An approach to modified heterocyclic analogues of huperzine A and isohuperzine A. Synthesis of the pyrimidone and pyrazole analogues, and their anticholinesterase activity

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Synthetic approaches to the pyrimidone and the pyrazole analogues of the naturally occurring acetylcholinesterase (AChE) inhibitor huperzine A and its unnatural regioisomer, isohuperzine, are described. The pyrimidone analogues of huperzine A were obtained starting from cyclohexane-1,4-dione monoethylene ketal by first annealing to this monocycle a pyrimidine ring and then constructing the unsaturated three-carbon bridge using the previously described palladium-catalysed bicycloannulation methodology. A major problem in this synthetic undertaking proved to be introduction of the ethylidene appendage onto tricycle 10. While both Wittig and Takai olefination protocols proved unsuccessful, the ethylidene moiety was eventually introduced using the Danheiser methodology which involves a two step reaction sequence consisting of the intermediate construction of a β-lactone, which in turn undergoes a [2 + 2] cycloreversion leading to the desired olefin. This β-lactone synthesis, which has not previously been applied to β-keto esters, was found to proceed with excellent diastereoselectivity. In turn, the β-lactone underwent a stereospecific decarboxylation reaction to provide the E-olefin product as the sole isomer. Additionally, starting from the bicyclo[3.3.1]nonene intermediate 2 we describe a synthetic strategy for procuring modified heterocyclic analogues of isohuperzine A. This chemistry provides an attractive approach to the synthesis of heterocyclic analogues with unsaturation in the 6,7 position. While none of these new analogues was found to rival huperzine A in its ability to act as a reversible inhibitor of AChE, the data reported herein should prove useful to modeling efforts aimed at acquiring a better understanding of huperzine A's binding topography within AChE.

Introduction

The role of acetylcholine (ACh) in the modulation of memory function in both the normal and pathological states has been extensively reviewed.[1] In general, the central cholinergic system is important in the regulation of memory and learning processes, and impairment of memory has been shown to occur following blockade of cholinergic function with antimuscarinic agents.[2] On the other hand, a variety of cholinergic agonists have been shown to improve memory in both man and animal.[3] Neurodegenerative conditions involving memory loss, such as dementia of the Alzheimer's type (AD), are accompanied by a loss of basal forebrain neurons and reduced cortical and hippocampal levels of the neurotransmitter acetylcholine. Treatment of dementia with cholinergic agonists has not generally proven to be therapeutically useful, especially for reasons relating to the manifestation of peripheral side effects. On the other hand, experimental findings regarding reduced muscarinic receptor density together with a reduction in ACh levels in the AD brain have prompted the investigation and development of inhibitors of the enzyme acetylcholinesterase (AChE). This enzyme is responsible for the rapid degradation of the important neurotransmitter ACh to choline and acetate ion. Thus, among the possible therapeutic approaches aimed at increasing cholinergic tone in the central nervous system (CNS) which includes, *inter alia*, the investigation of muscarinic and nicotinic agonists, 5-HT3 receptor antagonists, and facilitators of ACh release, the use of reversible AChE inhibitors is considered, at present, to represent one of the more attractive therapeutic approaches to the treatment of AD. While the well-known cholinesterase inhibitor physostigmine has been found to provide a moderate but consistent enhancement in memory function, its use has been limited by its short duration of action. On the other hand, the reversible AChE inhibitor tetrahydroaminoacridine (THA or Cognex) is currently marketed for use in the long-term palliative treatment of AD. Unfortunately, the severe liver toxicity associated with this drug as well as side effects stemming from its low target specificity (competing blockade of K^+ ion channels, M1 and M2 receptor antagonism, and inhibition of butyrylcholinesterase) conspire to limit its widespread applicability.[4]

Another reversible AChE inhibitor which is a natural product, and which has attracted considerable attention for its possible use in the treatment of AD is huperzine A. This compound was first isolated from the clubmoss *Huperzia serrata* by Liu and co-workers. This natural product has proven to be a very potent (K_i = 6.2 nmol l^{-1} for FBS AChE[7a]) and selective inhibitor of AChE with almost no action on BuChE. Additionally, when tested on nearly 40 other receptor and enzyme systems, huperzine A was found to have no activity. Several reports reveal huperzine A to produce a relatively long-term inhibition of AChE (about 6 h in rats), increasing the level of ACh in the cortical areas and hippocampus. In double blind-placebo controlled studies conducted in China, huperzine A has been found to dramatically improve the cognitive performance of individuals suffering from various forms of memory

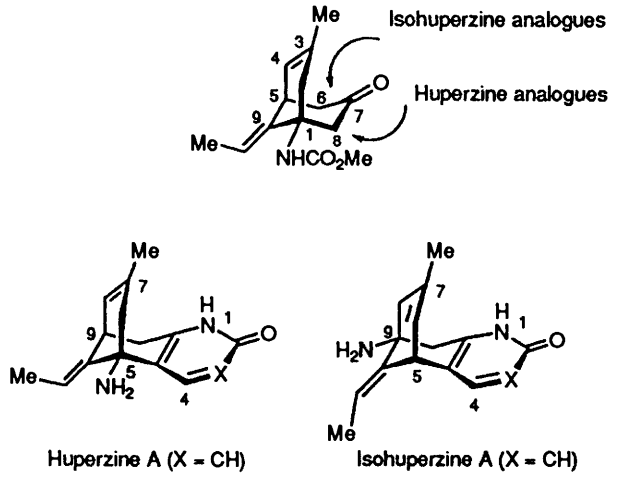
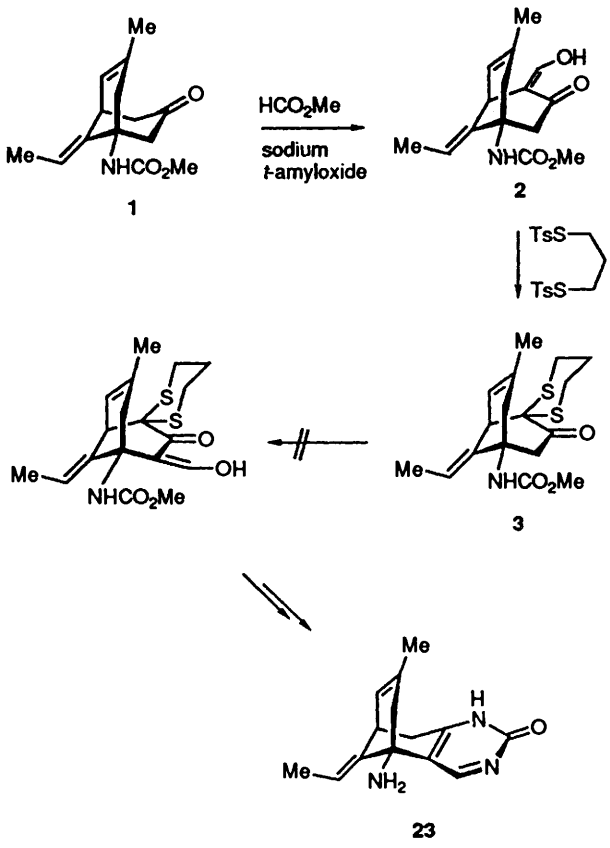


Fig. 1 Bicyclic precursor to huperzine and isohuperzine analogues

impairment.[5] Huperzine A thus appears to be a promising psychotherapeutic agent for the treatment of AD patients, and as such to be a worthy target for continued synthetic manipulations aimed at understanding the structural elements responsible for its *in vitro* and *in vivo* activity and selectivity.[6] Although we have previously reported on a number of modifications to this structure including alterations of the amino group, the three-carbon bridge, and the ethylidene side chain, few attempts have been made to examine alterations to its pyridone ring. Accordingly, we imagined that replacement of its pyridone ring by a pyrimidone ring might possibly lead to an analogue showing improved AChE inhibitory potency due to its ability to engage in additional H-bonding. Furthermore, starting from the bicyclic structure shown in Fig. 1 we have developed a synthetic strategy to modified heterocyclic analogues of the unnatural huperzine A regioisomer for which we propose the name isohuperzine A. In the course of these studies and as detailed herein we uncovered a novel application of Danheiser's β-lactone methodology for the stereoselective olefination of β-keto esters. Rather remarkably, this methodology is shown to provide solely the *E*-olefinic products.

Chemistry: Synthesis of the pyrimidone analogues of huperzine A

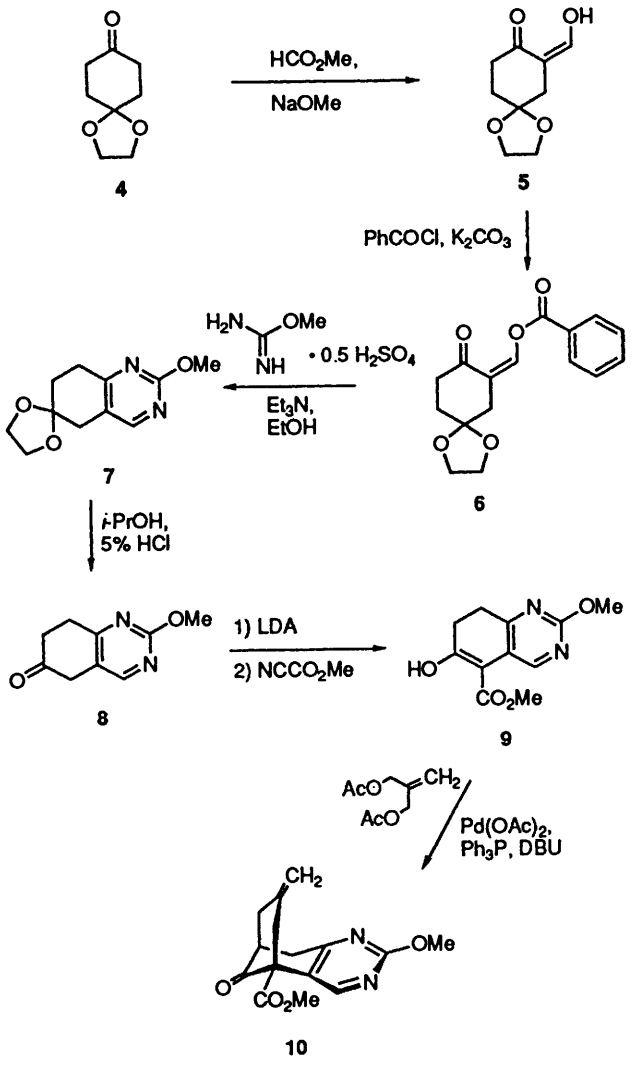
In one of our previous papers[7] we described the initial results and problems issuing from a strategy designed to procure modified heterocyclic huperzine A analogues using the bicyclo[3.3.1]nonane derivative **1** as a common intermediate. In that article we reported a possible approach to the synthesis of a thiazole analogue of huperzine A. On applying the Gewald aminothiazole synthesis to urethane **1**, we were able to obtain a single aminothiazole but, unfortunately, this product possessed the undesired regiochemistry. Apparently, for steric reasons, position 4 of urethane **1** is more reactive than position 2, the site at which functionalization is required in order to generate the desired regioisomer. On the basis of these negative results, and as delineated in Scheme 1, the first approach to the pyrimidone analogue **23** using urethane **1** that we chose to explore required that we block the C-2 position. This process was attempted by utilizing the thioketal blocking group strategy developed by Woodward.[8] The urethane **1** was thus reacted with methyl formate in the presence of sodium *tert*-amyloxide[9] to afford the hydroxymethylene intermediate **2**, which on treatment with trimethylene bis(thiotosylate) and potassium acetate[8] provided **3** in good overall yield. Unfortunately, while the bicycle **3** is suitably blocked at C-4, this intermediate failed to undergo hydroxymethylenation at the C-2 position, a prerequisite for further elaboration of the pyrimidone ring.



