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Volume Editor J. Mulzer

Natural Product Synthesis I

Targets, Methods, Concepts

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Natural Product Synthesis I

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Volume Editor: Johann Mulzer

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Preface

From its early days, the total synthesis of complex molecules, especially those that are natural products, has been the king's discipline in organic chemistry. The reasons for this are manifold: the challenge lying in a novel and intricate molecular architecture or the difficulty encountered when isolating the substance from its natural sources, or the possibility of finding a wide test ground for established methodology or the incentive to invent new methodology when the old one has failed, or simply the art and elegance which is so typical of a truly efficient synthetic sequence. In any case, everybody will agree that total synthesis is the best way to train young chemists and to prepare them for any kind of later employment.

In these two volumes, the contributions of a number of organic synthetic chemists from the German speaking area have been collected. It is the hope of the authors and the editor that these articles, which highlight all the various aspects of organic synthesis, will provide not only an insight into the basic strategy and tactics but also the purpose of organic syntheses.

Vienna, September 2004 Johann Mulzer

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Natural Product Synthesis II
Targets, Methods, Concepts

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Total Syntheses of Kelsoene and Preussin

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Abstract Total syntheses of the natural products kelsoene and preussin are comprehensively reviewed. Kelsoene is a sesquiterpene with a unique tricyclo[6.2.0.$0^{2,6}$]decane skeleton. It contains six stereogenic centers the selective construction of which has been addressed differently in the five syntheses known to date. Three syntheses employ an intermolecular [2+2]-photocycloaddition reaction as key step. One synthesis is based on a homo-Favorskii rearrangement and one on an intramolecular [2+2]-photocycloaddition. Preussin is a pyrrolidine alkaloid with three stereogenic centers which are all located within the central heterocyclic core (C-2, C-3, C-5). So far, 18 total syntheses of preussin

have been completed. Seven syntheses include the nucleophilic attack on an L-phenylalanine derived electrophile as key step, five use α-amino- or α-hydroxycarboxylic acids as chiral pool building blocks. Two syntheses are based on sugars as chiral starting materials and two are based on the desymmetrization of *meso*-compounds. In addition, there are two syntheses which use a chiral auxiliary to establish the first stereogenic element en route to preussin.

Keywords Alkaloids · Natural products · Photochemistry · Terpenes · Total synthesis

List of Abbreviations

Am	Amyl
ds	Diastereoselectivity
im	Imidazole
MSH	*O*-(Mesitylenesulfonyl)hydroxyl-amine
NOE	Nuclear Overhauser effect/enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
PPL	Pig pancreatic lipase
SES	Trimethylsilyl ethyl sulfonyl
TIBAL	Triisobutylaluminum
TPAP	Tetrapropylammonium perruthenate

1 Introduction

The title compounds kelsoene (*rac*-**1**) and (+)-preussin (**2**) have recently been synthesized in our laboratories using a stereoselective photochemical reaction as key step (Fig. 1). It is the purpose of this review to give a more detailed account on this work. In addition, other successful synthetic strategies to kelsoene and preussin will be comprehensively discussed. This intention has defined the way the content of the review was arranged. In two individual sections the target molecules are presented. Each section provides a short introduction to the target, a review on the syntheses conducted by other groups and finally an account of our own contribution.

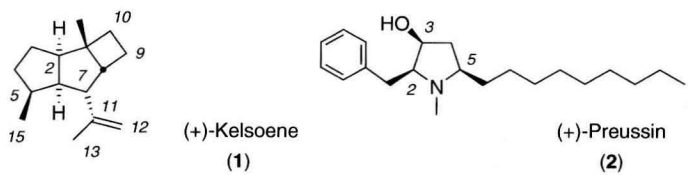
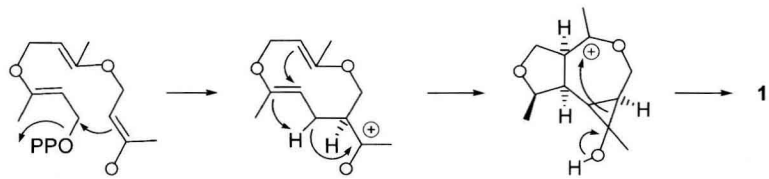


