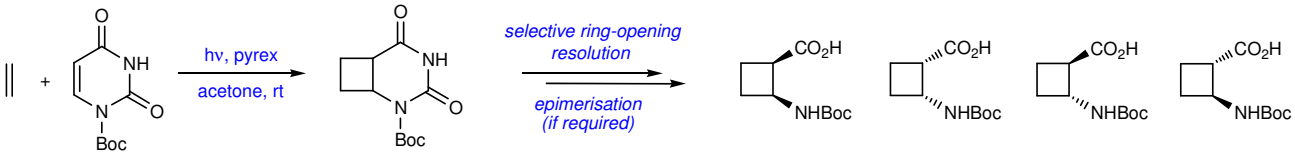
ORGANIC SYNTHESIS USING PHOTOCHEMISTRY

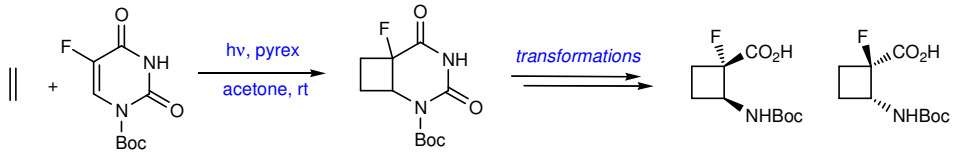
In the early 2000s, we began working on four-membered rings and in particular we were interested in the ability of small-ring β-amino acids to induce particular conformational preferences in peptides (see elsewhere for details of this programme). Six- and five-membered carbocyclic β-amino acids were already attracting considerable interest, yet the four-membered ring equivalents – derivatives of 2-aminocyclobutane-1-carboxylic acid (ACBC) – had not received the same attention, mainly due to the lack of convenient synthetic methods for the preparation of these molecular building blocks. Photochemical [2+2] cycloadditions involving nucleic bases were well known to biochemists, notably due to the deleterious effects that such reactions can have on DNA. However, organic chemists had not up to that point considered pyrimidinediones as photochemically-active enones having significant applications in preparative synthetic procedures. We therefore embarked on the objective of elaborating a photochemical strategy for the synthesis of the ACBC core structure, based on the [2+2] cycloaddition reaction of heterocyclic enones and simple alkenes.
This project has evolved progressively to consider other heterocyclic enone partners and to allow access to cyclobutane γ-amino acids too, and has also led us to examine other interesting examples of photochemical transformations of organic molecular architectures.
All of the reactions described in these pages are conducted on preparative scale, confirming that photochemistry is indeed a valuable addition to the synthetic chemist's toolbox.

PHOTOCHEMICAL SYNTHESIS OF CYCLOBUTANE β-AMINOACIDS

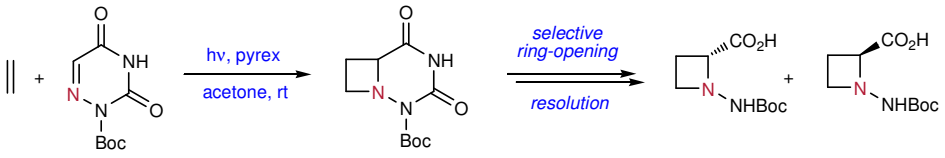
The core reaction in our early work was the facile [2+2] photocycloaddition reaction between uracil and ethylene. We used this reaction to provide a simple access to ACBC, the parent cyclobutane β-aminoacid. Over the last decade various means of controlling the stereochemistry have been examined and today this synthetic strategy represents the most convenient construction of any stereoisomer of this building block.
Amino Acids **2011**, *41*, 587, *J. Org. Chem.* **2009**, *74*, 3217, *Synthesis* **2007**, 2222, *Tetrahedron Lett.*, **2004**, *45*, 7095, *Tetrahedron Lett.* **2002**, *43*, 6177.



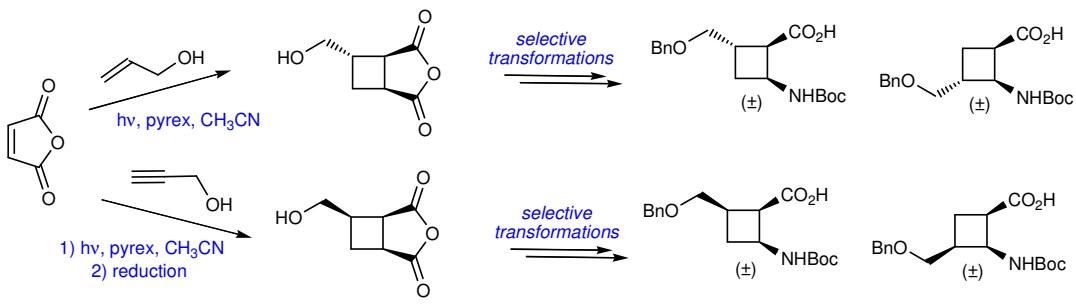
The reaction can be applied to a selection of 5- or 6-subsrituted uracils allowing the preparation of backbone-substituted ACBC derivatives. In a recent example, a *cis*- ACBC derivative with a fluorine on the Cα position was required; this material was prepared easily in enantiomerically pure form.
New J. Chem., **2015**, *39*, 3270, *Synlett* **2006**, 1394.



