Chimia 55 (2001) 1045–1048

ISSN 0009–4293

Radical Reactions as a Tool for Natural Product Synthesis

Philippe Renaud*

Abstract: Four examples of the synthesis of simple natural products and analogues bearing several adjacent stereogenic centers are presented. In all these syntheses, a highly stereocontrolled radical process is used as a key step.

Keywords: 1,2-Acyl migration · Cyclization · Lactones · Natural product · Radical

Introduction

Radical chemistry has advanced tremendously since Moses Gomberg's discovery of the triphenylmethyl radical in 1900 [1]. However, it was only in the mid 1980s that the synthetic potential of radicals emerged as a useful tool thanks to the pioneer works of Giese (tin hydride mediated radical addition to olefins) [2], Barton (radical decarboxylation [3] and deoxygenation [4]) and Curran (iodine atom transfer reaction) [5]. The first applications in natural product synthesis rapidly appeared and the work of Stork (prostaglandin) [6], Hart (alkaloid) synthesis [7] and Curran (triquinanes) [8] confirmed the unique power of radical reactions. Several reviews have appeared which highlight the importance of radical reactions in total synthesis and demonstrate their synthetic potential in terms of predictability, generality and variability [9–12]. In this account, selected examples of the synthesis of natural products and analogues from our research group will be presented in order to illustrate some important features of radical reactions such as the possibility of performing unique rearrangements and the high stereoselectivity.

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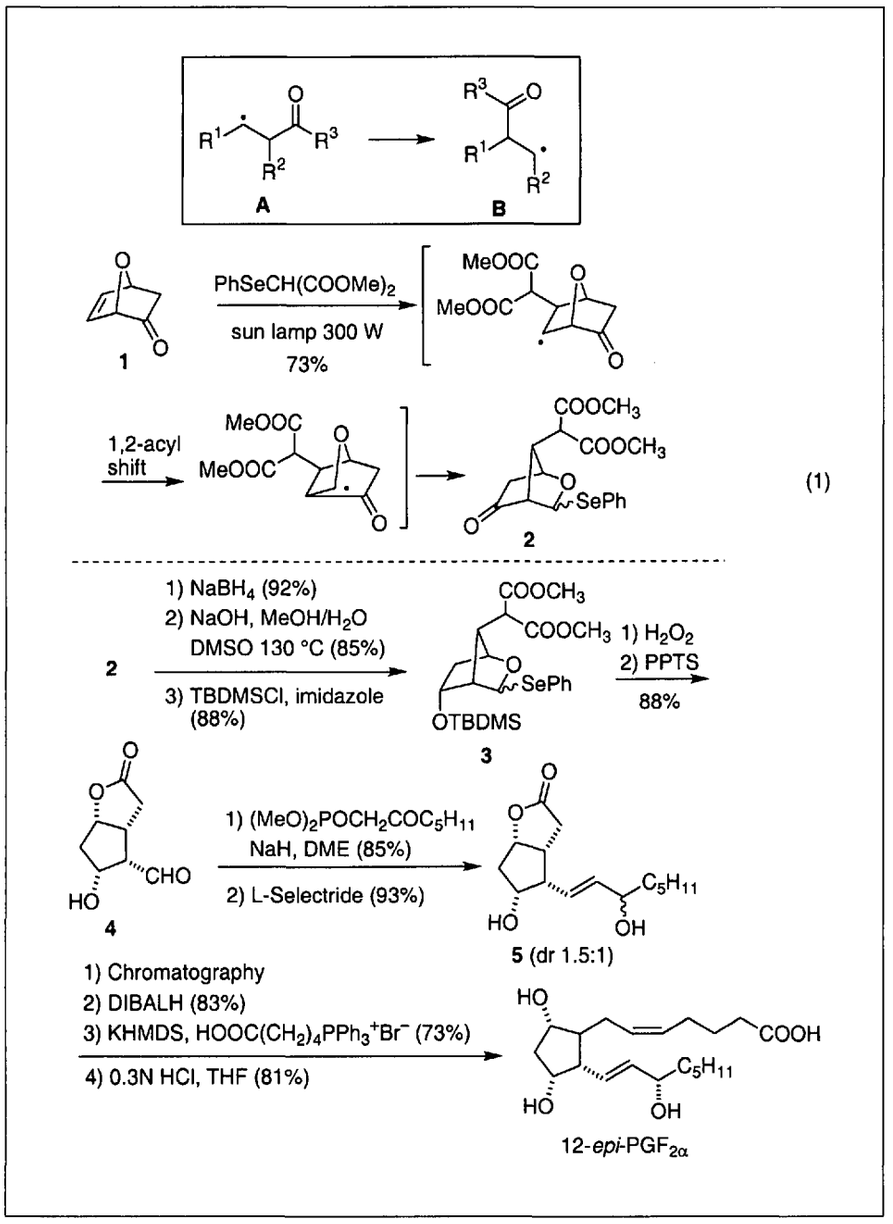
1,2-Acyl Migration in Bicyclic Systems