Fig. 1 Chemical structures of (+)-kelsoene (**1**) and (+)-preussin (**2**)

2
Kelsoene

(+)-Kelsoene (**1**) was first isolated from the sponge *Cymbastela hooperi* Van Soest, Desqueyroux-Faundez, Wright, König (Axinellidae, Halichondrida) collected from Kelso reef, Great Barrier Reef, Australia [1]. Its constitution and relative configuration was elucidated by König and Wright. It is a sesquiterpene with a tricyclo[6.2.0.$0^{2,6}$]decane skeleton rarely encountered in natural products. The compound was later also found in the liverworts *Ptychanthus striatus* [2], *Calypogeia muelleriana* [3], and *Tritomaria quinquedentata* [4]. Proof of the absolute configuration was obtained from total synthesis (see below) while initial NMR studies [5] had led to the conclusion that the natural product possessed the configuration of *ent*-**1**. Labeling studies (Scheme 1, ○=^{13}C label) with [2-^{13}C]-mevalonate indicated that the bio-



Scheme 1

synthesis proceeds from farnesyl diphosphate (**3**) via the germacradienyl cation (**4**) and the alloaromadendranyl cation (**5**) [2, 6].

From a synthetic point of view the stereoselective construction of the tricyclodecane skeleton and the installation of the methyl group at C-5 and of the 2-propenyl group at C-7 pose significant challenges which were addressed differently in the five syntheses of kelsoene known to date.

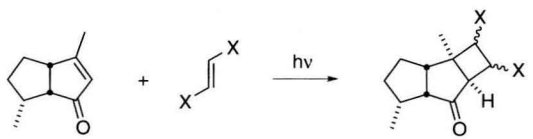
2.1
Syntheses by Other Groups

The following sections give an overview of the total syntheses of kelsoene that have been reported by other groups. With respect to the key step by which the tricyclic framework is constituted, they can be divided into two groups, the [2+2]-photocycloaddition approach and the homo-Favorskii strategy.

2.1.1
Intermolecular [2+2]-Photocycloaddition Approach

2.1.1.1
Intermolecular [2+2]-Photocycloaddition as the Key Step

The first total synthesis of kelsoene was achieved by Mehta and Srinivas [7, 8]. The tricyclic scaffold was established by an intermolecular [2+2]-photocycloaddition of diquinane enone *rac*-**6** and 1,2-dichloroethylene (**7**) as the key step (Scheme 2). As a consequence of the steric hindrance implemented



rac-**6** / *ent*-**6** / **6** **7** (X = Cl) *rac*-**9** / *ent*-**9** / **9** (X = Cl) 85%
rac-**6** **8** (X = H) *rac*-**10** (X = H) 90%

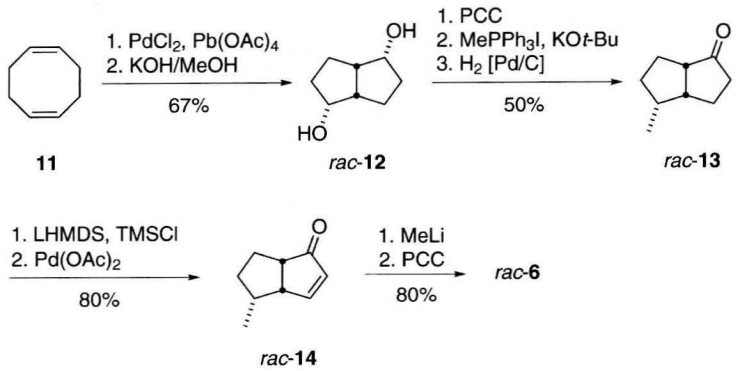
Scheme 2

in the bicyclic ring system of **6**, the alkene **7** is forced to attack exclusively from the *exo*-face of **6**. The perfect facial diastereoselectivity results in the formation of the tricyclodecane **9** the framework of which is connected in the requisite *cis-anti-cis* fashion [7]. In subsequent syntheses by others [9–11] and in the enantioselective synthesis by Mehta and Srinivas [12] an identical or almost identical photochemical key step was employed. In all syntheses, diquinane enone **6**, its enantiomer *ent*-**6**, or the racemate *rac*-**6** was used as the photoactive compound, the reaction partner was 1,2-dichloroethylene (**7**) [7–10, 12] or ethylene (**8**) [11].

