ANTONI RIERA

Asymmetric synthesis

Our group focuses on the synthesis of biologically active compounds for the various stages of drug development. Several of our projects are devoted to the development of basic synthetic methodology, with a special focus on asymmetric synthesis, while others address the synthesis of compounds of known therapeutic interest, in which emphasis is placed on the reliability, efficiency and scalability of the processes. Finally, other projects underway are related to drug discovery; these aim to prepare chemical libraries for biological screening.

Basic synthetic methodologies

New developments in the Pauson-Khand reaction. The Pauson-Khand reaction (PKR) is one of the most powerful reactions for the preparation of cyclopentanic compounds. The PKR is a cobalt-promoted or catalysed cycloaddition between an alkene and an alkyne, with the insertion of a carbon monoxide molecule to give a cyclopentenone. One of our main targets is to use these cyclopentenones as starting materials for the synthesis of biologically active substances such as carbanucleosides, prostaglandins and phytoprostanes. On route to a new approach for the synthesis of prostaglandins, a few years ago we uncovered a novel photochemical rearrangement (Figure 1). After studying the scope of this new reaction in 2007, this year, in collaboration with Santiago Olivella, we have published a study of the detailed mechanism of this unprecedented reaction (Olivella *et al*, 2008; Figure 2).

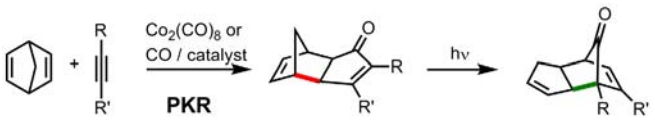


Figure 1. *Pauson-Khand reaction (PKR) and photochemical rearrangement of the PKR adducts.*

