

Combinatorial Chemistry

Synthesis, Analysis, Screening

Edited by
Günther Jung

 **WILEY-VCH**

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Prof. Dr. Günther Jung
Institut für Organische Chemie
Universität Tübingen
Auf der Morgenstelle 18
D-72076 Tübingen
Germany

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Preface

Since I edited *Combinatorial Peptide and Nonpeptide Libraries* – the first comprehensive book on the subject – in 1996, progress in the field of combinatorial chemistry has been truly dramatic. However, before I began to write this preface, I looked back and found the early work by no means outdated – as evidenced by the number of complimentary letters received from satisfied readers. A number of excellent books on combinatorial chemistry have appeared since then, covering different aspects of the subject. However, despite this earlier ‘boom’, I was encouraged to edit a second volume, and recognized that soon there will be very little overlap of *Combinatorial Chemistry* with the contents of other such books.

The past five years have seen the development and introduction of new and improved approaches to the combinatorial sciences, their practical applications having resulted in an almost ‘explosive’ increase in the number of experimental publications and new journals devoted exclusively to these areas. Thus, a comprehensive book which emphasizes the state of the art of most of the methods and instrumentation of combinatorial chemistry may be of value to those who may consider entering this exciting field. It is possible also that experts in combinatorial organic chemistry may find it interesting to examine more closely exciting new fields such as catalyst research, chemosensor development, new analytical tools, and the creation of biodiversity.

As a logical consequence of the demand for combinatorial chemists in industry, teaching the subject and related key technologies should be a major topic at our universities. It is hoped that some of the chapters of this book are sufficiently convincing as to encourage future scientists not only to use combinatorial methods in their research, but also to offer training for their students or co-workers. Indeed, for some years, I have offered public courses in multiple methods in peptide chemistry, and presently my group teaches theoretical and practical methods in combinatorial organic chemistry.

As we approach the end of the 20th century, we observe two major trends in the drug discovery process: first, the production of large numbers of single compounds and complex libraries in small scale (microgram) quantities; and second, the production of preparative-scale amounts (mg) of single compounds with complete analytical characterization and defined purity criteria, and less complex mixtures. At present, the nanoscale synthesis and on-line screening of 100 000 compounds per day remains a dream for organic chemists – except perhaps for primitive compounds and rather simple biological targets. Nonetheless, such wishes may be realized for oligomers accessible by repetitive synthetic steps.

Combinatorial Chemistry begins with a general overview on recent advances in the subject, with expert surveys provided on selected solid-phase organic reactions and – for the first time – also on solution-phase combinatorial chemistry. These chapters are followed by a detailed survey of the broad research into multicomponent reactions.

The chapter on solid supports in the first book has now been supplemented by a complete listing of the various solid-phase anchors and linkers used in organic chemistry – information which may be of particular value to newcomers in the field.

As a consequence of the progress and success of diverse oligomer libraries, experts in combinatorial synthetic oligomers, glycopeptide and oligosaccharide libraries, RNA- and DNA-aptamers have each contributed their news in these fields, while novel experimental examples of the use of templates in combinatorial chemistry for the solid-phase synthesis of multiple core structure libraries provide some insight to praxis-relevant work.

A complete chapter is devoted to novel combinatorial approaches to highly selective chemoreceptors designed for parallel analysis by sensor devices. An assay-oriented chapter on peptide libraries in T-cell-mediated immune response illustrates how libraries of extreme complexity (10^{13}) can lead directly to single molecules with activities that may be up to 100 000-fold higher than those of natural epitopes.

Results of combinatorial biosynthesis using gene clusters responsible for metabolites of potential pharmaceutical interest illustrate the state of the art in this field. Library design and diversity analysis are of increasing importance, and the present programs and approaches are discussed, together with expert views and opinions. In particular, the chapter on a miniaturized ultra-high throughput screening system highlights the immediate future in assay systems of this type.

Combinatorial approaches in materials sciences and solid-state catalysts are relatively new, and these are reviewed, together with expert contributions in the field.

Among the last five chapters, four are devoted to the important instrumentation used for analytical on- and off-bead controls. Whereas tagging concepts appear increasingly less interesting due to excessive time constraints and inherent problems introduced in the drug discovery process, a number of methods have proved suitable for routine single-bead analysis, including infra-red microscopy, separation techniques coupled to electrospray-mass spectrometry, and ion-cyclotron resonance-FT-mass spectrometry to determine the elemental composition of each component in a library. In addition, MAS-NMR has become a popular means of examining resin-bound intermediates during feasibility and optimization studies.

