rotamer are indicated by *. Column chromatography: Fluka silica gel 60 (40–63 μm). Compounds **24a**,**b** were prepared according to Ref. 16

4.2. Synthesis and characterization

4.2.1. Methyl 7-oxo-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonane-9-carboxylate (**21a**)

To a solution of **15a** (52 mg, 287 μmol) in CH_2Cl_2 (2 mL) was added MCPBA (193 mg, 861 μmol, 77%) and the mixture was stirred at rt for 2 days. The reaction mixture was filtered, the filtrate was diluted with CH_2Cl_2, dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give **21a** (43 mg, 220 μmol, 77%) as a colorless oil. R_f=0.21 (EtOAc/hexane 1:1). ^1H NMR (500 MHz, $CDCl_3$): δ 2.36–2.38 (m, 1H), 2.38–2.41 (m, 2H), 2.42–2.44 (m, 1H) (H_a-2, H_a-4, $H_{\bar{a}}$-2, $H_{\bar{a}}$-4), 2.65 (d, J=5.1 Hz, 1H), 2.67 (d, J=5.1 Hz, 1H), 2.69 (d, J=5.1 Hz, 1H), 2.72 (d, J=5.1 Hz, 1H) (H_b-2, H_b-4, $H_{\bar{b}}$-2, $H_{\bar{b}}$-4), 3.49 (d, J=3.0 Hz, 2H), 3.51 (d, J=3.0 Hz, 2H) (H-6, H-7, H*-6, H*-7), 3.75 (s, 6H, CH_3, $CH_{\bar{3}}$), 4.60 (d, J=4.4 Hz, 2H), 4.73 (d, J=4.4 Hz, 2H) (H-1, H-5, H*-1, H*-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.4, 42.5 (C-2, C-4, C-2*, C-4*), 52.1, 52.4 (C-1, C-5, C-1*, C-5*), 52.7, 53.1 (C-6, C-7, C-6*, C-7*), 53.0 (CH_3, $CH_{\bar{3}}$), 156.9 (COO, COO*), 205.0 (C-3, C-3*). IR (neat, cm^{-1}): ν_{max} 2959, 2916, 1695, 1447, 1384, 1330, 1294, 1192, 1103, 1036, 922, 867, 704. MS (ESI): m/z 220 $[MNa]^+$, 182, 164. HRMS (ESI, $[MNa]^+$): calcd for $C_9H_{11}NO_4$+Na 220.0586, found 220.0582.

4.2.2. Benzyl 7-oxo-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonane-9-carboxylate (**21b**)

Following the procedure described for **21a**, epoxide **21b** (19 mg, 70.0 μmol, 82%) was obtained as a colorless oil. R_f=0.34 (EtOAc/hexane 1:1). ^1H NMR (500 MHz, $CDCl_3$): δ 2.34–2.35 (m, 1H), 2.37–2.40 (m, 2H), 2.42–2.44 (m, 1H) (H_a-2, H_a-4, $H_{\bar{a}}$-2, $H_{\bar{a}}$-4), 2.63 (d, J=5.1 Hz, 1H), 2.67 (d, J=5.1 Hz, 1H), 2.69 (d, J=5.1 Hz, 1H), 2.73 (d, J=5.1 Hz, 1H) (H_b-2, H_b-4, $H_{\bar{b}}$-2, $H_{\bar{b}}$-4), 3.48 (d, J=3.0 Hz, 2H), 3.51 (d, J=3.0 Hz, 2H) (H-6, H-7, H*-6, H*-7), 4.63–4.66 (m, 2H), 4.73–4.76 (m, 2H) (H-1, H-5, H*-1, H*-5), 5.17 (s, 4H, CH_2Ph, CH_2Ph*), 7.29–7.38 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.4, 42.5 (C-2, C-4, C-2*, C-4*), 52.2, 52.5 (C-1, C-5, C-1*, C-5*), 52.7, 53.1 (C-6, C-7, C-6*, C-7*), 67.7 (CH_2Ph, CH_2Ph*), 128.1, 128.3, 128.4 (Ph, Ph*), 136.1 (C-1′, C-1′*), 156.4 (COO, COO*), 204.9 (C-3, C-3*). IR (neat, cm^{-1}): ν_{max} 2941, 2906, 1698, 1465, 1420, 1365, 1330, 1296, 1220, 1198, 1105, 1032, 992, 929, 857, 765, 739. MS (EI): m/z 273 $[M^+]$, 228, 186, 166, 139, 107, 91 ($[C_7H_7^+]$), 65. HRMS (APCI, $[MH]^+$): calcd for $C_{15}H_{15}NO_4$+H 274.1079, found 274.1078.

4.2.3. tert-Butyl 7-oxo-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonane-9-carboxylate (**21c**)

Following the procedure described for **21a**, epoxide **21c** (13 mg, 54.3 μmol, 55%) was obtained as a colorless oil. R_f=0.17 (EtOAc/hexane 1:2). ^1H NMR (500 MHz, $CDCl_3$): δ 1.47 [s, 18H, $C(CH_3)_3$, $C(CH_3)_{\bar{3}}$], 2.33–2.34 (m, 1H), 2.35–2.38 (m, 2H), 2.39–2.41 (m, 1H) (H_a-2, H_a-4, $H_{\bar{a}}$-2, $H_{\bar{a}}$-4), 2.64 (d, J=5.1 Hz, 1H), 2.68 (d, J=5.1 Hz, 2H), 2.71 (d, J=5.1 Hz, 1H) (H_b-2, H_b-4, $H_{\bar{b}}$-2, $H_{\bar{b}}$-4), 3.46 (d, J=3.0 Hz, 2H), 3.48 (d, J=3.0 Hz, 2H) (H-6, H-7, H*-6, H*-7), 4.54 (d, J=4.8 Hz, 2H), 4.68 (d, J=4.8 Hz, 2H) (H-1, H-5, H*-1, H*-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.3 [$C(CH_3)_3$, $C(CH_3)_{\bar{3}}$], 42.4, 42.5 (C-2, C-4, C-2*, C-4), 51.6, 52.7 (C-1, C-5, C-1*, C-5*), 52.8, 53.2 (C-6, C-7, C-6*, C-7*), 81.0 [$C(CH_3)_3$, $C(CH_3)_{\bar{3}}$], 155.9 (COO, COO*), 205.6 (C-3, C-3*). IR (neat, cm^{-1}): ν_{max} 2970, 2930, 1691, 1480, 1393, 1333, 1297, 1160, 1099, 1033, 963, 862, 705. MS (ESI): m/z 262 $[MNa]^+$, 224, 206, 184, 162, 145, 140, 122, 94, 84. HRMS (ESI, $[MNa]^+$): calcd for $C_{12}H_{17}NO_4$+Na 262.1056, found 262.1045.