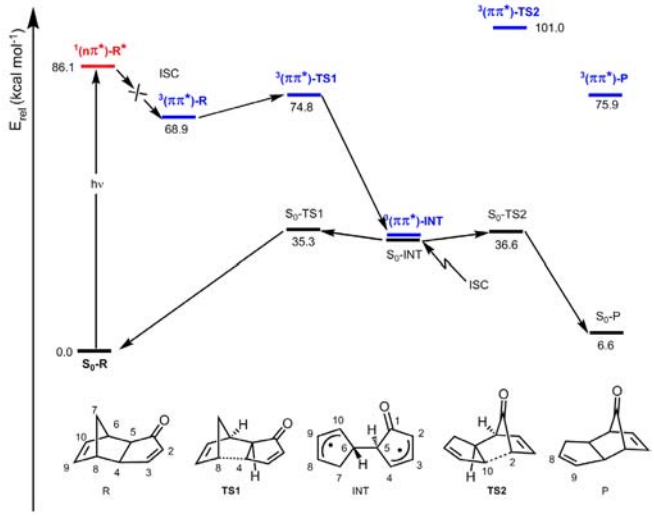
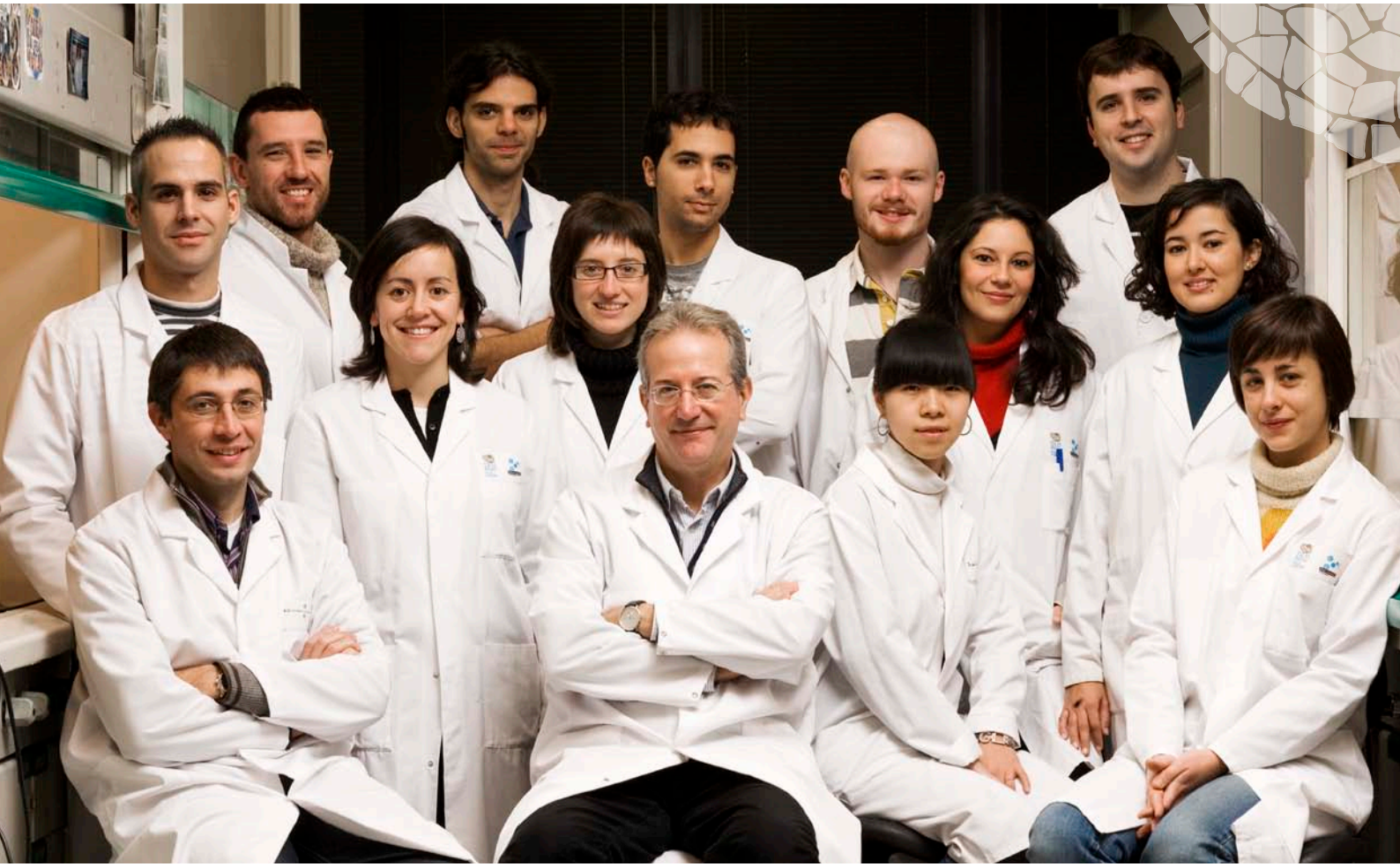


Figure 2. *Calculated mechanism of the photochemical rearrangement showing the relative energy of all intermediates and excited states along the reaction path.*

A new family of ligands for metal-catalysed reactions. To date, the best approach for an asymmetric version of the PKR is to use chiral ligands. In 2007 we designed an original family of hemilabile P,S-ligands with an unprecedented structure showing a backbone constituted by four linked heteroatoms (P-N-S-O). This year we have synthesised non-racemic *N*-phosphino-p-tolylsulfinamide ligands and studied their coordination behaviour towards dicobalthexacarbonyl complexes (Revés *et al*, 2008; Figure 3). We found that the presence of an aryl group on the sulfinamide reduces the hemilabile character of the sulfur-metal bond. Intermolecular PKR of the resulting complexes led to selectivities of up to 94% ee.

Applications of the new *N*-phosphinosulfinamide ligands to other metal-catalysed processes are now being studied in our lab. We have published the synthesis and the main structural features of several rhodium complexes of these ligands (Achard *et al*, 2009). The activity of these rhodium complexes towards cyclotrimerisation reactions is now being evaluated.

