Tetrahedron 70 (2014) 8183–8218

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 1051

# Protecting group-free syntheses of natural products and biologically active compounds

Radomir N. Saicic

*Faculty of Chemistry, University of Belgrade, Studentski trg 16, POB 51, 11158 Belgrade 118, Serbia*

ARTICLE INFO

*Article history:*
Received 17 January 2014
Available online 14 June 2014

*Keywords:*
Organic synthesis
Protecting groups
Natural products
Protecting group-free synthesis

**Contents**



*Abbreviations:* AIBN, azobisisobutyronitrile; 9-BBN, 9-borabicyclo[3.3.1]nonane; BER, borohydride exchange resin; BINOL, [1,1′-binaphthalene]-2,2′-diol; CDI, carbonyldiimidazole; cod, 1,5-cyclooctadiene; Cy, cyclohexyl; DABCO, 1,4-diazabicyclooctane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-quinone; DEAD, diethyl azodicarboxylate; DET, diethyl tartrate; DHP, 3,4-dihydro-2*H*-pyran; DIAD, diisopropyl azodicarboxylate; DIBAL, diisobutylaluminum hydride; DIPCl, β-chlorodiisopinocampheylborane; DIPEA, diisopropylethylamine; DMA, dimethyl acetamide; DMAP, 4-dimethylaminopyridine; DME, dimethoxyethane; DMF, dimethyl formamide; DMP, Dess–Martin periodinane; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone; DMSO, dimethyl sulfoxide; DPPA, diphenyl phosphoryl azide; DTBP, di-*tert*-butylpyridine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; Grubbs II, Grubbs catalyst second-generation; FGI, functional group interconversion; HFIP, hexafluoroisopropanol; HMPA, hexamethyl phosphoric triamide; HMPTA, hexamethylphosphorous triamide; HOAt, 1-hydroxy-7-azabenzotriazole; HOBt, 1-hydroxybenzotriazole; IBX, 2-iodoxybenzoic acid; Ipc, isopinocampheyl; JohnPhos, 2-(di-*tert*-butylphosphino)biphenyl; KHMDS, potassium hexamethyldisilazide; LDA, lithium diisopropylamide; *m*-CPBA, *meta*-chloroperoxybenzoic acid; Mes, 2,4,6-trimethylphenyl; MS, molecular sieves; MsCl, methanesulfonyl chloride; MTBE, methyl *tert*-butyl ether; MVK, methyl vinyl ketone; μw, micowave heating; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NIS, *N*-iodosuccinimide; NMM, *N*-methylmorfoline; NMO, *N*-methylmorfoline-*N*-oxide; *p*-ABSA, *p*-acetamidobenzenesulfonyl azide; PCC, pyridinium chlorochromate; PG, protecting group; PGF, protecting group free; PivOH, pivalic acid; PPTS, pyridinium *p*-toluenesulfonate; Py, pyridine; Ra-Ni, Raney nickel; (*R*)-Me-BoPhoz, (*R*)-*N*-methyl-*N*-diphenylphosphino-1-[*S*-2-(diphenylphosphino)ferrocenyl]ethylamine); TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBAF, tetrabutylammonium fluoride; TBAI, tetrabutylammonium iodide; TBHP, *tert*-butyl hydroperoxide; TEBAC, triethylbenzylammonium chloride; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxy; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TFDO, methyl(trifluoromethyl)dioxirane; THF, tetrahydrofuran; TMEDA, tetramethyl ethyenediamine; $TMSCHN_2$, trimethylsilyl diazomethane; TMSOK, potassium trimethylsilyloxide; T3P, propylphosphonic anhydride; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

E-mail addresses: rsaicic@chem.bg.ac.rs. rnsaicic@gmail.com.

http://dx.doi.org/10.1016/j.tet.2014.06.025

## 1. Introduction

At the beginning of the 21st century, the art and science of organic synthesis face the challenge of optimizing efficiency. One may assert that the need for efficiency has always been tacitly understood; however, when confronting the complex structure of a target molecule, a synthetic chemist has traditionally sought its total synthesis at any price. Some total syntheses of complex natural products are among the best scientific accomplishments of the 20th century; these syntheses have had a strong impact not only on the development of chemistry but also on biology, medicine, pharmacology, materials science, and even philosophy. Yet, these were more often than not lengthy procedures that consumed extended time and effort from devoted researchers, used hazardous reagents, produced toxic waste and were very costly, to obtain typically very small amounts of the desired products. In contrast, nature seems to produce its molecules without effort, and it does so in open vessels at room temperature without organic solvents and usually with high optical purity. Indeed, after 3.5 billion years of continuous experimenting, nature has evolved into an extremely good synthetic chemist, whose efficiency surpasses by far the current level of chemical science. The natural challenge to the human intellect is to emulate this efficiency by a rational design. The question is no longer 'can we synthesize a particular molecule?' but rather 'how can we synthesize it in the best possible way?' The focus is not to author the first synthesis of a molecule but to discover the best synthesis. This change of attitude—aiming for the ideal synthesis—is a natural step forward in the development of the field, inspired not only by academic thinking but also by the new role of organic synthesis in the scientific community.[1] Although chemistry still creates its own object,[2] it is increasingly involved in interdisciplinary research, such as life science or materials science, where it is expected to rapidly produce reasonable amounts of desired compounds, in economically and environmentally acceptable ways. These latter issues become of prime importance when any industrial application is considered. Thus, along with the increased use of domino, cascade, and multicomponent reactions to rapidly increase molecular complexity, additional attention is paid to other aspects, such as step-, atom- or redox-economy,[3] green chemistry, and protecting group-free synthesis (PGF synthesis). The provisional classification of these otherwise interconnected issues allows them to be analyzed separately and reviewed in more detail.