4.2.4. Methyl 6-(methoxymethoxy)-8H-spiro[8-azabicyclo-[3.2.1]octane-3,2′-[1,3]dioxolane]-8-carboxylate (**25a**)

To a cooled solution of **24a** (110 mg, 453 μmol) in CH_2Cl_2 (2 mL) were added MOMCl (170 μL, 2.26 mmol), i-Pr_2NEt (384 μL, 2.26 mmol), and DMAP (10 mg) and the reaction mixture was stirred for 30 min at 0 °C, then warmed to rt and stirred for 16 h. The mixture was diluted with CH_2Cl_2 (30 mL), washed with a satd NH_4Cl solution, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, EtOAc/hexane 2:1) to give **25a** (124 mg, 432 μmol, 95%) as a colorless oil. R_f=0.40 (EtOAc/hexane 2:1). ^1H NMR (500 MHz, $CDCl_3$): δ 1.71 (ddd, J=13.8, 4.1, 2.1 Hz, 2H, H_a-4, $H_{\bar{a}}$-4), 1.82–1.89 (m, 2H, H_a-7, $H_{\bar{a}}$-7), 1.86 (ddd, J=13.8, 2.4, 2.1 Hz, 2H, H_a-2, $H_{\bar{a}}$-2), 1.89–1.95 (br m, 1H, $H_{\bar{b}}$-4), 1.93 (dd, J=13.8, 4.1 Hz, 1H, H_b-2), 2.00–2.06 (br m, 2H, $H_{\bar{b}}$-2, H_b-4), 2.55 (dd, J=13.3, 7.3 Hz, 1H, H_b-7), 2.58 (dd, J=13.3, 7.3 Hz, 1H, $H_{\bar{b}}$-7), 3.36 (s, 3H, CH_2OCH_3), 3.37 (s, 3H, $CH_2OCH_{\bar{3}}$), 3.70 (s, 3H, $COOCH_3$), 3.71 (s, 3H, $COOCH_{\bar{3}}$), 3.80–3.86 (m, 4H, OCH_2, $OCH_{\bar{2}}$), 3.92–3.98 (m, 4H, OCH_2, $OCH_{\bar{2}}$), 4.21–4.24 (br m, 1H, H-1), 4.30–4.33 (br m, 1H, H*-1), 4.35–4.39 (br m, 1H, H*-5), 4.44 (dd, J=7.3, 2.4 Hz, 1H, H*-6), 4.45–4.48 (br m, 1H, H-5), 4.45 (dd, J=7.4, 2.4 Hz, 1H, H-6), 4.62 (d, J=7.2 Hz, 1H, $CH_aOCH_{\bar{3}}$), 4.64 (br s, 2H, CH_2OCH_3), 4.65 (d, J=7.2 Hz, 1H, $CH_bOCH_{\bar{3}}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.1 (C-7), 37.8 (C-7*), 38.5 (C-2*), 39.3 (C-2), 39.8 (C-4), 40.6 (C-4*), 52.4 ($COOCH_3$, $COOCH_{\bar{3}}$), 52.8 (C-5*), 52.9 (C-5), 55.4 (CH_2OCH_3), 55.5 ($CH_2OCH_{\bar{3}}$), 59.3 (C-1*), 59.6 (C-1), 63.5, 64.5 (OCH_2, $OCH_{\bar{2}}$), 78.8 (C-6*), 79.7 (C-6), 95.6 (CH_2OCH_3, $CH_2OCH_{\bar{3}}$), 106.9 (C-3, C-3*), 154.4 (COO*), 154.5 (COO). IR (neat, cm^{-1}): ν_{max} 2995, 2978, 2890, 1681, 1455, 1406, 1323, 1217, 1098, 1029, 982, 912, 868, 818, 760, 685, 641. MS (APCI): m/z 288 $[MH]^+$, 256, 226, 212, 194, 182, 151, 140. HRMS (APCI): calcd for $C_{13}H_{21}NO_6$+H 288.1447, found 288.1445.

4.2.5. Methyl 2,2-dimethyl-6-oxohexahydro-3aH-4,8-epiminocyclohepta[d][1,3]dioxole-9-carboxylate (**32a**)

Following the procedure described for **32b**, compound **32a** (34 mg, 133 μmol, 93%) was obtained as a colorless solid. Mp 121 °C. R_f=0.6 (EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.43 (dd, J=16.4, 9.4 Hz, 2H, H_a-2, H_a-4), 2.64 (dd, J=16.4, 5.3 Hz, 1H, H_b-4), 2.69 (dd, J=16.4, 5.3 Hz, 1H, H_b-2), 3.77 (s, 3H, CH_3), 4.43 (s, 2H, H-6, H-7), 4.48 (d, J=5.0 Hz, 1H, H-1), 4.59 (d, J=5.0 Hz, 1H, H-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 25.9 [$C(CH_3)_2$], 44.9, 45.1 (C-2, C-4), 52.9 (CH_3), 58.8 (C-1, C-5), 82.5, 83.0 (C-6, C-7), 111.6 [$C(CH_3)_2$], 155.4 (COO), 205.3 (C-3). IR (neat, cm^{-1}): ν_{max} 2991, 1697, 1451, 1402, 1204, 1113, 1047, 989, 869, 761, 693. MS (EI): m/z (%) 225 ($[M^+]$), 240 (100), 196 (15), 155 (65), 101 (20), 43 (25). $C_{12}H_{17}NO_5$ (255): calcd C, 56.46%; H, 6.71%; N, 5.49%. Found: C, 56.34%; H, 6.64%; N, 5.35%.

4.2.6. Benzyl 2,2-dimethyl-6-oxohexahydro-3aH-4,8-epiminocyclohepta[d][1,3]dioxole-9-carboxylate (**32b**)

To a stirred solution of **31b** (150 mg, 583 μmol) in acetone (5 mL) was added dimethoxypropane (340 μL, 3.26 mmol) and p-TsOH·H_2O (20 mg, 113 μmol) and the reaction mixture was kept at rt for 2 h. The reaction mixture was diluted with $NaHCO_3$ solution (5 mL) and extracted with EtOAc (10 mL). The extract was dried ($MgSO_4$) and EtOAc removed in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc/hexane 1:2) to give **32b** as a colorless solid (173 mg, 582 μmol, quant.). Mp 92 °C. R_f=0.22 (EtOAc/hexane 1:2). ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (CH_3, $CH_{\bar{3}}$), 1.35 (CH_3, $CH_{\bar{3}}$), 2.39 (br s, 1H), 2.43 (br s, 2H), 2.46 (br s, 1H) (H_a-2, H_a-4, $H_{\bar{a}}$-2, $H_{\bar{a}}$-4), 2.60 (dd, J=16.4, 5.3 Hz, 2H), 2.71 (dd, J=16.4, 5.3 Hz, 2H) (H_b-2, H_b-4, $H_{\bar{b}}$-2, $H_{\bar{b}}$-4), 4.44 (s, 4H, H-6, H-7, H*-6, H*-7), 4.54–4.58 (m, 2H), 4.61–4.65 (m, 2H) (H-1, H-5, H*-1, H*-5), 5.16–5.25 (m, 4H, CH_2Ph, CH_2Ph*), 7.29–7.40 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 25.9 (CH_3, $CH_{\bar{3}}$), 45.0, 45.2 (C-2, C-4, C-2*, C-4*), 58.8, 58.9 (C-1, C-5, C-1*, C-5*), 67.4 (CH_2Ph, CH_2Ph*),

82.5, 83.0 (C-6, C-7, C-6*, C-7*), 111.6 [$C(CH_3)_2$, $C(CH_3)_2$], 128.0, 128.2, 128.6 (Ph, Ph*), 136.3 (C-1′, C-1′*), 154.8 (CO, CO*), 205.3 (C-3, C-3*). IR (neat, cm^{-1}): ν_{max} 2985, 2934, 1716, 1700, 1418, 1367, 1232, 1205, 1123, 1053, 987, 870, 734, 695. MS (APCI): *m*/*z* 332 [MH^+], 302, 288, 244, 198, 182, 142, 91 [$C_7H_7]^+$. HRMS (ESI, [MNa]$^+$): calcd for $C_{18}H_{21}NO_5$+Na 354.1314, found 354.1318.

