# STUDIES IN NATURAL PRODUCTS CHEMISTRY

VOL. 1
PT. 1

# Studies in Natural Products Chemistry

## Volume 1
## Stereoselective Synthesis (Part A)

ELSEVIER SCIENCE PUBLISHERS B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

*Distributors for the United States and Canada:*

ELSEVIER SCIENCE PUBLISHING COMPANY INC.
52, Vanderbilt Avenue
New York, NY 10017, U.S.A.

ISBN 0-444-42970-0 (Vol. 1A)
ISBN 0-444-42971-9 (Series)



Printed in The Netherlands

# FOREWORD

The explosive growth in the natural sciences in this century has created an ever-growing need for books and journals which provide state-of-the-art overviews in specific fields of research. With the advances made in spectroscopy, as well as in chromatographic techniques, it has become possible to purify and unravel the structures of complex primary and secondary metabolites from the plant and animal kingdoms of an increasing order of complexity. While this has promoted a deeper understanding of some of the underlying chemistry which controls living processes, it has also provided organic chemists with complex synthetic targets, and posed new challenges to their genius for developing synthetic approaches to these substances. The study of the chemistry of natural products has therefore had a profound impact on the development of organic chemistry, having attracted the efforts of such giants as Woodward, Robinson, Todd and Perkin, to mention but a few. The Herculean efforts of Woodward and Eschenmoser which finally resulted in the first synthesis of vitamin $B_{12}$ two decades ago, constituted an important landmark, and heralded a new era in organic synthesis. Since the 1960's the emphasis has shifted to asymmetric synthesis, efforts having been directed by a number of leading groups towards the development of new synthetic methods which would afford the desired products with a high enantiomeric excess.

In view of these developments, it was felt that there was a strong need for a series of volumes which would provide comprehensive accounts by leading scientists in each area, covering the broad developments as well as highlighting the research contributions of the authors. The present volume is the first of a series of volumes which will be devoted to advances made in stereoselective synthesis of natural products. Other volumes in the series will be devoted to structure elucidation techniques and other selected areas of natural products chemistry. It is hoped that the series will provide a platform on which the major developments in the field can be presented by renowned experts and that it will prove to be an important and useful addition to the current literature.

This volume covers synthetic approaches to a wide variety of natural products including indole alkaloids, nucleoside antibiotics, anthracyclines and a number of other classes with diverse structures. The approaches adopted by the authors either highlight the various synthetic strategies used for a particular class of natural products or focus attention on the versatility of a certain approach to synthesising a wide diversity of natural products. All the contributors are eminent scientists who have made significant contributions to the progress of natural products chemistry. It is hoped that the articles will provide stimulat-

ing and enjoyable accounts of the work accomplished in each field, and will prove to be useful to a large community of synthetic organic chemists.

I wish to express my deep gratitude to Miss Khurshid Zaman for her assistance in the preparation of the manuscript.

March 1988 Atta-ur-Rahman, Editor

CONTRIBUTORS


| | |
|---|---|
| Jan Bergman | Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden |
| Josep Bonjoch | Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain |
| Joan Bosch | Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain |
| Michael T. Crimmins | Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514, U.S.A. |
| Philip Paul Garner | Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, U.S.A. |
| Gordon W. Gribble | Department of Chemistry, Dartmouth College, Hanover, NH 03755, U.S.A. |
| Miyoji Hanaoka | Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa, 920 Japan |
| W. Gary Hollis, Jr. | Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514, U.S.A. |
| Chihiro Kibayashi | Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan |
| Mauri Lounasmaa | Laboratory for Organic and Bioorganic Chemistry, Technical University of Helsinki, SF-02150 Espoo, Finland |
| Eugene A. Mash | Department of Chemistry, University of Arizona, Tucson, AZ 85721, U.S.A. |
| Fuyuhiko Matsuda | Sagami Chemical Research Centre, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan |
| C.J. Moody | Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, United Kingdom |

