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Studies towards a total synthesis of kainic acid

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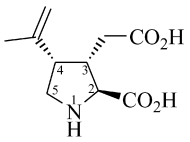
Abstract—The preparation of the fused bicycle **14** is reported together with its photocyclisation to the dioxinone **2**. Base induced fragmentation of the photoadduct **15** formed exclusively in the aforementioned photocylisation, followed by Wittig methylenation gave the kainoid derivative **18**. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The kainoid amino acids have attracted considerable interest in the fields of biology and neurobiology due to their pronounced insecticidal, anthelmintic and, principally, neuroexcitatory properties.[1] Kainic acid (**1**) has demonstrated extremely potent activity on both the vertebrate and invertebrate glutaminergic systems, leading to specific neuronal death in the brain,[2] and its pronounced neuroexcitatory properties have been well documented.[3] The pharmacological effects and the patterns of neuronal degeneration observed after the injection of kainoids have been shown to mimic the symptoms of neuronal conditions such as epilepsy,[4] Alzheimer's disease and Huntington's chorea.[5] Additionally, it has been proposed that the neuronal death induced by kainoids is a good experimental model for the neuronal cell loss observed in senile dementia.[2]



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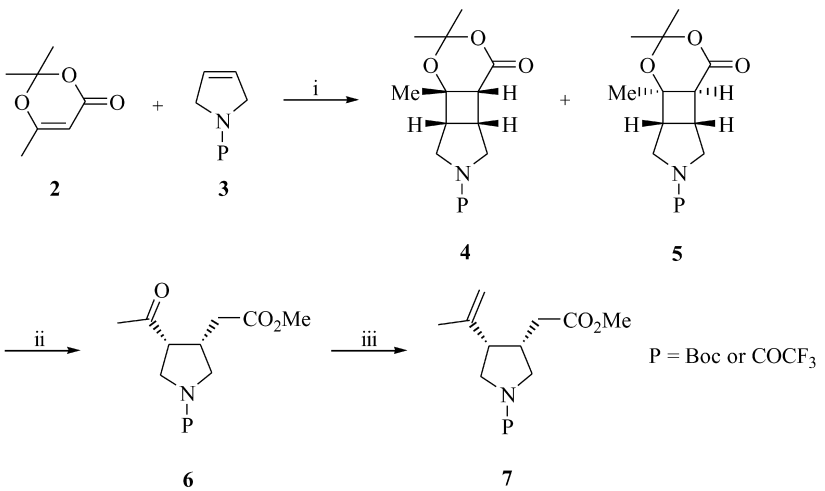
The authors have recently published initial results of a photochemical approach to the kainoid ring system.[6] The key step involves a [2+2] photocycloaddition of the dioxinone **2** to protected 3-pyrroline **3** to generate the diastereomeric cyclobutanes **4**,**5**. Subsequent methoxide induced cyclobutane fragmentation, and methylenation of the resultant ketone **6**, generates the desired C3/C4 functionality with the requisite *cis* stereochemistry (Scheme 1). Application of this approach to the elucidation of the full kainoid skeleton is detailed below.



Scheme 1. (i) *hv*/EtOAc; (ii) NaOMe (0.1 equiv.)/MeOH/reflus; (iii) Cp_2TiMe_2/THF/reflux.

Keywords: excitatory; kainate; photocyclisation; fragmentation; stereoselection.

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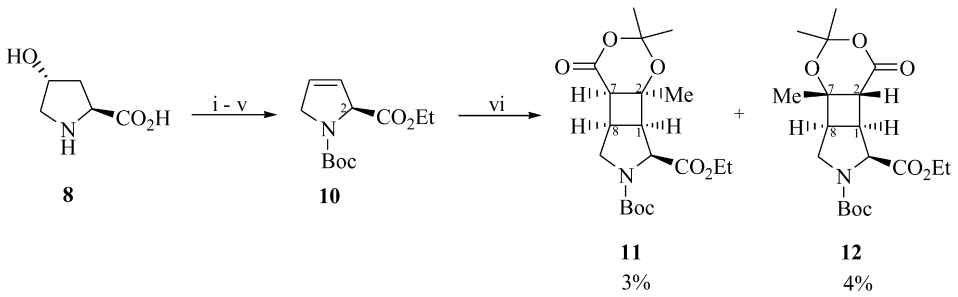


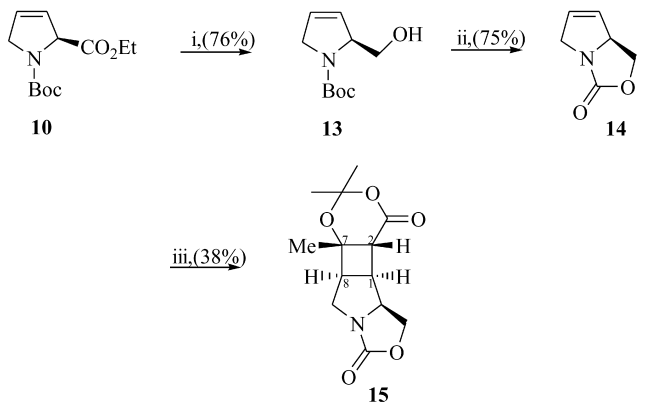
Scheme 2. (i) $SOCl_2$/MeOH; (ii) Boc_2O, ^{i}Pr2EtN, DMAP/Dioxane (96% over two steps); (iii) MsCI, Et_3N, DMAP/DCM (82%); (iv) Ph_2Se_2, $NaBH_4$/EtOH (86%); (v) 30% aq. H_2O_2sol^n, pyr./DCM (80%); (vi) **2**, *hv*/EtOAc.

2. Results and discussion

It was hoped that submission of alkene **10**, derived from *trans*-4-hydroxyproline, to the previously optimized photochemical conditions would generate a cyclobutane with the desired *trans*, *cis* stereochemistry around the pyrrolidine ring. As steric effects have previously been shown to play a strong role in directing photocycloadditions,[7] the bulk of the C-2 ester group was expected to induce the approach of the dioxinone from the opposite face of the 3-pyrroline system.

Unfortunately, no facial or regiochemical bias was observed, and the cyclobutane products **11**, **12** were recovered, after extensive column chromatography, in a disappointingly low yield (Scheme 2). Increasing the steric bulk of the C-2 (kainoid numbering) group to either the *tert*-butyl ester or the *tert*-butyldimethylsilyl protected alcohol offered no increase in yield or diastereoselectivity.

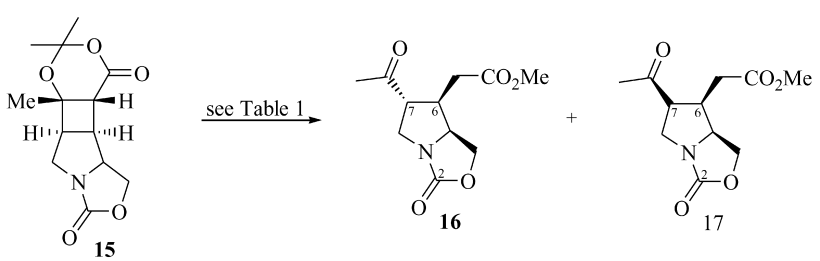
It was assumed that if the ester group of the proline derivative **10** could be tethered to the nitrogen in the form of an oxazolidinone ring then a 'butterfly' shaped molecule would be formed with a highly hindered concave face, generating a greater level of facial differentiation (Scheme 3). To this end the ester functionality was reduced to the alcohol **13**, with the intention of deprotecting the nitrogen functionality and forming the oxazolidinone ring by reaction with phosgene. Fortuitously, a recent publication by Zhao and Thurkauf[8] detailed the action of diethylaminosulfur trifluoride (DAST) on a Boc-protected 1,2-amino alcohol, where-by an oxazolidinone was unexpectedly generated in good yield, and none of the desired fluorinated compound was observed. Treatment of the alcohol **13** in dichloromethane with DAST at 0°C gave the desired bicyclic system **14** in a reasonable yield.



