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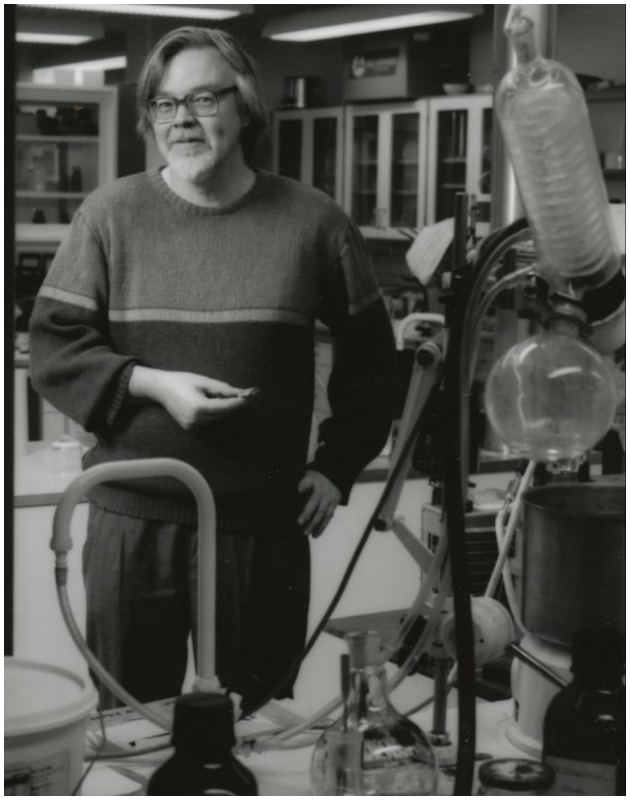
Tribute

Arkivoc **2020**, part vii, 1-15

Professor Jan Bergman

A Tribute



Dedicated to Prof. Jan Bargman on the occasion of his 80th anniversary

Published on line 02-27-2020

Professor Jan Olof Einar Bergman (Jan Bergman) was born on the 30th of April, 1941, in Spånga, Sweden, a small town later incorporated into its Eastern neighbor, Stockholm. Jan was the eldest of a family of two boys. His father was a stone-mason and his mother assisted her sister in a milliner's shop in the center of Stockholm. After grammar school in Spånga, Jan studied at the Royal Institute of Technology (*Kungliga Tekniska Högskolan*, commonly referred to as KTH), in Stockholm, graduating as Master of Engineering in 1964, specializing in Chemistry. Remaining in the same institution, he registered for the degree of PhD in 1965, though for the first year he was rarely in the Institute while he carried out part of his compulsory military service (two years – 1965-1966) at the Swedish Arméns Skyddsingenjörsskola (Army Protective Engineering School), in Stockholm. Earlier (1960), Jan spent one year of basic military service in Östersund and has been an avid supporter of Östersund FC ever since, despite their recent disappointments.

Already working in the KTH when Jan began his PhD studies, was Solveig Larsson who was to become Jan's lifetime assistant, both practically in the laboratory, as a supervisor of students at all levels, as an administrative Personal Assistant . . . and in July 1967, his wife. Their marriage produced three sons, Leif, Hans and Bengt, none of whom chose chemistry as a career, despite Jan's best efforts to encourage them in that direction; instead they chose computer-related paths. Finally, in 1971 Jan was awarded the degree of PhD for "Studies of Indole Derivatives", under the guidance of Professor Holger Erdtman – a topic that has continued to dominate much of Jan's subsequent research interests.

Jan Bergman was appointed to a Lectureship at KTH in 1967, and was promoted to Associate Professor in 1973; he was Studierektor in Organic Chemistry at KTH between 1970 and 1981 and served as Chairman of the Educational Committee at KTH between 1973 and 1977. In 1976 Jan was Visiting Professor at the University of Waterloo, Ontario, Canada. During 1980-1990 he chaired the KTH Committee for Safety and Environment dealing with the worst case during that period which was a severe explosion caused by 100 g of N-methylpyridinium perchlorate, intended as an ionic medium by an inorganic chemist. Debris from the explosion caused small holes, in the windows as if bullets from a shotgun had penetrated them. Animated meetings with lawyers, police, and student representatives, needed to be negotiated by the Chairman.