Radical 1,2-acyl migration (Scheme 1, **A** → **B**) is a well-established process that is involved in coenzyme-B12-dependent rearrangement catalyzed by methylmalonyl-CoA mutase. This rearrangement found applications in synthetic chemistry for one-carbon ring expansion reactions, a process commonly known as the 'Beck-with-Dowd' ring expansion reaction [13][14]. We have shown that a sequential reaction involving radical addition to bicyclo[2.2.1]hept-5-en-2-one (norbornenone) and 7-oxabicyclo[2.2.1]hept-5-en-2-one (7-oxanorbornenone) followed by a 1,2-acyl migration is feasible under phenylseleno transfer reactions [15]. For instance, addition of dimethyl phenylselenomalonate to 7-oxabicyclo [2.2.1]hept-5-en-2-one (**1**) under irradiation affords the selenoacetal **2** in 73% yield (Scheme 1, Eqn. 1). This product results from the completely stereoselective radical addition of the malonyl radical on the *exo* face of **1** followed by a 1,2-acyl migration. The efficiency of this process is caused by the slowness of the phenylseleno transfer reaction and the stability of the final O,Se-acetal **2**. Compound **2** is a useful building block that has been used for the synthesis of isoprostanes, a new class of natural products resulting from non-enzymatic lipid peroxidation [16], such as 12-*epi*-$PGF_{2\alpha}$ (Scheme 1). Indeed, **2** can be converted to **3** by stereoselective reduction, decarboxylation and silylation of the *endo* alcohol. Hydrolysis of the O,Se-acetal is achieved under oxidative conditions using hydrogen peroxide and treatment with pyridinium *para*-toluenesulfonate afforded the all-*cis* Corey lactone **4**. Introduction of the ω-chain was possible by reacting the formyllactone **4** with dimethyl 2-oxoheptylphosphonate/NaH. The ketone was reduced with L-Selectride and introduction of the α-chain *via* reduction of the lactone **5** to the lactol, Wittig reaction and deprotection afforded the desired 12-*epi*-$PGF_{2\alpha}$ [17]. The all-*cis* Corey lactone **4** has also served for the synthesis of an advanced intermediate of *epi*-thromboxanes [18].

The same intermediate **2** was used for a short synthesis of paraconic acids [19]. For instance, (±)-nephromopsinic acid has been prepared according to Scheme 2 [20]. Tin hydride reduction of **2** afforded **6**, which, upon Baeyer-Villiger oxidation, gives the bicyclic lactone **7**. Iodide mediated rearrangement of **7** to the disubstituted γ-lactone **8** is achieved by treatment with tetrabutylammonium iodide/BBr_3 followed by esterification of the free carboxylic acid with diazomethane. Decarboxylation and acidic hydrolysis gave the carboxylic acid **9** that was used for a mixed Kolbe electrolysis with tridecanoic acid. Finally, methylation with LDA and methyl iodide followed by oxidation of the vinyl group with ruthenium tetroxide yields (±)-nephromopsinic acid. Remarkably, this synthesis of (±)-nephromopsinic acid contains three different radical reactions, two of which deal with intermolecular carbon–carbon bond formation (conversion of **1** to **2** and the mixed Kolbe electrolysis of **9**).



