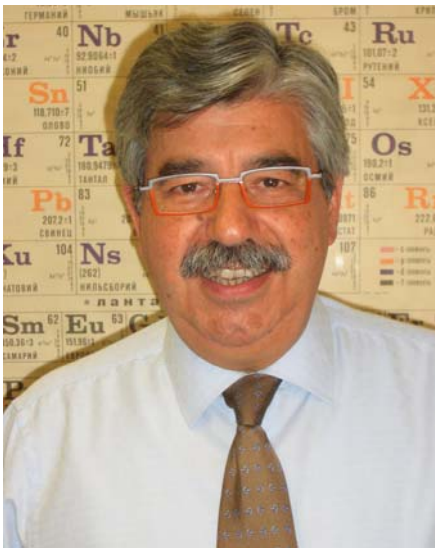
Professor Joan Bosch

A Tribute



This special issue of ARKIVOC is dedicated to Professor Joan Bosch to commemorate his 60th birthday and acknowledge his contribution to Spanish science through his achievements in organic synthesis.

Prof. Joan Bosch was born in Barcelona (Spain) on February 2, 1947. He graduated in Chemistry at the University of Barcelona in 1969, having developed a particular interest in Organic Chemistry, mainly due to the stimulating classes and charisma of his teacher, Prof. Ricardo Granados. After four years working on the synthesis of aminofurans under the supervision of Dr. Ramón Carreras in the Department of Organic Chemistry at the Faculty of Chemistry of the University of Barcelona, he received his Ph. D. in 1973. It should be mentioned that in the early seventies of the last century research in Spain was quite precarious. Very poor economical resources, limited access to scientific equipment and, most importantly, a lack of tradition converted research into a daunting task. However, the enthusiastic and obstinate personality of Joan prompted him to pursue a scientific career.

His academic career took off very early, in 1975, when at the age of 28 he was appointed to a permanent position as Associate Professor of Organic Chemistry at the Faculty of Pharmacy of the University of Barcelona. In 1981 he was promoted to the position of Full Professor and he moved to the Faculty of Pharmacy of the University of Valencia. After one academic year, he returned to the Faculty of Pharmacy of the University of Barcelona, where he has remained ever since. Always ready to assume academic responsibilities, he was Vice-Dean from 1983 to 1986, Dean from 1986 to 1992, Head of the Department of Pharmacology and Medicinal Chemistry from 1992 to 1998, and is currently Head of the Organic Chemistry Unit of this Department. His efforts have been instrumental in establishing this Unit in a competitive position in the field of Organic Chemistry.

The research interests of Joan Bosch have always focused on organic synthesis, in particular alkaloids and other bioactive nitrogen compounds. His scientific trajectory began with studies on the synthesis of analgesics related to benzomorphans in collaboration with a pharmaceutical company. The fact that the 2-azabicyclo[3.3.1]nonane nucleus is a common structural feature of both morphine-related analgesics and *Strychnos* indole alkaloids attracted his attention and led him to the fascinating area of the total synthesis of alkaloids. In this context, he became involved in the development of general synthetic methods and strategies of application to the total synthesis of indole alkaloids. During his research he has explored the reactivity of nitrogen heterocycles such as indole and pyridine. Worthy of particular mention are the preparation of new indole organometallics such as 3-lithioindoles and indolylzinc halides, and the use of pyridinium salts as starting materials and dihydropyridines as versatile synthetic intermediates for the synthesis of complex indole alkaloids. He has also been interested in developing syntheses, based on strategies that mimic the key steps of the alkaloid biosynthesis.