In 1990 Jan moved to a Professorship at the Karolinska Institute (KI) where he ran the Unit of Organic Chemistry in the Department of Biosciences at Novum, Huddinge, until 2011. Work during this period, mainly on biologically active nitrogen heterocyclic compounds, resulted in 306 scientific publications and 25 patents. During his career Jan Bergman has supervised more than 30 students through to their PhD degrees. He has welcomed post-doctoral workers into his laboratory from Australia, Chile, Finland, France, Hungary, Indonesia, Pakistan, Poland, Russia, Sri Lanka, and the USA. Jan Bergman has held Professor Emeritus status at KI since 2011 to the present day and currently operates from the Emeritus quarters at KI, though is often to be found in the laboratories of Vironova Medical AB, Stockholm.

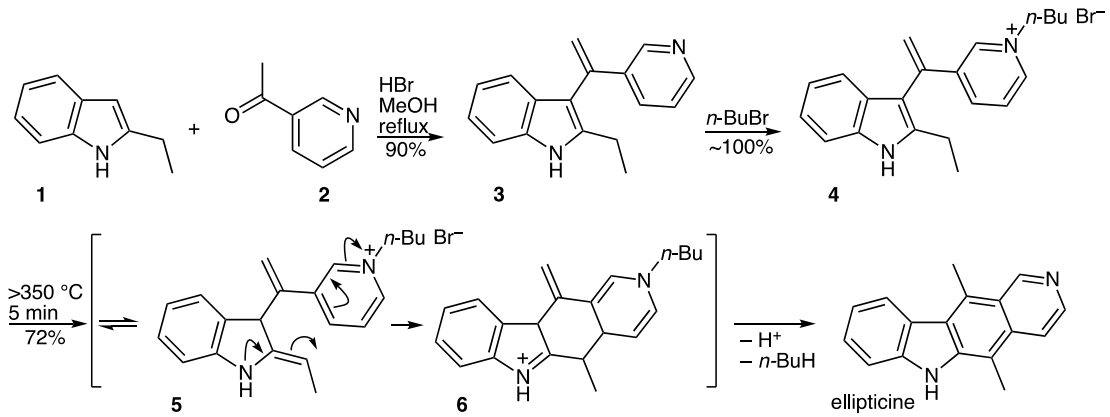
Amongst the many administrative duties and responsibilities outside his University base that Jan Bergman has undertaken one should note his Membership of the Board of the International Society of Heterocyclic Chemistry (ISHC) (1988-1996) and indeed its Presidency (1992-1994). Additionally he was a Member of the Editorial Board of the ISHC's annual publication, *Progress in Heterocyclic Chemistry* and Chairman of that Board (1992-1994). In 2000, Jan took over from Henk van der Plas as Chairman of the Scientific Committee for the biennial series of conferences initiated by Henk called initially, FEChem Conferences (Federation of European Chemical Societies, to emphasize the collegiate nature of the European contributors). Later is was rebranded as Bioheterocycles Conferences, to emphasize the subject matter, the most recent, being the 18th in the series, in Ghent, Belgium, in 2019 and the next, in 2021, to be at the Johannes Gutenberg-University, Mainz, Germany.

Professor Bergman has examined many PhD theses in Sweden and outside his home base, for example in England and Spain. Similarly, he has been called upon to evaluate Chair applications in the US, UK, Australia and New Zealand, amongst others. The Greek Ministry of Education called on his services to evaluate research activities in several Greek institutes. On several occasions, he has been appointed as an Expert Witness at the Court of Appeals in Stockholm.

In order to give a sense of the variety of research achievements of the Bergman group, given below are a few selected and typical examples taken from all parts of Jan's career. We hope by way of these examples, and this Tribute, to encapsulate the significance of Jan Bergman's major contributions to the world of chemistry.