Scheme 1. Synthesis of the isoprostane 12-*epi*-$PGF_{2\alpha}$ [17].

Ueno-Stork Radical Cyclizations Stereocontrolled by the Radical Center

More than fifteen years ago, Ueno and Stork independently reported the very efficient 5-*exo* radical cyclization of bromoacetals [21][22], easily prepared from allylic alcohols, and applied this reaction to various natural product synthesis [6][23–27]. In their strategy, the stereogenic center of the allylic alcohol was used to control the stereoselectivity of the cyclization process. Recently, we have shown that the stereochemistry of such cyclization reactions can be controlled from the stereogenic acetal center (**C** → **D**) [28]. This reaction was applied to a stereoselective synthesis of (±)-botryodiplodin (Scheme 3) [29]. The first and straightforward retrosynthetic analysis **I** proved not to be efficient for the control of the stereochemistry at C(3). Therefore, strategy **II** was used where the stereochemistry at C(3) is introduced in a subsequent reduction step (the stereochemistry at C(4) is controlled as expected from previous results during the radical cyclization). Starting from enolether **10**, bromoacetalization affords the allene **11** that cyclizes to **12** under tin hydride reducing condition. Reduction of **12** with the bulky tris(trimethylsilyl)silane affords the desired all-*cis* furane **13** in 80% ds. The stereochemical outcome is easily explained by model **E** where reduction occurs from the less hindered face *anti* to the adjacent substituents. Racemic botryodiplodin is obtained after hydrolysis of the acetal **13** followed by Wacker oxidation. The unstable botryodiplodin was acetylated for characterization purposes.

By controlling the absolute configuration of the acetal center with a chiral auxiliary, this approach can be used for the synthesis of enantiomerically pure compounds [28]. The utility of this approach was demonstrated by the preparation of the naturally occurring (+)-eldanolide, the pheromone of the male African sugarcane stem borer *Eldana saccharina* (Scheme 4) [30]. For this purpose, the bromoacetal **16** was prepared from (1*R*,2*S*)-2-phenylcyclohexanol *via* mercury(II) catalyzed transetherification followed by bromoacetalization of the chiral vinyl ether **14** with 1,4-pentadien-3-ol **15**. The haloacetalization step is not stereoselective, the required diastereomerically pure **16** could be obtained after

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VOL. 55 (2001)