The photochemical reaction also proceeds with 6-azauracil, providing an entry to the previously unknown aza-analogue of ACBC. Again, both enantiomers can be obtained through chiral resolution.
J. Org. Chem. **2011**, *76*, 708.

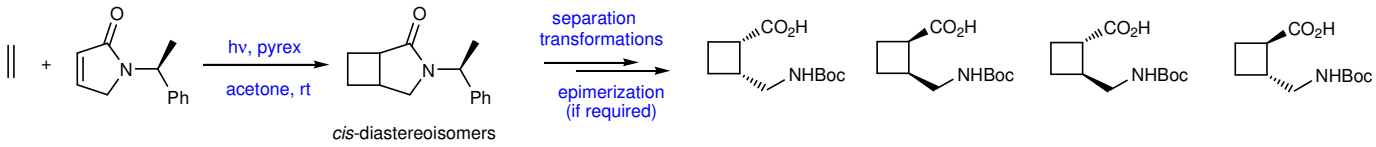


Maleic anhydride is a good partner for [2+2] photochemical cycloaddition reactions with non-symmetrical unsaturated hydrocarbons. In this strategy, the downstream selective transformations of the carboxylate motifs is the key for the controlled construction of the ACBC feature.
Org. Biomol. Chem. **2014**, *12*, 8212.

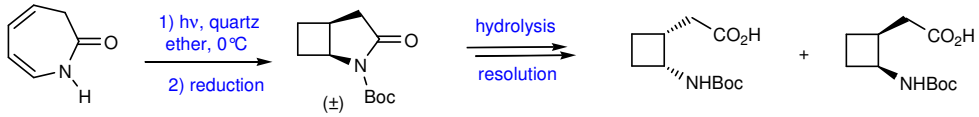


PHOTOCHEMICAL SYNTHESIS OF CYCLOBUTANE γ-AMINOACIDS

Conformationally-restricted analogues of the neurotransmitter γ-aminobutyric acid (GABA) are of considerable interest. In order to prepare a GABA analogue with a cyclobutane ring backbone restriction at Cα–Cβ, an unsaturated γ-lactam bearing a chiral appendage was engaged in a [2+2] photocycloaddition reaction with ethylene. All four stereoisomers of 2-(aminomethyl)cyclobutane-1-carboxylic acid were accessed via this route.
Tetrahedron, **2013**, *69*, 3571, *Tetrahedron Lett.,* **2011**, *52*, 1253.



To prepare a GABA analogue with a cyclobutane ring backbone restriction at Cβ–Cγ, a different photochemical approach was used: an azepin-2-one underwent an electrocyclization reaction to close the four-membered ring. After reduction, hydrolysis and resolution both enantiomers of *cis*-(2-aminocyclobutyl)acetic acid were obtained.
Eur. J. Org. Chem. **2014**, 7148.



OTHER PHOTOCHEMICAL STUDIES

In the course of the above noted studies, other unusual photochemical reactivities of heterocyclic molecules were encountered. These include the identification of new aryl-substituted uracil photodimers as well as the discovery of novel tandem photochemical transformations such as a [2+2]-cycloaddition/Norrish-1 cleavage process involving 5-acyl-uracils or a retro-[4+2]/[2+2] cycloaddition process observed for dihydropyridin-3-ones. These and the results of other studies can be found in a full list of publications on organic photochemistry provided below.