The fact that all approaches employing the intermolecular photocycloaddition key step used the same precursor for the construction of the four-membered ring renders enone **6** the key intermediate of the different synthetic strategies. It is therefore sensible to compare first the different strategies to synthesize precursor **6**. Afterwards, the different ways to complete the syntheses of kelsoene will be discussed.

2.1.1.2
Approaches to the Photocycloaddition Precursor

In the first total synthesis of kelsoene (*rac*-**1**) [7, 8], commercially available 1,5-cyclooctadiene (**11**) was chosen as the starting material (Scheme 3). Oxidative cyclization with a mixture of $PdCl_2$ and $Pb(OAc)_4$ in acetic acid led to the formation of a diquinane diacetate [13] that was saponified to give

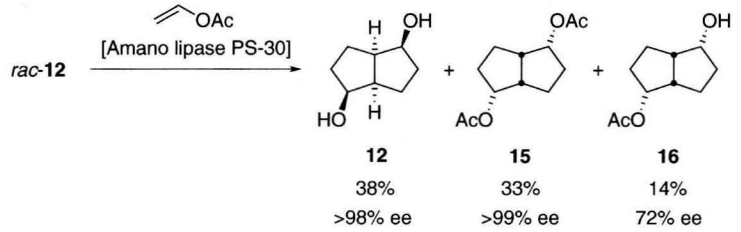


Scheme 3

2,6-dihydroxybicyclo[3.3.0]octane (*rac*-**12**). Oxidation of the two hydroxy groups followed by selective monomethylenation and catalytic hydrogenation furnished the *endo*-methyl diastereoisomer *rac*-**13** as the major product (dr=80/20). The observed diastereoselectivity was explained by the fact that the catalytic hydrogenation proceeded preferentially from the more easily accessible convex face of the diquinane framework [7].

Ketone *rac*-**13** was transformed into the corresponding silylenolether and by Pd(II)-mediated Saegusa oxidation [14] into α,β-unsaturated ketone *rac*-**14**. By alkylative enone transposition comprising methyl lithium addition and pyridinium chlorochromate (PCC) oxidation [15], *rac*-**14** was finally converted into the racemic photocycloaddition precursor *rac*-**6**. In conclusion, the bicyclic irradiation precursor *rac*-**6** was synthesized in a straightforward manner from simple 1,5-cyclooctadiene (**11**) in nine steps and with an overall yield of 21%.

In a succeeding publication, the same authors reported on an enantioselective approach to diquinane enones **6** and *ent*-**6** by combining the above-described synthesis with an enzymatic kinetic resolution (Scheme 4) [12]. After lipase-catalyzed enantioselective transesterification of diol *rac*-**12**,

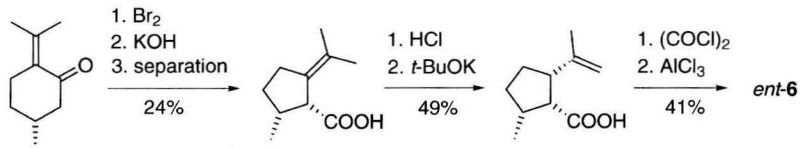


Scheme 4

enantiomerically pure diol **12** and diacetate **15** as well as monoacetate **16** were isolated in 38%, 33%, and 14% yield, respectively.

Continuing the synthesis of *rac*-**6** with enantiomerically pure diols **12** and *ent*-**12** (after saponification of **15** with KOH), both enantiomers **6** and *ent*-**6** were accessible. This allowed for an enantioselective synthesis of natural kelsoene (**1**) and its enantiomer (*ent*-**1**) (see below) with only one additional step as compared to the synthesis of the racemate (*rac*-**1**).