Frequency: Monthly
Erscheinungsweise: Monatlich

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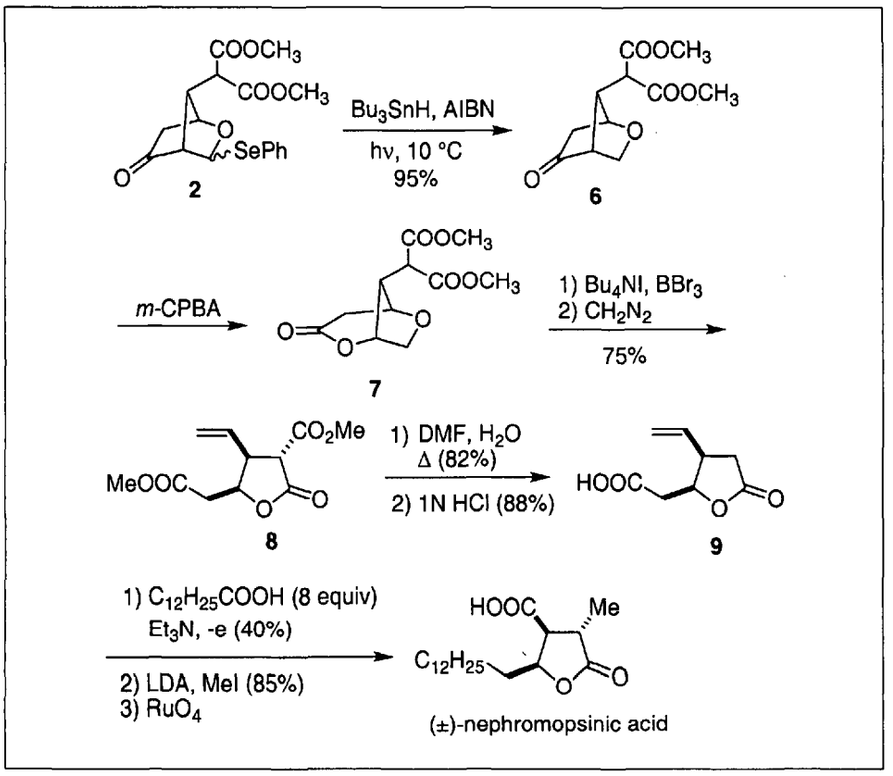
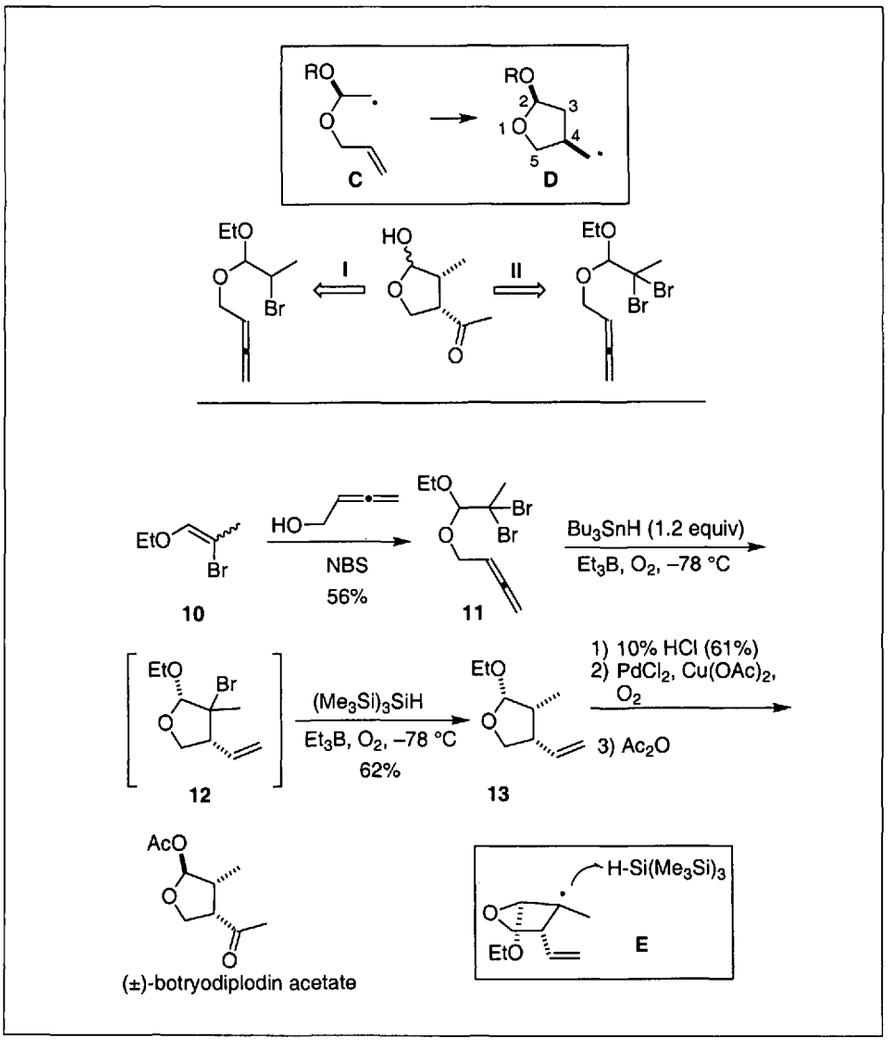


Scheme 2. Synthesis of (±)-nephromopsinic acid [20].



