New Trends in Natural Product Chemistry

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NEW TRENDS IN NATURAL PRODUCT CHEMISTRY

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Amsteldijk 166
1st Floor
1079 LH Amsterdam
The Netherlands

British Library Cataloguing in Publication Data

New trends in natural product chemistry
1. Natural products – Congresses 2. Natural products – Analysis – Congresses
I. Rahman, Atta-ur-, 1942- II. Choudhary, Muhammad Iqbal
547.7

ISBN 90-5702-287-7

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FOREWORD

Approaching the millennium, we can look back on the achievements of science in the past fifty years in awe of the spectacular advances that have been made on behalf of humankind. Natural product chemistry is certainly no exception, drawing as it does on the advances that have occurred in many intertwining fields, such as physics, organic chemistry, electronics, computers, and plant and mammalian biotechnology. In this volume, compiled from the outstanding presentations at the 6th International Symposium on Natural Products Chemistry held in Karachi, Pakistan, one can see immediately that research groups all over the world, in developing and developed countries, are tirelessly forging linkages for collaboration, and applying their collective and individual expertise to some of the most pressing health problems in the world.

Substantial new work is reported on the developments which will make a rare potent analgetic alkaloid from the skin of a frog available for extended pharmacological and hopefully clinical testing. There are several chapters devoted to various advances in the ongoing quest for improved anticancer agents from natural sources, be they from plants, from marine organisms or from microorganisms. Approaches to the developments of new antimalarial agents are reviewed, as are strategies for cancer chemopreventive agents.

One critical aspect of these important symposia does not appear in this volume, or any other symposium volume for that matter. It is the real, yet intangible camaraderie and understanding that is engendered when representatives from so many different countries and ethnic groups gather. While it is the science which draws these people together, it is their common humanity and desire to understand and develop fellowships which in the end is so critical. Thus the organizers and the sponsors who facilitate these gatherings are really to be thanked for their efforts to enhance both the science and level of human understanding that we all need in a time of instantaneous global interactions. This excellent volume stands as a testament to their efforts.

Geoffrey A. Cordell

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PREFACE

Chemical diversity in natural products is an immensely rich source of new pharmaceuticals, agrochemicals, industrial raw materials and other economically important chemicals. The renewed interest in natural product chemistry is largely based on many new developments in recent years. Asymmetric synthetic chemistry has largely reduced our dependence on natural sources by mimicking the synthesis of natural molecules. Cell-culture techniques have provided a means for sustainable use of biological resources without large-scale exploitation. Recent developments in spectroscopy have made it possible to determine the structures of very small quantities of samples in a short time. A number of new bench-top bioassays have been designed to facilitate the bioassay-directed isolation of natural products, besides the recently developed robotic-controlled bioassay techniques in industries for the rapid screening of several thousand samples in one day.

Compared with all this is the approach of chemists to focus on plant derived drugs as sources of new lead compounds which has contributed the recent progress in natural product chemistry. The so-called 'Green Wave' throughout the world has also created an atmosphere of acceptance of natural materials in contrast to synthetic materials.

The 6th International Symposium on Natural Product Chemistry was held in Karachi, Pakistan, 4–8 January, 1996. This symposia series has brought a galaxy of eminent chemists to Pakistan and developed a reputation of excellence in the field of natural products chemistry. It also provides a unique opportunity to scientists of the region to meet, interact and establish research collaborations with their colleagues in the developed world.

New Trends in Natural Products Chemistry is a compilation of articles based on the presentations during the symposium. These contributions are divided into two sections. Section A includes articles on routes developed to synthesise complex natural products, while section B is a compilation of discoveries of new natural products and their pharmacological properties.

