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Pierre Barbier* and **Josef Stadlwieser**

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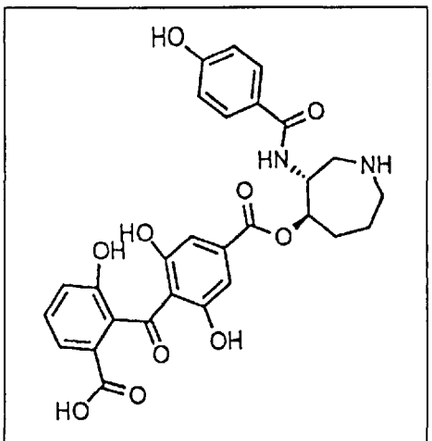
(–) Balanol (**1**, Azepinostatin), a potent inhibitor of protein kinase C enzymes, was isolated from the culture filtrates of different fungi (*Verticillium balanoides*, *Fusarium merismoides*) and its structure was elucidated by spectroscopic methods and chemical degradation [1][2]. Furthermore, the potential medical use of **1** was claimed in a recent patent [3]. The structural complexity as well as its biological activity make **1** a challenging synthetic target. Recently, independent syntheses of **1** were published by different groups [4–6].

In this communication, we wish to report a new synthesis of enantiomerically pure **1**, using tri-*O*-acetyl-D-glucal (**2**) as chiral template for the central azepane fragment of **1**. The synthesis of **15**, a fully protected and properly functionalized building block for the central azepane moiety, is outlined in *Scheme 1*.



(–)-Balanol (**1**)

The elaboration of **30**, a suitably protected building block for the highly functionalized benzophenone fragment of **1**, is outlined in *Scheme 2*. It is noteworthy, that direct alkylation of **16** with benzyl bromide under different conditions failed.

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The total synthesis of **1** was finally completed by assembling the individual building blocks **15**, **30** and **31** [10], followed by removal of the protective groups according to *Scheme 3*.

All compounds were fully characterized by spectroscopic methods (^{1}H-NMR, IR, MS) and microanalyses.

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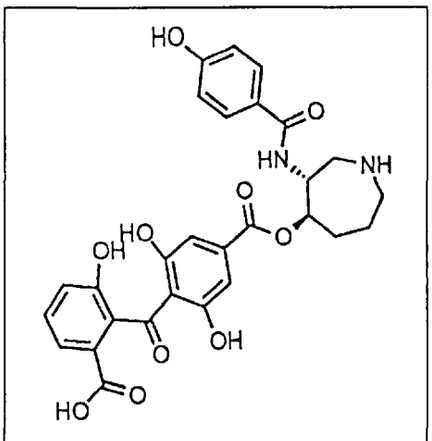