Synthesis of ellipticine

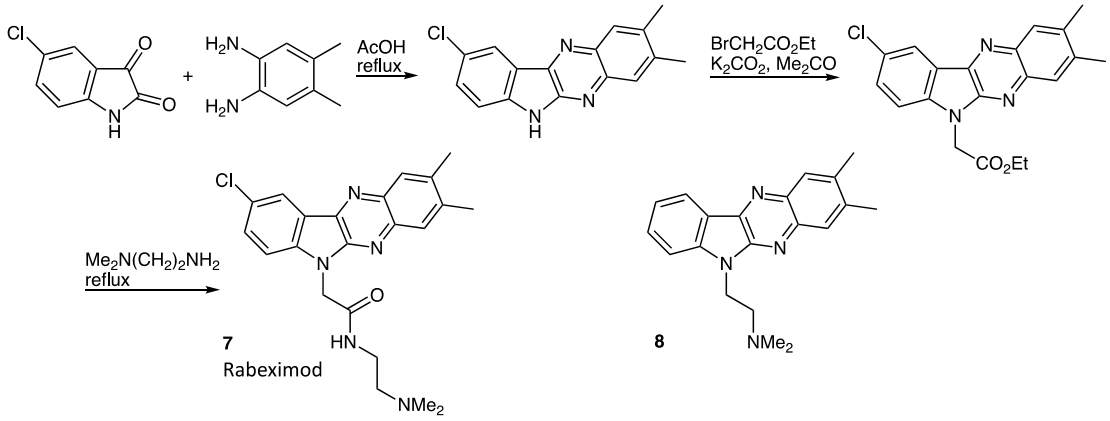
There have been many total syntheses of the indole alkaloid ellipticine, first isolated from the tropical evergreen tree, *Ochrosia elliptica*, and having the important property of inhibiting the enzyme topoisomerase II via intercalative binding to DNA. The Bergman synthesis (Scheme 1), which can be conveniently carried out on a gram scale, was one of the first [5]. A simple acid-catalysed alkylation/dehydration of 2-ethylindole (**1**) by 3-acetylpyridine (**2**) produced **3**. Pyridine N-alkylation with butyl bromide gave salt **4** which, on thermolysis, produced ellipticine. This conversion probably involves the tautomer **5**, where intramolecular enamine-alkylation (arrows on **5**) leads to **6**, deprotonation and loss of butane then forming the alkaloid. The crucial thermolysis step induced Jan's student assistant, René Carlsson, to develop a sublimation apparatus that was later commercialised.



Scheme 1. Synthesis of ellipticine.

Leading on from ellipticine studies, many analogues were assessed for biological activities. Isatins will condense with 1,2-diamino-aromatic compounds generating a new pyrazine ring, thereby forming indolo[2,3-*b*]quinoxalines. Explorations led to two active substances that are now in advanced stages of evaluation as drugs. Rabeximod **7** is for treatment of moderate or severe active rheumatoid arthritis. Compound **8** is a prospective anti-herpes treatment. Scheme 2 shows the main steps in the synthesis of rabeximod.

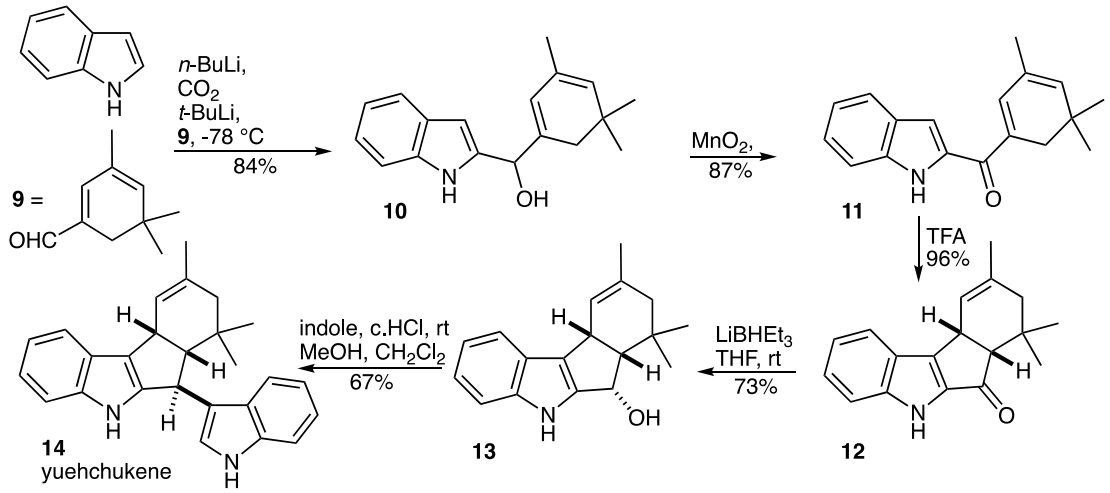
Indolo(2,3-*b*)quinoxalines



Scheme 2. Synthesis of Rabeximod and structure of anti-herpes candidate.