Scheme 3. (i) $LiAlH_4/Et_2O$ (76%); (ii) DAST/DCM/0°C(75%); (iii) **2**, *hv*/EtOAc (38%).

With the desired oxazolidinone **14** in hand, the photocycloaddition could be attempted. Irradiation of a continuously degassed solution of the oxazolidinone **14** and the dioxinone **2** gave a 38% yield of just one photoproduct **15**, together with isolated starting materials. The structure of **15** has been confirmed by X-ray crystallographic analysis. This reaction is noteworthy for two reasons: firstly, the photocycloaddition has occurred with complete regio- and stereoselectivity; Secondly, the dioxinone **2** has added onto the sterically hindered concave face of the oxazolidinone **14**, contrary to expectation. Whilst this reaction generates an all *cis* arrangement of the substituents around the pyrrolidine ring, the C2 centre (kainoid numbering) is readily epimerized at a later stage, and thus a rapid route into the kainoid ring system was envisaged.

The multiple ring fragmentation of photoadduct **15** with sodium methoxide in refluxing methanol was expected to proceed with good yields; as the chemistry of the lactone ring had been explored previously,[6] and oxazolidinone rings are known to open readily under these conditions.[9] It was therefore surprising that, when the photoadduct **15** was submitted to the previously optimized ring opening conditions, the oxazolidinone **16** was obtained in modest yield, despite the use of up to one equivalent of sodium



Scheme 4.

Table 1.

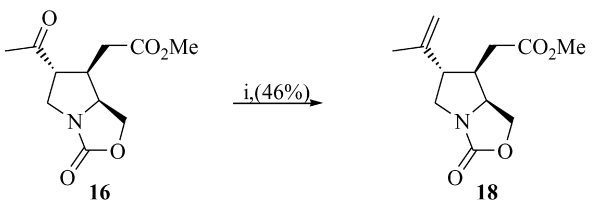
Conditions	% **16**	% **17**
NaOMe (1.0 equiv.)/methanol/reflux/24 h	49	0
$Ti(O^iPr)_4$ (0.1 equiv.)/methanol/rt/2 h	63	18
$AlMe_3$ (0.1 equiv.)/methanol/rt/2 h	65	15
BF_3OEt_2 (0.1 equiv.)/methanol/rt/2 h	33	10

methoxide (Scheme 4). In an attempt to avoid the epimerization at C-7, a variety of Lewis acid catalyzed fragmentations were conducted, the results of which are tabulated in Table 1.

The predominant product in each of these reactions was the epimerized oxazolidinone **16**. Ongoing studies within the group are concentrating on performing the lactone ring opening without the concomitant epimerization, so as to maintain the required C6/C7 *cis* stereochemistry.

To complete the synthesis of the kainoid skeleton, the ketone functionality was required to be converted to its *exo*-methylene analogue. In our previous studies this was achieved by the dimethyltitanocene (Cp_2TiMe_2) procedure of Petasis and Bzowej.[10] Unfortunately, submission of oxazolidinone **17** to the same procedure resulted in the recovery of starting material, with prolonged reaction times causing a small amount of decomposition. Another non-basic method developed by Takai et al.[11] in which the ketone is added to a solution of zinc, diiodomethane and titanium tetrachloride in tetrahydrofuran, was also attempted without success. In order to effect the methylenation, Wittig chemistry[12] was resorted to. Thus, the ylide formed from methyl triphenylphosphonium bromide using butyllithium was added to the ketone **16** to generate the *exo*-methylene compound **18** in a reasonable yield (Scheme 5). It should be noted however, that the use of this basic methodology on the real system **17** resulted in epimerization at C-7.

It can be seen that opening of the oxazolidinone ring of **18**, followed by oxidation of the resultant alcohol and subsequent deprotection would generate kainoid skeleton in a rapid fashion.



Scheme 5. (i) CH_3PPh_3Br, ^{n}BuLi/THF/−78°C (46%).

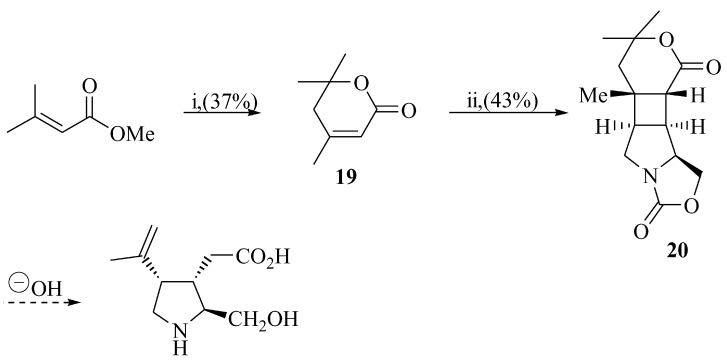
A shorter route to the kainoid skeleton, which avoids the problematic epimerization and subsequent methylenation steps, can be envisaged if the O-6 ether oxygen of the tetracycle **15** is replaced by a methylene group. Subsequent treatment of the resultant cyclobutane with strong base would drive the fragmentation of both the lactone and the oxazolidinone moieties with concomitant nitrogen deprotection and formation of the desired *exo*-methylene functionality in one step, without risk of epimerization (Scheme 6). In order for this to be possible the pyranone **19** was required to be synthesized and to undergo the photocycloaddition with the same regio- and stereoselectivity as the dioxinone **2**.

The pyranone **19** was formed according to the procedure of Dugger and Heathcock;[13] whereby methyl senecioate undergoes deprotonation with LDA followed by condensation with acetone, which subsequently undergoes intramolecular 1,2 nucleophilic substitution on the ester to yield pyranone **19**. The procedure was modified by the addition of 0.5 equiv. of cadmium chloride to promote the initial 1,5-nucleophilic addition to acetone.[14] Submission of the pyranone **19** and the oxazolidinone **14** to the standard photocycloaddition conditions gratifyingly gave just one photoadduct **20**. As with the previous oxazolidinone, the photoproduct **20** was a crystalline solid enabling an X-ray crystallographic confirmation of its structure; the desired C-6 methylene analogue of the previously obtained tetracycle **15**.

Base-induced fragmentation of photoadduct **20** was attempted by treatment with sodium hydroxide in methanol at reflux. Unfortunately, starting material was recovered quantitatively after 24 h. A range of acidic, basic and radical fragmentation methodologies were consequently investigated, (Table 2) all of which returned only starting material after prolonged reaction times.