We wish to record our indebtedness to a number of organizations which have contributed financially, materially or technically to the success of the 6th International Symposium of Natural Products Chemistry. We are particularly grateful to the National Science Foundation (USA), Office of Naval Research (USA), Third World Academy of Sciences (Italy), The Chemical Society of Pakistan and A.Q. Khan Research Laboratories. A number of private organizations have also contributed generously which include the Husein Ebrahim Jamal Foundation, Shahnawaz Limited, Technology Links (Pvt.) Ltd., AMS International, World Learning Bureau, Continental World Trading and the management of the Holiday Inn Crowne Plaza hotel group.

The symposium owes its success to the enthusiasm and dedicated hard work of the student volunteers, faculty and staff of the H.E.J. Research Institute of Chemistry (International Center for Chemical Sciences). We are also grateful to Harwood Academic Publishers for taking on the task of publishing the proceedings of the symposium.

Atta-ur-Rahman
M. Iqbal Choudhary

SECTION A

CONTENTS

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OPEN CHAIN 1,3-STEREOCONTROL

ASUNCION BARBERO, DAVID C. BLAKEMORE, IAN FLEMING* AND ROBERT C. WESLEY

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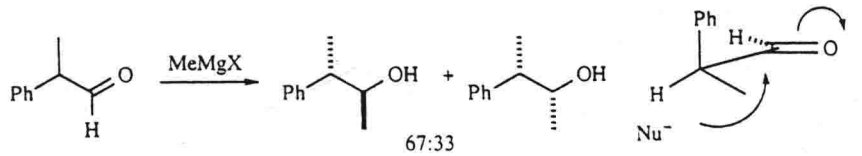
ABSTRACT

Several reactions of nucleophiles with aldehydes, ketones and α,β-unsaturated esters have been carried out in a search for a rule for open-chain 1,3-stereocontrol.

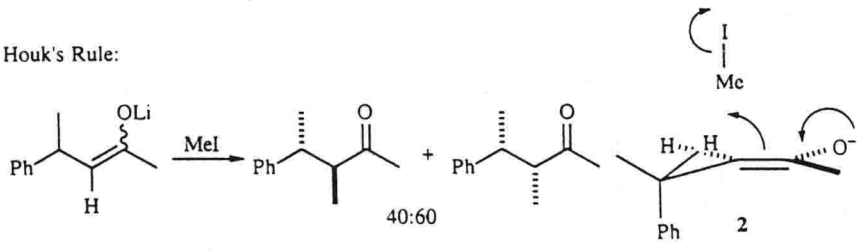
Cram's rule [1] for nucleophilic attack on a carbonyl group adjacent to a stereogenic centre is well known, and the explanation **1**, successively advanced by Karabatsos, Felkin, and Anh [2], is well accepted. We have pointed out [3] that the corresponding rule for electrophilic attack on a C=C double bond, developed successively by Zimmerman, Barton, and Houk [4], is in one sense the opposite of Cram's rule, because the preferred conformation at the time of reaction will have the hydrogen atom "inside" **2**.

Cram's Rule:



1

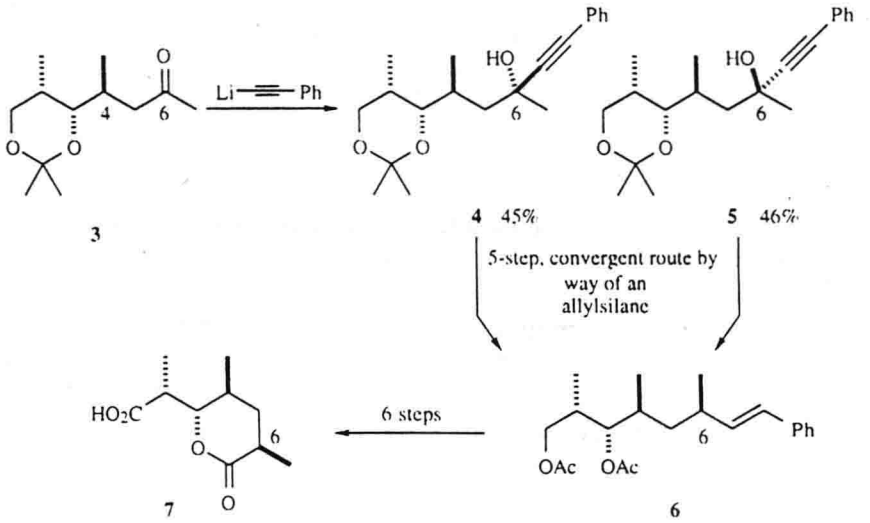
Houk's Rule:



2

The homologue of these reactions, in which the reaction site and the stereogenic centre are separated by a methylene group, is much less well understood. For good control in this situation, a cyclic substrate or transition structure is usually

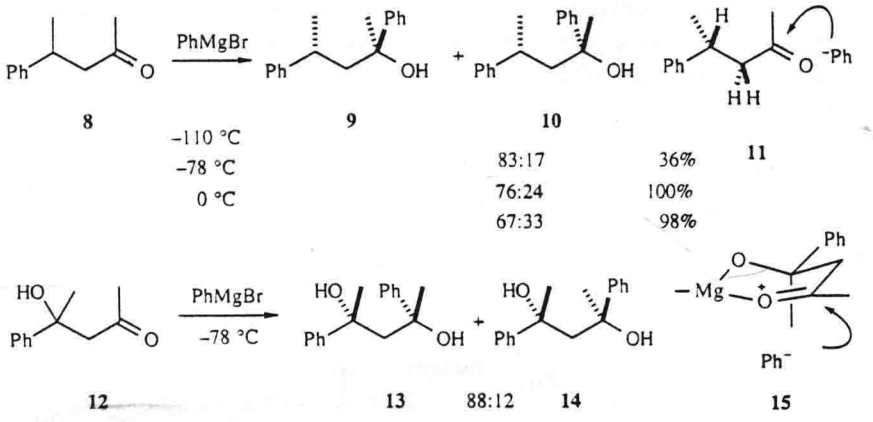
needed, and there are many such reactions, such as, for example, methods for controlling the relative stereochemistry of 1,3-diols by reduction of β-hydroxyketones [5]. In the absence of a ring, it is much more usual to get very low levels of diastereocontrol, as we found, for example, in our synthesis of the Prelog-Djerassi lactone **7** in which lithium phenylacetylide reacted with the ketone **3** having a stereogenic centre at C-4 to give both possible alcohols **4** and **5** at C-6 in equal amounts [6]. As it happens, that result was not a disappointment, since the whole point of that synthesis had been to demonstrate how our stereochemically complementary allylsilane syntheses, coupled to the predictably *anti* stereospecific protodesilylation of an allylsilane, allowed us to converge on a product **6** with the correct stereochemistry at C-6 from *both* diastereoisomers **4** and **5**.



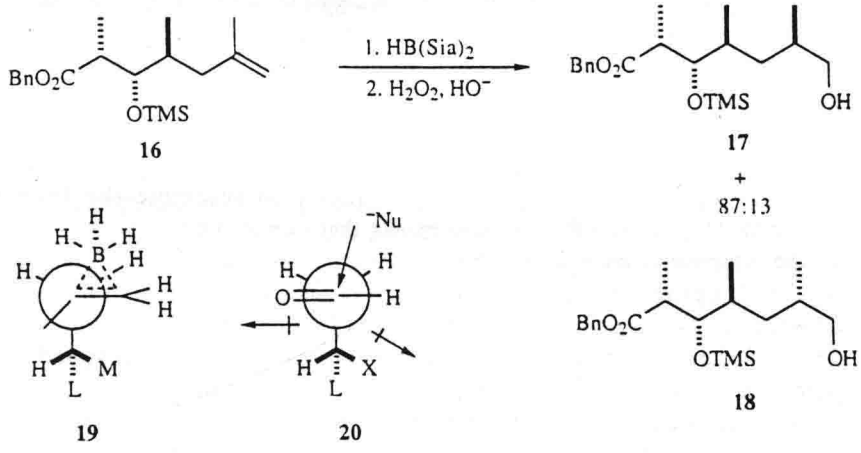
Nevertheless, it would be much easier if one were not obliged to use multistep sequences to achieve such control, but we need a rule with which to predict the sense of 1,3-selectivity in open-chain systems. We also need to be able to identify those features that lead to high levels of 1,3-stereocontrol, and, if such control is predictable, we can hope to save steps in syntheses.