| | |
|---|---|
| Kenji Mori | Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan |
| Yoshio Nishimura | Institute of Microbial Chemistry, 14-23 Kamiosaki 3-chome, Shinagawa-ku, Tokyo 141, Japan |
| Mugio Nishizawa | Faculty of Pharmaceutical Science, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan |
| Rosemary O'Mahony | Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514, U.S.A. |
| William H. Pearson | Department of Chemistry, The University of Michigan, Ann Arbor, MI 48109, U.S.A. |
| A.V. Rama Rao | Regional Research Laboratory, Hyderabad - 500 007, India |
| James H. Rigby | Department of Chemistry, Wayne State University, Detroit, MI 48202, U.S.A. |
| Shiro Terashima | Sagami Chemical Research Centre, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan |

CONTENTS

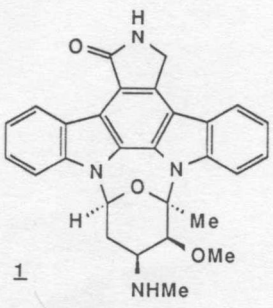
# Stereoselective Synthesis

# INDOLOCARBAZOLE ALKALOIDS

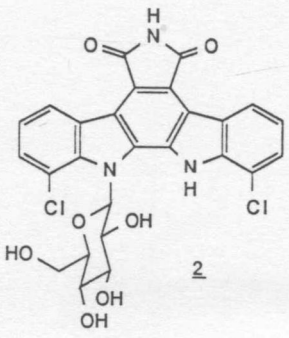
JAN BERGMAN

## INTRODUCTION

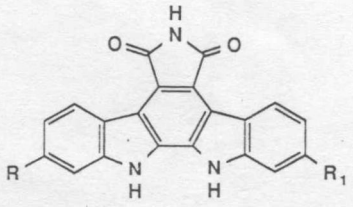
At present only a few natural products possessing an indolocarbazole unit are known. They include the antibiotics staurosporine (1) (from Streptomyces staruosporeus)[1-4], rebeccamycin (2) (a new antitumor antibiotic produced by Nocardia aeroligenes)[5] and the pigments[6] arcyriaflavin B (3b) and C (3c) from the slime mould Arcyria denudata. Arcyriarubin B (4b) and C (4c) as well as arcyroxepin A (5) are non-indolocarbazolic congeners to 3.