3. Conclusion

Whilst the initial photochemical route towards the kainoid skeleton has been shown to be successful, the facile epimerization of the C-4 center limits the synthetic viability



Scheme 6. (i) LDA, $CdCl_2/Et_2O$, then $(CH_3)_2C{=}O$ (37%); (ii) **14**, *hv*/EtOAc (43%).

Table 2.

Conditions	Time	Result
NaOMe (2 equiv.)/MeOH/reflux	72 h	Starting material recovered
Conc. H_2SO_4/MeOH/reflux	24 h	Starting material recovered
Cat. $HClO_4$/MeOH/reflux	24 h	Starting material recovered
Excess NaOH/MeOH/reflux	24 h	Starting material recovered
Bu_3SnH, AIBN/THF/reflux	8 h	Starting material recovered
SmI_2/THF/reflux	8 h	Starting material recovered

of such methodology. Further studies in this area are concentrating on the development of a non-basic fragmentation methodology to enable significant amounts of the C-3/C-4 *cis* compound to be generated. Conversely, the successful fragmentation of the highly inert, pyranone derived cyclobutane **20** would bypass the troublesome epimerization problem, and present an even more rapid route into the kainoid amino acids.

4. Experimental

4.1. General

Photoreactions were carried out in 150 ml or 350 ml reaction flasks with a quartz immersion well and photoexcited using a 125 W medium pressure mercury lamp (Model 3140) purchased from Photochemical Reactors Ltd, Blounts Farm, Blounts Court Road, Sonning Common, Reading, Berkshire, RG4 9PA.

Melting points were recorded on an electrothermal melting point apparatus, and are measured in degrees centigrade and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Advance AC-300 instrument measured at 300 MHz and a Bruker 500 at 500 MHz. ^{13}C NMR spectra were recorded on a Bruker Advance AC-300 instrument at 75 MHz and a Bruker 500 at 125 MHz. Chemical shifts are measured in ppm on the δ scale; coupling constants (denoted by J) are measured in hertz. Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrophotometer, as a thin film between sodium chloride plates, with ν_{max} measured in cm^{-1}. High resolution and low resolution mass spectra were recorded on a Fisons Instrument VG Autospec mass spectrometer.

4.1.1. (4*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-L-proline methyl ester.[15] The title compound was prepared by a modification of the procedure of Joullié et al.[15] To a stirred suspension of *trans*-4-hydroxy-L-proline (50.0 g, 381 mmol) in methanol (200 ml) at 0°C was added thionyl chloride (30.0 ml, 419 mmol). The reaction mixture was stirred at 0°C for 1 h then refluxed for 36 h. The reaction mixture was allowed to cool and then precipitated with diethyl ether. The precipitate was collected by filtration and washed with diethyl ether to give a quantitative yield of the desired methyl ester as a white solid.

To a stirred solution of the above proline ester (8.0 g, 55 mmol) in dioxane (30 ml) at room temperature was added diisopropylethylamine (17.0 ml, 94 mmol). Di-*tert*-butoxy dicarbonate (15.7 g, 72 mmol) in dioxane (70 ml) was added slowly and vigorous effervescence observed. The reaction mixture was stirred at room temperature for 2 h then 4-dimethylaminopyridine (0.13 g, 1.1 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was concentrated under reduced pressure and taken up in ethyl acetate (300 ml). The solution was washed with 1 M aqueous citric acid (100 ml), 1 M aqueous sodium bicarbonate solution (100 ml) and water (2×100 ml), dried over magnesium sulfate and concentrated under reduced pressure to give the pure, protected hydroxyproline as a yellow oil (13.0 g, 96%). TLC, (ethyl acetate) R_f=0.41; $[\alpha]_D^{30}$ −40.5 *c* 0.79 in chloroform (lit., $[\alpha]_D^{20}$ −64.9 *c* 0.98);[15] ν_{max} (thin film)/cm^{-1} 3443 (s, OH), 3004 and 2937 (s, CH_2/CH_3), 2885 (m, CH), 1751 (s, CO_2Me), 1685 (s, N−C=O), 1408 (s, OH), 1358 ($C(CH_3)_3$), 1215 (s, C−O), 1129 (s, C−OH); δ_H (300 MHz; $CDCl_3$) 4.51 (1H, br s, 4-H), 4.50–4.35 (1H, m, 2-H), 3.74 (3H, s, OMe), 3.68–3.38 (2H, m, 5-H), 2.37–2.22 (1H, m, 3-H), 2.15–2.02 (1H, m, 3-H), 1.50 and 1.45 (9H, 2×s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 174.1 (CO_2Me), 154.4 (N−C=O), 80.8 ($C(CH_3)_3$), 69.8 (C-4), 58.3 (C-2), 55.1 (C-5), 52.5 (OMe), 39.5 (C-3), 28.6 (^{t}Bu); *m/z* (FAB) 246 (M+H, 24%), 190 (79), 146 (85), 144 (M−Boc, 77), 130 (43), 57 (^{t}Bu, 100).

4.1.2. (4*S*)-*N*-*tert*-Butoxycarbonyl-4-methylsulfonyloxy-L-proline methyl ester.[16] To a stirred solution of (4*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-L-proline methyl ester (13.0 g, 56 mmol) in dichloromethane (300 ml) at 0°C was added triethylamine (8.5 ml, 61 mmol) followed by methanesulfonyl chloride (5.6 ml, 72 mmol). 4-Dimethylaminopyridine (2.0 g, 17 mmol) was added and the reaction mixture stirred at 0°C for 1 h then allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into ice/water (500 ml) and the layers were separated. The organic layer was washed with 1 M aqueous citric acid (500 ml), 1 M aqueous sodium bicarbonate solution (500 ml) and water (500 ml), dried over magnesium sulfate and concentrated under reduced pressure to leave a yellow oil. This was purified by column chromatography (50% petroleum ether/diethyl ether eluent) to give a colourless oil, which solidified upon prolonged standing (14.8 g, 82%). TLC, (ethyl acetate) R_f=0.59; mp 82–85°C (lit., 85–86°)[16] $[\alpha]_D^{35}$ −50.7, *c* 1.5 in chloroform (lit., $[\alpha]_D^{20}$ −52.3, *c* 1.6);[16] ν_{max} (thin film)/cm^{-1} 2922 and 2853 (s, CH_3/CH_2), 1747 (s, CO_2Me), 1698 (s, N−C=O), 1358 (s, $C(CH_3)_3$), 1215 (m, C−O), 1171 (m, $-SO_2O-$); δ_H (300 MHz; $CDCl_3$) 5.26 (1H, m, 4-H), 4.50–4.37 (1H, m, 2-H), 3.88–3.75 (2H, m, 5H), 3.76 (3H, s, CO_2Me), 3.06 (3H, s, SO_2Me), 2.70–2.53 (1H, m, 3-H), 2.31–2.19 (1H, m, 3-H), 1.47 and 1.32 (9H, 2×s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 173.1 (CO_2Me), 153.7 (N−C=O), 81.4 ($C(CH_3)_3$), 78.6 and 78.3 (C-4), 57.8 and 57.5 (C-2), 52.9 (CO_2CH_3), 52.7 and 52.6 (C-5), 39.2 (SO_2CH_3), 37.9 and 36.7 (C-3), 28.7 and 28.6 ($C(CH_3)_3$); *m/z* (FAB) 346 ([M+Na], 3%), 324 ([M+H], 22), 268 (78), 224 (84), 128 (76), 57 (^{t}Bu, 100), 55 (55).