Cram himself had already started on this route, finding low levels of selectivity in most cases but one reaction **8** → **9** + **10** with a high level, for which he offered the picture **11** to explain his result [7]. As in his work on 1,2-control, he also found that chelation made high levels of selectivity easier, as in the reaction **12** → **13** + **14**, which would now be explained by the picture **15** [8].

Evans found another example of substantial 1,3-selectivity in the hydroboration **16** → **17** + **18**, which he explained with a transition structure **19** [9]. This work led him into a substantial study of 1,3-selectivity in general, in the course

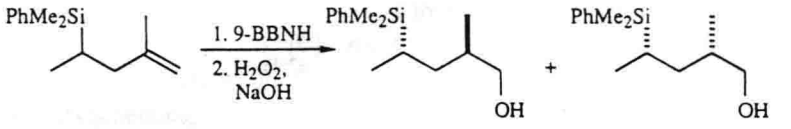


of which he found that nucleophilic attack on aldehydes gave high selectivity most reliably when the controlling stereogenic centre had a C-O bond to impart a dipolar influence on the transition structure **20** [10]. These transition structures are a development from the ideas of Jacques [11], and are significantly different from those of Cram.

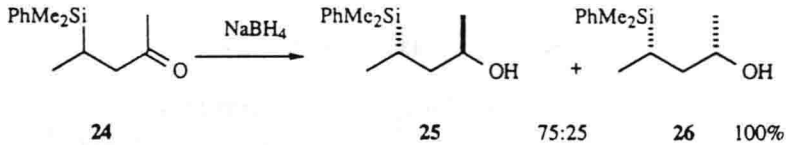


We also came across a stereoselective hydroboration reaction **21** → **22** + **23** and also a ketone reduction **24** → **25** + **26** [12]. To explain our hydroboration result, we drew yet another transition structure **27**, which is also based on Jacques', and is essentially the same as Evans's, but takes up a rather different perspective. This work led us into a larger study of the problem, the results of which we presented first in a lecture [13], and amplify now, one year later and with many more results, in another. Our work, like Evans's, is systematic and substantial. It is complementary to his, because we have chosen to study a system that we believe to be influenced only by steric effects free from polar

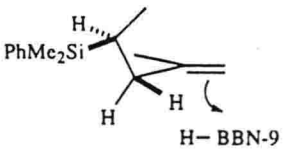
influences, but in consequence we have not been blessed with many examples of high levels of stereocontrol. Perhaps the single most powerful conclusion that our work provides is that Evan is probably right in identifying the dipolar effect as significant.