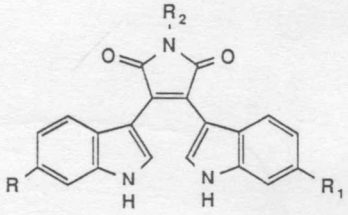

1



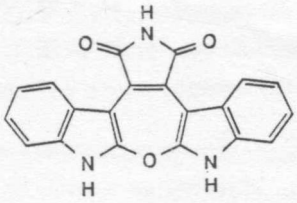

2



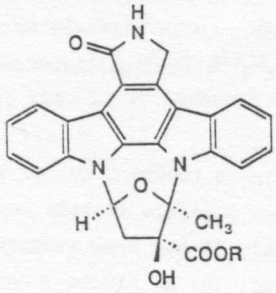

3 a R=R$_1$=H
b R=H, R$_1$=OH
c R=R$_1$=OH



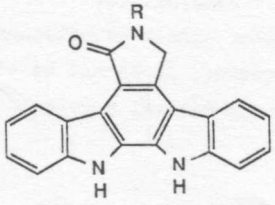

4 a R=R$_1$=R$_2$=H
b R=R$_2$=H, R$_1$=OH
c R=R$_1$=OH, R$_2$=H
d R=R$_1$=H, R$_2$=CH$_3$
e R=R$_1$=H, R$_2$=Bn



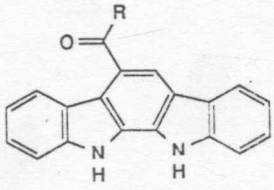
5



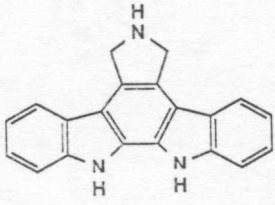
6 a R=$CH_3$
b R=H



7 a R=H
b R=Bn



8 a R=$NH_2$
b R=$OCH_3$

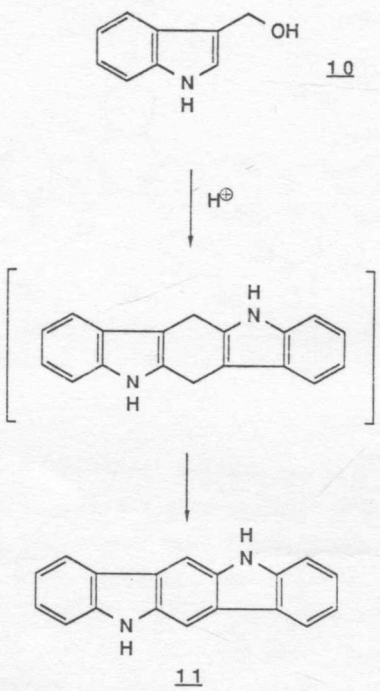


9

Staurosporine (1) is a potent platelet aggregation inhibitor[3] and likewise a potent inhibitor[4] of protein Kinase C. Subsequently similar inhibiting activity was reported for the new antibiotic 6 (and some congeners) isolated from Nocardiopsis sp. K-252. In this study, the indolocarbazole 7a (i.e. the aglycon of 1 and 6) was isolated as a natural product and also found to be a potent inhibitor of protein Kinase C. Compounds 1, 6 and 7a seriously affect the function of platelets, mast cells and several other cells and tissues. The availability of these indolocarbazoles should facilitate studies on the physiological role of protein Kinase C and calmodulin in the $Ca^{2+}$-messenger system. In this connection it appears to be of importance to evaluate the activity of "simplified" synthetic analogues of 7a such as 8a and 9.

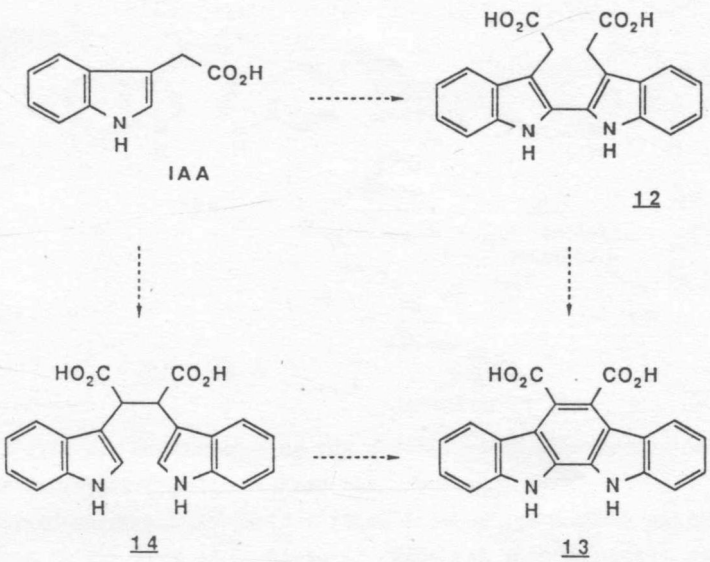
The first synthetic efforts in the field were reported 1980 by Steglich[6] who prepared the arcyriarubin analogue 4d from N-methyl-3,4-dibromomaleimide and the indole Grignard reagent. More recently several other routes, more or less related to the synthesis of staurosporine (1) or its aglycon 7a, have been reported[8-17].