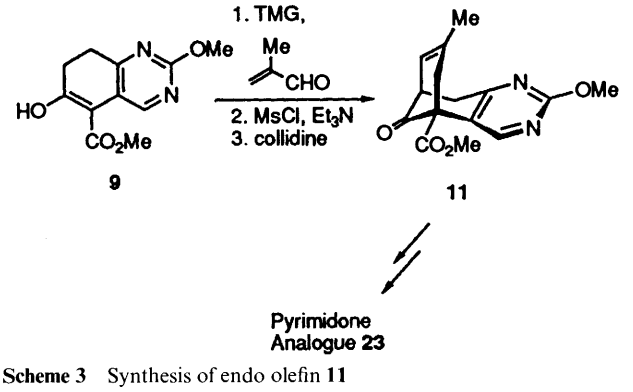
Scheme 1 First approach to the pyrimidone analogue **23**

Because of the above problem, we decided to redesign our original synthetic approach, and to begin anew by elaborating the pyrimidine ring at an earlier stage. This idea demanded that we prepare a pyrimidine bearing bicycle along synthetic lines similar to those followed in our construction of huperzine A itself.[10] Cyclohexane-1,4-dione monoethylene ketal **4** serves as a convenient starting material, for it contains both a free carbonyl group for elaborating the heterocyclic ring and a masked one which upon deprotection can be used to introduce the remaining three-carbon bridge and the ethylidene appendage.

Following this strategy, ketone **4** was hydroxymethylenated,[11] and **5** reacted in turn with benzoyl chloride and K_2CO_3 to provide the benzoate ester **6**.[12] Upon reaction of **6** with *O*-methylisourea hydrogen sulfate,[13] the quinazoline **7** was isolated in 68% yield. Deketalization of quinazoline **7**, followed by methoxycarbonylation using Mander's reagent[14] gave the β-keto ester **9** (Scheme 2). In our early efforts to graft the three-carbon bridge to **9**, we examined the combined Michael addition–aldol condensation sequence as described in the early synthesis of huperzine A.[10] The reaction of **9** with methacrolein using 1,1,3,3-tetramethylguanidine (TMG) as the base catalyst provided the expected cyclic ketol as a mixture of stereoisomers in 85% yield. This intermediate was mesylated, and the mesylate reacted in turn with collidine to effect elimination (Scheme 3). Because the elimination reaction to give **11** was found to proceed in only 8% yield, we chose at this stage to investigate the alternative palladium-catalysed bicycloannulation route to **11**.[15] As depicted in Scheme 2, this palladium-catalysed reaction using DBU as a base, 2-methyleneпropane-1,3-diol diacetate as the bis-electrophile, and tetrakis(triphenylphosphine)palladium(0) as the catalyst afforded the exocyclic olefin **10** in 76% yield.[16] Unfortunately, we were unable to isomerize **10** to its endocyclic counterpart **11** using either triflic acid or rhodium chloride.[15,17] In an effort to circumvent this problem, we decided to proceed with the other

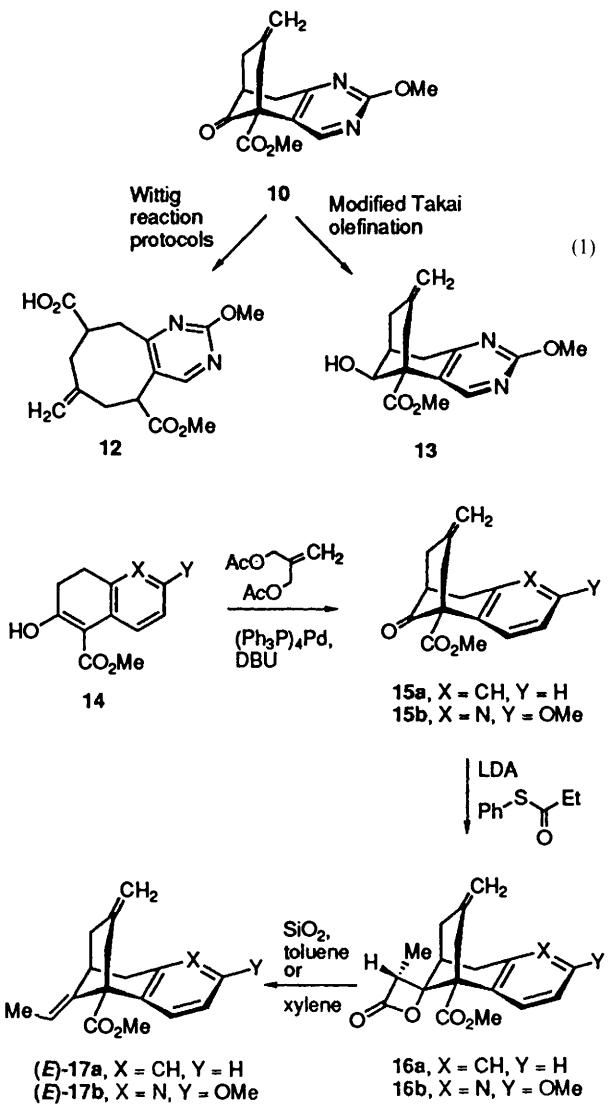


Scheme 2 Synthesis of intermediate **10**



Scheme 3 Synthesis of endo olefin **11**

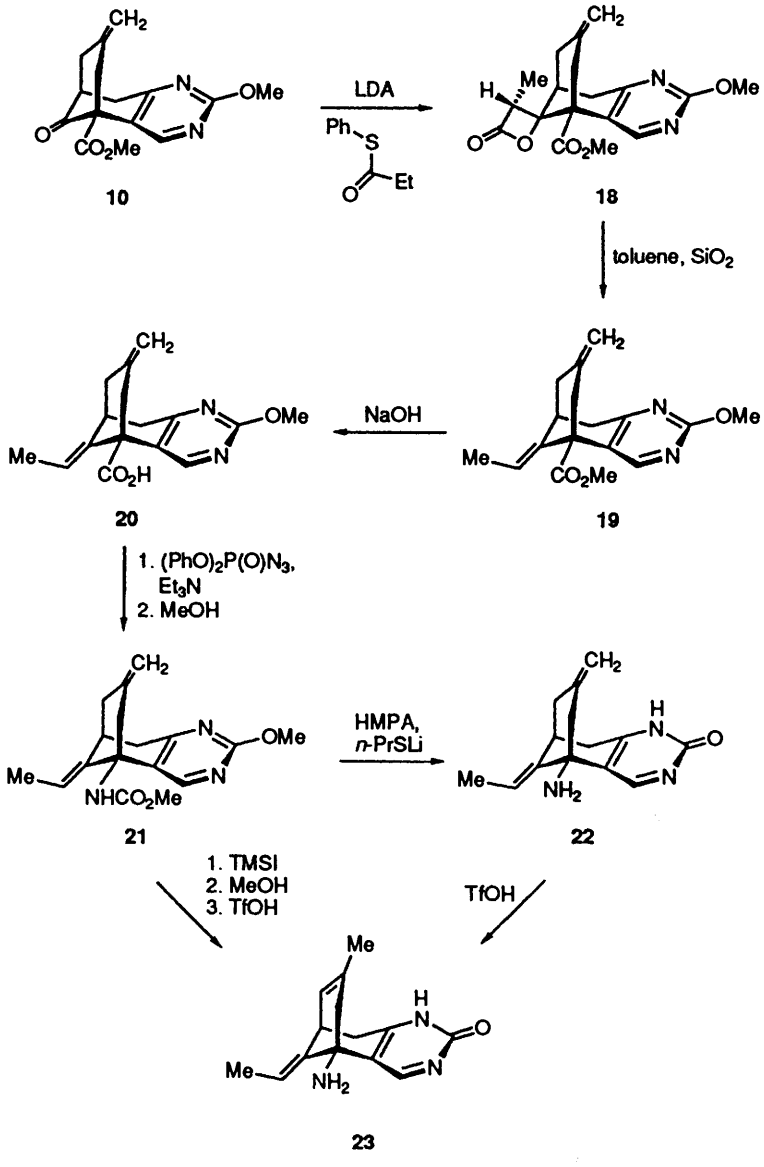
steps in the synthesis and to defer the double-bond isomerization step to the last stage of the synthesis. Thus, from the β-keto ester **10** installation of the (*E*)-ethylidene side chain at C-11 was required. Compound **10** was subjected to various olefination protocols [eqn. (1), and Schemes 4 and 5]. Wittig olefination with $Ph_3PEt^+ Br^-$ and BuLi was attempted under a variety of reaction conditions, but these attempts led to the formation of the fragmentation product **12**[18] in about 70% yield [eqn. (1)]. Examination of the Takai ethylidenation protocol[19] using 1,1-diiodoethane and $CrCl_2$ resulted in no reaction, while a modified procedure involving treatment with Zn, $TiCl_4$, and 1,1-diiodoethane[20] led solely to reduction to alcohol **13** in 85% yield [eqn. (1)].



Scheme 4 Synthesis of olefins **17** through a β-lactone intermediate

Further investigations eventually led us to the possibility of utilizing the method reported by Danheiser in 1991 for the construction of alkenes from β-lactone intermediates.[21] The anion of the benzenethiol ester of propionic acid was accordingly added to the ketone **10** to provide the sterically less crowded β-lactone diastereoisomer **18** with complete stereoselectivity. Upon heating of **18** in the presence of silica gel in toluene as solvent, [2 + 2] cycloreversion with elimination of carbon dioxide took place to afford the required *E*-configured olefinic product **19**.[21] This olefination strategy involved one more step than the classic Wittig reaction, but it proved to be the more practical and efficient method.