Synthesis of yuehchukene

The dimeric indole alkaloid yuehchukene (**14**) was isolated from various *Murruya* species and was reported to display strong anti-implantation activity in rats. The Bergman total synthesis (Scheme 3) required just five steps and proceeded with total regio- and stereochemical selectivity [23]. Using Katritzky's method for 2-lithiation of an indole by first protecting the nitrogen as a lithium carboxylate, reaction with the unsaturated aldehyde **9** produced alcohol **10**. After oxidation up to ketone (→ **11**), acid brought about ring closure giving tetracycle **12**. The corresponding alcohol **13** reacted with indole (or other indoles) [35] to produce the natural product via acid-catalysed displacement of the alcohol and electrophilic substitution at the indole 3-position.

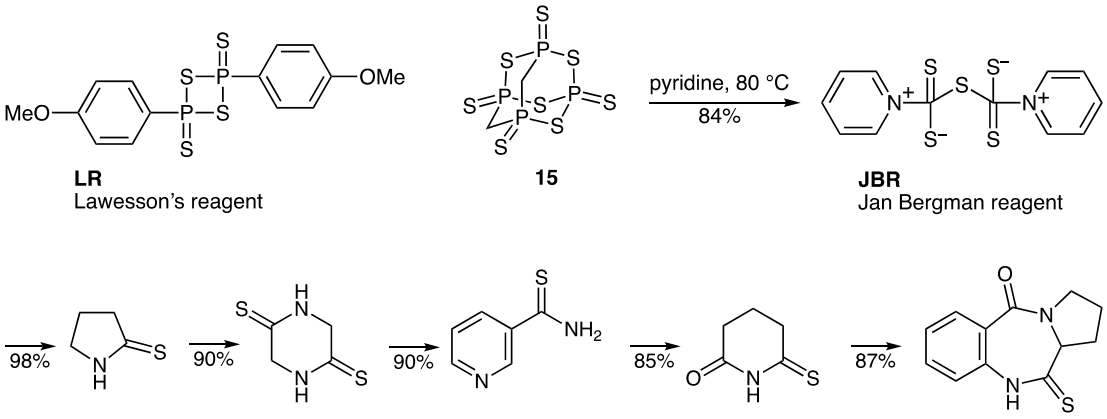


Scheme 3. Synthesis of yuehchukene.

Thionations with the Jan Bergman reagent

The traditional method for converting an amide carbonyl group NC=O into thiocarbonyl NC=S involved heating with tetraphosphorus decasulfide P_4S_{10} (**15**) in pyridine. An improvement on this method came with the introduction by the Swedish chemist Sven-Olov Lawesson of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disufide, now generally known as the Lawesson reagent (**LR**). Jan Bergman, in a

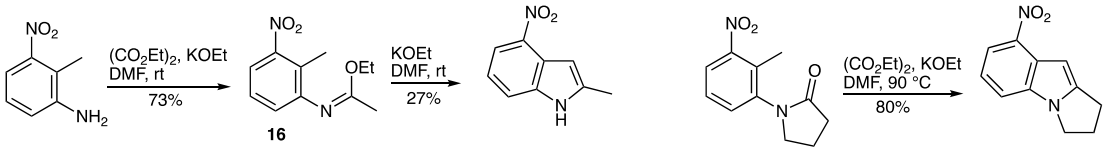
further improvement, showed how 1,1'-[thiobis(mercaptophosphinothioylidene)]-bis-pyridinium, bis(inner salt) (**JBR**) can be used in refluxing acetonitrile solution for efficient thionations [87]. Some products of its use in refluxing acetonitrile are shown in Scheme 4. The Jan Bergman reagent is prepared simply from pyridine and P_4S_{10} (**15**) and is crystalline and storable. Notably, it can be used for difficult thionations requiring higher temperatures, when **LR** cannot be used, for example in hot pyridine, or more extreme in dimethyl sulfone at 175 °C.



Scheme 4. Thionation of amides using the Jan Bergman Reagent.