As a result of these studies he has completed the total or formal synthesis, in some cases by several alternative routes, of more than 40 of the following indole alkaloids belonging to different structural types, both in the racemic series and enantiopure form: *Strychnos* alkaloids (tubifoline, tubifolidine, dihydroakuammicine, akuammicine, norfluorocurarine, echitamidine, 20-epilochneridine, tubotaiwine, Wieland-Gumlich aldehyde, and strychnine), alkaloids of the uleine group (dasycarpidone, nordasycarpidone, dasycarpidol, and uleine), alkaloids of the ervitsine-ervatamine group (ervitsine, ervatamine, 20-epiervatamine, dihydroervatamine, 6-oxosilicine, and 6-oxo-16-episilicine), indolopyridine alkaloids (nauclefine, angustine, dihydroangustine, naucletine, and 19-*O*-methylangustoline), indoloquinolizidine alkaloids (geissochizine, akagerine, and melinonine E), mavacurine-type alkaloids (vinoxine, 2,7-dihydropleiocarpamine), and others (ngouniensine, epingouniensine, deethylibophyllidine, tacamonine, eburnamonine, 20*S*- and 20*R*-dihydrocleavamine, camptothecin, and 20-deoxycamptothecin). Perhaps the most outstanding of all these achievements has been the enantioselective total synthesis of (-)-strychnine, a heptacyclic molecule that has always fascinated synthetic organic chemists.

During recent years he has explored the potential of aminoalcohol-derived lactams as chiral synthons for the synthesis of enantiopure piperidine-containing alkaloids and drugs. In this area, recent achievements include the enantioselective synthesis of the alkaloids (-)-coniine, (-)-dihydropinidine, (+)-*R*-decarbomethoxytetrahydrosecodine, (2*R*,6*R*)-lupetidine, (2*R*,6*R*)-solenopsin A, (-)-gephyrotoxin 167B, (+)-monomorine I, (-)-anabasine, and 1-deoxy-D-gulonojirimycin, the formal synthesis of the alkaloids of the uleine group, as well as the synthesis of the antidepressant drug (-)-paroxetine and the antipsychotic drug preclamol [(-)-3-PPP]. These studies have opened up a general and practical methodology for the synthesis of enantiopure piperidines bearing any substitution pattern.

All this work has been published in more than 250 scientific papers, most of them in highly reputed journals in the chemistry field.

His interest in maintaining close relationships with chemical and pharmaceutical companies has been constant throughout his career, resulting in many collaborative research projects aimed at the synthesis of new compounds with therapeutic potential or the development of new synthetic routes for drugs. As a consequence of this activity he is among the inventors of a large number of patents.

Joan Bosch has supervised as many as 35 Doctoral Theses and has decisively contributed to the training of a great number of researchers, many of whom currently hold positions either in universities or chemical and pharmaceutical companies.

In recognition of his scientific trajectory, in 2002 Joan Bosch was awarded the prestigious "Distinction for the Promotion of University Research" by the Catalan Government (Generalitat de Catalunya).

On the personal front, at home he breathes a scientific atmosphere. His wife, Prof. M. Carme Fusté, is a microbiologist specializing in bacterial population genetics. They have a daughter, Elena, also a biologist, who is carrying out post-doctoral research in human population genetics, and a son, Joan Bosch, Jr., a graduate in Pharmacy and in Food Science and Technology, who is now finishing his Ph. D. on volatile compounds in Catalan sparkling wine (cava). Joan Bosch recently became a grandfather when his daughter gave birth to Roger.

In his free time Joan enjoys walking in the countryside, especially in the mountains surrounding Vic (60 km from Barcelona) and the Pyrenees, where he and his wife, gourmets and mushroom connoisseurs, are able to pick more than twenty edible species. In summer he relaxes by the Mediterranean on the island of Menorca, where he likes to snorkel, sail his dinghy, read, and generally recharge his batteries for the next academic year.

Having had the privilege of doing research with Professor Joan Bosch, we feel honored to contribute this article to this special issue of ARKIVOC.

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Selected publications of Professor Joan Bosch

1. Bosch, J.; Bonjoch, J. Synthetic route to 6-functionalized 2-azabicyclo[3.3.1]nonanes. *J. Org. Chem.* **1981**, *46*, 1538.