4.1.3. (4*R*)-*N*-*tert*-Butoxycarbonyl-4-phenylselenyl-L-proline ethyl ester. To a stirred solution of diphenyl diselenide (7.50 g, 24 mmol) in ethanol (300 ml) at 0°C was added sodium borohydride (2.00 g, 52 mmol) portionwise. The solution was stirred until the yellow colouration had vanished. (4*S*)-*N*-*tert*-Butoxycarbonyl-4-methylsulfonyloxy-L-proline methyl ester (13.0 g, 40 mmol) in ethanol

(150 ml) was added and the solution refluxed for 3 h, then stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue taken up in diethyl ether (500 ml). The solution was washed with water (250 ml) followed by a saturated brine solution (250 ml), dried over magnesium sulfate and concentrated under reduced pressure. The resultant vivid yellow oil was purified by column chromatography (10% ethyl acetate/petroleum ether eluent) to give the desired product as a yellow oil (13.66 g, 86%). TLC, (ethyl acetate) R_f=0.59; $[\alpha]_D^{26}$ −28.0, *c* 2.1 in chloroform; ν_{max} (thin film)/cm^{-1} 3057 (w, aryl CH), 2976 and 2933 (s, CH_3/CH_2), 2872 (m, CH), 1745 (s, CO_2Et), 1703 (s, N–C═O), 1578 (m, C_6H_5), 1394 (s, C(CH_3)$_3$), 1251 (m) and 1190 (s, C═O), 741 (s, Ar-H), 693 (m, Ar-H); δ_H (300 MHz; $CDCl_3$) 7.55 (2H, dd, *J*=7.4, 1.8 Hz, 8-H), 7.30–7.25 (3H, m, 9- and 10H), 4.28–4.12 (3H, m, 2-H and OCH_2CH_3), 4.02–3.86 (1H, m, 4-H), 3.64–3.48 (1H, m, 5-H), 3.46–3.37 (1H, m, 5-H), 2.74–2.63 (1H, m, 3-H), 2.07–1.96 (1H, m, 3-H), 1.48 and 1.39 (9H, 2×s, ^{t}Bu), 1.28–1.23 (3H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 172.6 (*C*O_2Et), 153.5 (*C*O_2^tBu), 135.3 (C-8), 129.5 (C-9), 128.3 (C-10), 127.8 (C-7), 80.6 and 80.5 (*C*(CH_3)$_3$), 61.4 (C-5), 59.5 and 59.1 (C-4), 53.3 (C3), 38.2 and 37.6 (O*C*H_2CH$_3$), 36.8 and 36.7 (C-2), 28.6 and 28.5 (C(*C*H_3)$_3$), 14.5 (OCH$_2$*C*H$_3$); *m/z* (EI) 399 (M, 15%), 326 ([M− CO_2Et], 10), 298 ([M−Boc], 6), 157 (PhSe, 18), 77 (C_6H_5, 15), 57 (^{t}Bu, 100); HRMS (EI) found 395.0761, (M, $C_{18}H_{25}NO_4^{76}Se$ requires 395.0976).

4.1.4. *N-tert*-Butoxycarbonyl-3,4-didehydro-L-proline ethyl ester (10). The title compound was prepared by a modification of the procedure of Dormay.[17] To a stirred solution of (4*R*)-*N-tert*-Butoxycarbonyl-4-phenylselenyl-L-proline ethyl ester (13.00 g, 32.6 mmol) in dichloromethane (300 ml) at 0°C was added pyridine (4.0 ml, 49.0 mmol) followed by a 30% aqueous solution of hydrogen peroxide (9.3 ml, 82 mmol) gradually over 5 min. The reaction mixture was stirred at room temperature for 16 h then washed with 1 M aqueous citric acid (2×100 ml), saturated aqueous sodium bicarbonate solution (100 ml) and water (100 ml), dried over magnesium sulfate and concentrated under reduced pressure. The resultant yellow oil was purified by column chromatography (15% ethyl acetate/petroleum ether eluent) to give **10** as a pale yellow oil (6.21 g, 80%). TLC, (25% ethyl acetate/petroleum ether) R_f=0.45; $[\alpha]_D^{31}$ −230.0, *c* 11.3 in chloroform (lit., $[\alpha]_D^{20}$ −234.0, *c* 10.2);[17] ν_{max} (thin film)/cm^{-1} 2980 and 2936 (s, CH_3/CH_2), 1751 (s, CO_2Et), 1708 (s, N–C═O), 1450 (m, CH_2), 1396 and 1370 (s, C(CH_3)$_3$), 1319 and 1162 (s, C–O); δ_H (300 MHz; $CDCl_3$) 6.00–5.93 (1H, m, 4-H), 5.79–5.70 (1H, m, 3-H), 5.04–4.93 (1H, m, 2-H), 4.26–4.15 (4H, m, OC*H*2CH$_3$ and 5-H), 1.48 and 1.44 (9H, 2×s, ^{t}Bu), 1.31–1.24 (3H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 173.2 (*C*O_2Et), 155.9 (N–C═O), 131.8 and 131.7 (C-4), 127.4 and 127.3 (C-3), 82.7 and 82.6 (*C*(CH_3)$_3$), 69.2 and 68.9 (C-2), 63.7 (O*C*H_2CH$_3$), 56.0 and 55.8 (C-5), 30.9 and 30.8 (s, C(*C*H_3)$_3$), 16.8 and 16.6. (OCH$_2$*C*H$_3$); *m/z* (EI) 242 (M+H, 8%), 200 (47), 184 (M−^{t}Bu, 36), 154 (78), 68 (64), 57 (^{t}Bu, 100).

4.1.5. (1*R*,2*S*,7*R*,8*R*,11*S*)*N-tert*-Butoxycarbonyl-11-carboxy-2,4,4-trimethyl-6-oxo-10-aza-3,5-dioxatricyclo-[6.3.0.0^{2,7}]-undecane ethyl ester (11) and (1*S*, 2*R*, 7*S*, 8*R*, 11*S*) *N-tert*-Butoxycarbonyl-11-carboxy-5,5,7-trimethyl-3-oxo-10-aza-4,6-dioxa-tricyclo[6.3.0.0^{2,7}] undecane ethyl ester (12). A solution of the freshly distilled dioxinone **2** (0.47 g, 3.3 mmol) and prolinate **10** (1.20 g, 5.0 mmol) in dry, distilled ethyl acetate, under continuous degassing with nitrogen, was irradiated with a 125W medium pressure mercury lamp. After 2 h no dioxinone **2** remained by TLC and so the reaction mixture was concentrated under reduced pressure. The resultant yellow oil was purified by column chromatography three times (20 to 50% petroleum ether/diethyl ether eluent) to isolate two distinct cyclobutane products.