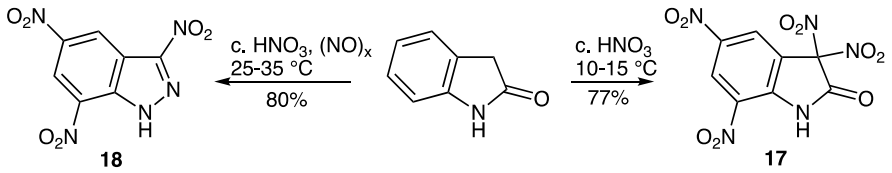
Nitro-indoles and 1,1-diamino-2,2-dinitroethylene

The development of a novel general route for the ring synthesis of 4- and 6-nitroindoles [30] is illustrated in Scheme 5 with two 4-nitro-examples; the key intermediates in this route are imidates, for example **16**.



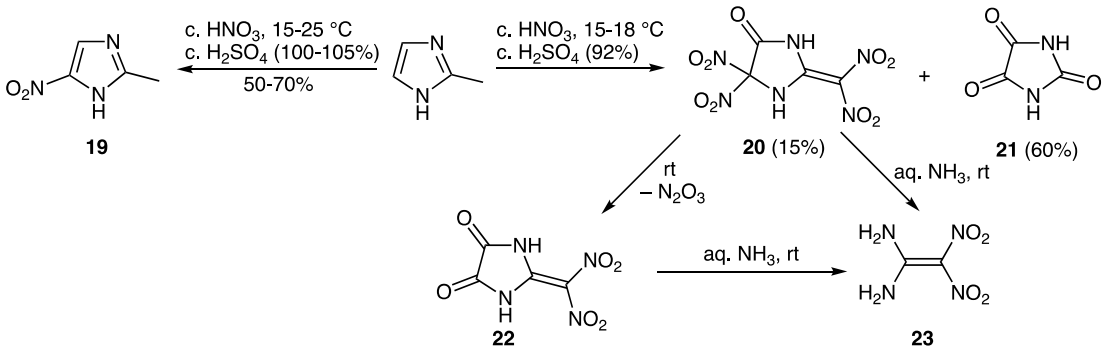
Scheme 5. Ring synthesis of 4- (shown) and 6-nitroindoles.

This approach also allowed the synthesis of 6-nitrooxindole (oxindole = 1,3-dihydro-2*H*-indol-2-one). Pursuing further nitro-oxindoles (Scheme 6), it was shown that oxindole itself, subjected to nitration with pure nitric acid, provides 3,3,5,7-tetranitrooxindole (**17**), but at only a slightly higher temperature, 3,5,7-trinitroindazole (**18**) is the product! These compounds are very high in nitrogen/oxygen content and indeed, compound **17** 'explodes with a flash' at 160 °C.



Scheme 6. Nitration of oxindole.

Interest in new energetic compounds with combined high efficiency and low sensitivity led to studies of nitrations of other heterocycles, and later to the first synthesis of 1,1-diamino-2,2-dinitroethylene (**23**) (Scheme 7)[44]. Reaction of 2-methylimidazole with nitric acid in 101-105% sulfuric acid produces mainly 2-methyl-4(5)nitroimidazole (**19**) in 50-70% yield, however in more dilute sulfuric acid, tetra-nitro product **20** (15%) and parabanic acid (**21**) (60%) are formed.

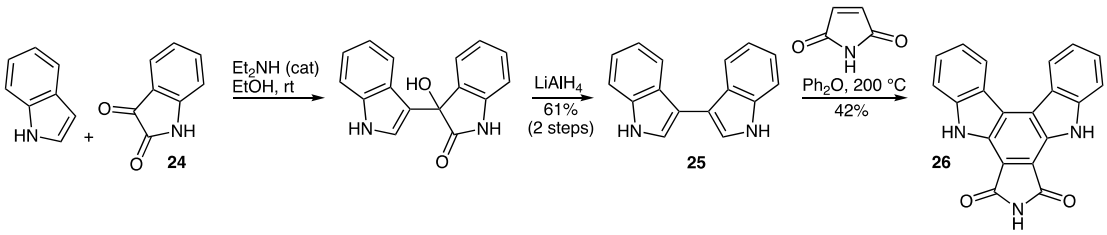


Scheme 7. Synthesis of 1,1-diamino-2,2-dinitroethylene (**23**).