In order to obtain additional information on the stereochemical course of this olefination methodology, which had not previously been applied to β-keto esters, we chose to synthesize the oxetanone derivatives **16** starting from the β-keto esters **15**. The oxetanone **16b** was a particularly useful model for this stereochemical study, owing to its more readily assignable NMR spectrum than that of **16a** or **18**. The two β-lactones **16a** and **16b** were in fact found to undergo facile [2 + 2] cycloreversion reactions to generate the (*E*)-olefins **17a** and **17b** in good overall yield, thus further confirming the stereospecificity of this olefination method at least for such tricyclic β-keto esters (Scheme 4). Of particular interest to this investigation was the stereochemical outcome of the β-lactone forming step. The orientation of the methyl group of the oxetanone in **16** and **18** was found to be *trans* to the carbomethoxy group on the basis of



Scheme 5 Synthesis of pyrimidone analogues **22** and **23**

detailed NMR analyses (Fig. 3). While further mechanistic considerations of this reaction are provided below, it is of some interest to note here that this olefination protocol may also represent a practical alternative route to the Wittig reaction and subsequent isomerization step used in our first synthesis of huperzine A.

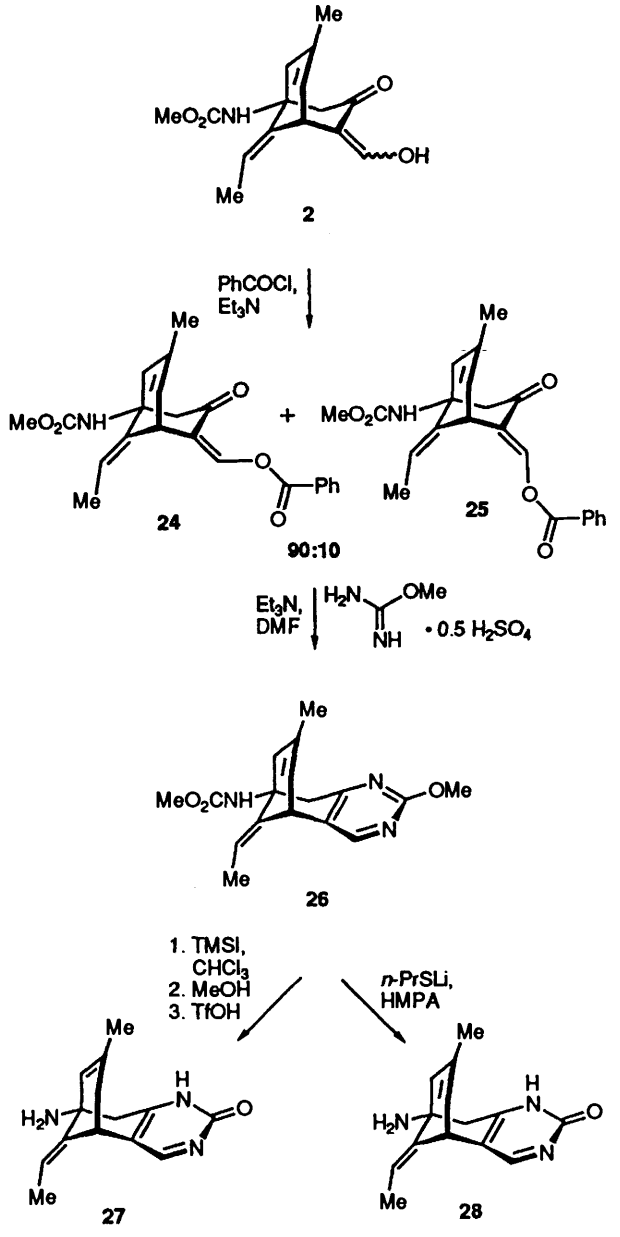
Having solved the olefination problem, we were now able to return to the main course of our synthetic endeavour. Saponification of **19** with sodium hydroxide yielded the crystalline acid **20** (Scheme 5). Curtius reaction of **20** by treatment with diphenyl azidophosphate and Et_3N, followed by methanolysis of the resulting isocyanate provided the urethane **21** (90% yield).[22] Trimethylsilyl iodide promoted deprotection of **21** in refluxing chloroform proceeded uneventfully, although partial isomerization of the exocyclic double bond to the endocyclic olefin was observed. By exposure of this mixture to triflic acid in dioxane at 92 °C the isomerization reaction was driven to completion, and the pyrimidone analogue **23** was isolated as the sole product in 87% yield.[15] To deprotect **21** without rearrangement of the exocyclic double bond, the urethane **21** was treated with lithium propylmercaptide.[23] This method provided the *exo*-methylene analogue **22**. Exposure of **22** in turn to triflic acid in a resealable tube at 90 °C gave **23** in 84% yield.

Synthesis of isohuperzine analogues bearing a modified heterocycle

We and others have over the past several years described a number of huperzine A analogues which embody various structural changes.[24] Among the structural elements believed to be relevant to huperzine A's interaction with acetylcholinesterase is the unsaturation present in the three-carbon bridge. While some attempts have been made to 'shift' the endocyclic double bond of huperzine A from the 7,8-position to 6,7-position, these attempts have proven unsuccessful. In fact, we have shown previously that the 7-methylene analogue of huperzine A can be isomerized under triflic acid conditions to afford solely huperzine A. No trace of the isomer with unsaturation in the 6,7-position could be detected, thus providing evidence that the isomer with unsaturation at the 7,8-position, *i.e.* huperzine A, is the thermodynamically favoured product.[15] This finding led us to hypothesize that the position of fusion of the heterocyclic ring to the bicyclo[3.3.1]nonene may affect isomer stability, and accordingly, the position of the double bond in the three-carbon bridge. This hypothesis, put forth in a previous paper,[7] is confirmed herein with the synthesis of four isohuperzine analogues, namely the pyrimidone and the pyrazole analogues. These analogues gave

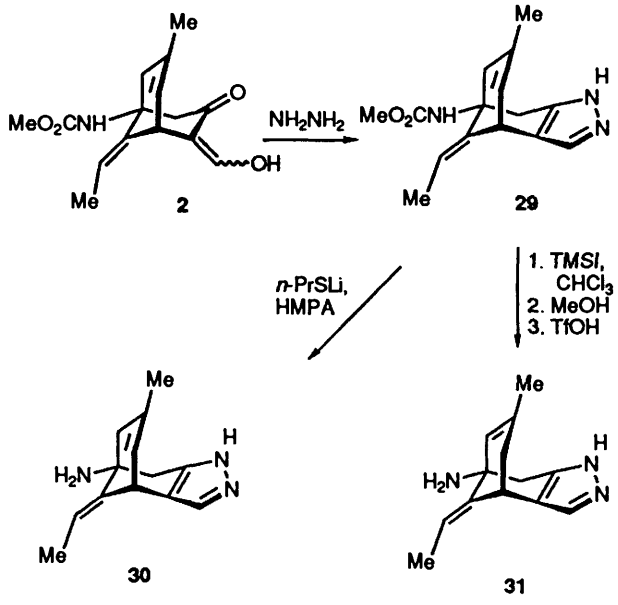
us the opportunity to investigate the rearrangement of the endocyclic double bond relative to the condensed heterocycle, and the influence that the position of this bond might have upon the interactions of these compounds with AChE.

The hydroxymethylene derivative **2** was found to be a versatile starting material for the preparation of the isohuperzine analogues featured in Schemes **6** and **7**. Thus,



Scheme 6 Synthesis of the pyrimidone analogues **27** and **28** of isohuperzine A

benzoylation of **2** afforded a mixture of the *cis*- and *trans*-esters **24** and **25** in a 9:1 ratio, respectively. Reaction of the mixture with *O*-methyl isourea hydrogen sulfate in DMF gave the urethane **26** in 37% yield. TMSI-promoted deprotection of **26** proceeded with the formation of a mixture of **28** and its double bond positional isomer **27**. Complete rearrangement of this mixture to **27** was brought about by exposure to triflic acid at 84 °C. Since a related double-bond rearrangement was not observed in the synthesis of huperzine A, and since **27** has the same relative positions of the endocyclic double bond and the heterocyclic ring as found in huperzine A, we conclude that isomer **27** is the thermodynamically favoured product. Rearrangement of the double bond of **26** could be avoided by using lithium propylmercaptide as the deprotection agent; **28**



Scheme 7 Synthesis of the pyrazole analogues **30** and **31** of isohuperzine A

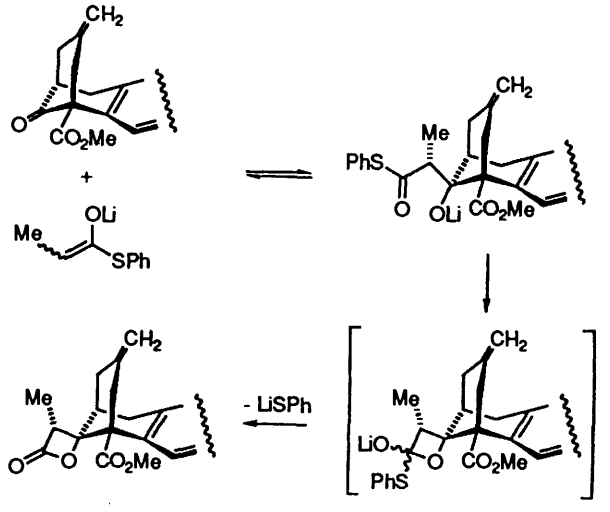


Fig. 2 Formation of the less congested tetrahedral intermediate

was formed as the sole product in 81% yield. In a similar manner the pyrazoles **30** and **31** were synthesized from **29**, an intermediate obtained from **2** by reaction with hydrazine hydrate (Scheme 7).[11]

Stereochemical course of β-lactone synthesis and structural assignments

Based upon the obtention of only the *E*-olefinic products from the β-lactone synthesis/cycloreversion protocol, we assume that only the sterically less crowded β-lactone diastereoisomers **18**, **16a** and **16b** were formed in each case. This notion finds support in the work of Danheiser and Nowick who suggest that the initial 'rapid and reversible aldol condensation' step of the thiol ester enolates is followed by the preferential cyclization of the aldolate that provides the less congested tetrahedral intermediate (Fig. 2).[21] In order to obtain experimental verification of the structure of one of our β-lactones, we carried out extensive NMR studies on **16b**. Stereochemical assignment of the protons of **16b** was made from ^{1}H decoupling and 2D COSY experiments, while the stereochemistry of the methyl group of **16b** was assigned from ^{1}H NMR NOE experiments (Fig. 3).