endo-Cyclobutane (**11**), a colourless oil (40 mg, 3.2%). TLC, (50% petroleum ether/diethyl ether) R_f=0.33; $[\alpha]_D^{26}$ 16.7, *c* 8.4 in chloroform; ν_{max} (thin film)/cm^{-1} 2962 (s, CH_3/CH_2), 2874 (m, CH), 1745 (s, CO_2Et), 1702 (s, CO_2^tBu), 1391 (s, C(CH_3)$_3$), 1365 (s, C(CH_3)$_3$), 1168 (s, C–O), 1087 (m, C–O); δ_H (500 MHz; $CDCl_3$) 4.93 and 4.76 (1H, 2×d, *J*=1.5 Hz, 11-H), 4.16 and 4.15 (2H, 2×q, *J*=7.1 Hz, OCH_2CH_3), 4.04 and 4.03 (1H, 2×d, *J*=12.0 Hz, 9-H), 3.24 and 3.21 (1H, 2×dd, *J*=5.4, 3.5 Hz, 9-H), 3.11–3.07 (1H, m, 8-H), 2.96–2.93 (1H, m, 7-H), 2.82–2.77 (1H, m, 1-H), 1.61 (3H, s, 2-Me), 1.58, 1.56, 1.54 and 1.53 (6H, 4×s, 4-Me), 1.47 and 1.43 (9H, 2×s, ^{t}Bu) 1.27–1.23 (3H, m, OCH_2CH_3); δ_C (125 MHz; $CDCl_3$) 172.4 and 172.2 (*C*O_2Et), 167.7 and 167.3 (C-6), 153.9 and 153.4 (N–C═O), 105.2 and 104.7 (C-4), 80.3 and 80.0 (*C*(CH_3)$_3$), 70.9 (C-2), 61.2 (O*C*H_2CH$_3$), 58.4 and 57.8 (C-11), 53.8 and 52.6 (C-1), 46.8 and 46.6 (C-9), 40.5 and 40.4 (C-7), 36.2 and 35.2 (C-8), 28.7, 28.6, 28.5, 28.4, 28.3 and 28.2 (4-Me, 2-Me and C(*C*H_3)$_3$), 14.3 and 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI) 328 (37%), 310 ([M−CO_2Et], 61), 282 ([M−Boc], 7), 210 (44), 185 (59), 143 (87), 68 (89), 57 (^{t}Bu, 100); HRMS (EI) found 310.1668, (M−CO_2Et, $C_{16}H_{24}NO_5$ requires 310.1654).

exo-Cyclobutane (**12**), a colourless oil (55 mg, 4.4%). TLC, (50% petroleum ether/diethyl ether) R_f=0.46; $[\alpha]_D^{26}$ −32.9, *c* 8.2 in chloroform; ν_{max} (thin film)/cm^{-1} 2979 (s, CH_3/CH_2), 2935 (s, CH_3/CH_2), 1740 (s, CO_2Et), 1702 (s, N–C═O), 1457 (m, CH_3/CH_2), 1391 (s, C(CH_3)$_3$), 1365 (s, C(CH_3)$_3$), 1186 and 1031 (s, C–O); δ_H (500 MHz; $CDCl_3$) 4.83 and 4.75 (1H, 2×s, 11-H), 4.17–4.09 (3H, m, 9-H and OCH_2CH_3), 3.36 and 3.33 (1H, 2×dd, *J*=11.8, 8.5 Hz, 9-H), 3.25 and 3.20 (1H, 2×dd, *J*=7.4, 9.8 Hz, 1-H), 3.04 (1H, dd, *J*=9.8, 1.8 Hz, 2-H), 2.71 (1H, m, 8-H), 1.58–1.56 (6H, m, 5-Me), 1.53–1.52 (3H, m, 7-Me), 1.45 and 1.42 (9H, 2×s, C(CH_3)$_3$), 1.25–1.23 (3H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 171.5 and 171.4 (*C*O_2Et), 167.8 and 167.4 (C-3), 153.8 (N–C═O), 105.3 and 104.8 (C-5), 80.3 and 80.0 (*C*(CH_3)$_3$), 70.9 and 70.8 (C-7), 61.3 and 61.2 (O*C*H_2CH$_3$), 60.1 and 59.6 (C-11), 48.7 and 47.8 (C-8), 44.6 and 44.5 (C-9), 41.0 and 40.8 (C-2), 39.9 and 39.1 (C-1), 28.61, 28.56, 28.39 and 28.24 (7-Me, 5-Me, and C(*C*H_3)$_3$), 14.2 and 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI) 383 (M, 4%), 382 ([M−H], 5), 328 (23), 310 ([M−CO_2Et], 60), 282 ([M−Boc], 44), 254 (88), 196 (100), 57 (^{t}Bu, 98). HRMS (EI) found 310.1656, (M−CO_2Et, $C_{16}H_{24}NO_5$ requires 310.1654).

4.1.6. (*S*)*N-tert*-Butoxycarbonyl-2-hydroxymethyl-3-pyrroline (13). To a stirred solution of prolinate **10** (10.0 g, 41 mmol) in diethyl ether (200 ml) at 0°C was added lithium

aluminium hydride (1.6 g, 41 mmol) portionwise. The reaction mixture was stirred overnight then poured into a 20% aqueous solution of Rochelle's salt (250 ml) and stirred for an hour. The layers were separated and the organic layer washed with water (2×50 ml), dried over magnesium sulfate and concentrated under reduced pressure to yield **13** as a colourless oil (6.26 g, 76%). TLC, (25% ethyl acetate/petroleum ether) R_f=0.12; $[\alpha]_D^{26}$ −107.2, *c* 13.9 in chloroform; ν_{max} (thin film)/cm^{-1} 3417 (s, OH), 3083 (m, H–C═), 2975 and 2931 (s, CH_3/CH_2), 2868 (s, CH), 1696 and 1679 (s, N–C═O), 1625 (s, C═C), 1471 and 1455 (s, CH_3/CH_2), 1407 (s, OH), 1367 (s, $C(CH_3)_3$), 1255 and 1174 (s, C–O); δ_H (300 MHz; $CDCl_3$) 5.83 (1H, m, 4-H), 5.63 (1H, m, 3-H), 4.73 (1H, m, 2-H), 4.20 (1H, d, *J*=15.7 Hz, 5-H_u), 4.08 (1H, dm, *J*=15.7 Hz, 5-H_d), 3.79, (1H, dd, *J*=11.3, 2.2 Hz, 6-H), 3.58 (1H, dd, *J*=11.3, 6.9 Hz, 6-H), 3.20 (1H, br s, OH), 1.50 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 157.0 (N–C═O), 127.2 (C-3), 127.0 (C-4), 81.0 ($C(CH_3)_3$), 68.1 (C-2), 67.7 (C-5), 54.6 (C-6), 28.8 ($C(CH_3)_3$); *m/z* (FAB) 222 (M+Na, 18%), 200 (M+H, 22), 168 ([M−CH_2OH], 16), 144 (69), 112 (75), 57 (^{t}Bu, 100); HRMS (EI) found 168.1041, (M−CH_2OH, $C_9H_{14}NO_2$ requires 168.1025).