The tetra-nitro compound (**20**) decomposes slowly forming the stable substance **22**; both **20** and **22** are converted by aqueous ammonia at pH 8-9 into the stable 1,1-diamino-2,2-dinitroethylene (**23**) – the first example of this push-pull system with no substituents on the amino groups. This substance has the properties of a high explosive with a performance close to that of the common high explosive RDX (1,3,5-trinitro-triazacyclohexane) but with lower sensitivity to impact and friction.

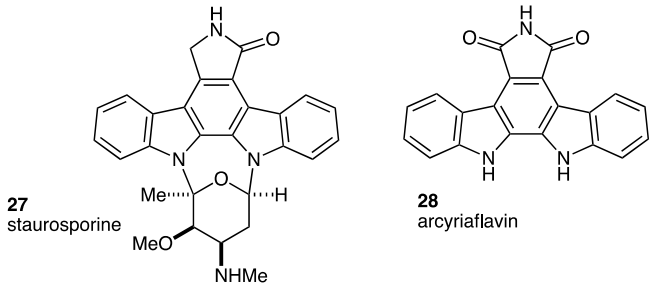
Indolo[2,3-*c*]carbazoles and indolo[2,3-*a*]carbazoles

Bergman's synthesis of 3,3'-biindolyls, e.g. **25**, (*Acta Chim. Scand.* **1971**, *25*, 1277) was at the basis of two strategies for the construction of indolo[2,3-*c*]carbazoles, one of which is shown in Scheme 8, producing **26**,[43]. 3,3'-Biindolyls e.g. **25**, are conveniently and simply made from an isatin, e.g. isatin itself, **24**, and an indole (unsubstituted examples shown in the Scheme). The central ring of the indolo[2,3-*c*]carbazoles is formed *via* a thermal electrocyclic process involving dienophiles such as ethyl propiolate, diethyl acetylenedicarboxylate and maleimide (shown).



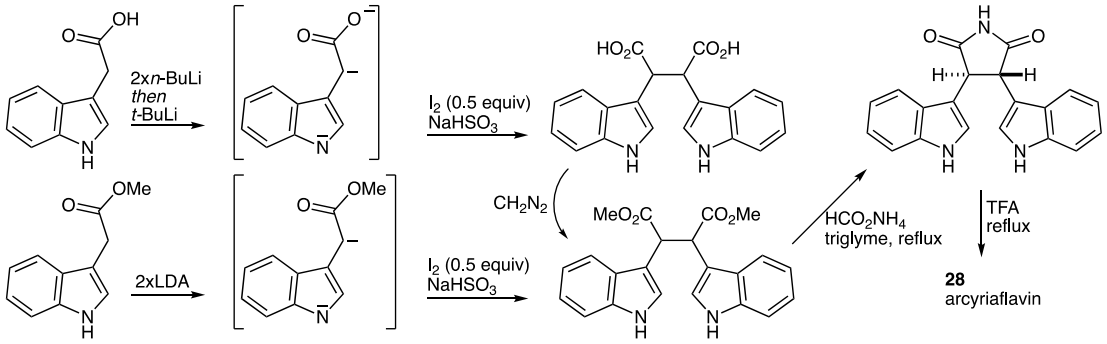
Scheme 8. A synthesis of indolo[2,3-*c*]carbazoles.

The isomeric indolo[2,3-*a*]carbazole nucleus occurs in staurosporine (**27**) and arcyriaflavin A (**28**) (the hexacycle being an indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole) (Scheme 9).

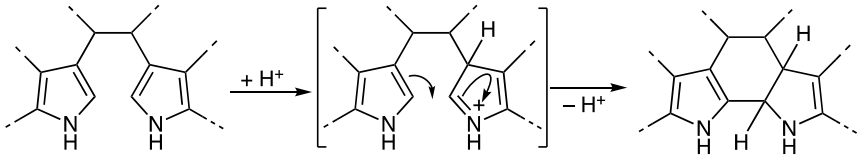


Scheme 9. Structures of staurosporine and arcyriaflavin.

The Bergman approach to this hexacycle centered on a 'dimerisation' of indol-3-acetic acid, or its dimethyl ester, as shown in Scheme 10. The construction of the central six-membered ring depends on the ability of an indole to be attacked by electrophiles at the 3-position or the 2-position, processes must take place in sequence, as illustrated in Scheme 11.