Principal Investigator Antoni Riera **Research Associate** Xavier Verdaguer **Postdoctoral Fellows** Thierry Achard, Cati Ferrer **PhD Students** Sean Doran, Yi Ning Ji, Pablo Antonio Martin, María Moreno, Rosario Ramon, Marc Revés, Ana María Vázquez **MSc Students** Thierry Leon, Albert Pesquer **Lab Technician** Ferran Santacana



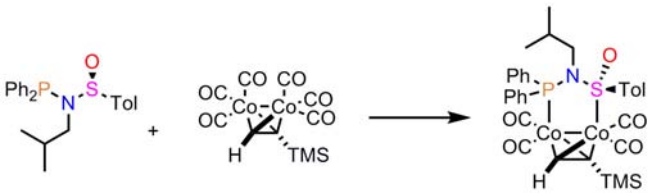


Figure 3. *Reaction of PNSO ligands with dicobalt complexes produces bridged-type complexes in which phosphorous (orange) and sulfur (magenta) are bonded to several cobalt atoms.*

Synthesis of biologically active compounds

Synthesis of five-membered-ring compounds. As mentioned, one of the best ways to prepare five-membered ring compounds is using the PKR. In 2007 we published an efficient enantioselective protocol for the preparation of cycloadduct 1 from trimethylsilylacetylene and norbornadiene. This year we have completed a new enantioselective approach for the synthesis of carbanucleosides starting from this useful Pauson-Khand adduct, thus showing its usefulness as a cyclopentenone synthon. Carbanucleosides are nucleosides in which the furanose ring has been substituted by a cyclopentane. Carbovir and Abacavir (Ziagen) are synthetic cyclopentanic carbanucleosides. They have shown major antiviral and anticancer activities. Due to its toxicity, Carbovir was not developed beyond the preclini-

cal phase; however, Abacavir was approved and launched for the treatment of HIV. In our synthetic approach, the PKR adduct was prepared in enantiomerically pure form using *N*-benzyl-*N*-diphenylphosphino-*tert*-butyl-sulfinamide as a chiral P,S ligand. From PKR adduct (−)-1, both (−)-Carbovir and (−) Abacavir were efficiently prepared in optically pure form (Vazquez *et al*, 2008; Figure 5).

In the field of phytoprostane and prostane synthesis, we have a fruitful collaboration with Paul Evans (Trinity College, Ireland). We have published a full paper in which we describe the use of the PKR adduct (+)-1 as starting material for the preparation of 5-alkylidenecyclopent-2-enones. This approach is exemplified by the short, stereoselective total syntheses of cyclopentenone phytoprostanes such as 13,14-dehydrophytoprostane J_1 (DPPJ1). We have also reported the capacity of this family of synthetic compounds to activate the peroxisome proliferator-activated receptor-γ (Figure 6).

Enantioselective synthesis of amino acids and alkaloids. The enantioselective synthesis of non-natural amino acids is attracting increasing interest due to the growing importance of modified peptides and drugs that contain fragments of amino acid derivatives. Cyclic α-amino acids are also present in many biologically relevant compounds. In particular, hydroxypipecolic acids can be considered as expanded hydroxylated homoprolines or as constrained serine derivatives.

(−)-*Cis*-4-hydroxypipecolic acid (−)-3 (Figure 7), isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*, has been identified as a constituent of cyclopeptide antibiotics such as virginiamycin S2. It has also been used as precursor in the preparation of selective *N*-methyl-D-aspartate (NMDA) receptor antagonists and in the synthesis of Palinavir, a potent peptidomimetic-based HIV protease inhibitor.

(−)-*Trans*-3-hydroxypipecolic acid (−)-2 is a non-natural cyclic β-hydroxy-α-amino acid that has been used as a precursor in the synthesis of (−)-swainsonine, a potent and specific inhibitor of α-D-mannosidase (Figure 7). We have described two new enantioselective entries to *cis*-4 and *trans*-3-hydroxypipecolic acids (−)-3 and (−)-2 with complete control of the stereochemistry of both stereogenic centres from enantiomerically enriched 2,3-epoxy-5-hexen-1-ol (−)-4 (Alegret *et al*, 2008). This useful epoxy alcohol is readily available in multigram scale by Sharpless asymmetric epoxidation.

The structural diversity and pharmacological activity associated with alkaloids found in amphibian skin have stimulated research into their synthesis. Many of these compounds have an indolizidine structure. For instance, alkylindolizidine alkaloids, isolated from the skin secretions of certain neotropical frogs of the *Dendrobatidae* family, have been demonstrated to non-competitively block neuromuscular transmission. We have shown the suitability of the same unsaturated epoxide used in the syntheses of pipecolic acids as starting material for a stereocontrolled synthesis of indolizidine alkaloid *trans*-209D. The key intermediate of this synthesis was enantiomerically pure *N*-Boc-baikiain (−)-5, the preparation of which was described by our group some years ago (Figure 7).