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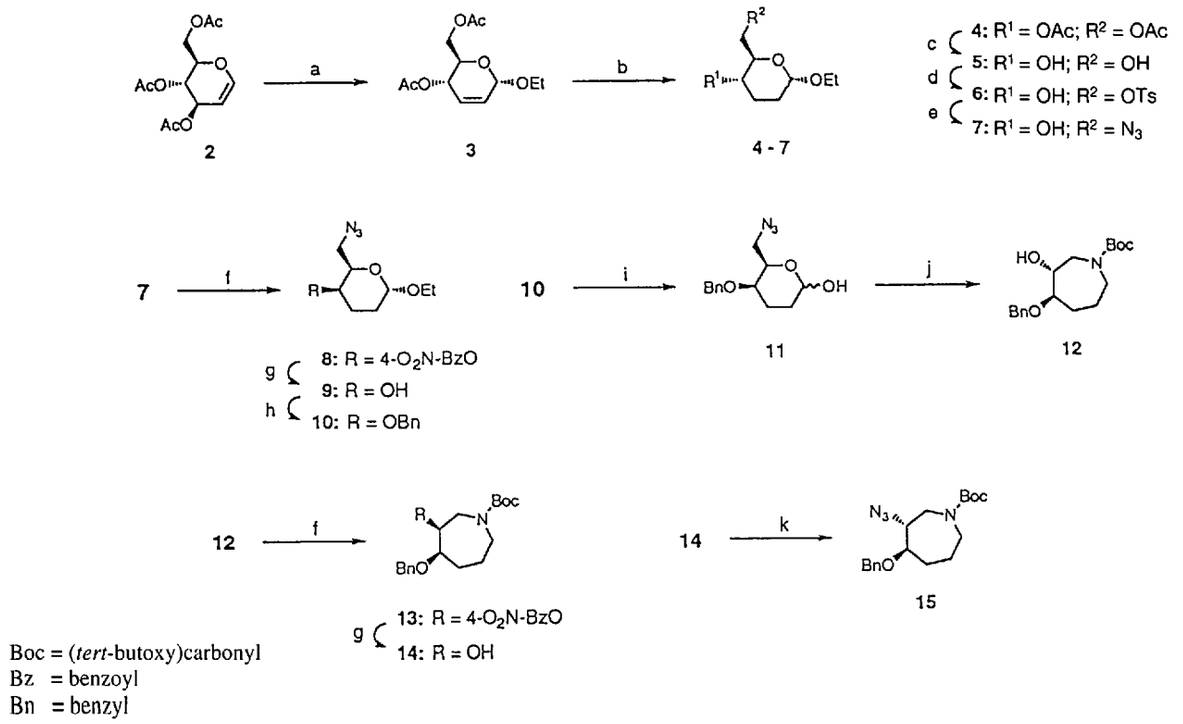
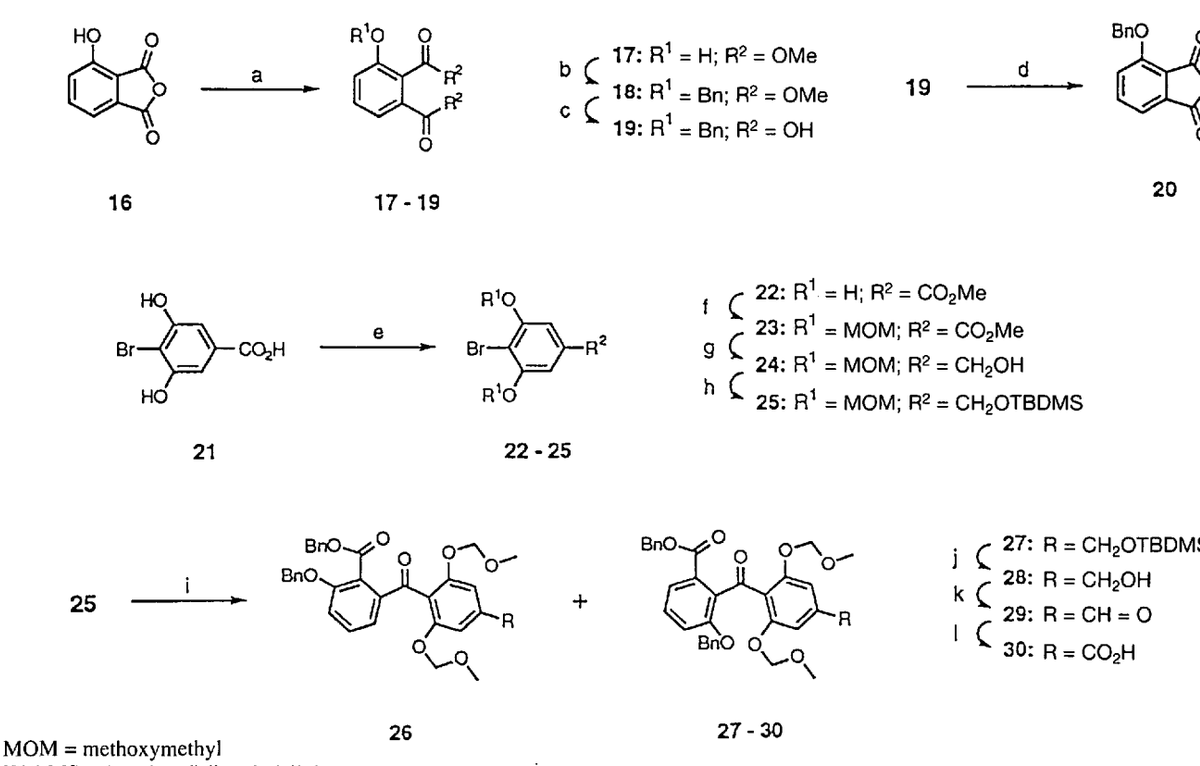
Scheme 1



a) [7][8]. b) H_2, PtO_2, AcOEt. c) NaOEt, EtOH. d) *p*-TsCl, pyridine. e) NaN_3, TBAHS, DMF. f) 4-O_2N–C_6H_4–CO_2H, Ph_3P, DEAD, THF. g) KOH, EtOH. h) 1. NaH, THF; 2. BnBr, $(Bu)_4NI$, THF. i) 1N H_2SO_4, acetone. j) 1. H_2, Pd/C, THF; 2. Boc_2O, dioxane. k) HN_3, Ph_3P, DEAD, THF, toluene.

Scheme 2



a) MeOH, H_2SO_4. b) BnBr, K_2CO_3, butan-2-one. c) KOH, MeOH, Δp, DT. d) Ac_2O, toluene. e) MeOH, HCl (g). f) 1. NaH, THF, DMF; 2. MOM-Cl. g) $LiAlH_4$, THF. h) TBDMS-Cl, imidazole, DMF. i) 1. BuLi, THF; 2. + **20**; 3. BnBr; 4. separation of isomeres. j) $(Bu)_4NF$, THF. k) MnO_2, CH_2Cl_2. l) MMPP, DMF.