Scheme 10. Synthesis of arcyriaflavin A (**28**).



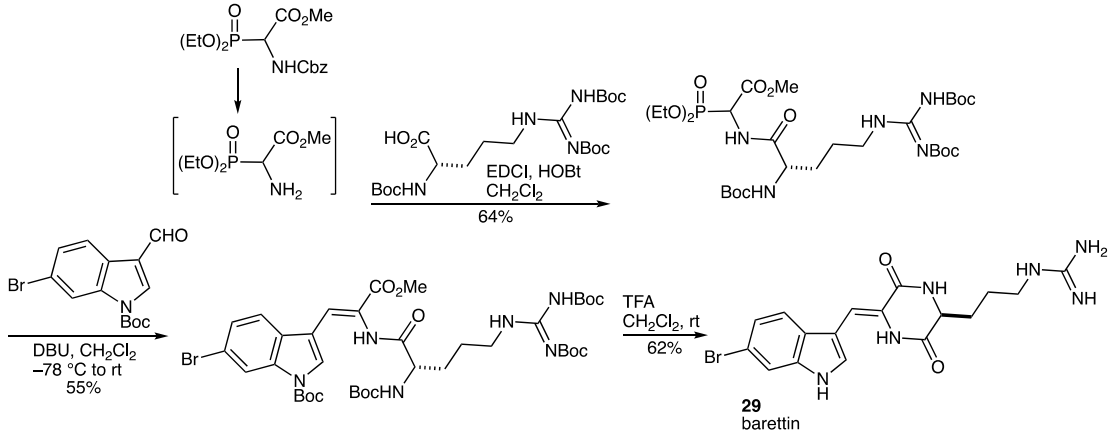
Scheme 11. Acid-promoted formation of the six-membered carbocyclic ring of the indolo[2,3-*a*]carbazole system.

The whole area of indolo-carbazole chemistry was recently reviewed. [95]

Barettin, caulersin and caulerpine

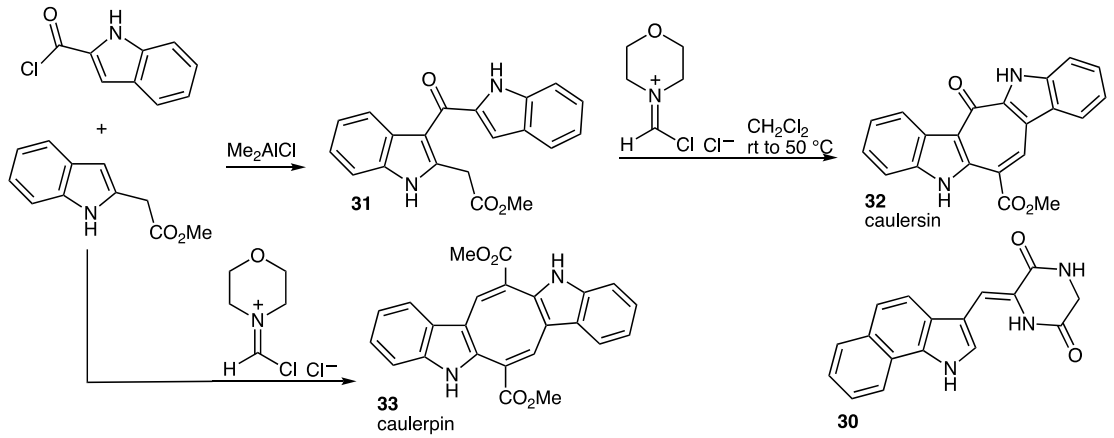
The sessile sponge *Geodia baretti* lives on the Atlantic continental shelf at depths down to 500 m; fiords are a favorite habitat. Its body surface is completely free of invading pests, which suggested that the animal produces efficacious antifouling compounds, one of which is barettin (**29**). One complicating factor in structural studies of the sea alkaloid was that the highly basic guanidino group of the arginine unit (pK_a 12.5) ensures that barettin is positively charged under all relevant conditions, thus, initial Swedish structural investigations were misleading (*Phytochem. Rev.* **2013**, *12*, 487) but the structure (**29**) was finally settled by

total synthesis (Scheme 12)[66]. With barettin as a 'lead' structure, other synthetic compounds were examined. For example structure **30** (Scheme 13), in which the bromine (essential for activity) has been replaced by an aromatic ring, has a greater antifouling effect than barettin. Additionally, other powerfully antifouling substances have subsequently been isolated from *Geodia baretti*.