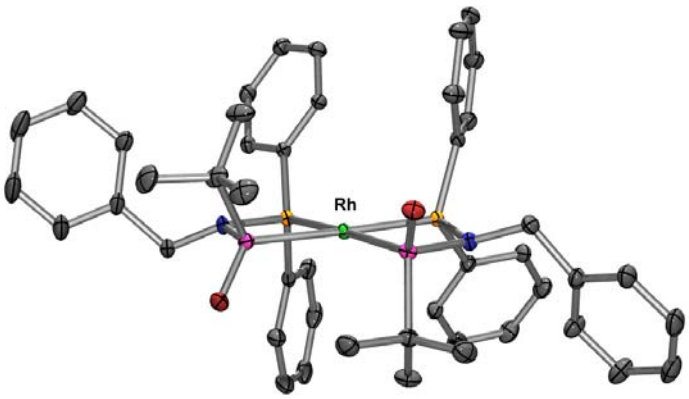


Figure 4. *Crystal structure of a Bis-PNSO-Rhodium complex. The Rhodium (green) centre is coordinated to phosphorous (yellow) and sulfur (magenta).*

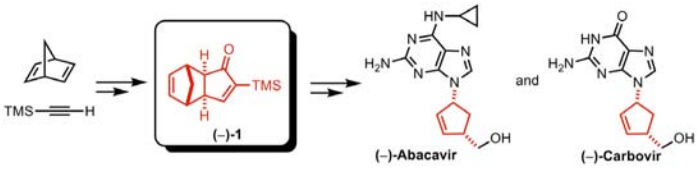


Figure 5. *Scheme of the enantioselective syntheses of Abacavir and Carbovir performed by our group at IRB Barcelona.*

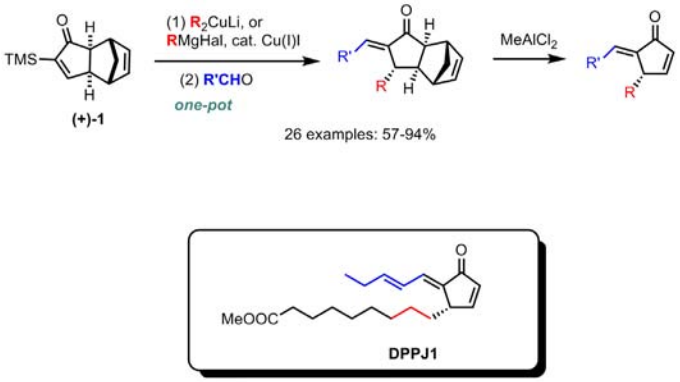


Figure 6. *Enantioselective syntheses of dehydrophytoprostanes developed in collaboration with Paul Evans's group.*

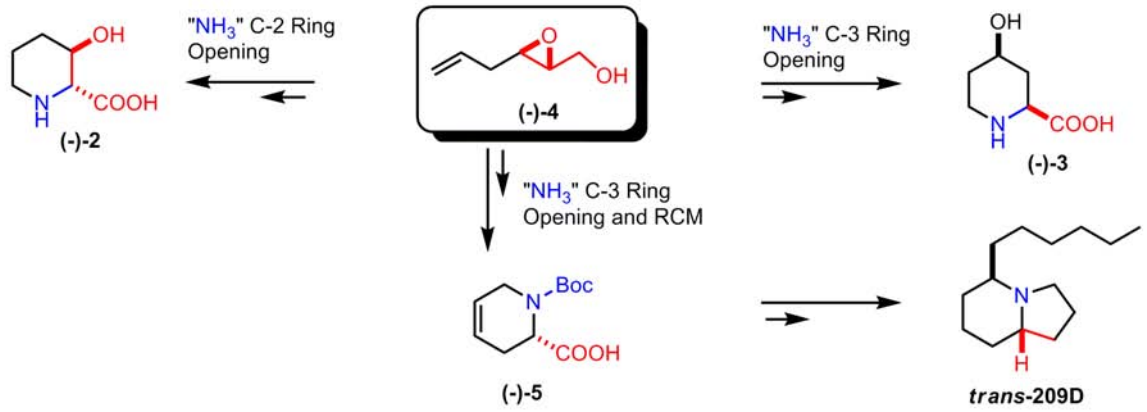


Figure 7. *Enantioselective syntheses of pipecolic acids and alkaloid trans-209D performed by our group.*