All the indolocarbazoles isolated so far are indolo[2,1-b]carbazoles; no members of the other four possible systems have been reported as a unit in natural products. Recently it has been suggested[18,19] that an acid-induced selfcondensation (cf. ref. 20) of indole-3-carbinol (10) is responsible for the antitumor effect associated with 10, since indolo[3,2-b]carbazole(11) binds to the TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) receptor almost as efficiently as TCDD itself, whereas 10 seems not to bind at all. However, it should be stressed that 11 (or a derivative) has yet to be isolated from a natural source.




Scheme 1

Nothing is known about the biosynthesis of the indolocarbazole alkaloids but an obvious candidate for involvement, as speculated in Scheme 2, is tryptophan or indole-3-acetic acid (IAA). An un-confirmed report[21] which states that 12 is responsible for the plant hormone effect of IAA is of interest in this connection.

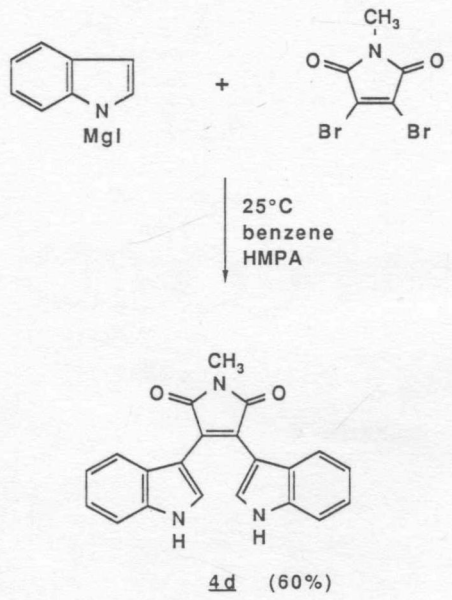



Scheme 2

Synthetic Studies

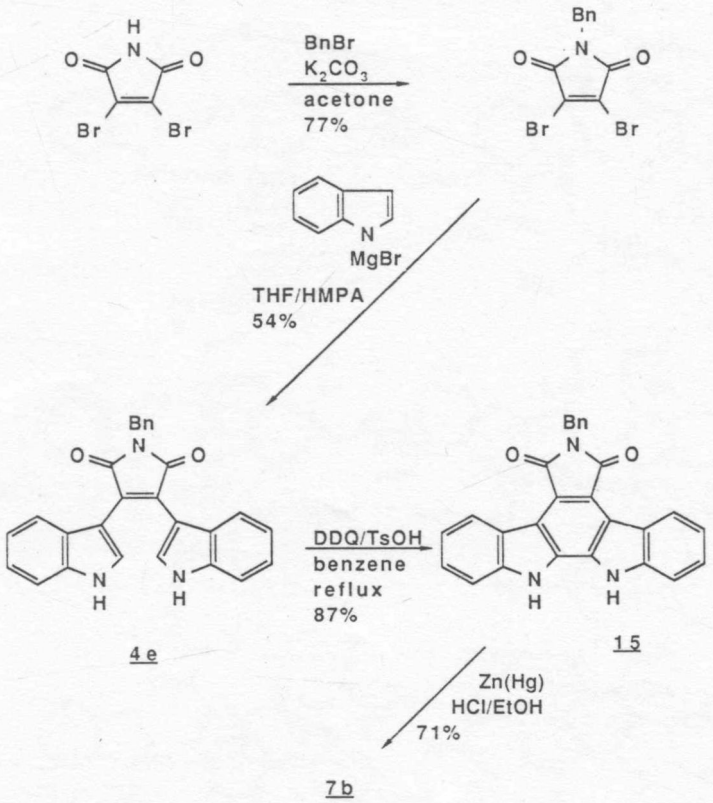
In connection with the isolation work of the pigments from Arcyria denudata Steglich[6] synthesized 4d in a straightforward manner by reacting indolylmagnesium iodide with N-methyl-3,4-dibromomaleimide in benzene in the presence of HMPA (Scheme 3). This efficient coupling methodology was later adopted by Weinreb[10] in a slightly modified form for the synthesis of 4e, as outlined in Scheme 4. Attempts to reduce the imide from the 2,2'-coupling reaction with $LiAlH_4$ and related reagents were unsuccessful because only partial reduction to the hydroxy lactam occurred, even under forcing conditions.