4.1.7. (5*R*)2-Oxo-1-aza-3-oxabicyclo[3.3.0]oct-6-ene (14). To a stirred solution of alcohol **13** (7.40 g, 37 mmol) in dry dichloromethane (200 ml) at 0°C was added *N*,*N*-diethylaminosulfur trifluoride (6.45 g, 40 mmol) dropwise. The reaction mixture was stirred for 4 h then quenched with saturated aqueous sodium bicarbonate solution (200 ml). The layers were separated and the aqueous extracted with dichloromethane (2×200 ml). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure. The resultant oil was purified by column chromatography (diethyl ether eluent) to give **14** as a colourless oil (3.46 g, 75%). TLC, (diethyl ether) R_f=0.29; $[\alpha]_D^{31}$ −18.0, *c* 25.0 in chloroform; ν_{max} (thin film)/cm^{-1} 2983 and 2918 (m, CH_2), 2880 (m, CH), 1751 (s, N–C═O), 1604 (m, C═C); δ_H (300 MHz; $CDCl_3$) 6.08–6.04 (1H, m, 7-H), 5.93–5.89 (1H, m, 6-H), 4.75–4.70 (1H, m, 5-H), 4.62 (1H, dd app t, *J*=8.7 Hz, 4-H), 4.40 (1H, dddd app ddt, *J*=15.6, 3.1, 2.0 Hz, 8H), 4.25 (1H, dd, *J*=8.5, 5.1 Hz, 4-H), 3.87–3.79 (1H, m, 8-H); δ_C (75 MHz; $CDCl_3$) 162.5 (C-2), 131.0 (C-7), 128.9 (C-6), 68.7 (C-4), 64.6 (C-5), 54.8 (C-8); *m/z* (EI) 125 (M, 60%), 95 ([M−CH_2O], 85), 67 ([M−CO_2CH_2], 100); HRMS (EI) found 125.0487, (M, $C_6H_7NO_2$ requires 125.0477).

4.1.8. (1*S*,2*R*,7*S*,8*R*,14*R*)5,5,7-Trimethyl-3,11-dioxo-10-aza-4,6,12-trioxa-tetracyclo[6.6.0.0.^{2,7}0^{10,14}]tetradecane (15). A solution of (5*R*) 2-Oxo-1-aza-3-oxabicyclo[3.3.0]-oct-6-ene (**14**) (3.75 g, 22.0 mmol) and the dioxinone **2** (2.13 g, 11.0 mmol) in ethyl acetate (400 ml), under continuous degassing with nitrogen, was irradiated with a 125 W medium pressure mercury lamp until no dioxinone **2** remained by TLC. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (diethyl ether eluent) to give **15**, which was recrystallized from ethyl acetate (1.32 g, 33%). TLC, (diethyl ether) R_f=0.19; mp (ethyl acetate) 178–180°; $[\alpha]_D^{31}$ −4.2, *c* 26.5 in chloroform; ν_{max} (thin film)/cm^{-1} 2921 and 2853 (s, CH_3/CH_2), 1739 (br s, C═O), 1384 and 1376 (s, $(CH_3)_2$), 1089 (m, C–O); δ_H (300 MHz; $CDCl_3$) 4.16 (1H, dd, *J*=9.6, 2.6 Hz, 13-H) 3.69 (1H, d, *J*=12.8 Hz, 9-H_d), 3.66 (1H, dd, *J*=9.5, 8.4 Hz, 13-H), 2.75 (1H, m, 14-H), 2.41–2.34 (1H, m, 1-H), 2.302.16 (3H, m, 2-H, 8-H and 9-H_u), 1.34 (3H, s, 5-Me), 0.97 (3H, s, 7-Me), 0.93 (3H, s, 5-Me); δ_C (75 MHz; $CDCl_3$) 168.5 (C-11), 160.9 (C-3), 105.6 (C-5), 75.3 (C-7), 63.9 (C-13), 59.5 (C-14), 50.2 (C-2), 45.1 (C-9), 43.9 (C-1), 38.1 (C-8), 29.4 (5-Me), 28.7 (7-Me), 22.3 (5-Me);*m/z* (EI) 268 ([M+H], 7%), 210 (45), 143 (dioxinone, 14), 125 ([M−dioxinone], 94), 85 (oxazolidinone, 100); HRMS (EI) found 268.1185, (M+H, $C_{13}H_{18}NO_5$ requires 268.1185).

4.1.9. (5*R*,6*S*,7*S*)7-Acetyl-6-carboxymethyl-2-oxo-1-aza-3-oxabicyclo[3.3.0]octane methyl ester (16) and (5*R*,6*S*,7*R*)7-Acetyl-6-carboxymethyl-2-oxo-1-aza-3-oxabicyclo[3.3.0]octane methyl ester (17). To a stirred solution of the tetracycle **15** (0.134 g, 0.50 mmol) in dry methanol (2 ml) was added a 2 M solution of trimethylaluminium in hexane (0.125 ml, 0.25 mmol). The reaction mixture was stirred for 2 h then quenched with saturated aqueous sodium bicarbonate solution (5 ml) and extracted with ethyl acetate (2×5 ml). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure. The resultant colourless oil was purified by column chromatography (ethyl acetate eluent) to give a small quantity of the desired *cis* product **17** and a reasonable yield of the *trans* product **16**.

trans-Oxazolidinone (**16**), (a colourless oil, 0.146 g, 65%). TLC, (ethyl acetate) R_f=0.50; $[\alpha]_D^{31}$ −4.9, *c* 8.1 in chloroform; ν_{max} (thin film)/cm^{-1} 2957 (s, CH_3/CH_2), 1751 (br s, N–C═O and C^{10}═O), 1711 (s, C^{11}═O), 1363 (s, $COCH_3$); δ_H (300 MHz; $CDCl_3$) 4.39 (1H, dd, *J*=8.1, 10.0 Hz, 4-H), 4.15 (1H, dd, *J*=2.9, 10.0 Hz, 4-H), 4.08–4.03 (1H, m, 5-H), 3.78 (1H, dd, *J*=11.8, 8.7 Hz, 8-H), 3.65 (3H, s, OMe), 3.26 (1H, dd, *J*=11.8, 5.1 Hz, 8-H), 3.10–3.04 (1H, m, 7-H), 2.78–2.73 (1H, m, 6-H), 2.46 (1H, dd, *J*=16.7, 5.9 Hz, 9-H), 2.21 (3H, s, 12-H), 2.16 (1H, dd, *J*=16.7, 9.6 Hz, 9H); δ_C (75 MHz; $CDCl_3$) 207.1 (C-11), 172.4 (C-10), 161.4 (C-2), 64.1 (C-4), 60.3 (C-5), 56.9 (C-7), 52.5 (OMe), 46.4 (C-8), 39.6 (C-6), 33.1 (C-9), 29.8 (C-12); *m/z* (EI) 241 (M, 22%), 210 ([M−OMe], 25), 198 ([M−CH_3CO], 21), 171 (100), 43 (CH_3CO, 75); HRMS (EI) found 241.0934, (M, $C_{11}H_{15}NO_5$ requires 241.0950).

cis-Oxazolidinone (**17**), (colourless crystals, 0.146 g, 15%). TLC, (ethyl acetate) R_f=0.32; mp (ethyl acetate) 97–101°; $[\alpha]_D^{23}$ −6.7, *c* 3.0 in chloroform; ν_{max} (thin film)/cm^{-1} 2924 (br s) and 2853 (s, CH_3/CH_2), 1728 (br s, N–C═O and C^{10}═O), 1707 (s, C^{11}═O), 1459 (s, CH_3/CH_2); δ_H (300 MHz; CD_2Cl_2) 4.41–4.27 (3H, m, 4-H and 5-H), 3.76 (1H, dd, *J*=11.4, 5.8 Hz, 8H), 3.65 (3H, s, OMe), 3.54–3.41 (1H, m, 7-H), 3.25 (1H, dd, *J*=11.7, 7.5 Hz, 8-H), 2.96–2.81 (1H, m, 6-H), 2.47–2.34 (2H, m, 9-H), 2.21 (3H, s, 12-H); δ_C (75 MHz; CD_2Cl_2) 208.0 (C-11), 173.1 (C-10), 162.1 (C-2), 65.1 (C-4), 62.0 (C-5), 55.4 (OMe), 52.8 (C-7), 47.8 (C-8), 40.1 (C-6), 31.6 (C-12), 29.5 (C-9); *m/z* (EI) 241 (M, 9%), 210 ([M−OMe], 40), 198 ([M−CH_3CO], 21), 171 (77), 55 (88), 43 (CH_3CO, 100); HRMS (EI) found 241.0951, (M, $C_{11}H_{15}NO_5$ requires 241.0950).