Finally, *Combinatorial Chemistry* closes with a critical discussion of the various attempts to automate combinatorial synthesis, with a presentation of a newly developed workstation used to perform fully automated parallel synthesis, including all steps through work-up to sample preparation for screening modules.

I would like to close this Preface by expressing my gratitude to all authors and co-authors who spent their precious time in contributing to this work. I also acknowledge the present and former co-workers of my group who contributed novel experimental results.

I am very grateful to Mrs. Ursula Sanzenbacher for her help during the editorial work, and to Dr. Gudrun Walter and Dr. Peter Göllitz from Wiley-VCH for their continuous interest on this edition.

During the past few years – and in parallel with combinatorial chemistry – communication via the Internet and the availability of published material from databases have emerged exponentially. However, I am confident that a broad readership may still – from time to time – enjoy reading a scientific book such as *Combinatorial Chemistry*.

Tübingen, September 1999

Günther Jung

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List of Abbreviations

| | |
|----------|--|
| A-3CR | Asinger – three component reaction |
| Aba | 2-aminobenzoic acid |
| Ac | acetyl |
| ACN | acetonitrile |
| ACP | acyl carrier protein |
| ADME | absorption, distribution, metabolism, excretion |
| ADPV | 5-(4-aminomethyl-3,5-dimethoxy-phenoxy)-valeric acid |
| Alloc | allyloxycarbonyl |
| AM | aminomethyl |
| AMCA | 7-amino-4-methyl-coumarin-3-acetic acid |
| ANP | 3-amino-3-(2-nitrophenyl) propionic acid |
| APCI | atmospheric pressure chemical ionization |
| ATP | adenosine triphosphate |
| ATR-IR | attenuated total reflection infrared spectroscopy |
| BAL | backbone amide linker |
| BAP | borane/pyridine complex |
| BB-4CR | Berg-Bucherer – four component reaction |
| BBTO | bis-(tributyl)tin oxide |
| BEMP | 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine |
| BHA | benzyhydramine |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn, Benz | benzyl |
| Boc | tert.-butoxycarbonyl |
| BOP | benzotriazolyl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate |
| Bz | benzoyl |
| CAD | collision activated dissociation |
| CALD | computer assisted library design |
| CAN | ceric ammonium nitrate |
| CBP | carbohydrate binding proteins |
| Cbz | benzyloxycarbonyl |
| CD | circular dichroism |
| CDI | N,N-carbonyldiimidazole |
| CE | capillary electrophoresis |

XXIV *List of Abbreviations*

| | |
|--------|---|
| CHC | a-cyano-4-hydroxy-cinnamic acid |
| CHO | chinese hamster ovary (cells) |
| Chx | cyclohexyl |
| CID | collision induced decay |
| CID | collision induced decomposition |
| CLEAR | cross-linked ethoxylate acrylate resin |
| CLF | chain length factor protein |
| CLIP | class II-associated invariant chain peptide |
| CMPP | chloromethyl phenyl pentyl polystyrene |
| CoA | coenzyme A |
| Cod | cyclooctadienyl |
| CPG | controlled pore glass |
| CRD | carbohydrate recognition domain |
| CTL | cytotoxic T lymphocytes |
| cHex | cyclohexyl |
| Cy | cyclohexyl |
| CZE | capillary zone electrophoresis |
| Da | dalton |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBE | double bond equivalent |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCI | desorption chemical ionization |
| DCM | dichloromethane |
| Dde | 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl |
| DDQ | dichlorodicyano-p-benzochinon |
| DEAD | diethylazodicarboxylate |
| DEBS | 6-deoxyerythronolide B synthase |
| DH | dehydratase |
| DIAD | diisopropyl azodicarboxylate |
| DIBAH | diisobutylaluminium hydride |
| DIBAL | diisobutylaluminium hydride |
| DIC | diisopropylcarbodiimide |
| DIEA | diisopropylethylamine |
| DMAE | dimethylaminoethanol |
| DMAP | 4-N,N-dimethylaminopyridine |
| DMF | N,N-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DMTST | dimethyl(methylthio)sulfonium-trifluoromethylsulfonate |
| DNA | desoxyribonucleic acid |
| DRIFTS | diffuse reflectance infrared Fourier transform spectroscopy |
| DSB | 4-(2,5-dimethyl-4-methylsulfinylphenyl)-4-hydroxybutyric acid |
| DVB | divinylbenzene |
| EA | enzyme acceptor |
| EBV | Epstein-Barr virus |
| ED | enzyme donor |