The conditions for the Clemmensen reduction step (15→7b) was originally worked out by Raphael[9] in connection with his approach to arcyriaflavin B, which is outlined in Scheme 5.




4d (60%)

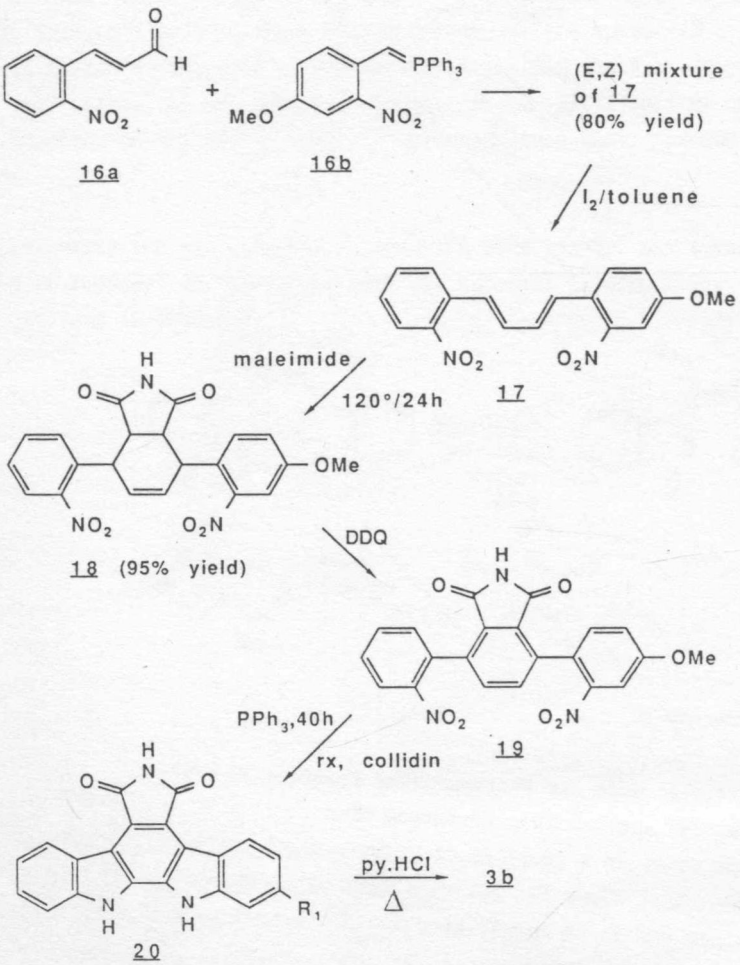
Scheme 3




Scheme 4

The ylid was generated from the corresponding phosphonium bromide ($K_2CO_3$/18-crown-6/$CH_2Cl_2$) and was then condensed with o-nitrocinnamaldehyde to yield a (Z,E)-diene mixture which was quantitatively converted to the pure (E,E)-diene 17. Reaction with maleimide subsequently gave the desired Diels-Alder adduct in excellent yield. Dehydrogenation of this adduct (18) with DDQ in t-butylbenzene gave the required substituted terphenyl 19(75-80% yield). The crucial double indolization by nitrene insertion was effected (65% yield) with $PPh_3$ in refluxing (40h) collidine. Minor byproducts in this step included two isomeric mononitrene carbonyl insertion products. The final demethylation required some experimentation but was finally effected by Prey's method (heating with neat pyridine-HCl).

N-benzylmaleimide reacted similarly with the parent compound of 17 (i.e. 1,4-di(o-nitrophenyl)butadiene) to give a Diels-Alder adduct which could in steps be converted to 7b (cf Scheme 4).




Scheme 5