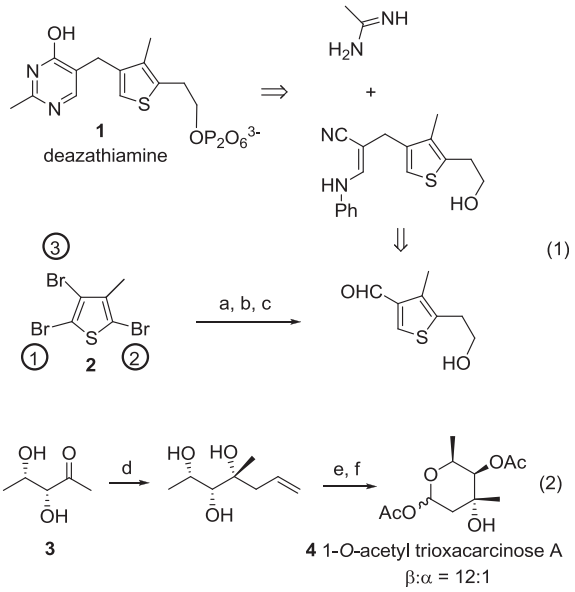
An important prerequisite for synthetic efficiency is to minimize the use of protecting groups: using fewer protecting groups reduces the number of steps, increases the overall yield, and improves the economy of the process. Excellent reviews on this topic have stimulated the creativity and invention of synthetic chemists in this regard,[4] and PGF syntheses have been reported at an increasing pace. This review covers the PGF syntheses of natural products since 2009, when the topic was comprehensively reviewed most recently.[4b]

For a successful PGF synthesis, several principles should be followed: (1) If a target molecule contains several reactive functional groups (FGs), the construction of the carbon skeleton should rely on reactions that are known to be tolerant of a range of functionalities. In this respect, the use of organotransition metal-catalyzed reactions has found widespread application. Radical reactions are also known to tolerate groups that need protection under ionic conditions, as well as most pericyclic reactions and a number of rearrangements. (2) Reactive functional groups should be introduced in later stages of synthesis. This logical principle has become the basis for a new, two-phase retrosynthetic strategy. It may also prove useful to implement reactive functional groups into precursors in their latent form; while this may be considered a type of protection, such FG equivalents do not have to be introduced into the synthetic intermediates during synthesis but are present from the beginning as synthetic equivalents. (3) A biomimetic approach often allows for the most efficient and economical access to natural products. It is not necessary to use enzymes, but the goal is to emulate the mechanistic principle of the envisaged transformation and the structural pattern of proposed biosynthetic intermediates. (4) A deeper understanding of the reactivity of a substrate molecule can allow for chemoselectivity to be achieved without the need to block the centers of unwanted reactivity. In addition, new catalysts and reagents are continuously being discovered that can alter the order of reactivity of competitive FGs and modify the chemoselectivity of a given reaction. This understanding has led to the modified chiron approach, in which chiral synthons from natural sources are implemented in target compounds without PG manipulations. (5) Probably most importantly, the challenges of PGF synthesis are also opportunities for invention, and the solutions of particular problems that involve new reactions and strategies can permanently enrich the synthetic armamentarium.

An attempt was made to group the examples from the literature according to (one of the aforementioned) principles whose application enabled PGF synthesis. However, and especially in the syntheses of complex molecules, it is usually not a single factor but rather a combination of these that contributes to the success of the PGF sequence. Therefore, some level of inherent inconsistency was inevitable when arranging material for this review.

## 2. Syntheses based on metal-mediated reactions

Metal-mediated reactions have dominated PGF synthesis, with a preponderance of organotransition metal-catalyzed reactions, whereas reactions of organometallic nucleophiles were scarce and usually limited to molecules with a low level of functionalization.[5]




**Scheme 1.** Reagents and conditions: (a) Zn powder, AcOH, reflux overnight, 80%; (b) *n*-BuLi (1.0 equiv), ethylene oxide, $BF_3{\cdot}Et_2O$, −78 °C to 0 °C, 3 h, 64%; (c) *n*-BuLi (2.0 equiv), DMF, −78 °C to rt, 3 h, 64%; (d) allyl bromide, In, water, rt; (e) $O_3$, MeOH, −78 °C, then $Me_2S$; (f) $Ac_2O$, DMAP, 42% over three steps.