Scheme 3. Synthesis of (±)-botryodiplodin [29].

flash chromatography. However, since the separation of the diastereomers is easier after the cyclization reaction, the mixture of diastereomers was used for the next step. The bromoacetal **16** (1:1 mixture of two diastereomers) was submitted to cyclization conditions to afford **17** as a 1:1 mixture of two diastereoisomers, the cyclization process is completely diastereoselective (ds >98%) for each diastereomer of **16**. At this stage, the two diastereomers were separated by flash chromatography and compound (2*S*,4*S*,5*R*)-**17** was used for the rest of the synthesis. The γ-chain was modified in a straightforward manner by hydroboration, Swern oxidation, and Wittig reaction. Finally, hydrolysis of the acetal **18** furnished the lactol together with recovered (1*R*,2*S*)-2-phenylcyclohexanol (62%). Oxidation of the lactol with PCC gave the desired enantiomerically pure (+)-eldanolide.

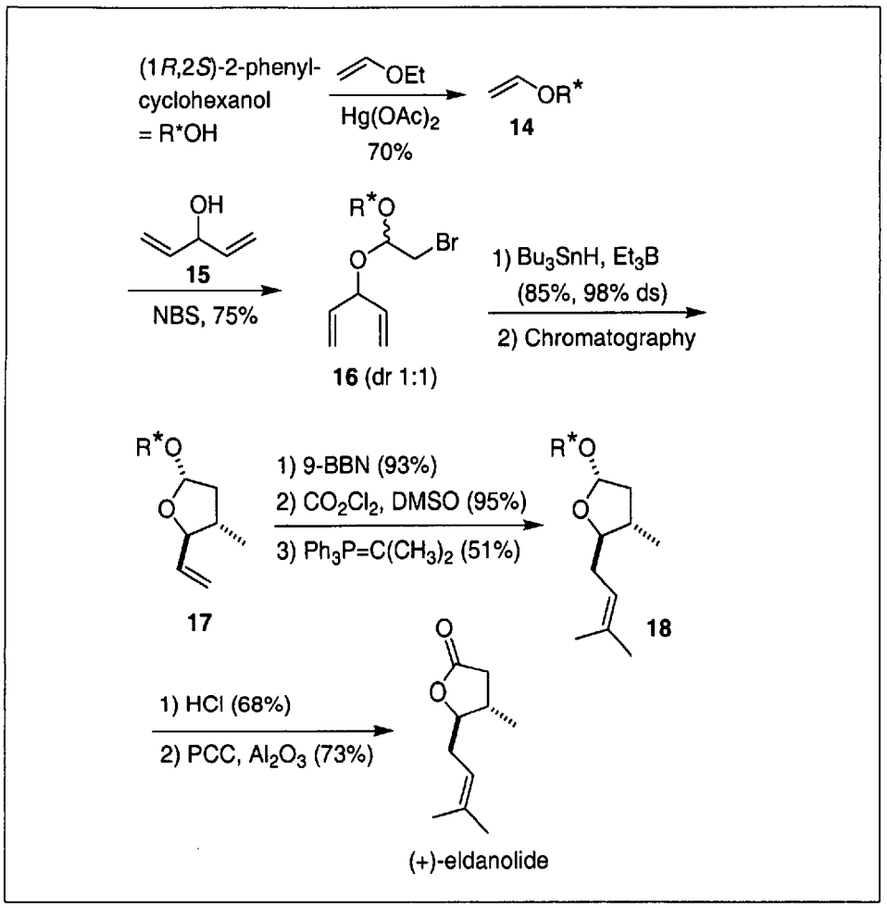
Conclusions

The four syntheses presented here serve to illustrate the potential of radical reactions for the preparation of functionalized natural products bearing several adjacent stereogenic centers. Taking advantage of radical rearrangement, cyclization and intermolecular addition reactions opens new opportunities to achieve short and efficient preparation of desired target molecules.

Acknowledgements

We wish to thank the Swiss National Science Foundation and the Federal Office for Education and Science for their financial support.

Received: October 17, 2001



Scheme 4. Synthesis of (+)-eldanolide [30].

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