SCIENTIFIC OUTPUT

Publications

Alegret C, Ginesta X and Riera A. Asymmetric synthesis of cis-4- and trans-3-hydroxypipecolic acids. *Eur J Org Chem*, **10**, 1789-96 (2008)

Alegret C and Riera A. Enantioselective synthesis of indolizidine alkaloid trans-209D. *J Org Chem*, **73**(21), 8661-64 (2008)

Iqbal M, Duffy P, Evans P, Cloughley G, Allan B, Lledo A, Verdaguer X and Riera A. The conjugate addition-Peterson olefination reaction for the preparation of cross-conjugated cyclopentenone, PPAR-gamma ligands.*Org Biomol Chem*, **6**(24), 4649-61 (2008)

Olivella S, Sole A, Lledo A, Ji Y, Verdaguer X, Suau R and Riera A. Theoretical and experimental studies on the mechanism of norbornadiene Pauson-Khand cycloadducts photorearrangement. Is there a pathway on the excited singlet potential energy surface? *J Am Chem Soc*, **130**(50), 16898-07 (2008)

Revés M, Achard T, Sola J, Riera A and Verdaguer X. N-phosphino-p-tolylsulfinamide ligands: Synthesis, stability, and application to the intermolecular Pauson-Khand reaction. *J Org Chem*, **73**(18), 7080-87 (2008)

Vázquez-Romero A, Rodríguez J, Lledo A, Verdaguer X and Riera A. Enantioselective syntheses of carbanucleosides from the Pauson-Khand adduct of trimethylsilylacetylene and norbornadiene. *Org Lett*, **10**(20), 4509-12 (2008)

Research networks and grants

Identificación de inhibidores específicos de la actividad transcripcional de la beta-catenina en cáncer de colon
'La Caixa' Foundation, BM-05-68-0 (2005-2008)
Principal investigator: Antoni Riera

Identificació d'inhibidors específics de l'activitat transcripcional de la beta-catenina en la progressió tumoral
'La MTV3' Foundation, 050630/31/32 (2006-2008)
Principal investigator: Antoni Riera

Síntesis enantioselectiva de moléculas bioactivas mediante catálisis asimétrica: Reacciones de Pauson-Khand, organocatálisis y oxidaciones de Sharpless
Spanish Ministry of Science and Innovation, CTQ2005-00623/BQU (2006-2008)
Principal investigator: Antoni Riera

Collaborations

Asymmetric catalysis
Miquel Pericàs, Institute of Chemical Research of Catalonia (Barcelona, Spain)

Molecular orbital calculations
Santiago Olivella, Spanish National Research Council (Barcelona, Spain)

NMR studies of peptide structures
Maria Macias, IRB Barcelona (Barcelona, Spain)

Synthesis and biological activity of phytoprostanes
Martin Müller, Julius-von-Sachs-Institut of Biosciences, Universität Würzburg (Würzburg, Germany)

Synthesis and biological activity of phytoprostanes
Paul Evans, Trinity College, University of Dublin (Dublin, Ireland)

Synthesis of peptide analogues
Berta Ponsati, Jimena Fernández-Carneado and Marc Gómez, BCN Peptides SL (Barcelona, Spain)

Synthesis of pharmaceutically active compounds
Llorenç Rafecas, Alex Comely and Nicolas Tesson, Enantia SL (Barcelona, Spain)

Synthesis of specific inhibitors of β-catenin
Antonio Garcia de Herreros, Parc de Recerca Biomèdica de Barcelona and Pompeu Fabra University (Barcelona, Spain)

Synthesis of specific inhibitors of β-catenin
Mireia Duñach, Autonomous University of Barcelona (Barcelona, Spain)

Other funding sources

Two contract research projects with Enantia SL and one with BCN Peptides SA through the 'Bosch i Gimpera' Foundation