4.2.7. Methyl 2,2-dimethyl-7-oxohexahydro-3aH-4,9-epimino[1,3]dioxolo[4,5-d]oxocine-10-carboxylate (**33a**)

Following the procedure described for **33b**, compound **33a** (18 mg, 66.4 μmol, 50%) was obtained as a colorless oil. R_f=0.26 (EtOAc/hexane 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 6H, CH_3, CH_3), 1.49 (s, 6H, CH_3, CH_3), 2.67–2.92 (br m, 4H, H_a-5, H_a-5, H_b-5, H_b-5), 3.69–3.75 (m, 2H, H_a-2, H_a-2), 3.73 (s, 6H, OCH_3, OCH_3), 3.79–3.96 (m, 2H, H_b-2, H_b-2), 4.06 (br, 1H, H*-1), 4.14 (br, 1H, H-1), 4.28–4.42 (br m, 2H, H-6, H*-6), 4.57 (d, *J*=5.8 Hz, 1H, H*-7), 4.58 (d, *J*=5.8 Hz, 1H, H-7), 4.74 (br, 1H, H-8), 4.76 (br, 1H, H*-8). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 27.3 (CH_3, CH_3), 36.8 (br, C-5*), 37.4 (br, C-5), 53.0 (OCH_3, OCH_3), 61.0, 61.9 (br, C-6, C-6*), 62.4, 63.0 (br, C-2, C-2*), 66.2 (br, C-1*), 67.1 (br, C-1), 81.2 (br, C-8), 82.0 (br, C-8*), 83.6 (br, C-7*), 84.0 (br, C-7), 112.2 [$C(CH_3)_2$, $C(CH_3)_2$], 155.8, 156.1 (CO, CO*), 174.7 (C-4, C-4*).

4.2.8. Benzyl 2,2-dimethyl-7-oxohexahydro-3aH-4,9-epimino[1,3]dioxolo[4,5-d]oxocine-10-carboxylate (**33b**)

To a stirred solution of **32b** (124 mg, 375 μmol) in dichloroethane (6 mL) was added MCPBA (252 mg, 1.46 mmol, 77%) and 2,4,6-tri(*tert*-butyl)phenol (2 mg). After stirring at 55 °C for 3 days, the reaction mixture was cooled, the solid filtered off and the filtrate diluted with CH_2Cl_2 (6 mL). The filtrate was washed successively with aqueous solutions of Na_2SO_3 and $NaHCO_3$ (3 mL each) and brine (3 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel, EtOAc/hexane=1:2) to give **33b** (72 mg, 207 μmol, 55%) as a colorless oil. R_f=0.21 (EtOAc/hexane 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (s 3H), 1.28 (s, 3H) (CH_3, CH_3), 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.79 (dd, *J*=16.5, 1.8 Hz, 1H, H_a-5), 2.89 (dd, *J*=16.5, 1.8 Hz, 1H, H_a-5), 3.06 (dt, *J*=16.5, 5.8 Hz, 2H, H_b-5, H_b-5), 4.23 (d, *J*=13.3 Hz, 1H, H_a-2 or H_a-2), 4.31 (d, *J*=13.3 Hz, 1H, H_a-2 or H_a-2), 4.36 (dd, *J*=13.3, 4.5 Hz, 1H, H_b-2 or H_b-2), 4.35–4.38 (m, 1H, H-6 or H*-6), 4.41 (dd, *J*=13.3, 4.5 Hz, 1H, H_b-2 or H_b-2), 4.44 (dt, *J*=5.8, 1.4 Hz, 1H, H-6 or H*-6), 4.52 (d, *J*=4.6 Hz, 1H, H-1 or H*-1), 4.57 (d, *J*=5.6 Hz, 2H, H-7, H*-7), 4.62 (d, *J*=4.6 Hz, 1H, H-1 or H-1*), 4.88 (d, *J*=5.6 Hz, 2H, H-8, H*-8), 5.15 (d, *J*=12.3 Hz, 1H), 5.16 (d, *J*=12.3 Hz, 1H), 5.21 (d, *J*=12.3 Hz, 1H), 5.22 (d, *J*=12.3 Hz, 1H) (CH_2Ph, CH_2Ph*), 7.31–7.39 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 25.9 (CH_3, CH_3), 41.1 (C-5), 41.6 (C-5*), 57.8, 57.9 (C-6, C-6*), 62.4, 62.6 (C-1, C-1*), 67.6 (CH_2Ph, CH_2Ph*), 71.3, 71.4 (C-2, C-2*), 80.4, 81.0 (C-8, C-8*), 82.6, 83.1 (C-7, C-7*), 111.9 [$C(CH_3)_2$, $C(CH_3)_2$], 128.0, 128.4, 128.6 (Ph, Ph*), 136.1 (C-1′, C-1′*), 154.2, 154.3 (CO, CO*), 171.9, 172.0 (C-4, C-4*). IR (neat, cm^{-1}): ν_{max} 2987, 2939, 1697, 1411, 1323, 1208, 1118, 1050, 869, 813, 697. MS (APCI): *m*/*z* 348 [MH^+], 304, 256, 240, 138, 91 [$C_7H_7]^+$. HRMS (ESI, [MNa]$^+$): calcd for $C_{18}H_{21}NO_6$+Na 370.1264, found 370.1267.