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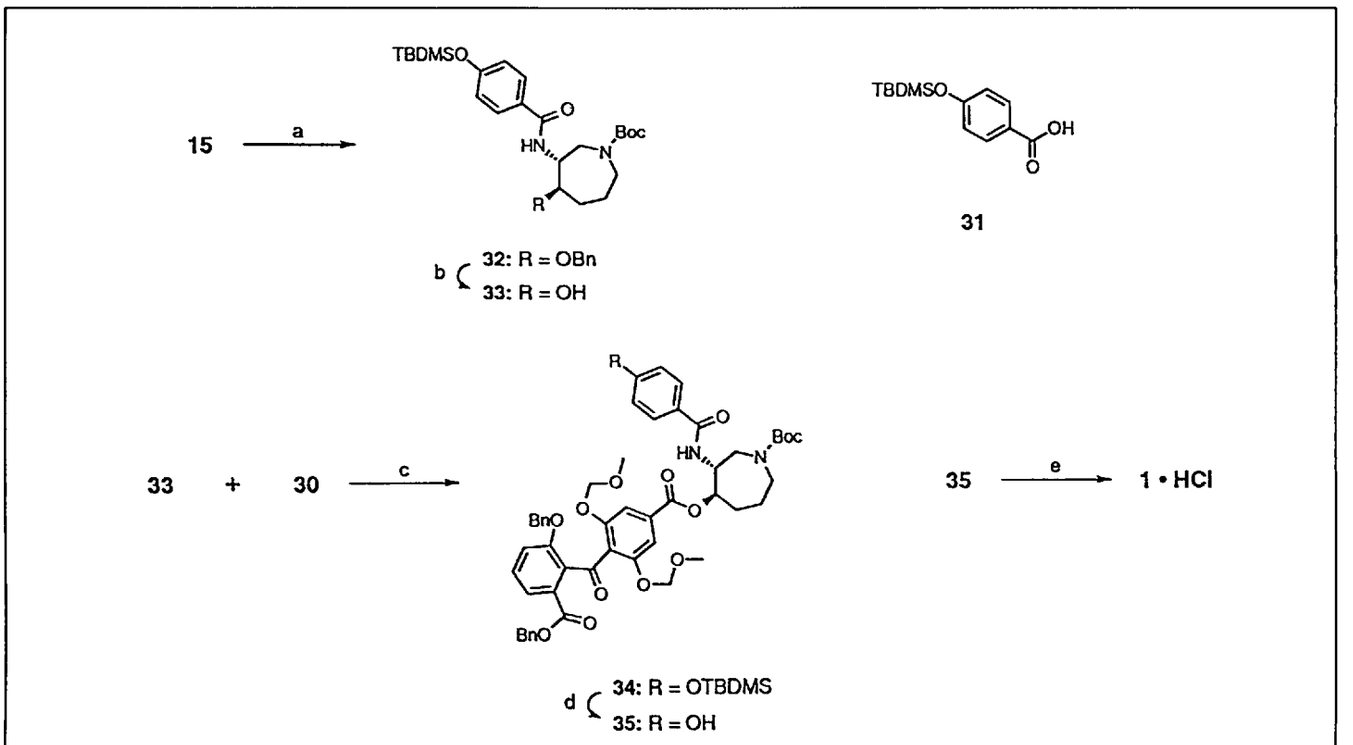
Scheme 3



a) 1. H_2, Pd/C, THF; 2. + **31**, *N*-[3-(dimethylamino)propyl]-*N'*-ethyl-carbodiimide hydrochloride (EDC), DMAP, CH_2Cl_2. b) H_2, Pd/C, MeOH. c) *p*-TsCl, DMAP, CH_2Cl_2. d) $(Bu)_4NF$, THF. e) 1. H_2, Pd-C, THF; 2. HCl (g), i-PrOH, DME.

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Synthesis of the HIV-Proteinase Inhibitor Saquinavir: A Challenge for Process Research

Wolfgang Göhring, Surendra Gokhale, Hans Hilpert*, Felix Roessler, Markus Schlageter and Peter Vogt

Abstract. The task of process research, namely developing efficient, economically and technically as well as ecologically feasible syntheses in time, is demonstrated on the HIV-proteinase inhibitor Saquinavir (**1**), a complex molecule comprising six stereocentres. Based on the first 26-step research synthesis furnishing a 10% overall yield, process research established a new, short 11-step synthesis affording a 50% overall yield.

1. Introduction

In 1986, the HIV-proteinase, an enzyme that catalyses the processing of the group antigen (gag) polyprotein p55 to the core proteins p24, p17 and p15, was recognized by *Kramer* [1] as a challenging new target to combat acquired immunodeficiency syndrome (AIDS). Subsequently, industry as well as academia started an intensive search for inhibitors of the HIV-proteinase. At our research laboratories in Welwyn, England, a number of potent inhibitors were synthesized and structurally optimized leading finally to the selection of the peptide mimetic Saquinavir (**1**) (Ro 31-8959) as a development candidate in 1989 [1].

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