The benzylic protons h and i were determined by their diagnostic chemical shifts at δ 2.18 (i) and at about δ 2.7

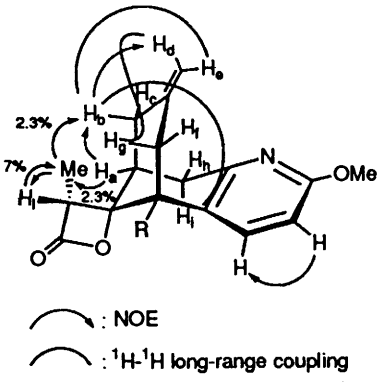


Fig. 3 NMR analysis of **16b**

Table 1 Extent of AChE inhibition by the compounds tested

Compound number	IC_{50}[a] (μmol l^{-1})	(*n*)
(±)-Huperzine A	0.02 ± 0.005	3
22	> 300	3
23	30.8 ± 10.0	3
27	16.6 ± 4.0	3
28	0.73 ± 0.10	3
30	3.48 ± 0.15	3
31	100 ± 9.6	

[a] IC_{50} values are the mean ± standard deviation. The IC_{50} values provided for compounds **22**, **23**, **27**, **28**, and huperzine A are for the inhibition of FBS AChE. The IC_{50} values provided for **30** and **31** are for the inhibition of rat cortex AChE. Although different enzyme preparations have been used, comparisons between the IC_{50} values for the two sets of compounds are reasonable, for IC_{50} values similar to those reported above were obtained for **27** and **28** when tested for their inhibition of rat cortex AChE: 19.0 ± 3.4 μmol l^{-1} and 2.4 ± 0.6 μmol l^{-1}, respectively.

(h). Furthermore, the 2D COSY spectrum revealed a long-range coupling between proton i and proton b. In the ^{1}H NMR and COSY spectra, a correlation between proton h and proton a was also observed, while no coupling was found between proton a and proton i due to a dihedral angle of about 80°. Proton c appeared at δ 2.32 as a doublet of doublets; the smaller equatorial–equatorial coupling showed the expected coupling constant ($J_{a\text{-}c}$ = 1.74 Hz), while the geminal coupling ($J_{b\text{-}c}$) was about 13 Hz. Further examination of the COSY spectral data indicated that the two axial protons b and g at δ 3.25 were coupled to proton c at δ 2.32 and proton f at δ 2.82 ($J_{g\text{-}f}$ = 19.0 Hz), respectively. Moreover, the axial protons b and g presented a long-range coupling with the exocyclic methylene protons e and d, respectively.

The stereochemistry of the methyl group of the β-lactone moiety together with the orientation of its ring oxygen were deduced primarily from the NOE experiments. Irradiation of **16b** at δ 1.34 (CH_3) produced enhancements at δ 3.25 (2.3%, axial protons b and g), δ 4.26 (7%, proton l), and at δ 2.68 (2.3%, proton a). Irradiation of **16b** at δ 4.26 (proton l) produced enhancement only at δ 1.34 (CH_3), while no enhancement was observed at δ 2.18 (proton i).

From these NMR results we conclude that the 3-methyloxetan-2-one ring of **16b** is oriented so that its ring oxygen assumes an axial-like position at the spiro centre of the six-membered ring. The methyl group is accordingly located syn to the methinyl carbon bearing H_a. Further support for the NMR-based stereochemical assignments derive from the silica gel promoted [2 + 2] cycloreversion reaction of the β-lactones **16a**, **16b** and **18**, all of which lead solely to the *E*-olefins.

Biological activity and discussion

The AChE inhibitory data for the new analogues are provided in Table 1 along with IC_{50} value for racemic huperzine A.[25,26] In view of the relatively more dramatic structural alterations embodied by the alternately fused pyridone and pyrazole analogues **27**, **28**, **30** and **31**, it is not surprising to find that these compounds are less active than huperzine A itself. Pyrimidone **27** is about 800-fold less active, while **28** is only about 36-fold less active. Somewhat less expected, however, is the finding that compounds **22** and **23** are even less active than **27** and **28** (> 15 000-fold and 1540-fold, respectively), in spite of the fact that the former structures are more closely related to huperzine A. Apparently, the extra nitrogen atom present in these structures must confer an undesirable electrostatic interaction with the enzyme in addition to the unfavourable change in the energetics of desolvation. The approximately 30-fold difference observed in the activity of pyrazoles **30** and **31** is also striking and parallels the 24-fold difference found in the activity of pyrimidones **27** and **28**; in both cases the more active isomer has, like huperzine A itself, the double bond in the three-carbon bridge directed away from the NH_2 group. The present work serves to further underscore the importance of huperzine A's electronic field to its interaction with AChE. An in depth understanding of the ability of the alternatively fused pyrimidones **27** and **28** to serve as a modestly active AChE inhibitors will require the docking of these molecules to the X-ray structure available for *T. californica* AChE, a study now underway.

Conclusions

The present work delineates concise methodology for procuring huperzine A analogues bearing heterocyclic replacements for its pyridone ring. These synthetic efforts have led to the discovery of a useful application of the β-lactone/[2 + 2] cycloreversion approach for the stereoselective construction of a trisubstituted olefin.

In terms of biological activity, this work reveals that even the rather modest alteration made to the huperzine A structure through the replacement of one of its pyridone ring CH groups by nitrogen causes a major reduction in AChE inhibitory activity. While the drop in activity found for **23** can be related in part to changes in the energetics of desolvation, it is surprising to find that this activity difference is greater than 1500-fold. Also noteworthy was the finding that the pyrimidone analogues **27** and **28** of isohuperzine are more active than the pyrimidone analogues **22** and **23**. It is obvious that **27** and **28** must find modes for binding to AChE which are different from those of huperzine A itself. Through the use of X-ray co-crystallization studies and computer modeling methods, we currently seek a better understanding of these binding modalities, as well as of the nature of the interaction between the unsaturation in huperzine A's three-carbon bridge and AChE. While preliminary studies in this direction have been published,[27] more definitive studies will be reported in due course.

Experimental

General experimental information can be found in reference 4. IR spectra were obtained on a Perkin-Elmer FT-1600 instrument. GC–MS analyses were performed on a Hewlett-Packard 5890 II instrument.

(9*E*)-(±)-[9-Ethylidene-6-(hydroxymethylene)-3-methyl-7-oxobicyclo[3.3.1]non-3-en-1-yl]carbamic acid methyl ester 2

To a solution of **1** (40 mg, 0.17 mmol) in dry toluene (0.4 ml) was slowly added sodium *tert*-amyloxide (25.6 mg, 0.22 mmol) in dry benzene (0.4 ml). The mixture was stirred for 1 h at room temp. under argon, then cooled in an ice-water bath, and methyl formate (21 μl, 0.34 mmol) was added dropwise. After the addition was complete, the mixture was allowed to warm to room temp. and stirred for 24 h. The reaction was quenched with water, and the mixture was extracted with dichlorometh-

ane. The organic layer was removed, and the aqueous layer was adjusted to pH 4 with 6 mol l^{-1} HCl and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material (39 mg), which by ^1H NMR analysis consisted of a 9:1 mixture of the (*E*)- and (*Z*)-hydroxymethylene derivatives **2**, was used in the next step without further purification.

(9*E*)-(±)-[9-Ethylidene-3-methyl-7-oxo-6,6-(trimethylenedithio)bicyclo[3.3.1]non-3-en-1-yl]carbamic acid methyl ester 3

A solution of urethane **2** (217 mg, 0.78 mmol), trimethylene dithiotosylate (324 mg, 0.78 mmol), and anhydrous potassium acetate (260 mg) in anhydrous ethanol (3.9 ml) was refluxed for 3 h under argon. After cooling, the solvent was removed under vacuum, and the residue was partitioned between cold 2 mol l^{-1} NaOH and chloroform. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography using benzene as the eluent to afford **3** (192 mg, 70% yield) as colourless prisms: mp 130–131 °C (hexanes); R_f = 0.26 (benzene); ν_{max}(KBr)/cm^{-1} 1715, 1520, 737; δ_H($CDCl_3$) 5.64 (m, 1 H), 5.61 (q, 1 H, *J* 6.8), 4.79 (s, NH), 4.27 (d, 1 H, *J* 15.4), 3.67 (m, 4 H), 3.56 (dt, 1 H, *J* 13.4 and 2.9), 2.68–2.60 (m, 3 H), 2.47–2.30 (m, 3 H), 2.08 (m, 1 H), 1.82 (d, 3 H, *J* 6.8), 1.75 (m, 1 H), 1.64 (s, 3 H); δ_C($CDCl_3$) 13.7, 22.7, 24.7, 27.6, 28.1, 44.0, 48.1, 48.2, 52.0, 57.8, 60.1, 116.3, 120.3, 131.9, 135.1, 155.1, 202.3; *m/z* 353 (5%, M^+), 321, 278, 250, 192, 161 (100%) (Calc. for $C_{17}H_{23}NO_3S_2$ *M*, 353.1119, Found *M*, 353.1124. Calc. for $C_{17}H_{23}NO_3S_2$: C, 57.77; H, 6.56; N, 3.96. Found: C, 58.04; H, 6.50; N, 3.93%).

4,4-(Ethylenedioxy)-2-(hydroxymethylene)cyclohexan-1-one 5

To a mixture of sodium (0.44 g, 19.2 mmol) and dry diethyl ether (38.3 ml) was added cyclohexane-1,4-dione monoethylene ketal **4** (3 g, 19.2 mmol), methyl formate (1.68 ml, 28.8 mmol), and then dry methanol (95 µl, 2.9 mmol). The reaction mixture was placed in an ice–water bath and stirred under argon. After 6 h, methanol (5 ml) was added, and the mixture was stirred for 1 h at room temp. Water (10 ml) was added, and the mixture was extracted with diethyl ether. The aqueous phase was adjusted to a pH of 5 with 6 mol l^{-1} HCl and extracted with diethyl ether. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by distillation (70 °C/5 mmHg) to give 2.58 g (74%) of **5** as a colourless oil; R_f = 0.3 (10% ethyl acetate in chloroform); δ_H($CDCl_3$) 11.13 (d, 1 H, *J* 3.4), 8.55 (d, 1 H, *J* 3.1), 4.02 (m, 4 H), 2.59 (m, 4 H), 1.87 (m, 2 H); *m/z* 184 (23%, M^+), 167, 155, 127, 86 (100%) (Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.71; H, 6.53%).

2-(Benzoyloxymethylene)-4,4-(ethylenedioxy)cyclohexan-1-one 6

To a slurry of the hydroxymethylene derivative **5** (383 mg, 2.08 mmol) and K_2CO_3 (287 mg, 2.08 mmol) in dry dichloromethane (5 ml) was added benzoyl chloride (240 µl, 2.08 mmol) within 30 min, and the suspension was stirred at room temp. under argon for 24 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness under vacuum. Flash chromatography (10% hexanes in chloroform) afforded 550 mg (92%) of benzoate ester **6**: mp 138–140 °C (10% dichloromethane in hexanes); R_f = 0.47 (10% ethyl acetate in chloroform); ν_{max}(KBr)/cm^{-1} 1730, 1693, 1055, 704; δ_H($CDCl_3$) 8.39 (m, 1 H), 8.10 (m, 2 H), 7.66 (m, 1 H), 7.48 (m, 2 H), 4.05 (m, 4 H), 2.95 (d, 2 H, *J* 0.9), 2.67 (app. t, 2 H, *J* 7.0), 2.08 (app. t, 2 H, *J* 7.0); *m/z* 288 (15%, M^+), 260, 183, 105 (100%) (Calc. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.81; H, 5.63%).