4.2.9. Benzyl 6-oxo-8H-spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane]-8-carboxylate (**28**)

Trifluoroacetic anhydride (36 μL, 0.256 mmol) was added dropwise to a solution of DMSO (36 μL, 513 μmol) in CH_2Cl_2 (1 mL) at −78 °C. Then a solution of **24b** (50 mg, 157 μmol) in CH_2Cl_2 (100 μL) and DMSO (10 μL) was added dropwise. After stirring for 30 min, NEt_3 (70 μL) was added and the mixture warmed to rt and stirred for 3 h. EtOAc (20 mL) was added and the mixture washed with water (3×10 mL) and aqueous NaCl solution (3×10 mL). The organic layer was dried (Na_2SO_4) and evaporated. Purification by column chromatography (silica gel, EtOAc/hexane 1:1) gave **28** (35 mg, 110 μmol, 70%) as a colorless oil. R_f=0.38 (EtOAc/hexane 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.85 (br d, *J*=13.8 Hz, 2H, H_a-2, H_a-2), 1.93–2.14 (br m, 4H, H_a-4, H_a-4, H_b-4, H_b-4), 2.16–2.33 (m, 2H, H_b-2, H_b-2), 2.54 (dd, *J*=17.6, 7.6 Hz, 2H, H_a-7, H_a-7), 2.69 (d, *J*=17.6 Hz, 2H, H_b-7, H_b-7), 3.83–3.88 (m, 4H, OCH_2, OCH_2), 3.89–3.97 (m, 4H, OCH_2, OCH_2), 4.16–4.29 (br m, 2H, H-5, H*-5), 4.68–4.81 (br m, 2H, H-1, H*-1), 5.10–5.22 (br m, 4H, CH_2Ph, CH_2Ph*), 7.29–7.41 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.8 (br, C-2), 39.2 (br, C-2*), 39.6 (br, C-4*), 40.1 (br, C-4), 42.5 (br, C-7), 42.9 (br, C-7*), 51.2 (br, C-1), 51.4 (br, C-1*), 59.8 (br, C-5, C-5*), 64.1, 64.8 (OCH_2, OCH_2), 67.4 (CH_2Ph, CH_2Ph*), 106.3 (C-3, C-3*), 128.1, 128.3, 128.6 (Ph, Ph*), 136.1 (C-1′, C-1′*), 153.5 (COO, COO*), 210.9 (br, C-6, C-6*). IR (neat, cm^{-1}): ν_{max} 3034, 2958, 2916, 2849, 1765, 1701, 1603, 1563, 1406, 1357, 1304, 1200, 1116, 1097, 1046, 948, 823, 698, 641. MS (ESI): *m*/*z* 340 [MNa^+], 318.1 [MH^+], 274, 212, 91 [$C_7H_7]^+$. HRMS (ESI, [MH]$^+$): calcd for $C_{17}H_{19}NO_5$+H 318.1341, found 318.1336.

4.2.10. Benzyl 7′-oxo-9′H-spiro[1,3-dioxolane-2,3′-[6]oxa[9]azabicyclo[3.3.1]nonane]-9′-carboxylate (**29**)

MCPBA (111 mg, 495 μmol, 77%) and $NaHCO_3$ (17 mg) were added to a stirred solution of **28** (30 mg, 94.6 μmol) in CH_2Cl_2 (2 mL) at rt. After stirring overnight, CH_2Cl_2 (10 mL) was added and the mixture washed successively with aqueous solutions of Na_2SO_3 (5 mL) and $NaHCO_3$ (3 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give the **29** (18 mg, 54.0 μmol, 57%) as a colorless oil. R_f=0.29 (EtOAc/hexane 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (br d, *J*=14.1 Hz, 1H, H_a-6), 1.98 (dd, *J*=14.1, 3.3 Hz, 1H, H_a-8), 2.12 (ddd, *J*=14.0, 4.8, 1.0 Hz, 1H, H_b-6), 2.36 (br d, *J*=14.1 Hz, 1H, H_b-8), 2.66 (d, *J*=18.0 Hz, 1H, H_a-4), 2.76–2.96 (br m, 1H, H_b-4), 3.87–3.96 (m, 2H, OCH_2), 3.99–4.07 (m, 2H, OCH_2), 4.78 (br s, 1H, H-5), 5.18 (d, *J*=12.1 Hz, 1H, CH_aPh), 5.23 (d, *J*=12.1 Hz, 1H, CH_bPh), 6.39 (br s, 1H, H-1), 7.33–7.41 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9 (br, C-4), 38.7 (br, C-8), 38.9 (br, C-6), 45.3 (br, C-5), 63.8 (OCH_2), 65.1 (OCH_2), 68.5 (CH_2Ph), 81.6 (C-1), 105.0 (C-7), 128.3, 128.6, 128.7 (C-2′, C-3′, C-4′), 135.3 (C-1′), 153.3 (NCOO), 167.3 (C-3). IR (neat, cm^{-1}): ν_{max} 2925, 2854, 1747, 1708, 1422, 1388, 1343, 1262, 1213, 1116, 1054, 960, 912, 887, 754, 695, 671. MS (APCI): *m*/*z* 334 [MH^+], 290, 246, 230, 204, 186, 149, 117, 91 [$C_7H_7^+$]. HRMS (APCI, [MH]$^+$): calcd for $C_{17}H_{19}NO_6$+H 334.1290, found 333.1286.

4.2.11. Benzyl 4-(hydroxymethyl)-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate (**36**)

To a solution of **33b** (482 mg, 1.39 mmol) in MeOH (15 mL) was added K_2CO_3 (20 mg, 147 μmol) and the reaction mixture stirred at rt overnight. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give **36** (496 mg, 1.31 mmol, 94%) as a colorless oil. R_f=0.24 (EtOAc/hexane 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 6H, CH_3, CH_3), 1.47 (s, 6H, CH_3, CH_3), 1.63–1.84 (m, 6H, CH_2COOMe, CH_2COOMe*, OH, OH*), 3.57 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.62–3.74 (m, 2H, CH_2OH, CH_2OH*), 3.85 (d, *J*=10.6 Hz, 1H, CH_aOH*), 3.93 (d, *J*=10.6 Hz, 1H, CH_bOH), 4.04–4.12 (br m, 1H, H*-2), 4.12–4.20 (br m, 1H, H-2), 4.41 (br t, *J*=7.1 Hz, 2H, H-5, H*-5), 4.52 (2d, *J*=5.7 Hz, 2H, H-4, H*-4), 4.69–4.74 (br m, 1H, H-3), 4.74–7.80 (br m, 1H, H*-3), 5.07–5.18 (m, 4H, CH_2Ph, CH_2Ph*), 7.29–7.38 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.3, 27.3 (CH_3, CH_3), 36.8 (CH_2COOMe*), 37.6 (CH_2COOMe), 51.9 (OMe), 52.1 (OMe*), 61.1 (C-5), 61.7 (C-5*), 62.7 (CH_2OH*), 63.1 (CH_2OH), 66.5 (C-2*), 67.3 (C-2), 67.4 (CH_2Ph*), 67.5 (CH_2Ph), 81.2 (C-3), 82.0 (C-3*), 83.5 (C-4*), 84.1 (C-4), 112.2 [$C(CH_3)_2$, $C(CH_3)_2$], 127.7, 128.1, 128.6 (Ph, Ph*), 136.1, 136.3 (C-1′, C-1′*), 154.8 (CO*), 155.4 (CO), 171.5 (COOMe), 172.2 (COOMe*). IR

(neat, cm^{-1}): ν_{max} 3462, 2987, 2950, 1735, 1698, 1409, 1325, 1209, 1120, 1053, 869, 698. MS (EI): *m/z* (%) 379 ([M^+], 5), 348 (15), 304 (30), 214 (5), 186 (5), 156 (5), 91 ([$C_7H_7^+$], 100), 65 (5), 43 (5). HRMS (ESI, [MNa]$^+$): calcd for $C_{19}H_{25}NO_7$+Na 402.1529, found 402.1528. HPLC: Chromasil ODH, hexane/isopropanol (70:30), flow rate 0.5 mL min^{-1}, t_R=10.84 min and t_R=12.65 min.