2. Feliz, M.; Bosch, J.; Mauleón, D.; Amat, M.; Domingo, A. Synthetic applications of 2-cyano-1,2,3,6-tetrahydropiridines. Improved synthesis of the fundamental tetracyclic framework of dasycarpydone. *J. Org. Chem.* **1982**, *47*, 2435.
3. Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. Synthetic applications of 2-cyano-1,2,3,6-tetrahydropyridines. II. Synthesis of isodasycarpidone and related systems, the ervitsine skeleton, and its benzo analogue. *J. Org. Chem.* **1985**, *50*, 1516.
4. Bosch, J.; Bennasar, M.-L.; Zulaica, E.; Massiot, G.; Massoussa, B. Total synthesis of indole alkaloids ngouniensine and epingouniensine. *Tetrahedron Lett.* **1987**, *28*, 231.
5. Rubiralta, M.; Díez, A.; Bosch, J.; Solans, X. Studies on the synthesis of the indolo[2,3-*a*]quinolizidine system. *J. Org. Chem.* **1989**, *54*, 5591.
6. Amat, M.; Linares, A.; Bosch, J. A new synthetic entry to pentacyclic *Strychnos* alkaloids. Total synthesis of (±)-tubifolidine, (±)-tubifoline and (±)-19,20-dihydroakuammicine. *J. Org. Chem.* **1990**, *55*, 6299.
7. Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. A general method for the synthesis of bridged indole alkaloids. Nucleophilic addition of indoleacetic ester enolates to *N*-alkylpyridinium salts. *J. Org. Chem.* **1990**, *55*, 1156.
8. Amat, M.; Bosch, J. Studies on the synthesis of pentacyclic *Strychnos* alkaloids. Closure of E ring by Pummerer cyclization. *J. Org. Chem.* **1992**, *57*, 5792.
9. Bonjoch, J.; Solé, D.; Bosch, J. A new, general synthetic pathway to *Strychnos* indole alkaloids. First total synthesis of (±)-echitamidine. *J. Am. Chem. Soc.* **1993**, *115*, 2064.
10. Bennasar, M.-L.; Vidal, B.; Bosch, J. First total synthesis of the indole alkaloid ervitsine. A straightforward, biomimetic approach. *J. Am. Chem. Soc.* **1993**, *115*, 5340.
11. Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. Studies on the synthesis of mavacurine-type indole alkaloids. First total synthesis of (±)-2,7-dihydropleiocarpamine. *J. Org. Chem.* **1993**, *58*, 7756.
12. Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. Preparation and reactions of 1-(tert-butyldimethylsilyl)-3-lithioindole. Regioselective synthesis of 3-substituted indoles. *J. Org. Chem.* **1994**, *59*, 10.
13. Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. Total synthesis of uleine-type and *Strychnos* alkaloids through a common intermediate. *J. Org. Chem.* **1994**, *59*, 3939.
14. Quirante, J.; Escolano, C.; Bosch, J.; Bonjoch, J. First total synthesis of (±)-melinonine-E. *J. Chem. Soc. Chem. Commun.* **1995**, 2141.
15. Fernández, J.-C.; Valls, N.; Bosch, J.; Bonjoch, J. A straightforward route to ibophyllidine alkaloids by a double transannular cyclization. *J. Chem. Soc. Chem. Commun.* **1995**, 2317.
16. Bonjoch, J.; Solé, D.; Bosch, J. Studies on the synthesis of *Strychnos* indole alkaloids. Synthesis of (±)-dehydrotubifoline. *J. Am. Chem. Soc.* **1995**, *117*, 11017.
17. Bosch, J.; Bonjoch, J.; Amat, M. The *Strychnos* alkaloids. *The Alkaloids* (G.A. Cordell, ed.) **1996**, *48*, 75.

18. Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. Total syntheses of the *Strychnos* indole alkaloids (-)-tubifoline, (-)-tubifolidine, and (-)-19,20-dihydroakuammicine. *Tetrahedron: Asymmetry* **1997**, *8*, 935.
19. Amat, M.; Hadida, S.; Pschenichnyi, G.; Bosch, J. Palladium(0)-catalyzed heteroarylation of 2- and 3-indolylzinc derivatives. An efficient general method for the preparation of (2-pyridyl)indoles and their application to indole alkaloid synthesis. *J. Org. Chem*. **1997**, *62*, 3158.
20. Bennasar, M.-L.; Vidal, B.; Bosch, J. Biomimetic total synthesis of ervitsine and indole alkaloids of the ervatamine group *via* 1,4-dihydropyridines. *J. Org. Chem*. **1997**, *62*, 3597.
21. Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. A general synthetic entry to *Strychnos* alkaloids of the curan type via a common 3a-(2-nitrophenyl)hexahydroindol-4-one intermediate. Total syntheses of (±)-tubifolidine, (±)-akuammicine, (±)-19,20-dihydroakuammicine, (±)-norfluorocurarine, (±)-echitamidine, and (±)-20-epilochneridine. *J. Am. Chem. Soc*. **1997**, *119*, 7230.
22. Lavilla, R.; Coll, O.; Kumar, R.; Bosch, J. Electrophilic oxidative additions upon 1,4-dihydropyridines. *J. Org. Chem*. **1998**, *63*, 2728.
23. Lavilla, R.; Barón, X.; Coll, O.; Gullón, F.; Masdeu, C.; Bosch, J. Non-biomimetic oxidations of dihydropyridines. *J. Org. Chem*. **1998**, *63*, 10001.
24. Lavilla, R.; Gullón, F.; Bosch, J. A unified synthetic strategy for the indolopyridine alkaloid group. *Eur. J. Org. Chem*. **1999**, 373.
25. Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. Total synthesis of (-)-strychnine via the Wieland-Gumlich aldehyde. *Angew. Chem. Int. Ed.* **1999**, *38*, 395.
26. Lavilla, R.; Coll, O.; Nicolàs, M.; Sufi, B.A.; Torrents, J.; Bosch, J. Iodocyclisation of 1,4-dihydropyridines: synthesis and reactivity of 1-iodoindolo[2,3-*a*]quinolizidines. *Eur. J. Org. Chem.* **1999**, 2997.
27. Bennasar, M.-L.; Jiménez, J.-M.; Vidal, B.; Sufi, B.A.; Bosch, J. Nucleophilic addition of 1-acetylindole enolates to pyridinium salts. Stereoselective formal synthesis of (±)-geissoschizine and (±)-akagerine via 1,4-dihydropyridines. *J. Org. Chem.* **1999**, *64*, 9605.
28. Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. Enantioselective total synthesis of Wieland-Gumlich aldehyde and (-)-strychnine. *Chem. Eur. J.* **2000**, *6*, 655.
29. Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. Synthesis of enantiopure *trans*-3,4-disubstituted piperidines. An enantiodivergent synthesis of (+)- and (-)-paroxetine. *J. Org. Chem*. **2000**, *65*, 3074.
30. Lavilla, R.; Kumar, R.; Coll, O.; Masdeu, C.; Spada, A.; Bosch, J.; Espinosa, E.; Molins, E. Introduction of heteroatom-based substituents on 1,4-dihydropyridines through a non-biomimetic, halogen-mediated, oxidative protocol. Diamination, sulfinylation, disulfanylation, and halophosphonylation processes. *Chem. Eur. J.* **2000**, *6*, 1763.
31. Lavilla, R.; Spada, A.; Bosch, J. Oxidative diphosphonylation of 1,4-dihydropyridines and pyridinium salts. *Org. Lett.* **2000**, *2*, 1533.

32. Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A.; Bosch, J. A synthetic entry to ervatamine alkaloids. Synthesis of (±)-6-oxo-16-episilicine and (±)-6-oxosilicine. *Eur. J. Org. Chem*. **2000**, 3019.
33. Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Bosch, J. A biomimetic synthesis of (-)-$N_{(a)}$-methylervitsine. *Chem. Commun.* **2001**, 1166.
34. Lavilla, R.; Coll, O.; Bosch, J.; Orozco, M.; Luque, F.J. General access to tacamine and vinca-eburna alkaloids through tandem non-biomimetic oxidation of dihydropyridines/Zn-mediated radical addition processes. Unexpected facial selectivity of flattened cyclohexyl-type radicals. *Eur. J. Org. Chem*. **2001**, 3719.
35. Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. Unprecedented oxidation of a phenylglycinol-derived 2-pyridone: enantioselective synthesis of polyhydroxypiperidines. *Org. Lett*. **2001**, *3*, 3257.
36. Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. Dynamic kinetic resolution and desymmetrization of enantiotopic groups by cyclodehydration of racemic or prochiral δ-oxoesters with (*R*)-phenylglycinol. Enantioselective synthesis of piperidines. *Angew. Chem. Int. Ed.* **2002**, *41*, 335.
37. Amat, M.; Cantó, M.; Llor, N.; Bosch, J. Enantioselective synthesis of 2-arylpiperidines from chiral lactams. A concise synthesis of (-)-anabasine. *Chem. Commun*. **2002**, 526.
38. Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. Dynamic kinetic resolution of racemic δ-aryl-γ-oxoesters. Enantioselective synthesis of 3-arylpiperidines. *J. Org. Chem*. **2002**, *67*, 5343.
39. Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. Addition of ester enolates to *N*-alkyl-2-fluoropyridinium salts: total synthesis of (±)-20-deoxycamptothecin and (+)-camptothecin. *J. Org. Chem*. **2002**, *67*, 7465.
40. Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. Enantioselective synthesis of piperidine, indolizidine, and quinolizidine alkaloids from a phenylglycinol-derived δ-lactam. *J. Org. Chem*. **2003**, *68*, 1919.
41. Amat, M.; Huguet, M.; Llor, N.; Bassas, O.; Gómez, A. M.; Bosch, J.; Badia, J.; Baldoma, L., Aguilar, J. Enantioselective synthesis of 1-deoxy-D-gulonojirimycin from a phenylglycinol-derived lactam. *Tetrahedron Lett*. **2004**, *45*, 5355.
42. Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, J.; Molins, E.; Bosch, J. Conjugate additions to phenylglycinol-derived unsaturated δ-lactams. Enantioselective synthesis of uleine alkaloids. *J. Org. Chem.* **2004**, *69*, 8681.
43. Amat, M.; Bassas, O., Pericàs, M.-A.; Pastó, M.; Bosch, J. Highly enantioselective dynamic kinetic resolution and desymmetrization processes by cyclocondensation of chiral aminoalcohols with racemic or prochiral δ-oxoacid derivatives. *Chem. Commun*. **2005**, 1327.
44. Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. Biogenetically inspired enantioselective approach to indolo[2,3-*a*]- and

benzo[*a*]quinolizidine alkaloids from a synthetic equivalent of secologanin. *Org. Lett.* **2005**, *7*, 2817.

45. Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, J. An enantioselective entry to *cis*-perhydroisoquinolines. *Org. Lett*. **2005**, *7*, 3653.
46. Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E. Bosch, J. Alkylation of phenylglycinol-derived oxazolopiperidone lactams. Enantioselective synthesis of β-substituted piperidines. *J. Org. Chem*. **2006**, *71*, 3804.
47. Soteras, I.; Lozano, O.; Gómez-Esqué, A.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, J. On the origin of the stereoselectivity in the alkylation of oxazolopiperidone enolates. *J. Am. Chem. Soc*. **2006**, *128*, 000.