6,6-(Ethylenedioxy)-5,6,7,8-tetrahydro-2-methoxyquinazoline 7

To a stirred solution of the ester **6** (316 mg, 1.1 mmol) and Et_3N (185 µl, 1.32 mmol) in absolute ethanol (1.14 ml) was added *O*-methyl isourea hydrogen sulfate (227 mg, 1.32 mmol). The resulting mixture was heated at reflux under argon for 24 h and then concentrated *in vacuo*. The concentrated mixture was dissolved in dichloromethane, washed with 20% $NaHCO_3$ and brine, and dried ($MgSO_4$). Concentration followed by flash chromatography (1:1:1 chloroform–ethyl acetate–hexanes) afforded 165 mg (68%) of quinazoline **7** as a waxy solid: R_f = 0.22 (1:1:1 chloroform–ethyl acetate–hexanes); ν_{max}(KBr)/cm^{-1} 1599, 1465, 1043, 731; δ_H($CDCl_3$) δ 8.18 (s, 1 H), 4.03 (m, 4 H), 3.97 (s, 3 H), 3.02 (app. t, 2 H, *J* 6.9), 2.88 (s, 2 H), 2.02 (app. t, 2 H, *J* 7.1); δ_C($CDCl_3$) 30.6, 30.8, 34.8, 54.6, 64.6 (2 C), 107.1, 120.7, 159.0, 164.1, 167.0; *m/z* 222 (30%, M^+), 192, 177, 163, 149 (100%), 120 (Calc. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.62; H, 6.38; N, 12.68%).

7,8-Dihydro-2-methoxyquinazolin-6(5*H*)-one 8

A solution of ketal **7** (103 mg, 0.46 mmol) in acetone (1 ml) and 5% HCl (1.17 ml) was heated at reflux under argon for 3 h. After cooling, the mixture was evaporated, neutralized and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Evaporation and flash chromatography of the residue (30% chloroform in ethyl acetate) gave 74 mg (91%) of ketone **8** as a yellowish solid: mp 84–85 °C (10% chloroform in hexanes); R_f = 0.31 (30% chloroform in ethyl acetate); ν_{max}(KBr)/cm^{-1} 1718, 1589, 1574, 1379, 794; δ_H($CDCl_3$) 8.25 (s, 1 H), 4.01 (s, 3 H), 3.53 (s, 2 H), 3.17 (app. t, 2 H, *J* 7.2), 2.67 (app. t, 2 H, *J* 7.3); δ_C($CDCl_3$) 30.7, 37.1, 39.6, 54.9, 119.3, 128 (br), 157.9, 164.7, 167.4; *m/z* 178 (20%, M^+), 163, 135, 120, 107.

5,6,7,8-Tetrahydro-2-methoxy-6-oxoquinazoline-5-carboxylic acid methyl ester 9

BuLi (1.5 ml, 1.6 mol l^{-1} in hexanes) was added to a stirred solution of diisopropylamine (336 µl, 2.4 mmol) in anhydrous THF (5 ml) at −20 °C under argon. After 30 min, the temperature was lowered to −78 °C, a solution of ketone **8** (356 mg, 2 mmol) in anhydrous THF (3 ml) was added, and then stirring was continued at 0 °C for 30 min. The solution was cooled again to −78 °C, and HMPA (204 µl, 2.4 mmol) was added, followed by methyl cyanoformate (204 mg, 2.4 mmol). After 1.5 h at 0 °C, the mixture was poured into cold water (15 ml), and the product was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue using 30% chloroform in hexanes as the eluent gave 303 mg (64%) of **9** as a yellowish solid. This product proved to be stable only if stored in the freezer: mp 72–73 °C (hexanes); R_f = 0.51 (30% chloroform in hexanes); ν_{max}(KBr)/cm^{-1} 2955, 1645, 1585, 1471, 1246; δ_H($CDCl_3$) 12.32 (s, 1 H), 8.74 (s, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 2.93 (app. t, 2 H, *J* 6.5), 2.65 (app. t, 2 H, *J* 7.4); δ_C($CDCl_3$) 29.0, 29.6, 52.0, 54.6, 95.9, 118.9, 154.1, 162.8, 164.8, 171.4, 176.6 (Calc. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.03; H, 5.21; N, 11.83%).

(±)-7,8,9,10-Tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[*d*]pyrimidine-5(6*H*)-carboxylic acid methyl ester 10

Palladium diacetate (51.2 mg, 0.21 mmol) and triphenylphosphine (239 mg, 0.91 mmol) were stirred at room temp. in dry dioxane (23 ml) under argon for 30 min. A solution of the β-keto ester **9** (1.08 g, 4.56 mmol), DBU (0.95 ml, 6.43 mmol), and 2-methylenepropane-1,3-diol diacetate (0.73 ml, 4.56 mmol) in dry dioxane (7.7 ml) was then added dropwise to the palladium complex over a period of 10 min. After stirring for 20 min at room temp. a solution of DBU (0.48 ml, 3.24 mmol) in dry dioxane (3 ml) was added dropwise. After an additional 20 min, the mixture was refluxed for 3.5 h. Concentration and flash chromatography of the residue using 20% ethyl acetate in hexanes as the eluent gave 1.0 g (76%) of the methylene-bridged adduct **10** as a colourless oil: R_f = 0.39 (20% ethyl acetate in hexanes); ν_{max}(neat)/cm^{-1} 2955, 1747, 1739, 1589, 1257, 734; δ_H($CDCl_3$) 8.00 (s, 1 H), 4.91 (m, 1 H), 4.58 (m, 1 H), 3.99 (s, 3 H), 3.84 (s, 3 H), 3.41 (dd, 1 H, *J* 19.0, 6.7), 3.25 (d, 1

H, *J* 14.8), 3.13 (d, 1 H, *J* 18.9), 3.00 (t, 1 H, *J* 5.9), 2.80 (m, 1 H), 2.58 (m, 2 H); $\delta_C(CDCl_3)$ 40.2, 43.7, 45.0, 48.1, 52.9, 54.9, 60.3, 117.7, 124.1, 137.9, 158.2, 164.6, 165.1, 170.1, 206.4; *m/z* 288 (65%, M^+), 256 (100%), 229, 201, 185, 161 (Calc. for $C_{15}H_{16}N_{20}O_4$ *M*, 288.1106. Found *M* 288.1109. Anal. calc. for $C_{15}H_{16}N_2O_4$: C, 62.48; H, 5.60; N, 9.72. Found: C, 62.52; H, 5.62; N, 9.78%).

(±)-9,10-Dihydro-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*d*]pyrimidine-5(6*H*)-carboxylic acid methyl ester 11

The β-keto ester **9** (500 mg, 2.11 mmol) was stirred with methacrolein (0.35 ml, 4.22 mmol) and 1,1,3,3-tetramethylguanidine (26 μl, 0.211 mmol) in dry CH_2Cl_2 at room temp. for 48 h. Concentration and flash chromatography of the residue using 30% ethyl acetate in hexanes as the eluent gave 588 mg of the bridged alcohol as mixture of isomers. This mixture was used in the next step without further purification: R_f = 0.23–0.42 (30% ethyl acetate in hexanes); *m/z* 306 (88%, M^+), 274, 236, 219, 189 (100%), 161.

Mesyl chloride (163 μl, 2.11 mmol) was added dropwise to a mixture of the alcohols (540 mg, 1.76 mmol) prepared as described above, triethylamine (320 μl, 2.28 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (6.5 mg, 0.053 mmol) in dry CH_2Cl_2 (7.7 ml) at room temp. The solution was stirred at room temp. for 3 h, diluted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. Flash chromatography using 25% hexanes in ethyl acetate as eluent gave 620 mg (91%) of the desired mesylate as a mixture of isomers: *m/z* 384 (9%, M^+), 325, 305, 260, 218, 201 (100%), 175.

The mixture of mesylates (250 mg, 0.65 mmol) was heated with 2,4,6-trimethylpyridine (2.5 ml) at reflux for 24 h under argon. After cooling, the solution was decanted from the tarry precipitate, and the solvent was removed under vacuum. Both the precipitate and the distillation residue were taken up in 10% methanol in dichloromethane. The organic solution was washed with 5 ml of 5% H_3PO_4, then with brine, and finally with a saturated aqueous $NaHCO_3$. After evaporation, the residue was purified by flash chromatography using 25% ethyl acetate in toluene as the eluent to afford 15 mg (8%) of **11** as a pale yellow oil: R_f = 0.54 (25% ethyl acetate in toluene); $\delta_H(CDCl_3)$ 8.11 (s, 1 H), 5.43–5.42 (m, 1 H), 4.00 (s, 3 H), 3.79 (s, 3 H), 3.50 (d, 1 H, *J* 18.2), 3.38 (dd, 1 H, *J* 17.8 and 4.9), 3.29 (dd, 1 H, *J* 17.7 and 1.8), 3.19 (m, 1 H), 2.52 (d, 1 H, *J* 17.4), 1.63 (s, 3 H); *m/z* 288 (32%, M^+), 256, 229, 201 (100%), 185.

Preparation of the benzene analogue 15a

This compound was prepared starting from **14** by methods analogous to those used to prepare the β-keto ester **10**. Flash chromatography was performed using 20% EtOAc in hexanes as eluent, and **15a** was obtained in 89% yield as colourless prisms: mp 105–106 °C (2% EtOAc in hexanes); R_f = 0.36 (20% EtOAc in hexanes); $\nu_{max}(KBr)/cm^{-1}$ 1740, 1720, 1590, 735; $\delta_H(CDCl_3)$ 7.50–7.05 (m, 3 H), 6.93–6.72 (m, 1 H), 4.73 (m, 1 H), 4.41 (m, 1 H), 3.81 (s, 3 H), 3.50 (dd, 1 H, *J* 17.4 and 6.4), 3.17 (dd, 1 H, *J* 8.8 and 1.2), 3.09 (d, 1 H, *J* 17.3), 2.92 (t, 1 H, *J* 5.3), 2.80 (m, 1 H), 2.68 (dd, 1 H, *J* 13.7 and 2.9), 2.55 (dt, 1 H, *J* 13.9 and 2.4 Hz); $\delta_C(CDCl_3)$ 37.9, 43.9, 45.7, 48.6, 52.4, 63.7, 115.3, 126.7, 126.9, 127.3, 127.5, 133.8, 137.3, 139.4, 171.8, 209.2 (Calc. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.98. Found: C, 74.72; H, 7.08%).