Scheme 12. Total synthesis of barettin (**29**).

Caulersin (**32**) is a component isolated from the alga *Caulerpa serrulata*, which is a fast-spreading pest, for example in the Mediterranean Sea. Scheme 13[73] shows the neat synthesis of this substance. 3-Acylation of methyl indole-2-acetate with indole-2-carbonyl chloride produces ketone **31** (and other products) and reaction of this substance with the Vilsmeier reagent, chloromethylenemorpholinium chloride, leads directly to the natural product, the first additional carbon-carbon bond probably being formed via attack at the indole 3-position. The co-occurring caulerpine (**33**) results from reaction of methyl indole-2-acetate with the same Vilsmeier reagent.

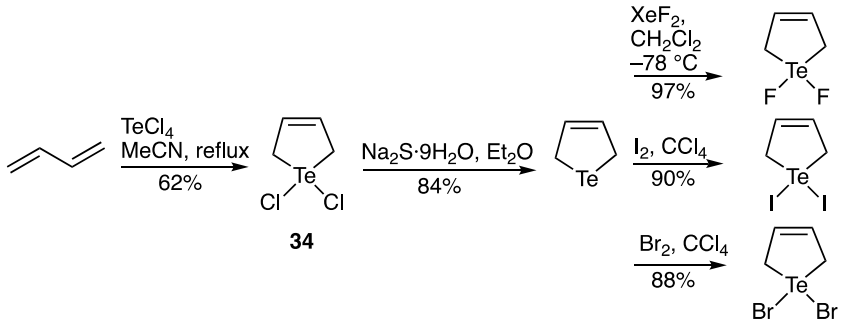


Scheme 13. Total syntheses of caulersin (**32**) and caulerpine (**33**).

Selenium and tellurium chemistry

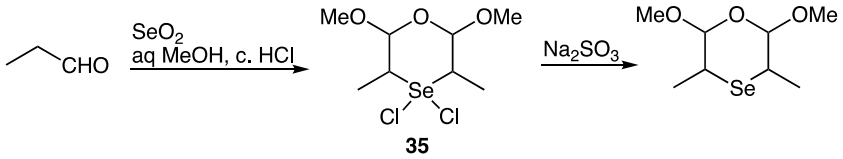
The Bergman group has made several significant contributions to organo-selenium and organo-tellurium chemistry - a couple of examples chosen at random are given below.

It was shown that tetralkyl ammonium borohydrides react with elemental selenium or tellurium in refluxing toluene to generate dialkylselenides/tellurides in good yields (*Synthesis* **1980**, 569). Naphthalene and $TeCl_4$, when heated together at 110 °C, yield 2-naphthyltellurium trichloride, which on treatment with degassed Raney Ni affords 2,2'-binaphthyl in excellent yield (*Tetrahedron* **1980**, *36*, 1275). 2,5-Dihydrotellurophene 1,1-dichlorides, e.g. **34**, are formed when 1,3-dienes react with tellurium tetrachloride [13]. Scheme 14 shows some chemistry of the parent – all these substances having 'obnoxious odours'.



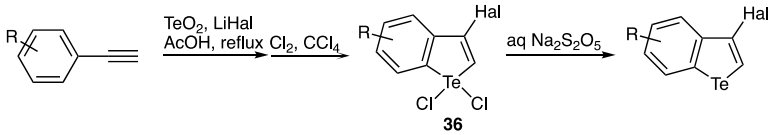
Scheme 14. 2,5-Dihydrotellurophene 1,1-dihalides.

Aliphatic aldehydes react with SeO_2 in an alcohol with aqueous HCl producing crystalline, albeit unstable, 2,6-dialkoxy-3,5-dialkyl-1,4-oxaselenane 4,4-dichlorides **35** (*Heterocycles* **1985**, *23*, 37), as exemplified in Scheme 15.



Scheme 15. 1,4-Oxaselenanes.

3-Halo-benzo[*b*]tellurophenes **36** can be produced from aryl alkynes as shown in Scheme 16.[9]



Scheme 16. Synthesis of 3-halo-benzo[*b*]tellurophenes.

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Selected Publications

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