4.2.12. Benzyl 4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-5H-[1,3]-dioxolo[4,5-c]pyrrole-5-carboxylate (**37**)

A solution of **36** (254 mg, 0.67 mmol) in DMF (1.5 mL) was added to a solution of *tert*-butyldimethylsilylchloride (136 mg, 0.89 mmol) and imidazole (61 mg, 0.89 mmol) in DMF (1.5 mL). After stirring overnight, the reaction mixture was diluted in CH_2Cl_2 (15 mL) and washed with brine (10 mL) and water (10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:4) to give **37** (321 mg, 651 μmol, 97%) as a colorless oil. R_f=0.59 (EtOAc/hexane 1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 [s, 6H, Si(CH_3)$_2$], 0.05 [s, 3H, Si(CH_3)$_2$], 0.06 [s, 3H, Si(CH_3)$_2$], 0.87 [s, 9H, C(CH_3)$_3$], 0.89 [s, 9H, C(CH_3)$_3$], 1.32 (s, 6H, CH_3, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.59 (dd, *J*=15.9, 10.5 Hz, 1H, CH_aCOOCH_3), 2.67 (dd, *J*=15.9, 10.5 Hz, 1H, CH_aCOOCH_3), 2.76 (dd, *J*=15.9, 4.5 Hz, 1H, CH_bCOOCH_3), 2.93 (dd, *J*=15.9, 4.5 Hz, 1H, CH_bCOOCH_3), 3.63–3.70 (m, 2H, CH_2OSi*), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.73 (dd, *J*=10.5, 2.7 Hz, 1H, CH_aOSi), 3.85 (dd, *J*=10.5, 2.7 Hz, 1H, CH_bOSi), 4.07–4.10 (br m, 1H, H*-2), 4.15–4.18 (br m, 1H, H-2), 4.35 (dd, *J*=4.5, 1.7 Hz, 1H, H-5), 4.37 (dd, *J*=4.5, 1.7 Hz, 1H, H*-5), 4.50 (dd, *J*=5.9, 1.7 Hz, 1H, H-4), 4.53 (dd, *J*=5.9, 1.7 Hz, 1H, H*-4), 4.67 (d, *J*=5.9 Hz, 1H, H-3), 4.70 (d, *J*=5.9 Hz, 1H, H*-3), 5.08 (d, *J*=12.3 Hz, 1H, CH_aPh or CH_aPh*), 5.18 (s, 2H, CH_2Ph or CH_2Ph*), 5.18 (d, *J*=12.3 Hz, 1H, CH_bPh or CH_bPh*), 7.28–7.37 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.6 [Si(CH_3)$_2$], −5.4 [Si(CH_3)$_2$], 18.4 [*C*(CH_3)$_3$, *C*(CH_3)$_3$], 25.2 [C(*C*H_3)$_2$, *C*(CH_3)$_2$], 26.0 [C(*C*H_3)$_3$, C(*C*H_3)$_3$], 27.3 [C(*C*H_3)$_2$, *C*(CH_3)$_2$], 36.9 (*C*H_2COOCH_3), 37.8 (*C*H_2COOCH_3), 51.7 (OCH_3, OCH_3), 61.7, 62.4 (C-5, C-5*), 62.8 (CH_2OSi), 63.5 (CH_2OSi*), 65.8 (C-2*), 66.6 (C-2), 67.0, 67.1 (*C*H_2Ph, *C*H_2Ph*), 81.1 (C-3), 82.1 (C-3*), 84.0 (C-4*), 84.8 (C-4), 111.8 [*C*(CH_3)$_2$, *C*(CH_3)$_2$], 127.6, 127.9, 128.0, 128.1, 128.5 (Ph, Ph*), 136.5 (C-1′, C-1′*), 154.2, 154.3 (CO, CO*), 171.4, 171.5 (*C*OOCH$_3$, *C*OOCH$_3$). IR (neat, cm^{-1}): ν_{max} 2952, 2857, 1741, 1704, 1409, 1383, 1327, 1255, 1160, 1118, 1065, 836, 632. MS (ESI): *m/z* 494 ([MH^+]), 462, 450, 404, 392, 358, 318, 286, 260, 232, 210, 168, 152, 91 ([$C_7H_7^+$]). HRMS (ESI, [MNa]$^+$): calcd for $C_{25}H_{39}NO_7Si$+Na 516.2394, found 516.2381.

4.2.13. Benzyl 4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-6-(2-hydroxyethyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo-[4,5-c]pyrrole-5-carboxylate (**38**)

A solution of **37** (617 mg, 1.25 mmol) in Et_2O (15 mL) was added dropwise to a cooled (0 °C) suspension of $LiAlH_4$ (95 mg, 2.50 mmol) in Et_2O (10 mL). After stirring at rt for 1 h, the reaction mixture was diluted with Et_2O (10 mL), hydrolyzed with a satd Na_2SO_4 solution (2 mL) and filtered. The filtrate was evaporated and purified by flash chromatography (silica gel, EtOAc/hexane 1:2) to give in a first fraction **39** (12 mg, 35.0 μmol, 3%) as a colorless oil and in a second fraction **38** (548 mg, 1.18 mmol, 94%) as the major product. Compound **38**: R_f=0.28 (EtOAc/hexane 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.02 [s, 3H, Si(CH_3)$_2$], 0.00 [s, 3H, Si(CH_3)$_2$], 0.86 [br s, 9H, C(CH_3)$_3$], 1.32 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.59 (dt, *J*=11.8, 2.6 Hz, 1H, CH_aCH$_2$OH), 1.82–1.90 (m, 1H, CH_bCH$_2$OH), 3.53 (td, *J*=11.8, 2.6 Hz, 1H, CH$_2$CH_aOH), 3.58–3.64 (m, 1H, CH$_2$CH_bOH), 3.62 (dd, *J*=10.5, 4.8 Hz, 1H, CH_aOSi), 3.69 (dd, *J*=10.5, 3.3 Hz, 1H, CH_bOSi), 4.05–4.08 (m, 1H, H-2), 4.38 (dd, *J*=11.8, 4.1 Hz, 1H, H-5), 4.41 (d, *J*=5.7 Hz, 1H, H-4), 4.73 (dd, *J*=5.7, 2.1 Hz, 1H, H-3), 5.13 (d, *J*=12.4 Hz, 1H, CH_aPh), 5.24 (d, *J*=12.4 Hz, 1H, CH_bPh), 7.29–7.38 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.6, −5.5 [Si(CH_3)$_2$], 18.4 [*C*(CH_3)$_3$], 25.4 [C(*C*H_3)$_2$], 25.9 [C(*C*H_3)$_3$], 27.4 [C(*C*H_3)$_2$], 36.3 [*C*H$_2$CH$_2$OH], 58.5 [CH$_2$*C*H$_2$OH], 61.2 (C-5), 63.2 (CH_2OSi), 66.8 (C-2), 67.6 (*C*H_2Ph), 81.6 (C-3), 84.7 (C-4), 111.8 [*C*(CH_3)$_2$], 127.8, 128.2, 128.6 (Ph), 136.3 (C-1′), 156.4 (CO). IR (neat, cm^{-1}): ν_{max} 3460, 2952, 2930, 2857, 1680, 1410, 1360, 1328, 1252, 1212, 1159, 1119, 1065, 966, 939, 835, 777, 734, 697. MS (ESI): *m/z* 466 [MH^+], 422, 408, 364, 334, 290, 272, 226, 204, 91 [$C_7H_7^+$]. HRMS (ESI, [MH]$^+$): calcd for $C_{24}H_{39}NO_6Si$+H 466.2626, found 466.2611.