21 **22** 75:25 **23** 94%

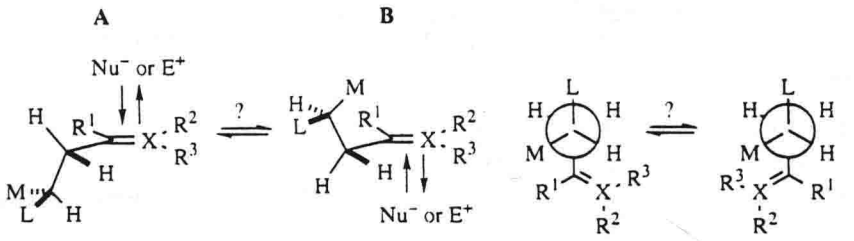


24 **25** 75:25 **26** 100%

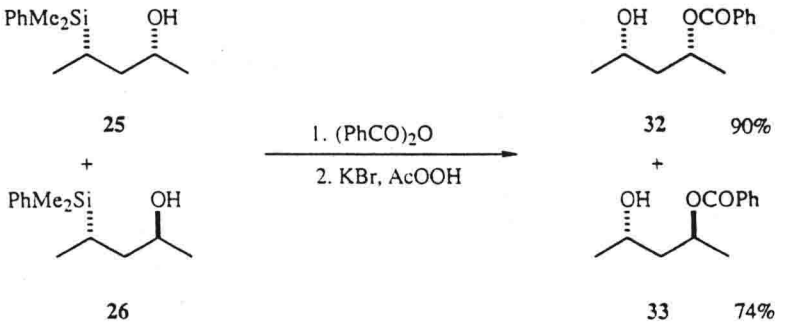


27

As a basis for thinking about what the factors affecting selectivity might be, we have chosen to use the drawings **28** and **29**, which we find easier to visualise. The argument that these pictures are likely to resemble the favoured conformation goes like this: we can expect that one of the two hydrogen atoms on the intervening methylene group will more or less eclipse the double bond; we can also expect that the large group L will take up a position in the segment between the two methylene hydrogen atoms. There are then two conformations, **28** and **29**; in the former the top face is more exposed to a reagent and in the latter the bottom face is more exposed. The Newman projections **30** and **31** provide an alternative view, and reveal that the difference between the conformations **28** and **29** is in the segments that the medium-sized group occupies. What we want to know is (i) which, if either, of these conformations is preferred, (ii) how is the position of equilibrium between the conformations affected by changing the variables, and (iii) do the experimental results match the predictions based on these considerations. We shall call attack from above, in the sense **28**, attack **A**, and attack from below, in the sense **29**, attack **B**, where the letters **A** and **B** are intended to be independent of any explanation, and we have used the same absolute configuration in all our drawings.