Preparation of 17a

To a solution of LDA (0.75 mol l^{-1} in 1:1 hexanes and THF, 1.07 ml, 0.79 mmol) cooled to −78 °C was slowly added a solution of *S*-phenyl propanethioate (130 mg, 0.78 mmol) in anhydrous THF (0.5 ml). After 30 min, a solution of the β-keto ester **15a** (200 mg, 0.78 mmol) in anhydrous THF (0.5 ml) was added over a period of 30 min. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to 0 °C over 2 h. A half-saturated NH_4Cl solution (5 ml) was added, and the resulting mixture was partitioned between water and EtOAc. The organic layer was washed with a 10% aqueous K_2CO_3 and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give the β-lactone **16a** (152 mg, 62% yield) as a colourless oil which was used in the next step without further purification; R_f = 0.24 (5% EtOAc in chloroform); $\nu_{max}(KBr)/cm^{-1}$ 1805, 1740; $\delta_H(CDCl_3)$ 7.20–7.03 (m, 3 H), 6.70 (m, 1 H), 4.58 (m, 1 H), 4.39 (q, 1 H, *J* 7.6), 4.26 (m, 1 H), 3.74 (s, 3 H), 3.21 (d 1 H, *J* 17.2, 6.3), 3.08 (m, 2 H), 2.76 (d, 1 H, *J* 17.0), 2.60 (m, 1 H) 2.36 (d, 1 H, *J* 1.7), 2.12 (dt, 1 H, *J* 13.4 and 2.1), 1.26 (d, 3 H, *J* 7.5).

A mixture of β-lactone **16a** (53 mg, 0.17 mmol), 230–400 mesh silica gel (100 mg), and anhydrous xylene (6 ml) was refluxed for 10 h under argon and then allowed to cool to room temp. The solvent was removed, and the residue was purified by flash chromatography (10% EtOAc in hexanes) to give the (*E*)-olefin **17a** (41 mg, 91% yield) as a white solid: mp 81–82 °C (hexanes); R_f = 0.42 (5% EtOAc in hexanes); $\nu_{max}(KBr)/cm^{-1}$ 1755, 1599, 760; $\delta_H(CDCl_3)$ 7.28–7.05 (m, 3 H), 6.80 (m, 1 H), 5.22 (q, 1 H, *J* 6.8), 4.55 (m, 1 H) 4.25 (m, 1 H), 3.81 (s, 3 H), 3.36 (m, 1 H), 3.20 (dd, 1 H, *J* 16.9 and 6.4), 2.87 (d, 1 H, *J* 14.2), 2.59 (d, 1 H, *J* 17.1), 2.48 (d, 1 H, *J* 12.9), 2.40 (m, 2 H), 1.73 (d, 3 H, *J* 6.9); $\delta_C(CDCl_3)$ 12.7, 31.9, 36.7, 43.0, 49.0, 51.9, 57.8, 112.2, 115.5, 125.9, 126.3, 126.5, 127.9, 135.6, 138.7, 139.3, 143.0, 175.7 (Calc. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.93; H, 7.39%).

3-Methyloxetan-2-one derivative 16b

To a solution of diisopropylamine (0.1 ml, 0.76 mmol) in anhydrous THF (3 ml) cooled to 0 °C was added BuLi (2.5 mol l^{-1} in hexanes, 0.28 ml, 0.72 mmol) over 5 min under argon. After 15 min, the ice bath was replaced with dry ice–acetone bath (−78 °C), and a solution of *S*-phenyl propanethioate (116 mg, 0.7 mmol) in anhydrous THF (0.3 ml) was added. After 30 min, a solution of the β-keto ester **15b** (200 mg, 0.7 mmol) in anhydrous THF (0.5 ml) was added over a period of 30 min. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to room temp. over 2 h. A half-saturated NH_4Cl solution (5 ml) was added, and the resulting mixture was partitioned between water and EtOAc. The organic layer was washed with a 10% aqueous K_2CO_3, and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10% EtOAc in chloroform) to give **16b** (192 mg, 81% yield) as colourless prisms: mp 172–173 °C (EtOAc and hexanes); R_f = 0.44 (10% EtOAc in chloroform); $\nu_{max}(KBr)/cm^{-1}$ 2850, 1815, 1739; $\delta_H(CDCl_3)$ 7.07 (d, 1 H, *J* 8.8), 6.53 (d, 1 H, *J* 8.7), 4.69 (m, 1 H), 4.37 (m, 1 H), 4.26 (q, 1 H, *J* 7.8), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.25 (m, 2 H), 2.82 (d, 1 H, *J* 19.0), 2.75 (m, 2 H), 2.32 (dd, 1 H, *J* 13.5 and 1.7), 2.21 (dt, 1 H, *J* 11.2 and 1.7), 1.34 (d, 3 H, *J* 7.7); $\delta_C(CDCl_3)$ 9.3, 34.7, 37.0, 38.3, 42.2, 49.5, 52.9, 53.4, 55.4, 81.6, 108.9, 113.5, 123.2, 138.2, 140.0, 151.9, 162.7, 171.2, 172.6 (Calc. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.63; H, 5.89; N, 4.16%).

(11*E*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[b]pyridine-5(6*H*)-carboxylic acid methyl ester 17b

A mixture of β-lactone **16b** (100 mg, 0.29 mmol), 230–400 mesh silica gel (150 mg), and anhydrous toluene (6 ml) was refluxed for 45 h under argon and then allowed to cool to room temp. The solvent was removed, and the residue was purified by flash chromatography (30% EtOAc in toluene) to give the olefin **17b** (76 mg, 88% yield) as a white solid whose spectroscopic data were identical to those reported previously:[15] $\delta_H(CDCl_3)$ 6.95 (d, 1 H, *J* 8.4), 6.48 (d, 1 H, *J* 8.4), 5.18 (q, 1 H, *J* 6.7), 4.63 (m, 1 H), 4.30 (m, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.40 (m, 1 H), 3.14 (dd, 1 H, *J* 17.8 and 6.6), 2.87 (d, 1 H, *J* 12.6), 2.78 (d, 1 H, *J* 17.8), 2.39 (m, 3 H), 1.73 (d, 3 H, *J* 6.7).

3-Methyloxetan-2-one derivative 18

To a solution of diisopropylamine (0.29 ml, 2.1 mmol) in anhydrous THF (9 ml) cooled to 0 °C was added BuLi (1.6 mol l^{-1} in hexanes, 1.18 ml, 1.97 mmol) over 5 min under argon. After 15 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and a solution of *S*-phenyl propanethioate (320 mg, 1.91 mmol) in anhydrous THF (1.5 ml) was added. After 30 min, a solution of the β-keto ester **10** (550 mg, 1.91 mmol) in anhydrous THF (2.2 ml) was added over a period of 30 min. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to room temp. over 2 h. A half-saturated NH_4Cl solution (10 ml) was added, and the resulting mixture was partitioned between water and EtOAc. The organic layer was washed with 10% aqueous K_2CO_3 and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 10% EtOAc in chloroform as the eluent to give **18** (545 mg, 84% yield) as colourless prisms: mp 153–154 °C (EtOAc and hexanes); R_f = 0.23 (10% EtOAc in chloroform); ν_{max}(KBr)/cm^{-1} 2860, 1815, 1740; δ_H($CDCl_3$) 8.11 (s, 1 H), 4.77 (m, 1 H), 4.45 (m, 1 H), 4.16 (q, 1 H, *J* 7.7), 3.98 (s, 3 H), 3.88 (s, 3 H), 3.31 (d, 1 H, *J* 13.2), 3.15 (m, 1 H), 2.70 (m, 3 H), 2.35 (dd, 1 H, *J* 13.7 and 1.6), 2.22 (d, 1 H, *J* 13.0), 1.32 (d, 3 H, *J* 7.6); δ_C($CDCl_3$) 9.2, 34.2, 36.8, 38.1, 42.5, 49.6, 53.2, 53.6, 54.9, 80.7, 114.9, 122.7, 139.0, 158.7, 164.3, 165.9, 170.4, 171.5 (Calc. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.89; H, 5.88; N, 8.21%).

(11*E*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*d*]pyrimidine-5(6*H*)-carboxylic acid methyl ester 19

A mixture of the β-lactone **18** (260 mg, 0.75 mmol), 230–400 mesh silica gel (300 mg), and anhydrous toluene (12 ml) was refluxed for 40 h under argon and then allowed to cool to room temp. The solvent was removed, and the residue was purified by flash chromatography (30% EtOAc in toluene) to give the olefin **19** (150 mg, 67% yield) as a white solid: mp 154–156 °C (10% chloroform in hexanes); R_f = 0.46 (30% EtOAc in toluene); ν_{max}(KBr)/cm^{-1} 1750, 1600, 1480, 770; δ_H($CDCl_3$) 7.93 (s, 1 H), 5.21 (q, 1 H, *J* 6.7), 4.70 (m, 1 H), 4.36 (m, 1 H), 3.95 (s, 3 H), 3.83 (s, 3 H), 3.42 (m, 1 H), 3.06 (dd, 1 H, *J* 19.0 and 6.6), 2.94 (d, 1 H, *J* 12.7), 2.81 (d, 1 H, *J* 18.8), 2.39 (m, 3 H), 1.73 (d, 3 H, *J* 6.7); δ_C($CDCl_3$) 12.9, 31.2, 39.2, 42.8, 48.5, 52.3, 54.7, 114.5, 117.1, 126.1, 137.4, 141.2, 157.0, 163.9, 167.5, 174.0; *m*/*z* 300 (60%, M^+), 257, 241 (100%), 213, 173 (Calc. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.02; H, 6.83; N, 9.38%).

(11*E*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*d*]pyrimidine-5(6*H*)-carboxylic acid 20

Ester **19** (335 mg, 1.11 mmol) was dissolved in 5.2 ml of methanol–THF 2:1, and 2 mol l^{-1} NaOH (2.22 ml) was added. The mixture was heated at 70 °C under argon for 24 h. After cooling, the solution was adjusted to pH 5–6 with 5% aqueous HCl, and the methanol and THF were evaporated. The aqueous residue was extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography using ethyl acetate as eluent to give 210 mg (66%) of the acid **20** as colourless prisms: mp 217–218 °C (ethyl acetate and hexanes); R_f = 0.26 (ethyl acetate); ν_{max}(KBr)/cm^{-1} 2941, 1694, 1599, 1440, 737; δ_H($CDCl_3$) 8.19 (s, 1 H), 5.53 (q, 1 H, *J* 6.6), 4.72 (m, 1 H), 4.40 (m, 1 H), 3.97 (s, 3 H), 3.45 (m, 1 H), 3.12 (dd, 1 H, *J* 18.8 and 6.7), 2.97 (d, 1 H, *J* 13.0), 2.84 (d, 1 H, *J* 18.8), 2.45 (m, 3 H), 1.76 (d, 3 H, *J* 6.8); δ_C($CDCl_3$) 12.6, 31.2, 39.2, 42.9, 49.1, 54.1, 55.2, 112.7, 116.4, 128.3, 137.8, 143.2, 158.2, 163.1, 167.0, 179.2; *m*/*z* 286 (11%, M^+), 241, 149, 84 (100%) (Calc. for $C_{16}H_{18}N_2O_3$: C, 67.10; H, 6.34; N, 9.78. Found: C, 67.43; H, 6.52; N, 9.66%).