4.2.14. 4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2,2-dimethyl-hexahydro[1,3]dioxolo[3,4]pyrrolo[1,2-c][1,3]oxazine (**39**)

R_f=0.44 (EtOAc/hexane 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.53 [s, 3H, Si(CH_3)$_2$], 0.55 [s, 3H, Si(CH_3)$_2$], 0.88 [s, 9H, C(CH_3)$_3$], 1.32 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.58–1.75 (br m, 1H, H_a-4), 1.89 (d, *J*=12.5 Hz, 1H, H_b-4), 2.53–2.63 (br m, 1H, H-4a), 2.78–2.86 (m, 1H, H-7), 3.45 (td, *J*=11.8, 2.7 Hz, 1H, H_a-3), 3.76–3.82 (m, 2H, CH_2OSi), 3.97 (d, *J*=8.4 Hz, 1H, H_a-1), 4.06 (dd, *J*=11.8, 4.8 Hz, 1H, H_b-3), 4.21–4.29 (br m, 1H, H-5), 4.33 (dd, *J*=7.0, 3.8 Hz, 1H, H-6), 4.86 (d, *J*=8.4 Hz, 1H, H_b-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.5, −5.4 [Si(CH_3)$_2$], 18.2 [*C*(CH_3)$_3$], 25.1 [C(*C*H_3)$_2$], 25.9 [C(*C*H_3)$_3$], 27.1 [C(*C*H_3)$_2$], 29.7 (C-4), 64.9 (CH_2OSi), 66.6 (C-3), 67.2 (C-4a), 68.2 (C-7), 81.1 (C-6), 83.0 (C-5), 83.9 (C-1), 113.8 [*C*(CH_3)$_2$]. IR (neat, cm^{-1}): ν_{max} 2930, 2856, 1471, 1380, 1253, 1209, 1189, 1168, 1109, 1068, 976, 872, 837, 777, 632. GC–MS (EI): *m/z* (%) 343 ([M^+], 5), 328 (5), 286 (10), 270 (5), 228 (5), 198 (100), 156 (5), 140 (5), 124 (5), 101 (5), 73 (5), 59 ([$COOCH_3^+$], 5), 41 (5). $C_{17}H_{33}NO_4Si$ (343.54): calcd C, 59.44; H, 9.68; N, 4.08. Found: C, 59.60; H, 9.62; N, 3.92.

4.2.15. Benzyl 4-(2-bromoethyl)-6-({[tert-butyl(dimethyl)-silyl]oxy}methyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]-pyrrole-5-carboxylate (**40**)

To a solution of **38** (35 mg, 75.3 μmol) in CH_2Cl_2 (1 mL) was added tetrabromoethane (35 mg, 105 μmol) and triphenylphosphine (24 mg, 90.3 μmol) and the mixture was stirred at rt for 2 h and then diluted with water (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×2 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue purified by flash chromatography (silica gel, EtOAc/hexane 1:5) to give **40** (38 mg, 72 μmol, 96%) as a yellow oil. R_f=0.58 (EtOAc/hexane 1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02–0.06 [m, 12H, Si(CH_3)$_2$, Si(CH_3)$_2$], 0.88 [s, 9H, C(CH_3)$_3$], 0.89 [s, 9H, C(CH_3)$_3$], 1.32 (s, 6H, CH_3, CH_3), 1.43 (s, 6H, CH_3, CH_3), 2.03–2.11 (m, 2H, CH_aCH$_2$Br, CH_aCH$_2$Br*), 2.22–2.32 (m, 1H, CH_bCH$_2$Br), 2.33–2.42 (m, 1H, CH_bCH$_2$Br*), 3.28–3.51 (m, 4H, CH_2Br, CH_2Br*), 3.64 (dd, *J*=10.5, 3.5 Hz, 1H, CH_aOSi), 3.70 (dd, *J*=10.5, 2.3 Hz, 1H, CH_bOSi), 3.75 (dd, *J*=10.5, 2.3 Hz, 1H, CH_aOSi*), 3.82 (dd, *J*=10.5, 3.5 Hz, 1H, CH_bOSi*), 4.06–4.11 (br m, 3H, 2-H*, H-5, H*-5), 4.16 (br s, 1H, H-2), 4.38 (d, *J*=5.7 Hz, 1H, H-4), 4.41 (d, *J*=5.7 Hz, 1H, H*-4), 4.68 (d, *J*=5.7 Hz, 1H, H-3), 4.71 (d, *J*=5.7 Hz, 1H, H*-3), 5.11 (d, *J*=12.4 Hz, 1H, CH_aPh), 5.18 (d, *J*=12.4 Hz, 3H, CH_bPh, CH_2Ph*), 7.29–7.39 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.5 [Si(CH_3)$_2$), −5.4 (Si(CH_3)$_2$], 18.4 [*C*(CH_3)$_3$, *C*(CH_3)$_3$], 25.4 [C(*C*H_3)$_2$, C(*C*H_3)$_2$], 26.0 [C(*C*H_3)$_3$, C(*C*H_3)$_3$], 27.4 [C(*C*H_3)$_2$, C(*C*H_3)$_2$], 29.1 (CH_2Br, CH_2Br*), 37.1 (*C*H$_2$CH$_2$Br), 37.3 (*C*H$_2$CH$_2$Br*), 62.9 (CH_2OSi*), 63.5 (CH_2OSi), 63.6 (C-5), 64.6 (C-5*), 66.0 (C-2*), 66.7 (C-2), 67.1 (*C*H_2Ph), 67.2 (*C*H_2Ph*), 81.1 (C-3*), 82.0 (C-3), 84.0 (C-4*), 84.6 (C-4), 111.9 [*C*(CH_3)$_2$, *C*(CH_3)$_2$], 127.8, 128.0, 128.1, 128.5 (Ph, Ph*), 136.4 (C-1′*), 136.5 (C-1′), 155.0 (CO, CO*). IR (neat, cm^{-1}): ν_{max} 2953, 2930, 2857, 1703, 1462, 1409, 1383, 1326, 1254, 1212, 1160, 1117, 1067, 1004, 836, 779, 632. MS (ESI): *m/z* 528 ([MH^+]), 484, 470, 426, 392, 358, 334, 314, 294, 226, 187, 168, 91 ([$C_7H_7^+$]). HRMS (ESI, [MH]$^+$): calcd for $C_{24}H_{38}BrNO_5Si$+H 528.1782, found 528.1775.