4.1.10. 7-Isopropenyl-6-carboxymethyl-2-oxo-1-aza-3-oxabicyclo[3.3.0]octane methyl ester (18). To a stirred

solution of methyl triphenylphosphonium bromide (0.214 g, 0.5 mmol) in tetrahydrofuran (5 ml) was added a 2.5 M solution of *n*-butyl lithium in hexane (0.24 ml, 0.6 mmol). The reaction mixture was stirred at room temperature for 1 h then cooled to −78° and the *epi-oxazolidinone* (*epi*-**16**) (0.124 g, 0.5 mmol) in tetrahydrofuran (1 ml) added dropwise. The reaction mixture was allowed to warm to room temperature then quenched with saturated aqueous ammonium chloride solution (10 ml) and extracted with ethyl acetate (2×10 ml). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure. The resultant yellow oil was purified by column chromatography (diethyl ether eluent) to give the desired product.

epi-Oxazolidinone (**18**), (a colourless oil, 0.054 g, 46%. TLC, (ethyl acetate) R_f=0.43; ν_{max} (thin film)/cm^{-1}3078 (w, C=CH$_2$), 2982, 2950 and 2920 (m, CH$_3$/CH$_2$), 1755 (br s, C=O), 1645 (m, C=C), 899 (m, C=CH$_2$); δ_H (300 MHz; $CDCl_3$) 4.89 (1H, s, 13-H), 4.81 (1H, s, 13-H), 4.43 (1H, ddd app q, *J*=9.0 Hz, 4-H), 4.37–4.31 (1H, m, 5-H), 4.12–4.07 (1H, m, 4-H), 3.81 (1H, dd, *J*=11.8, 7.2 Hz, 8-H), 3.67 (3H, s, OMe), 2.99 (1H, dd, *J*=11.8, 8.9 Hz, 8-H), 2.60–2.53 (1H, m, 7-H), 2.46 (1H, dd *J*=16.9, 5.5 Hz, 9-H), 1.73 (3H, s, 12-H); δ_c (75 MHz; $CDC1_3$) 172.9 (C-10), 162.0 (C-2), 143.2 (C-11), 113.9 (C-13), 65.2 (C-4), 60.0 (C-5), 53.1 (C-6), 52.4 (OMe), 50.6 (C-8), 41.2 (C-7), 33.9 (C-9), 20.6 (C-12); $^m/_z$ (EI) 239 (M, 25%), 208 ([M−OMe], 17), 154 (59), 55 (100), 41 (CH$_3$C=CH$_2$, 24); HRMS (EI) found 239.1171, (M, $C_{12}H_{17}NO_4$ requires 239.1158).

4.1.11. 4,6,6-Trimethyl-5,6-dihydropyran-2-one (19). To a stirred solution of preformed lithium diisopropylamide (171 mmol) in dry tetrahydrofuran (100 ml) at −78°C was added methyl senecioate (13.0 g, 114 mmol) dropwise over 1 h. The reaction mixture was stirred for 30 min before addition of cadmium chloride (11.6 g, 57 mmol) (ground in a mortar and dried overnight in a vacuum oven at 110°C). The resulting suspension was stirred for a further 30 min at −78°C before addition of acetone (8.37 ml, 114 mmol) dropwise over 1 h. The reaction mixture was allowed to warm to 10°C then quenched with saturated aqueous ammonium chloride solution (100 ml). The reaction mixture was filtered through celite and the layers separated. The aqueous was extracted with diethyl ether (2×100 ml) and the combined organics washed with a saturated brine solution (100 ml), dried over magnesium sulfate and concentrated under reduced pressure. The resultant yellow oil was purified by column chromatography (diethyl ether eluent) and then by distillation (110°C/3 mmHg) to give the desired product as a colourless oil (3.32 g, 21% (36% based on recovered starting material)). TLC, (diethyl ether) R_f=0.55; ν_{max} (thin film)/cm^{-1} 3060 (w, C=CH), 2978 and 2935 (s, CH$_3$/CH$_2$), 1704 (br s, C=O), 1651 (m, C=C), 1383 (s, C(CH$_3$)$_3$); δ_H (300 MHz; $CDCl_3$) 5.84–5.83 (1H, m, 3-H), 2.34 (2H, s, 5-H), 1.97 (3H, m, 4-Me), 1.44 (6H, s, 6-Me); δ_C (75 MHz; $CDCl_3$) 178.0 (C-2), 155.2 (C-4), 115.8 (C-3), 79.3 (C-6), 40.8 (C-5), 27.6 (6-Me), 23.2 (4-Me); *m/z* (EI) 141 ([M+H], 25%), 140 (M, 16), 125 ([M−Me], 88), 82 ([M−(CH$_3$)$_2$CO], 100); HRMS (EI) found 140.0848, (M, $C_8H_{12}O_2$ requires 140.0837).