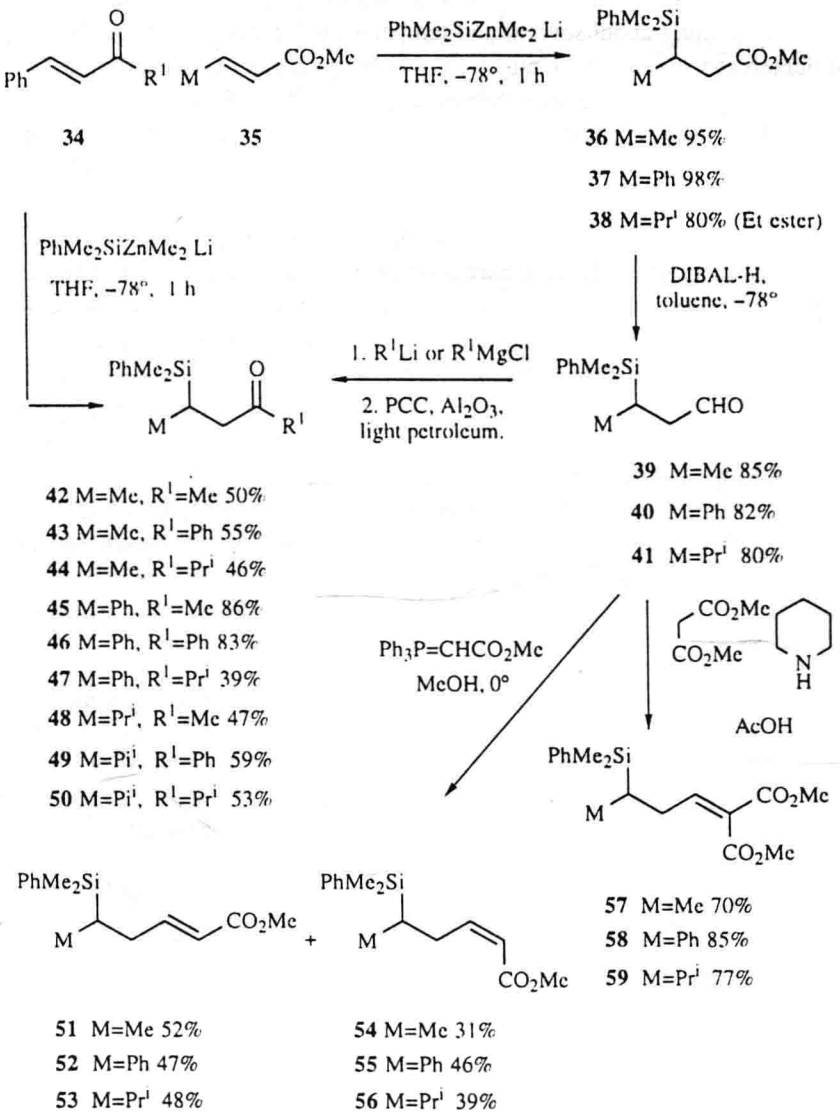
Our first problem was the infinite number of possibilities with six structural variables, L, M, R^1-R^3 and X, and a large number of possible reagents, E^+ or Nu^-, to say nothing about solvent and temperature. To begin with we chose to limit ourselves to nucleophilic attack on a carbonyl group (X=O) and on a C=C double bond carrying electron-withdrawing groups (X=C, R^1=H, and R^2 and/or R^3=CO_2Me). We have chosen to use three representative carbon-based groups, namely methyl, phenyl and isopropyl, both as the medium-sized groups M and as the substituent R^1. Perhaps most significantly, and least surprisingly, given that it is we who are doing this work, we have chosen the phenyldimethylsilyl group as the large group L. This particular choice has several virtues. The silyl group is unambiguously *large*, although it may prove to be less sterically *demanding* than we might like. It is unlikely to coordinate either to reagents or to functional groups within the molecule, either of which might give rise to cyclic transition structures. Most important, it can be converted with retention of configuration into a hydroxyl group [14], which makes it ideal for proving the relative configurations in the products. Thus we had easily proved the relative configuration of the alcohols **25** and **26** that we had already prepared by converting them into the diol monobenzoates **32** and **33** of known relative configuration. The major product **25**, which is the product of attack on the ketone **29** with M=R^1=Me, X=O and Nu^-="H^-", was therefore the product of attack taking place in the sense **B**.



Even with these limitations, there is still a formidable number of possible reactions. So far we have prepared the twenty-one substrates **39-59** by one or

more of the methods illustrated, using such reactions as silyl-zincation [15] of the ketone **34** and the esters **35**, and by aldol and Wittig reactions on the aldehydes **39-41**.

We have carried out 89 reactions involving nucleophilic attack on these substrates, using such nucleophiles as lithium aluminium hydride and sodium borohydride on the ketones, and Grignard and lithium reagents on the aldehydes, and cuprate reagents on α,β-unsaturated esters. In essentially every case we proved which diastereoisomer was the major product using reactions like those illustrated for the alcohols **25** and **26** giving the diol derivatives **32**



34 **35**

36 M=Me 95%
37 M=Ph 98%
38 M=Pr^i 80% (Et ester)

39 M=Me 85%
40 M=Ph 82%
41 M=Pr^i 80%

42 M=Me, R^1=Me 50%
43 M=Me, R^1=Ph 55%
44 M=Me, R^1=Pr^i 46%
45 M=Ph, R^1=Me 86%
46 M=Ph, R^1=Ph 83%
47 M=Ph, R^1=Pr^i 39%
48 M=Pr^i, R^1=Me 47%
49 M=Pi^i, R^1=Ph 59%
50 M=Pi^i, R^1=Pr^i 53%

57 M=Me 70%
58 M=Ph 85%
59 M=Pr^i 77%

51 M=Me 52%
52 M=Ph 47%
53 M=Pr^i 48%

54 M=Me 31%
55 M=Ph 46%
56 M=Pr^i 39%

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