The approach of Schulz et al. to enantiomerically pure diquinane enone *ent*-**6** employed (*R*)-(+)-pulegone (**17**) as chiral pool starting material [9, 10] (Scheme 5). Bromination and Favorskii rearrangement of **17** generated a



17 **18** **19**

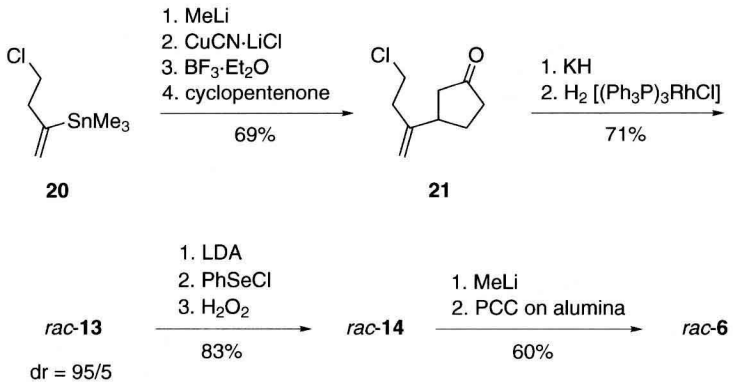
Scheme 5

mixture of *cis*- (**18**) and *trans*-pulegonic acids [16] that was separated by column chromatography. Acid-induced lactonization of the desired *cis*-substituted acid **18** followed by elimination with a bulky base led to the formation of the all-*cis*-substituted acid **19** with a terminal double bond [16, 17].

The photocycloaddition precursor *ent*-**6** was obtained from **19** by transformation into the corresponding acid chloride and $AlCl_3$-mediated intramolecular acylation of the double bond. While the conciseness of this strategy is appealing, drawbacks are the low yields achieved in the individual reaction steps giving *ent*-**6** in an overall yield of only 5%.

Racemic diquinane enone *rac*-**6** was prepared by Piers and Orellana starting from cyclopentenone (Scheme 6) [11]. After the preparation of the heterocuprate from stannane **20**, conjugate addition to cyclopentenone in the presence of $BF_3{\cdot}Et_2O$ provided carbonyl compound **21**. It was expected that conversion of **21** by intramolecular alkylation and subsequent hydrogenation should provide the desired *endo*-substituted diquinane *rac*-**13**. While other hydrogenation methods proved to be rather unselective, reduction in the presence of Wilkinson's catalyst finally resulted in the formation of *rac*-**13** with good facial diastereoselectivity [11].

The introduction of the double bond of *rac*-**14** was performed by conversion of *rac*-**13** into its α-phenylselenide, subsequent peroxide oxidation, and elimination. Following the synthesis reported by Mehta and Srinivas, an alkylative enone transposition was used as the last step towards irradiation



Scheme 6

precursor *rac*-**6**. Not taking into account the preparation of 4-chloro-2-trimethylstannylbut-1-ene (**20**), this synthetic route offers another elegant access to *rac*-**6** with a reported overall yield of 24% exceeding those of the other syntheses.

In conclusion, the three groups which applied the intermolecular photocycloaddition as the key step in their approach to kelsoene (**1**) reported different strategies to synthesize the irradiation precursor **6** in racemic or enantiomerically pure form. After the photocycloaddition step the syntheses of kelsoene were completed in different ways. The next section describes the different strategies employed in the second half of the way to kelsoene.

2.1.1.3 Completion of the Syntheses

The first report on the construction of the complete 5-5-4-fused tricyclic framework of kelsoene and later on the first total synthesis of racemic kelsoene *rac*-**1** was published by Srinivas and Mehta in 1999 [7, 8]. As discussed in the last section, the insertion of an enzymatic kinetic resolution step allowed for the analogous synthesis in an enantioselective manner [12]. The intermolecular [2+2]-photocycloaddition as the key step in their approach was performed by irradiating diquinane enone **6** with 1,2-dichloroethylene (**7**) (Scheme 2). This led to the formation of a mixture of *cis*- and *trans*-dichlorosubstituted cycloaddition products **9** in 85% yield. The perfect facial diastereoselectivity resulting from the attack of alkene **7** on the *exo*-face of **6** led to the exclusive formation of the desired *cis-anti-cis* connected tricyclodecane **9**. After protection of the carbonyl group as an acetal, the chlorine atoms were removed by reductive dehalogenation with sodium naphthalenide. Originally, the resulting cyclobutene was then hydrogenated and deprotected to yield cyclobutane **10** (Scheme 7).