4.2.16. 4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2,2-dimethyl-hexahydro-6H-[1,3]-dioxolo[4,5-a]pyrrolizin-6-one (**41**)

A solution of **40** (133 mg, 252 μmol) in THF (3.5 mL) was added dropwise to a cooled solution of *t*-BuLi (478 μL, 758 μmol, 1.7 M in pentane) in THF (1 mL) at −78 °C. After stirring for 1 h at −78 °C,

a satd NH_4Cl solution (1 mL) was added and the solvent was removed. The residue was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give **41** (51 mg, 149 μmol, 59%) as a yellow oil. R_f=0.34 (EtOAc/hexane 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.49 [s, 3H, $Si(CH_3)_2$], 0.64 [s, 3H, $Si(CH_3)_2$], 0.88 [s, 9H, $C(CH_3)_3$], 1.34 [s, 3H, $C(CH_3)_2$], 1.54 [s, 3H, $C(CH_3)_2$], 1.77 (ddt, *J*=12.2, 10.0, 8.8 Hz, 1H, H_a-7), 2.30–2.35 (m, 1H, H_b-7), 2.38 (dd, *J*=16.5, 8.8 Hz, 1H, H_a-6), 2.58 (dddd, *J*=16.5, 12.2, 7.9, 1.3 Hz, 1H, H_b-6), 3.71 (dd, *J*=10.3, 2.0 Hz, 1H, CH_aOSi), 3.84–3.86 (br m, 1H, H-4), 3.96 (dt, *J*=10.0, 6.1 Hz, 1H, H-7a), 4.23 (dd, *J*=6.1, 5.7 Hz, 1H, H-7b), 4.59 (dd, *J*=10.3, 2.8 Hz, 1H, CH_bOSi), 4.75 (dd, *J*=5.7, 0.9 Hz, 1H, H-3a). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.7 [$Si(CH_3)_2$], −5.5 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 25.7 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 26.9 (C-7), 28.0 [$C(CH_3)_2$], 36.2 (C-6), 58.6 (CH_2OSi), 61.2 (C-4), 69.2 (C-7a), 81.7 (C-7b), 87.5 (C-3a), 112.5 [$C(CH_3)_2$], 173.3 (C-5). IR (neat, cm^{-1}): ν_{max} 2929, 2857, 1698, 1605, 1471, 1382, 1329, 1257, 1214, 1157, 1116, 1074, 1008, 967, 838, 779. GC–MS (CI): *m*/*z* (%) 342 ([MH^+], 50), 326 (20), 284 (100), 268 (5), 226 (10), 210 (10), 143 (5), 89 (5), 75 (5), 43 (5). HRMS (ESI, $[MH]^+$): calcd for $C_{17}H_{31}NO_4Si$+H 342.2100, found 342.2080.

4.2.17. 4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2,2-dimethylhexahydro-4H-[1,3]dioxolo[4,5-a]pyrrolizine (**42**)

To a solution of **41** (10 mg, 29.3 μmol) in THF (0.5 mL) was added dropwise $BH_3 \cdot SMe_2$ (31 μL, 293 μmol) and the reaction mixture stirred for 6 h. Then the mixture was diluted slowly with MeOH (0.2 mL) and concentrated. The residue was dissolved in MeOH (0.5 mL), refluxed for 5 h, concentrated, and purified by flash chromatography (silica gel, EtOAc/MeOH 10:1) to give **42** (5.8 mg, 17.7 μmol, 60%) as a colorless oil. R_f=0.23 (EtOAc/MeOH 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.07 [s, 3H, $Si(CH_3)_2$], 0.08 [s, 3H, $Si(CH_3)_2$], 0.90 [s, 9H, $C(CH_3)_3$], 1.32 [s, 3H, $C(CH_3)_2$], 1.53 [s, 3H, $C(CH_3)_2$], 1.54–1.70 (br m, 1H, H-7), 1.79–1.94 (br m, 2H, H-6), 2.08–2.20 (br m, 1H, H-7), 2.83 (br s, 2H, H-5), 3.27 (br s, 1H, H-4), 3.54 (br s, 1H, H-7a), 3.80 (dd, *J*=11.2, 5.8 Hz, 1H, CH_aOSi), 3.96 (d, *J*=11.2 Hz, 1H, CH_bOSi), 4.36 (dd, *J*=6.4, 3.8 Hz, 1H, H-7b), 4.61–4.68 (m, 1H, H-3a). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.6 [$Si(CH_3)_2$], −5.5 [$Si(CH_3)_2$], 18.3 [$C(CH_3)_3$], 25.5 [$C(CH_3)_2$], 25.9 [$C(CH_3)_3$], 26.6 (C-6), 27.6 [$C(CH_3)_2$], 28.8 (C-7), 48.2 (C-5), 61.6 (CH_2OSi), 67.9 (C-4), 70.9 (C-7a), 82.5 (C-3a), 85.3 (C-7b), 113.4 [$C(CH_3)_2$]. IR (neat, cm^{-1}): ν_{max} 2929, 2857, 2360, 2341, 1636, 1541, 1462, 1379, 1254, 1211, 1109, 1068, 836, 777, 631. GC–MS (CI): *m*/*z* (%) 328 ([MH^+], 20), 312 (15), 298 (5), 270 (20), 254 (5), 212 (5), 182 (100), 124 (5), 96 (5), 73 (5). HRMS (ESI, $[MH]^+$): calcd for $C_{17}H_{33}NO_3Si$+H 328.2308, found 328.2307.

4.2.18. 6,7-Dihydroxy-5-(hydroxymethyl)hexahydro-3H-pyrrolizin-3-one (**34**)

To a solution of **41** (10 mg, 29.3 μmol) in THF (0.5 mL) was added TFA (67 μL, 870 μmol) in water (200 μL) and the reaction mixture refluxed for 1.5 h. After azeotropic codestillation with toluene (0.5 mL), the residue was directly purified by flash chromatography (silica gel, EtOAc/MeOH 5:1) to give **34** (5.5 mg, 29.3 μmol, quant.) as a colorless amorphous solid. R_f=0.17 (EtOAc/MeOH 5:1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.87 (tt, *J*=12.3, 9.3 Hz, 1H, H_a-1), 2.31 (dddd, *J*=12.3, 8.3, 6.1, 1.0 Hz, 1H, H_b-1), 2.45 (dd, *J*=16.5, 8.8 Hz, 1H, H_a-2), 2.72 (dddd, *J*=16.5, 12.3, 8.3, 1.5 Hz, 1H, H_b-2), 3.53–3.56 (m, 1H, H-5), 3.76 (dd, *J*=11.7, 4.1 Hz, 1H, CH_aOH), 3.81 (dd, *J*=8.5, 4.9 Hz, 1H, H-7), 4.00–4.05 (m, 1H, H-7a), 4.07 (dd, *J*=11.7, 4.1 Hz, 1H, CH_bOH), 4.16 (dd, *J*=4.9, 1.5 Hz, 1H, H-6). ^{13}C NMR (125 MHz, CD_3OD): δ 27.1 (C-1), 37.1 (C-2), 59.8 (CH_2OH), 66.2 (C-5), 67.1 (C-8), 76.2 (C-7), 78.9 (C-6), 176.2 (C-3). IR (neat, cm^{-1}): ν_{max} 3277, 2888, 2361, 2341, 1647, 1547, 1426, 1375, 1203, 1113, 1046, 721, 630. MS (ESI): *m*/*z* 188 [MH^+], 170, 152, 124, 110. HRMS (ESI, $[MH]^+$): calcd for $C_8H_{13}NO_4$+H 188.0923, found 188.0907.