(11*E*)-(±)-(11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocyclo-octa[*d*]pyrimidin-5(6*H*)-yl)-carbamic acid methyl ester 21

A mixture of acid **20** (220 mg, 0.768 mmol), dry triethylamine (106.3 μl, 0.768 mmol), diphenyl azidophosphate (163.3 μl, 0.768 mmol), and dry toluene (3.2 ml) was heated at 85 °C for 3.5 h. After cooling, the solvent was removed by rotary evaporation, and the residue was dissolved in dry methanol (3.2 ml). The resulting solution was heated under reflux for 18 h. Evaporation and silica gel flash chromatography using 30% dichloromethane in ethyl acetate as the eluent gave the urethane **21** (217 mg, 90%) as a colourless solid: mp 181–182 °C (hexanes and ethyl acetate); R_f = 0.51 (ethyl acetate); ν_{max}(KBr)/cm^{-1} 3340, 1725, 1600, 1395, 750; δ_H($CDCl_3$) 8.30 (s, 1 H), 5.50 (q, 1 H, *J* 6.8), 5.01 (s, NH), 4.74 (m, 1 H), 4.39 (m, 1 H), 3.95 (s, 3 H), 3.65 (s, 3 H), 3.44 (m, 1 H), 3.10 (dd, 1 H, *J* 18.6 and 6.5), 2.77 (d, 1 H, *J* 18.7), 2.57 (d, 1 H, *J* 10.8), 2.36 (m, 3 H), 1.75 (d, 3 H, *J* 6.8); δ_C($CDCl_3$) 12.5, 31.1, 38.7, 42.8, 52.1, 52.5, 54.4, 58.9, 114.4, 115.0, 127.4, 136.4, 140.7, 154.6, 154.9, 163.9, 167.5; *m*/*z* 315 (100%, M^+), 300, 272, 260, 225, 186 (Calc. for $C_{17}H_{21}N_3O_3$: C, 64.73; H, 6.71; N, 13.32. Found: C, 64.51; H, 6.55; N, 13.27%).

(11*E*)-(±)-5-Amino-11-ethylidene-5,6,7,8,9,10-hexahydro-7-methylene-5,9-methanocycloocta[*d*]pyrimidin-2(1*H*)-one 22

To a solution of the carbamate **21** (135 mg, 0.43 mmol) in dry HMPA (0.8 ml) was added lithium propylmercaptide in HMPA (1.79 ml, 5.54 mmol) at room temp. under argon. The resulting mixture was heated at 90 °C for 6 h. After cooling, the mixture was treated at 0 °C with water and then extracted with 5% methanol in ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography using 15% methanol in chloroform as the eluent to afford **22** (97 mg) in 92% yield as colourless prisms: mp 240 °C (d) (ethyl acetate); R_f = 0.41 (18% methanol in chloroform); ν_{max}(KBr)/cm^{-1} 3400–3300, 1650, 1390, 1215, 740; δ_H(D_2O) 8.31 (s, 1 H), 5.74 (q, 1 H, *J* 6.8), 4.88 (m, 1 H), 4.60 (m, 1 H), 3.57 (m, 1 H), 3.04 (dd, 1 H, *J* 19.6 and 6.9), 2.76 (d, 1 H, *J* 19.4), 2.41 (m, 4 H), 1.78 (d, 3 H, *J* 6.8); δ_C(CD_3OD) 12.7 (CH_3), 31.4 (CH), 38.4 (CH_2), 42.7 (CH_2), 53.2 (CH_2), 56.0 (C), 114.8 (CH_2), 115.9 (CH), 123.9 (C), 140.7 (C), 143.7 (C), 151.2 (br, CH), 158.7 (C), 171.5 (br, C); *m*/*z* 243 (80%, M^+), 228 (100%), 214, 202, 188, 162 (Calc. for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.05; N, 17.28. Found: C, 68.74; H, 7.10; N, 16.93%).

(11*E*)-(±)-5-Amino-11-ethylidene-5,6,9,10- tetrahydro-7-methyl-5,9-methanocycloocta[*d*]pyrimidin-2(1*H*)-one 23

Iodotrimethylsilane (125.6 μl, 0.88 mmol) was added to a solution of the carbamate **21** (70 mg, 0.22 mmol) in dry chloroform (7 ml) under argon at room temp., and the solution was refluxed for 5.5 h. After cooling and evaporation, the residue was dissolved in methanol (7 ml) and the solution was refluxed for 18 h. The solvent was removed by rotary evaporation, the residue was dissolved in dry dioxane (2.5 ml), and trifluoromethanesulfonic acid (44 μl, 0.44 mmol) was added. The solution was heated at 92 °C for 24 h. Evaporation of the solvent afforded a residue which was partitioned between a 10% aqueous $NaHCO_3$ and 10% methanol in chloroform. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (15% methanol in chloroform) gave 46 mg (87%) of pyrimidone **23** as a white solid: mp 203 °C (d) (ethyl acetate); ν_{max}(KBr)/cm^{-1} 3420–3340, 1645, 737; δ_H(D_2O) 8.49 (s, 1 H), 5.62 (q, 1 H, *J* 6.8), 5.55 (m, 1 H), 3.75 (m, 1 H), 2.95 (dd, 1 H, *J* 18.4 and 4.9), 2.79 (dd, 1 H, *J* 17.8 and 1.4), 2.41 (ABq, 2 H, *J* 17.3), 1.70 (d, 3 H, *J* 6.7), 1.55 (s, 3 H); δ_C(CD_3OD) 12.6 (CH_3), 22.6 (CH_3), 33.9 (CH), 39.6 (CH_2), 51.1 (CH_2), 54.7 (C), 114.0 (CH), 124.4 (C), 125.7 (CH), 135.0 (C), 141.6 (C), 154.9 (br, CH), 158.9 (C), 169.0 (br, C);

m/z 243 (100%, M^+), 228, 214, 200, 188, 174 (Calc. for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.05; N, 17.28. Found: C, 69.23; H, 7.12; N, 17.43%).

Preparation of pyrimidone 23 from 22

A mixture of pyrimidinone **22** (29 mg, 0.119 mmol), trifluoromethanesulfonic acid (24 μl, 0.23 mmol), and dry dioxane (0.5 ml) was heated at 93 °C in a resealable tube under argon for 24 h. The solvent was removed, and the residue was partitioned between aqueous $NaHCO_3$ and 10% methanol in ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and filtered. Concentration and flash chromatography (15% methanol in chloroform) gave **23** (25 mg) in 86% yield. Spectral data are as given above.

(9*E*)-(±)-[6-(Benzoyloxymethylene)-3-methyl-7-oxobicyclo[3.3.1]non-3-en-1-yl]carbamic acid methyl esters 24 and 25

To a slurry of the hydroxymethylene derivative **2** (46 mg, 0.166 mmol) and K_2CO_3 (23 mg, 0.166 mmol) in dry dichloromethane (0.8 ml) was added benzoyl chloride (19 μl, 0.166 mmol) within 30 min. The resulting suspension was stirred at room temp. under argon for 24 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness under vacuum. Flash chromatography using 5% hexanes in chloroform as the eluent afforded 54 mg (85%) of the (*Z*)-benzoate ester **24** and 6 mg (9.5%) of the (*E*)-benzoate ester **25**.

24. mp 160–162 °C (5% ethyl acetate in hexanes); R_f = 0.29 (25% hexanes in chloroform); $\nu_{max}(CHCl_3)/cm^{-1}$ 3338, 1743, 1730, 1255, 1066, 707; $\delta_H(CDCl_3)$ 8.13 (m, 3 H), 7.67 (m, 1 H), 7.52 (m, 2 H), 5.45 (m, 2 H), 4.87 (s, NH), 4.74 (d, 1 H, *J* 5.5), 3.67 (s, 3 H), 3.25 (d, 1 H, *J* 18.2), 2.84 (d, 1 H, *J* 18.2), 2.48 (br s, 2 H), 1.79 (d, 3 H, *J* 6.7), 1.67 (s, 3 H); *m/z* 382 (15%, MH^+), 326, 307 (100%), 289, 257, 220 (Calc. for $C_{22}H_{24}NO_5$ M + H, 382.1648. Found MH^+, 382.1607. Calc. for $C_{22}H_{24}NO_5$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.42; H, 6.04; N, 3.60%).

25. mp 144–146 °C (5% ethyl acetate in hexanes); R_f = 0.33 (25% hexanes in chloroform); $\delta_H(CDCl_3)$ 8.17 (m, 1 H), 7.63–7.45 (m, 5 H), 5.47 (q, 1 H, *J* 6.8), 5.40 (m, 1 H), 4.79 (s, NH), 3.97 (d, 1 H, *J* 5.5), 3.67 (s, 3 H), 3.40 (d, 1 H, *J* 15.4), 2.76 (d, 1 H, *J* 17.4), 2.44 (br s, 2 H), 1.78 (d, 3 H, *J* 6.8), 1.66 (s, 3 H) (Calc. for $C_{22}H_{23}NO_5$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.05; H, 6.05; N, 3.62%).

(11*E*)-(±)-(11-Ethylidene-5,8,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*d*]pyrimidin-9-yl)carbamic acid methyl ester 26

To a stirred solution of the esters **24** and **25** (38 mg, 0.097 mmol) and Et_3N (16.8 μl, 0.12 mmol) in dry DMF (0.3 ml) was added *O*-methyl isourea hydrogen sulfate (21 mg, 0.12 mmol). The resulting mixture was heated at 80 °C under argon for 24 h after which time the reaction mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane, washed with 20% aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Concentration followed by flash chromatography (1:1:1 chloroform–ethyl acetate–hexanes) afforded 11 mg (37%) of pyrimidine **26** as colourless prisms: mp 184–185 °C (5% ethyl acetate in hexanes); R_f = 0.28 (1:1:1 chloroform–ethyl acetate–hexanes); $\nu_{max}(KBr)/cm^{-1}$ 3335, 1724, 1465, 1043, 731; $\delta_H(CDCl_3)$ 8.13 (s, 1 H), 5.47 (m, 1 H), 5.31 (q, 1 H, *J* 6.7), 4.96 (s, NH), 4.21 (d, 1 H, *J* 5.8), 3.93 (s, 3 H), 3.66 (s, 3 H), 3.52 (d, 1 H, *J* 19.0), 3.25 (d, 1 H, *J* 19.0), 2.52 (ABq, 2 H, *J* 16.6), 1.71 (d, 3 H, *J* 6.8), 1.61 (s, 3 H); $\delta_C(CDCl_3)$ 13.0, 22.5, 35.8, 47.2, 48.9, 51.9, 54.6, 55.4, 112.8, 125.2, 127.4, 132.0, 135.3, 154.3, 155.2, 164.1, 168.7; *m/z* 315 (85%, M^+), 300, 268, 253, 240 (100%), 225 (Calc. for $C_{17}H_{21}N_3O_3$ *M*, 315.1584. Found *M*, 315.1576. Calc. for $C_{17}H_{21}N_3O_3$: C, 64.73; H, 6.71; N, 13.33. Found: C, 64.51; H, 6.64; N, 13.08%).