| | |
|--------|---|
| EDC | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride |
| EI | electron impact |
| ELISA | enzyme-linked immunosorbent assay |
| ER | endoplasmatic reticulum |
| ER | enoyl reductase |
| ESI | electrospray ionization |
| ES-MS | electrospray-mass spectrometry |
| Et | ethyl |
| FAB | fast atom bombardment |
| FCS | fluorescence correlation spectroscopy |
| FITC | fluoresceinisothiocyanate |
| FMN | flavinemononucleotide |
| Fmoc | fluorenylmethyloxycarbonyl |
| FP | fluorescence polarization |
| FRET | fluorescence resonance energy transfer |
| FT | Fourier transform |
| FT-IR | Fourier transform infrared spectroscopy |
| Fuc | L-fucose |
| GalNAc | N-acetyl-D-galactosamine |
| GC | gas chromatography |
| GlcNAc | N-acetyl-D-glucosamine |
| HFIP | hexafluoroisopropanol |
| HHR | hammer head ribozyme |
| HIV | human immunodeficiency virus |
| hKGF | human keratinocyte growth factor |
| HLA | human leukocyte antigen (MHC) |
| HMBA | 4-hydroxymethylbenzoic acid |
| HMPB | 4-hydroxymethyl-3-methoxyphenoxybutyric acid |
| HMP-PS | p-benzyloxybenzyl alcohol polystyrene |
| HMQC | heteronuclear correlation quantum coherence |
| HOBT | hydroxybenzotriazole |
| HPLC | high performance liquid chromatography |
| HPSEC | high-performance size-exclusion chromatography |
| HQN | hydroxy-quinuclidine |
| HTE | high-throughput experimentation |
| HTS | high-throughput screening |
| HR | high resolution |
| iPr | isopropyl |
| IR | infrared |
| ICR-MS | ion cyclotron resonance mass spectrometry |
| ICR | ion cyclotron resonance |
| IRMDP | multiphoton infrared photodissociation |
| kDa | kilodalton |
| KHMDS | potassium bis(trimethylsilyl)amide |
| KR | ketoreductase |

XXVI *List of Abbreviations*

| | |
|------------|---|
| KS | ketosynthase |
| Lau | lauric acid |
| LC | liquid chromatography |
| LCAA-CPG | long-chain alkyl amino controlled pore glass |
| LC-MS | liquid chromatography-mass spectrometry |
| LD | laser desorption |
| M-3CR | Mannich – three component reaction |
| MALDI | matrix assisted laser ionization |
| MAMP | alpha-methoxy-phenyl (4-methoxy-benzhydryl) |
| Man | mannose |
| MAS-NMR | magic angle spinning-nuclear magnetic resonance |
| MBHA | 4-methylbenzhydrylamine |
| MBP | myelin basic protein |
| mCPBA | meta-chloroperoxobenzoic acid |
| MCPS | multiple column peptide synthesis |
| MCR | multicomponent reaction |
| MCSL | multiple core structure libraries |
| Me | methyl |
| Me-Du-Phos | 1,2-bis(2,5-dimethylphospholano)benzene |
| MHC | major histocompatibility complex |
| MOBHA | 4-methoxybenzhydrylamine |
| MPR | mannose-phosphate receptor |
| Ms | mesyl, methanesulfonyl |
| MS | mass spectrometry |
| MsCL | methanesulfonylchloride |
| MTBD | 7-methyl-1,5,7-triazabicyclo[4,4,0]elec-5-ene |
| MTP | microtiter plate |
| Mtr | 4-methoxy-2,3,6-trimethyphenyl-sulfonyl |
| Nasyl | naphthylsulfonyl |
| NBA | 4-aminomethyl-3-nitrobenzoic acid |
| Nbb-PS | aminobenzhydryl-polystyrene |
| NBHA | ortho-nitrobenzylhydramino (2-nitrobenzhydrylamine) |
| NeuAc | N-acetyl-neuraminic acid |
| NIS | N-iodosuccinimide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| NPE | 4-hydroxyethyl-3-nitro-benzoic acid |
| Npss | 2-methoxy-5-(2-(2-nitrophenyl)dithio-1-oxypropylphenylacetic ac |
| NSG | N-substituted oligoglycine |
| NBS-Cl | o-nitrobenzenesulfonyl chloride |
| P | partition coefficient |
| P-3CR | Passerini – three component reaction |
| PAAs | poly-N-acylated amines |