4.2.19. 7a-epi-Hyacinthacine A_1 (7a-epi-**7**)

A solution of **42** (5.8 mg, 16.2 μmol) in a (2:1) mixture of MeOH/H_2O (450 μL) was refluxed for 1 h. The solvent was removed and the residue diluted with water and purified on DOWEX 1×8 (OH^-) to give 7a-*epi*-**7** (2.8 mg, 16.2 μmol, quant.) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD): δ 1.49 (ddt, *J*=12.6, 10.6, 7.7 Hz, 1H, H_a-7), 1.64–1.74 (m, 1H, H_a-6), 1.83–1.89 (m, 1-H, H_b-6), 2.11–2.17 (m, 1H, H_b-7), 2.76 (ddd, *J*=10.3, 9.5, 5.8 Hz, 1H, H_a-5), 2.88 (ddd, *J*=9.5, 6.6, 2.7 Hz, 1H, H_b-5), 3.19 (ddd, *J*=8.5, 8.2, 4.2 Hz, 1H, H-3), 3.36 (dt, *J*=7.7, 2.7 Hz, 1H, H-7a), 3.75 (dd, *J*=5.4, 2.7 Hz, 1H, H-1), 3.79–3.89 (m, 3H, CH_2OH, H-2). ^{13}C NMR (125 MHz, CD_3OD): δ 27.3 (C-6), 31.0 (C-7), 48.6 (C-5), 61.3 (CH_2OH), 67.0 (C-3), 71.3 (C-7a), 72.7 (C-2), 77.4 (C-1). IR (neat, cm^{-1}): ν_{max} 3367, 2923, 2360, 2341, 1622, 1572, 1418, 1338, 1302, 1103, 978, 823, 669, 592. MS (ESI): *m*/*z* 174 [MH^+], 156, 138, 125, 120, 110, 100, 96. HRMS (ESI, $[MH]^+$): calcd for $C_8H_{15}NO_3$+H 174.1130, found 174.1117.

4.2.20. Benzyl 4-[(acetyloxy)methyl]-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate (**43**)

Ac_2O (8.4 μL, 84.4 μmol) was added to a solution of **36** (16 mg, 42.2 μmol), DMAP (2 mg), and NEt_3 (20 μL) in CH_2Cl_2 (1 mL) and the mixture stirred at rt for 0.5 h. Then CH_2Cl_2 was added (2 mL) and the mixture washed successively with 0.1 N NaOH and brine (2 mL each). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane 1:2) to give **43** (16 mg, 38.0 μmol, 90%) as a colorless oil. R_f=0.21 (EtOAc/hexane 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 6H, CH_3, CH_3^*), 1.46 (s, 6H, CH_3, CH_3^*), 2.08 (s, 6H, Ac-CH_3, Ac-CH_3^*), 2.51 (dd, *J*=15.6, 10.0 Hz, 2H, CH_aCOOCH_3, $CH_aCOOCH_3^*$), 2.76 (dd, *J*=15.6, 4.0 Hz, 1H, $CH_bCOOCH_3^*$), 2.90 (dd, *J*=15.6, 4.0 Hz, 1H, CH_bCOOCH_3), 3.66 (s, 3H, OCH_3^*), 3.69 (s, 3H, OCH_3), 4.09–4.22 (m, 4H, CH_2OAc, CH_2OAc^*), 4.24 (br s, 1H, H-2), 4.32 (br s, 1H, H*-2), 4.37–4.44 (m, 2H, H-5, H*-5), 4.56–4.62 (m, 2H, H-4, H*-4), 4.63 (dd, *J*=5.8, 1.5 Hz, 2H, H-3, H*-3), 5.15 (br s, 4H, CH_2Ph, CH_2Ph^*), 7.29–7.38 (m, 10H, Ph, Ph*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9 (Ac-CH_3, Ac-CH_3^*), 25.1, 27.2 (CH_3, CH_3^*), 37.2 (CH_2COOCH_3), 38.1 ($CH_2COOCH_3^*$), 51.9 (OCH_3, OCH_3^*), 61.5, 62.2 (C-5, C-5*), 63.2 (C-2), 63.6 (CH_2OAc^*), 63.9 (C-2*), 64.1 (CH_2OAc), 67.4 (CH_2Ph, CH_2Ph^*), 81.3 (C-3*), 82.1 (C-3), 83.6 (C-4), 84.5 (C-4*), 112.3 [$C(CH_3)_2$, $C(CH_3)_2^*$], 127.8, 127.9, 128.2, 128.6 (Ph, Ph*), 136.2 (C-1′, C-1′*), 154.4 (CO, CO*), 170.4 ($OCOCH_3$, $OCOCH_3^*$), 170.9 ($COOCH_3^*$), 171.1 ($COOCH_3$). IR (neat, cm^{-1}): ν_{max} 2987, 2952, 1737, 1699, 1498, 1407, 1381, 1324, 1232, 1158, 1123, 1059, 870, 770, 699, 632. MS (EI): *m*/*z* 422 [MH^+], 378, 364, 348, 320, 304, 286, 272, 260, 240, 228, 121, 170, 91 [$C_7H_7^+$]. HRMS (ESI, $[MH]^+$): calcd for $C_{21}H_{27}NO_8$+H 422.1815, found 422.1810. HPLC: Chromasil ODH, hexane/isopropanol (70:30), flow rate 0.5 mL min^{-1}, t_R=14.53 min and t_R=16.20 min.

4.2.21. Enzymatic resolution of benzyl 4-(hydroxymethyl)-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ((±)-**36**)

To a solution of *rac*-**36** (67 mg, 177 μmol) in toluene (3 mL) was added vinyl acetate (82 μL, 883 μmol), molecular sieves (4 Å; 10 pellets), and Chirazyme L-6 (122 mg). The mixture was stirred at rt for 1.5 h, and then filtered through Celite. The filtrate was concentrated and the residue purified by flash chromatography (EtOAc/hexane 1:1) to give as a colorless oil in the first fraction (−)-**43** (31 mg, 73.6 μmol, 42%); $[\alpha]_D^{20}$ −19.3 (*c* 1.00, $CHCl_3$), 98.5% ee, and in the second fraction (+)-**36** (32 mg, 84.3 μmol, 48%); $[\alpha]_D^{20}$ +12.4 (*c* 1.00, $CHCl_3$), 75% ee.

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