(11*E*)-(±)-9-Amino-11-ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*d*]pyrimidin-2(1*H*)-one 27

Iodotrimethylsilane (93.3 μl, 0.65 mmol) was added to a solution of carbamate **26** (52 mg, 0.16 mmol) in dry chloroform (5.1 ml) at room temp., and the mixture was refluxed for 5.5 h under argon. After cooling and evaporation, the residue was dissolved in methanol (5.1 ml), and the solution was refluxed for 15 h under argon. The solvent was removed under vacuum, the residue was dissolved in dry dioxane (1 ml) and triflic acid (60 μl, 0.68 mmol) was added. The solution was heated at 84 °C for 11 h. The solvent was evaporated, and the crude product was partitioned between a 10% aqueous $NaHCO_3$ and ethyl acetate. Purification by flash chromatography using 15% methanol in chloroform as eluent gave 35 mg (90%) of pyrimidinone **27** as colourless prisms: mp 167 °C (decomp.); R_f = 0.33 (15% methanol in chloroform); $\nu_{max}(KBr)/cm^{-1}$ 3471–3390, 1645, 1087, 738; $\delta_H(D_2O)$ 8.04 (s, 1 H), 5.35 (q, 1 H, *J* 6.7), 5.15 (s, 1 H), 4.00 (m, 1 H), 2.65 (ABq, 2 H, *J* 17.6), 2.35 (app. d, 1 H, *J* 16.3), 1.85 (d, 1 H, *J* 17.3), 1.52 (d, 3 H, *J* 6.7), 1.35 (s, 3 H); $\delta_C(D_2O)$ 14.2, 24.2, 35.1, 43.0, 47.9, 55.4, 116.4, 122.6, 130.2, 138.0, 139.9, 159.1, 162.7, 169.2; *m/z* 243 (75%, M^+), 236, 228 (100%), 215, 200, 188 (Calc. for *M*, $C_{14}H_{17}N_3O$ 243.1373. Found *M*, 243.1365. Calc. for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.05; N, 17.28. Found: C, 69.21; H, 7.13; N, 17.36%).

(11*E*)-(±)-9-Amino-11-ethylidene-5,8,9,10-tetrahydro-7-methyl-5,9- methanocycloocta[*d*]pyrimidin-2(1*H*)-one 28

To a solution of carbamate **26** (64 mg, 0.204 mmol) in dry HMPA (0.5 ml) was added lithium propylmercaptide in HMPA (4.65 ml, 2.32 mmol, 0.5 mol l^{-1} solution) at room temp. under argon. The resulting mixture was heated at 90 °C for 6 h. After cooling to 0 °C, the mixture was treated with water and then extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 20% methanol in chloroform as the eluent to afford 40 mg (81%) of **28** as a white solid: mp 175 °C (decomp.); R_f = 0.46 (20% methanol in chloroform); $\nu_{max}(KBr)/cm^{-1}$ 3475–3380, 1642, 1599, 1083, 754; $\delta_H(D_2O)$ 7.74 (s, 1 H), 5.35 (m, 2 H), 4.10 (d, 1 H, *J* 5.8), 2.96 (d, 1 H, *J* 19.5), 2.62 (d, 1 H, *J* 19.5), 2.13 (ABq, 2 H, *J* 17.5), 1.49 (d, 3 H, *J* 6.7), 1.38 (s, 3 H); $\delta_C(D_2O)$ 14.6, 24.0, 37.1, 49.3 (br), 51.1, 54.8, 116.5, 123.7, 127.8, 136.2, 140.9, 151.4, 162.5, 174.7 (Calc. for $C_{14}H_{17}N_3O$ *M*, 243.1373. Found *M*, 243.1380. Calc. for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.05; N, 17.28. Found: C, 69.33; H, 7.19; N, 17.40%).

(10*E*)-(±)-(10-Ethylidene-1,4,7,9-tetrahydro-6-methyl-4,8-methanocycloocta[*c*]pyrazol-8-yl)carbamic acid methyl ester 29

To a solution of the hydroxymethylene derivative **2** (90 mg, 0.325 mmol) in ethanol (0.32 ml) was slowly added $N_2H_4 \cdot H_2O$ (16 μl, 0.325 mmol), and the mixture was stirred at room temp. for 1 h. The solvent was removed, and the residue was purified by flash chromatography (1:1:1 chloroform–ethyl acetate–hexanes) to afford the pyrazole **29** in 85% yield (75 mg) as colourless crystals: mp 129–131 °C (from hexanes and ethyl acetate); R_f = 0.31 (1:1:1 chloroform–ethyl acetate–hexanes); $\nu_{max}(KBr)/cm^{-1}$ 3338, 1714, 1518, 731; $\delta_H(CDCl_3)$ 7.24 (s, 1 H), 5.65 (m, 1 H), 5.27 (q, 1 H, *J* 6.7), 5.11 (s, carbamate NH), 4.26 (d, 1 H, *J* 6.3), 3.69 (s, 3 H), 3.37 (d, 1 H, *J* 15.7), 3.13 (d, 1 H, *J* 15.8), 2.63 (ABq, 2 H, *J* 17.7), 1.71 (d, 3 H, *J* 6.7), 1.57 (s, 3 H); $\delta_C(CDCl_3)$ 13.2, 22.4, 31.2, 40.1, 47.6, 51.9, 58.4, 111.4, 121.4, 126.4, 127 (br), 132.6, 138.1, 143.4 (br), 155.6 (br); *m/z* 273 (8%, M^+), 226, 198 (100%), 183, 156 (Calc. for $C_{15}H_{19}N_3O_2$ *M*, 273.1478. Found *M*, 273.1469. Calc. for $C_{15}H_{19}N_3O_2$: C, 65.90; H, 7.01; N, 15.38. Found: C, 66.21; H, 7.13; N, 15.43%).

(10*E*)-(±)-8-Amino-10-ethylidene-4,7,8,9-tetrahydro-6-methyl-1*H*-4,8-methanocycloocta[*c*]pyrazole 30

To a solution of carbamate **29** (21 mg, 0.076 mmol) in dry

HMPA (0.5 ml) was added lithium propylmercaptide in HMPA (0.8 ml, 0.4 mmol, 0.5 mol l^{-1} solution) at room temp. under argon. The resulting mixture was stirred at room temp. under argon for 24 h. After cooling to 0 °C, the mixture was treated with water and then extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (22% methanol in chloroform) to afford **30** (15 mg) in 92% yield as a white solid: mp 118–120 °C (10% ethyl acetate in hexanes); R_f = 0.50 (22% methanol in chloroform); ν_{max}(KBr)/cm $^{-1}$ 3270, 3173, 1599, 1083, 754; δ_H($CDCl_3$) 7.24 (s, 1 H), 5.64 (m, 1 H), 5.51 (q, 1 H, *J* 6.7), 4.25 (d, 1 H, *J* 6.2), 3.14 (d, 1 H, *J* 16.5), 2.70 (dd, 1 H, *J* 16.5 and 1.7), 2.46 (d, 1 H, *J* 18.0), 2.15 (d, 1 H, *J* 18.1), 1.72 (d, 3 H, *J* 6.7), 1.54 (s, 3 H); δ_C($CDCl_3$) 13.0, 22.5, 31.5, 41.7, 50.6, 53.8, 111.1, 122.3, 126.5 (br), 127.1, 132.5, 144.1, 144.7 (br); *m*/*z* 215 (32%, M^+), 200 (100%), 183, 160, 133, 120 (Calc. for $C_{13}H_{17}N_3$: *M*, 215.1424. Found *M*, 215.1430. Calc. for $C_{13}H_{17}N_3$: C, 72.51; H, 7.96; N, 19.53. Found: C, 72.73; H, 8.14; N, 19.68%).

(10*E*)-(±)-8-Amino-10-ethylidene-4,5,8,9-tetrahydro-6-methyl-1*H*-4,8-methanocycloocta[*c*]pyrazole 31

Iodotrimethylsilane (53.3 μl, 0.37 mmol) was added to a solution of carbamate **29** (50 mg, 0.18 mmol) in dry chloroform (5.5 ml) at room temp. and the mixture was refluxed for 5.5 h under argon. After cooling and evaporation, the residue was dissolved in methanol (5.5 ml), and the solution was refluxed for 15 h under argon. The solvent was evaporated, and the crude product was partitioned between a 10% aqueous $NaHCO_3$, and ethyl acetate. Purification by flash chromatography using 15% methanol in chloroform as the eluent gave 35 mg (89%) of pyrazole analogue **31** as colourless prisms: mp 91–92 °C (from 5% ethyl acetate in hexanes); R_f = 0.63 (15% methanol in chloroform); ν_{max}(KBr)/cm^{-1} 3271, 3175, 1599, 1087, 738; δ_H(DMSO-d_6) 7.31 (s, 1 H), 5.49 (q, 1 H, *J* 6.7), 5.20 (s, 1 H), 4.01 (d, 1 H, *J* 3.6), 2.68 (d, 1 H, *J* 15.3), 2.36 (d, 1 H, *J* 15.3), 2.27 (d, 1 H, *J* 14.0), 1.84 (d, 1 H, *J* 16.6), 1.62 (d, 3 H, *J* 6.7), 1.46 (s, 3 H); δ_C(DMSO-d_6) 12.2, 22.6, 29.2, 40.7, 54.1, 110.6, 119.6, 131.6, 132.1, 143.7; *m*/*z* 215 (100%, M^+), 200, 183, 159, 133 (Calc. for $C_{13}H_{17}N_3$ *M*, 215.1424. Found *M*, 215.1439. Calc. for $C_{13}H_{17}N_3$: C, 72.51; H, 7.96; N, 19.53. Found: C, 72.59; H, 8.03; N, 19.50%).

Determination of AChE inhibitory activity

For experimental details of the inhibition of rat cortex AChE, see reference 15; for experimental details regarding the inhibition of FBS AChE, see references 25–27.

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