PUBLICATIONS from the Aitken group dealing with SYNTHETIC ORGANIC PHOTOCHEMISTRY

- *Conformational preferences in the β-peptide oligomers of cis-2-amino-1-fluorocyclobutane-1-carboxylic acid*. A. HASSOUN, C. M. GRISON, R. GUILLOT, T. BODDAERT, D. J. AITKEN, *New J. Chem.*, 2015, **39**, 3270-3279.
- *Practical syntheses of both enantiomers of the conformationally restricted GABA analogue cis-(2-aminocyclobutyl)acetic acid*. H. AWADA, S. ROBIN, R. GUILLOT, O. YAZBECK, D. NAOUFAL, N. JABER, A. HACHEM, D. J. AITKEN, *Eur. J. Org. Chem.*, 2014, 7148-7155.
- *Stereoselective intermolecular [2 + 2]-photocycloaddition reactions of maleic anhydride: stereocontrolled and regiocontrolled access to 1,2,3-trifunctionalized cyclobutanes*. F. HERNVANN, G. RASORE, V. DECLERCK, D. J. AITKEN, *Org. Biomol. Chem.*, 2014, **12**, 8212-8222.
- *Photochemical transformation of a 1,2-dihydropyridin-3-one: an original tandem retro-[4+ 2] / [2+2] cycloaddition process*. D. J. AITKEN, A FRONGIA, X. GAUCHER, J. OLLIVER, H. RAFIQUE, C. SAMBIAGIO, F. SECCI, *Tetrahedron Lett.*, 2013, **54**, 2825-2827.
- *Molecular structures of the photodimers of 5-phenyluracil and 6-phenyluracil*. A VIDAL, R. PAUGAM, S. FAURE, E. PEREIRA, D. J. AITKEN, *Tetrahedron Lett.*, 2013, **54**, 2536-2537.
- *A unified synthesis of all stereoisomers of 2-(aminomethyl)cyclobutane-1-carboxylic acid*. V. ANDRE, M. GRAS, H. AWADA, R. GUILLOT, S. ROBIN, D. J. AITKEN, *Tetrahedron*, 2013, **69**, 3571-3576.
- *Photochemical synthesis of four-membered ring amino acids*. D. J. AITKEN, *European Photochemistry Association Newsletter*, December 2012, 34-37.
- *Rapid access to cis-cyclobutane g-amino acids in enantiomerically pure form*. V. ANDRE, A. VIDAL, J. OLLIVIER, S. ROBIN, D. J. AITKEN, *Tetrahedron Lett.*, 2011, **52**, 1253-1255.
- *A refined synthesis of enantiomerically pure 2-aminocyclobutane carboxylic acids*. V. DECLERCK, D. J. AITKEN, *Amino Acids*, 2011, **41**, 587-595.
- *Endo-6-(Hydroxymethyl)bicyclo[3.2.0]hept-3-en-2-one esters and the photochemical challenge: [2+2] cycloaddition versus skeletal rearrangement*. M. LE LIEPVRE, J. OLLIVIER, D. J. AITKEN, *Tetrahedron: Asymmetry*, 2010, **21**, 1480-1485.
- *Expedient preparation of all isomers of 2-aminocyclobutane-1-carboxylic acid in enantiomerically pure form*. C. FERNANDES, E. PEREIRA, S. FAURE, D. J. AITKEN, *J. Org. Chem.*, 2009, **74**, 3217-3220.
- *Synthesis of functional bicyclo[3.2.0]heptanes: a study of the [2+2] photocycloaddition reactions of 4-hydroxycyclopent-2-enone derivatives*. M. LE LIEPVRE, J. OLLIVIER, D. J. AITKEN, *Eur. J. Org. Chem.*, 2009, 5953-5962.
- *Efficient synthesis of 3-hydroxymethylated cis- and trans-cyclobutane b-amino acids using an intramolecular photocycloaddition strategy*. A. MONDIÈRE, R. PENG, R. REMUSON, D. J. AITKEN, *Tetrahedron*, 2008, **64**, 1088-1093.
- *Photochemical behaviour of 5-formyl and 5-acetyl uracils in the presence of ethene*. E. PEREIRA, S. FAURE, D. J. AITKEN, *Tetrahedron Lett.*, 2008, **49**, 1968-1970.
- *Synthesis of (+)-coniceine via reductive photocyclization of dienamides: an entry to indolizidines*. T. HJELMGAARD, D. GARDETTE, D. TANNER, D. J. AITKEN, *Tetrahedron: Asymmetry*, 2007, **18**, 671-678.
- *[2+2] Photocycloadditions with chiral uracil derivatives: access to all four stereoisomers of 2-aminocyclobutanecarboxylic acid*. C. FERNANDES, C. GAUZY, Y. YANG, O. ROY, E. PEREIRA, S. FAURE, D. J. AITKEN, *Synthesis*, 2007, 2222-2232.
- *A solution to the component instability problem in the preparation of peptides containing C2-substituted cis-cyclobutane b-aminoacids: synthesis of a stable Rhodopeptin analogue*. O. ROY, S. FAURE, D. J. AITKEN, *Tetrahedron Lett.*, 2006, **47**, 5981-5984.
- *Synthesis of the constrained glutamate analogues (2S,1'R,2'R)- and (2S,1'S,2'S)-2-(2'-carboxy-cyclobutyl)glycines L-CBG-II and L-CBG-I by enzymatic transamination*. X. GU, M. XIAN, S. ROY-FAURE, J. BOLTE, D. J. AITKEN, T. GEFFLAUT, *Tetrahedron Lett.*, 2006, **47**, 193-196.
- *The [2+2] photocycloaddition of uracil derivatives with ethylene as a general route to cis-cyclobutane β-aminoacids* . C. GAUZY, B. SABY, E. PEREIRA, S. FAURE, D. J. AITKEN, *Synlett*, 2006, 1394-1398.
- *Synthesis of (+)-(1S,2R) and (–)-(1R,2S)-2-aminocyclobutane-1-carboxylic acids*. C. GAUZY, E. PEREIRA, S. FAURE, D. J. AITKEN, *Tetrahedron Lett.*, 2004, **45**, 7095-7097.
- *A short synthesis of the cis-cyclobutane b-aminoacid skeleton using a 2+2 cycloaddition strategy*. D. J. AITKEN, C. GAUZY, E. PEREIRA, *Tetrahedron Lett.*, 2002, **43**, 6177-6179.