



Concise syntheses of stereoisomeric hexahydroazepine derivatives related to the protein kinase inhibitor balanol

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ABSTRACT

A stereodivergent route to four stereoisomeric azepane derivatives related to the important protein kinase inhibitor balanol is developed which utilises (–)- or (+)-serine as starting material, and a ring-closing metathesis as the key ring forming step.

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Protein kinase C is a prime target for therapeutic agents, since unregulated protein kinase activities are linked to a myriad of diseases including carcinogenesis.¹ Of the various known protein kinase C (PKC) inhibitors, the fungal metabolite² balanol (**1**, Fig. 1) was demonstrated as one of the most potent, having inhibitory activity in the nanomolar range. This, in turn, has rendered it an attractive synthetic target over the last 15 years.³ One feature of balanol, as remarkable as its high potency, is its lack of isozyme selectivity.⁴ Compounds that selectively modulate certain PKC isozymes hold promise in the development of novel therapeutics. In the dual quest for delineating the functional requirements for PKC inhibition and achieving selectivity, several balanoids with modification at one or more positions have been prepared and evaluated.⁵ The perhydroazepine ring has remained the centre of focus of most of these studies, since very subtle changes in this moiety have resulted in compounds of desired potency and/or selectivity. A number of elegant routes to the azepane core in (–)-balanol have been described.⁶ However, a general preparation of all the stereoisomers of this important moiety has not been reported to the best of our knowledge. In continuation of our studies⁷ on the asymmetric synthesis of bioactive molecules utilising chiral pool materials and our interest⁸ in medium ring heterocyclic systems, we became interested in developing a flexible synthetic route to balanoids. Ophiocordin (**2**) is a closely related metabolite which shows antifungal activity.⁹ Herein, we report a concise synthesis of all four stereoisomers of the hexahydroazepine subunit common to these two important natural products.

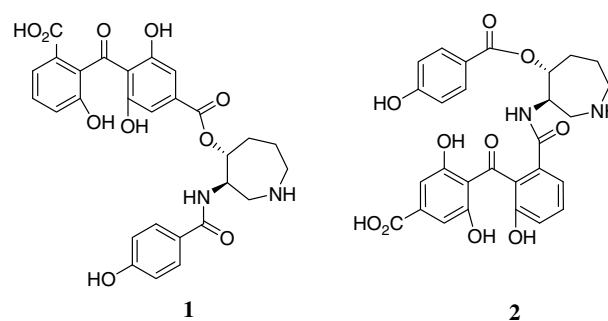


Figure 1. Balanol (**1**) and ophiocordin (**2**).

Our retrosynthetic analysis (Fig. 2) of the azepane unit **3** of natural configuration, hinged on the successful outcome of two crucial steps, viz. ring-closing metathesis (RCM) of the diene **5** for construction of the tetrahydroazepine ring and a chelation-controlled addition of vinylmagnesium bromide to the α -chiral aldehyde **6** to establish the desired *anti*-configuration of the stereogenic centres present in **3**. The aldehyde **6** was thought to be obtainable from functional group manipulation of the known¹⁰ L-serine derived Garner's aldehyde **7**.

Thus, compound **7** (Scheme 1), prepared following a modified procedure,¹¹ was converted to the corresponding *N*-allylimine **8** by dehydrative condensation with allylamine. Compound **8** was obtained essentially pure for carrying over to the next step. Reduction of the imine **8** with sodium borohydride followed by protection of the resulting amine **9** with Cbz-Cl in the usual manner

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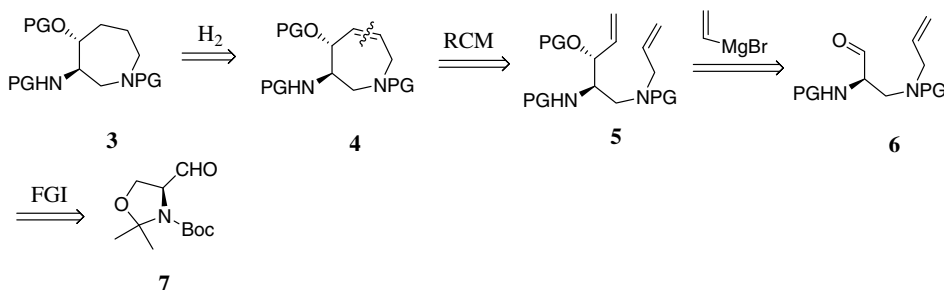
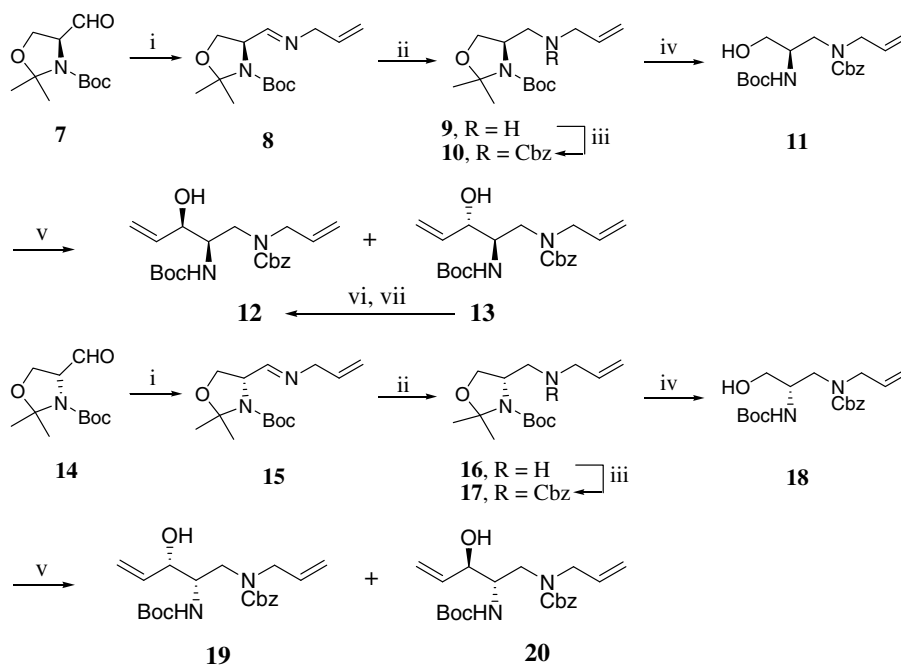