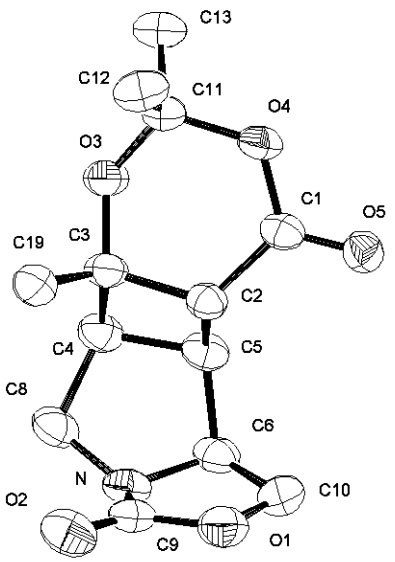
4.1.12. (1*S*,2*R*,7*S*,8*R*,14*R*)5,5,7-Trimethyl-3,11-dioxo-10-aza-4,12-dioxa-tetracyclo[6.6.0.0.^{2,7}0^{10,14}] tetradecane (20). A solution of (5*R*) 2-oxo-1-aza-3-oxabicyclo[3.3.0]-oct-6-ene (**14**) (2.25 g, 18.0 mmol) and 4,6,6-trimethyl-5,6-dihydropyran-2-one (**19**) (1.26 g, 9.0 mmol) in ethyl acetate, under continuous degassing with nitrogen, was irradiated with a 125 W medium pressure mercury lamp until no pyranone **19** remained by TLC. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (diethyl ether eluent) to give **20**, which recrystallized from ethyl acetate (0.766 g, 32% (43% based on recovered starting material)). TLC, (diethyl ether) R_f=0.21; mp 184–189°C; $[\alpha]_D^{25}$ 4.2, *c* 16.8 in chloroform; ν_{max} (thin film)/cm^{-1} 2956 and 2924 (s, CH$_3$/CH$_2$), 1737 (s, N–C=O), 1722 (C^3=O), 1369 (m, C–O); δ_H (300 MHz; $CDCl_3$) 4.66 (1H, dd, *J*=9.6, 3.0 Hz, 13-H), 4.58 (1H, dd, *J*=9.6, 8.4 Hz, 13-H), 4.05 (1H, dd, *J*=13.7, 1.3 Hz, 9-H$_u$), 4.02–3.98 (1H, m, 14-H), 3.10 (1H, dd, *J*=13.6, 8.0 Hz, 9-H$_d$), 3.04–3.00 (1H, m, 1-H), 2.60 (1H, dddd app tt, *J*=7.8, 1.2 Hz, 8H), 2.44–2.42 (1H, m, 2-H), 2.07 (1H, d, *J*=14.8 Hz, 6-H$_d$), 1.90 (1H, dd, *J*=14.8, 1.0 Hz, 6-H$_u$), 1.48 (3H, s, 5-Me$_d$), 01.42 (3H, s, 5-Me$_u$), 1.23 (3H, s, 7-Me); δ_C (75 MHz; $CDCl_3$) 172.8 (C-3), 167.3 (C-11), 82.5 (C-5), 63.4 (C-13), 60.1 (C-14), 50.1 (C-8), 46.0 (C-9), 45.3 (C-6), 44.0 (C-1), 39.2 (C-2), 33.7 (C-7), 31.1 (5-Me$_d$), 28.8 (5-Me$_u$), 23.5 (7-Me); *m/z* (EI) 265 (M, 17%), 210 (37), 141 (pyranone, 100), 123 ([cyclobutane–pyranone], 67); HRMS (EI) found 265.1320, (M, $C_{14}H_{19}NO_4$ requires 265.1314).

Diffraction data were measured on a Nonius KappaCCD diffractometer at 173 K using Mo Kα radiation and refined on F^2.

Crystal data for **15**: $C_{13}H_{17}NO_5$, *M* 267.3, Orthorhombic, $P2_12_12_1$ (No. 19), *a* 6.1730 (6), *b* 9.8187 (9), *c* 20.7031 (19)Å, *V* 154.8 (2)Å^3, *Z* 4, μ 0.11 mm^{-1}. 6184 Measured reflections, 2214 unique (R_{int} 0.084), R_1 0.058 (for 1678 reflections with $I>2\sigma I$), *wR*2 0.141 (for all reflections).

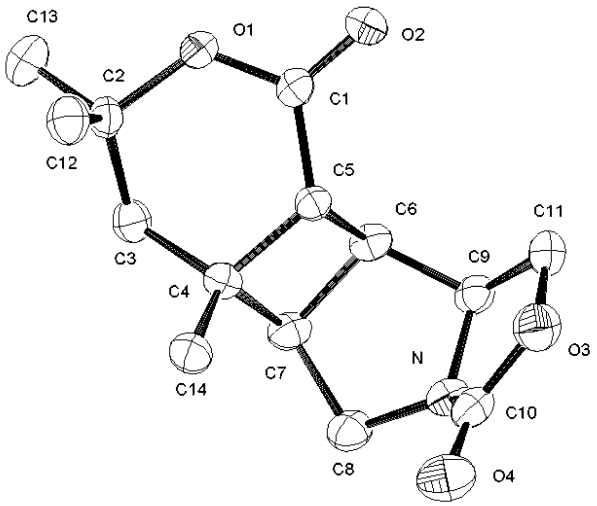
4.2. X-Ray data

4.2.1. (1*S*,2*R*,7*S*,8*R*,14*R*)5,5,7-Trimethyl-3,11-dioxo-10-aza-4,6,12-trioxa-tetracyclo[6.6.0.0.^{2,7}0^{10,14}]tetradecane (15).



Crystal data for **20**: $C_{14}H_{19}NO_4$, *M* 265.30, Orthorhombic, $P2_12_12_1$ (No. 19), *a* 6.1728 (3), *b* 10.0767 (6), *c* 20.4092 (15)Å, *V* 1274.5 (15)Å^3, *Z* 4, μ 0.10 mm^{-1}. 4747 Measured reflections, 2160 unique (R_{int} 0.042), R_1 0.042 (for 1849 reflections with $I>2\sigma I$), *wR*2 0.098 (for all reflections).

4.2.2. (1*S*,2*R*,7*S*,8*R*,14*R*)5,5,7-Trimethyl-3,11-dioxo-10-aza-4,12-dioxa-tetracyclo[6.6.0.0.^{2,7}0^{10,14}]tetradecane (20).



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References

1. For a comprehensive review, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.
2. (a) Shinozaki, H.; Knoishi, S. *Brain Res.* **1970**, *24*, 368. (b) Ishida, M.; Shinozaki, H. *Brain Res.* **1988**, *474*, 386. (c) Shinozaki, H.; Ishida, M.; Okamoto, T. *Brain Res.* **1986**, *399*, 395. (d) Maruyama, M.; Takeda, K. *Brain Res.* **1989**, *504*, 328. (e) Shinozaki, H.; Ishida, M.; Gotoh, Y.; Kwak, S. *Brain Res.* **1989**, *503*, 330.
3. (a) In *Kainic Acid as a Tool in Neurobiology*; McGeer, E. G., Olney, J. W., McGeer, P. L., Eds.; Raven: New York, 1978. (b) In *Excitatory Amino Acids*; Simon, R. P., Ed.; Thieme Medical: New York, 1992. (c) In *Amino Acids and Synaptic Transmissions*; Wheal, H. V., Thomson, A. M., Eds.; Academic: London, 1991. (d) Watkins, J. C.; Krogsgaard-Larsen, P.; Honore, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25.
4. Sperk, G. *Prog. Neurobiol. (Oxford)* **1994**, *42*, 1.
5. (a) Coyle, J. T.; Schwarcz, R. *Nature (London)* **1976**, *263*, 244. (b) McGeer, E. G.; McGeer, P. L. *Nature (London)* **1976**, *263*, 517.
6. Greenwood, E. S.; Parsons, P. J. *Synlett* **2002**, 167.
7. see Bach, T. *Synthesis* **1998**, 683, and references therein.
8. Zhao, H.; Thurkauf, A. *Synlett* **1999**, 1280.
9. (a) Hirai, Y.; Chintani, M.; Yamazaki, T.; Momose, T. *Chem. Lett.* **1989**, 1449. (b) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1991**, *47*, 155. (c) Horikawa, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 331. (d) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (e) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321. (f) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.
10. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
11. Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.
12. Wittig, G.; Schoellkopf, U. *Ber* **1954**, *87*, 1318.
13. Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181.
14. Lei, B.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 1450.
15. Schumacher, K. K.; Jiang, J.; Joullié, M. M. *Tetrahedron Asymmetry* **1998**, *9*, 47.
16. Abraham, D. J.; Mokotoff, M.; Sheh, L.; Simmons, J. E. *J. Med. Chem.* **1983**, *26*, 549.
17. Dormoy, J.-R. *Synthesis* **1982**, 753.