| | |
|------------|---|
| PAL | peptide amide linker: 5-[4[9-fluorenylmethoxycarbonylaminomethyl]-3,5-dimethoxyphenoxy]valeric acid |
| PAM | phenylacetamidomethyl |
| PBS | phosphate buffered saline |
| PCA | principal component analysis |
| PCR | polymerase chain reaction |
| PDC | pyridinium dichromate |
| PDTs | pharmacophor definition triplets |
| PEG | polyethyleneglycol |
| PEGA | polyethylene glycol-polyacrylamide co-polymer |
| PEG-PS | polyethylene glycol-polystyrene |
| PET | photo-induced electron transfer effect |
| Pfp | pentafluorophenyl |
| Ph | phenyl |
| PhFl Resin | 9-phenylfluorene-9-yl-PS/DVB |
| Pip | piperidine |
| PK | pharmacokinetics |
| PKSs | polyketide synthases |
| PNAs | peptide nucleic acids |
| PNP | para-nitrophenyl |
| POEPOP | polyoxyethylene-epichlorohydrine derivative |
| POEPS | polyoxyethylene-cross-linked-oligostyrene |
| Ppa | phenylpropionic acid |
| PS | polystyrene |
| PS-DVB | polystyrene-divinylbenzene copolymer |
| PSD | post-source decay |
| PS-PEG | polystyrene-polyethyleneglycol graft polymer |
| PyBroP | bromo-tris-pyrrolidino-phosphonium-hexafluorophosphate |
| QSAR | quantitative structure-activity relationship |
| R | alkyl |
| RCM | ring closure metathesis |
| relSI | relative stimulation index |
| REMPI | laser-induced resonant multiphoton ionization |
| Rev | reverse transcriptase (HIV) |
| RIfS | reflectometric interference spectroscopy |
| RP-HPLC | revers phase-high performance liquid chromatography |
| RRE | Rev-responsive element |
| S-3CR | Strecker – three component reaction |
| SAR | structure-activity relationship |
| SASRIN | super acid sensitive resin |
| SDS-PAGE | sodium dodecylsulfate-polyacrylamide gel electrophoresis |
| SI | stimulation index |
| S-Le | sialyl – Lewis |
| SMSI | string metal support interaction |
| SPOC | solid-phase organic chemistry |

XXVIII *List of Abbreviations*

| | |
|---------|---|
| SPOCC | polyoxyethylene-oxetane derivative |
| SPOS | solid phase organic synthesis |
| SPPS | solid phase peptide synthesis |
| ssRNA | single stranded ribonucleic acid |
| TAR RNA | trans-activation response region |
| TAP | transporter associated with antigen processing |
| TBAF | tetrabutylammonium fluoride |
| Tbf | tetrabenz[a,c,g,i]fluorene |
| tBu | tert.-butyl |
| TCC | CD4 ⁺ T-cell clones |
| TCR | T-cell receptor |
| TE | thioesterase |
| TEA | triethyl amine |
| Tf | trifluoromethylsulfonyl |
| TFA | trifluoroacetic acid |
| TFE | trifluoroethanol |
| TFMSA | trifluoromethanesulfonic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIC | total ion current |
| TIPS | triisopropylsilane (TIS) |
| TIS | triisopropylsilane (TIPS) |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TMOF | trimethylsilyl trifluoromethanesulfonate |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| Tn | tags for labeling |
| TOCSY | total correlation spectroscopy |
| TOF | time-of-flight |
| TPAP | thrombin receptor activating peptide |
| Ts | tosyl, para-toluenesulfonyl |
| U-4CR | Ugi – four component reaction |
| uHTS | ultra high-throughput screening |
| UV | ultra-violet |
| UVDD | ultra-violet photodissociation |
| VEGF | vascular endothelial growth factor |
| VLSIPS | very large-scale immobilized polymer synthesis |
| VPF | vascular permeability factor |
| WHIM | weighted holistic invariant molecular (indices) |
| Z | benzyloxycarbonyl |

Further special abbreviations of linkers and resins are found in Chapter 5.