Figure 2.



Scheme 1. Reagents and conditions: (i) allyl amine, molecular sieves 4 Å, CH₂Cl₂, 0 °C, 24 h; (ii) NaBH₄, THF, 0 °C to rt, 15 h; (iii) benzyl chloroformate, NaHCO₃, EtOAc, rt, 12 h, **10** (89%), **17** (87%); (iv) HCl (5%), MeOH, rt, 6 h, **11** (90%), **18** (92%); (v) oxalyl chloride, DMSO, *N,N*-DIPEA, –78 to –35 °C, 1 h, then vinylmagnesium bromide, THF, –78 °C to rt, 8 h, **12** + **13** (64%), **19** + **20** (61%); (vi) DEAD, PPh₃, *p*-nitrobenzoic acid, THF, 0 °C to rt, 2 h, 89%; (vii) K₂CO₃, MeOH–H₂O, 1 h, 91%.

provided the protected amine **10** in an overall yield of 89% over three steps. Acid-catalysed deprotection of the oxazolidinone unit in the latter followed by oxidation of the resulting alcohol **11** under modified Swern conditions¹² led to the corresponding chiral aldehyde which was used as such in the next step. Addition of this aldehyde to vinylmagnesium bromide in one-pot furnished the *syn*- and *anti*-allyl alcohols **12**, [α]_D –8 (c 1.5, CHCl₃), and **13**, respectively, in a combined yield of 64%. The isomers were readily separated by column chromatography, and the diastereomeric ratio was observed to be 68:32 in favour of the *syn*-alcohol **12**. Similarly, starting from the *D*-serine derived Garner's aldehyde **14**, the amino alcohols **19** and **20** were prepared in comparable yield and selectivity (63:37) following an identical sequence of events.

Chelation-controlled addition of Grignard reagents to α -chiral α -amino aldehydes has been studied¹³ extensively, and such additions usually proceed with high level of selectivity. However, addition to α -chiral α,β -diamino aldehydes has not been studied in detail, to the best of our knowledge. Although the *syn*-selectivity in the present instance is somewhat less, the amount of the *syn*-product could be raised by simple Mitsunobu-type inversion¹⁴ of the *anti*-isomer **13** to the desired *syn*-isomer **12**.

With the four stereoisomeric diene precursors in hand, we next focused on their RCM reaction for construction of the tetrahydroazepine ring. Initial attempts on RCM of diene **12** with Grubbs' first and second generation catalysts under a range of conditions met with failure. Problems associated with RCM of allyl alcohols have been recognised in many instances.¹⁵ We, therefore, converted the alcohol **12** to the corresponding acetate **21** (Scheme 2) under conventional conditions. However, attempted RCM of **21** in the presence of Grubbs' first generation catalyst, benzylidenebis(tricyclohexylphosphino)ruthenium(IV) dichloride, proved to be sluggish and low yielding. Pleasingly, use of Grubbs' second generation catalyst, benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium¹⁶ (**22**), effected smooth ring closure and the desired cycloalkene **23**, [α]_D +12 (c 2.0, CHCl₃), was obtained in an isolated yield of 89%. Sequential removal of the protecting groups from compound **23**, that is, hydrolysis of the acetyl group leading to the alcohol **24**, removal of the Boc-group to afford amine **25** and subsequent hydrogenolytic removal of the Cbz-group in the latter with concomitant saturation of the double bond led to the parent azepane derivative **26** in an overall yield of 41% from **13** over five steps. Similarly, each of the stereoisomeric dienes **13**, **19** and **20**

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