Tetrahedron Letters 49 (2008) 5498–5501

Contents lists available at ScienceDirect

Tetrahedron Letters

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

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

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ARTICLE INFO

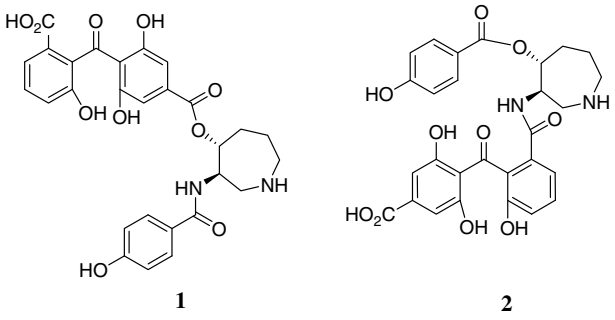
Article history:
Received 30 May 2008
Revised 27 June 2008
Accepted 5 July 2008
Available online 9 July 2008

Keywords:
Balanol
Ring-closing metathesis
Garner's aldehyde
Azepane

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.

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 metabolite[2] 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 studies[7] on the asymmetric synthesis of bioactive molecules utilising chiral pool materials and our interest[8] 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.



1 **2**

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 known[10] 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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doi:10.1016/j.tetlet.2008.07.031

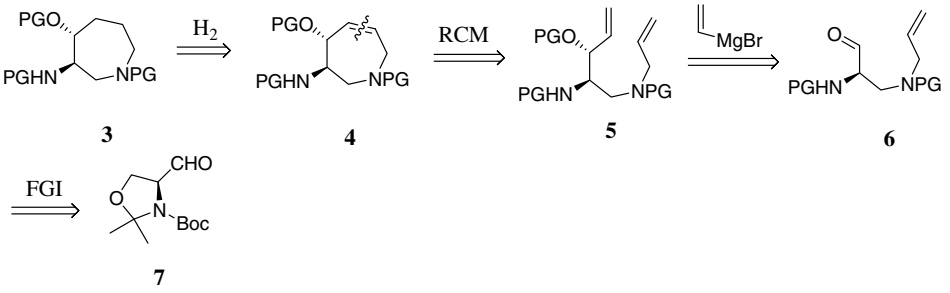
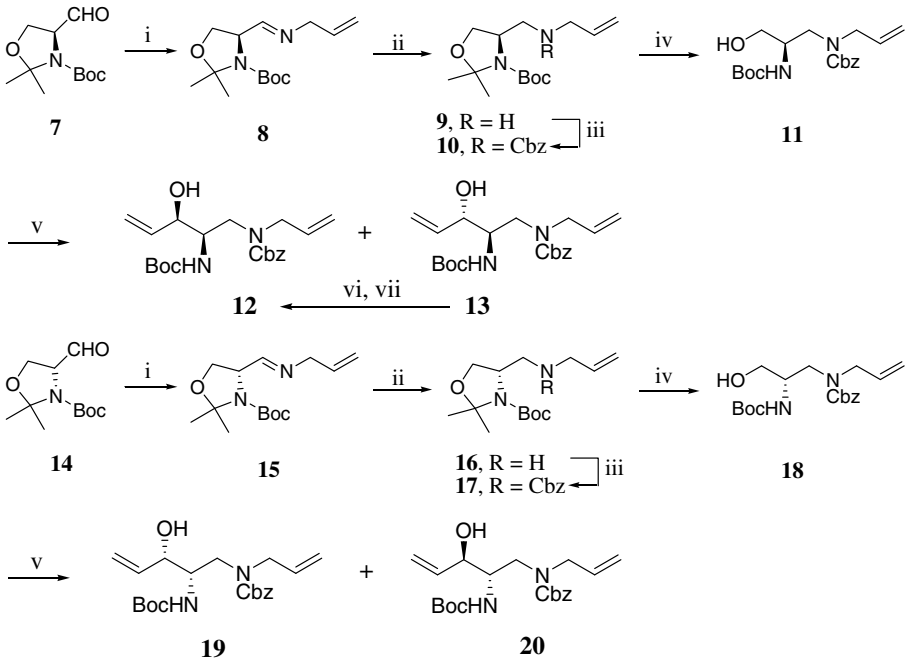


Figure 2.

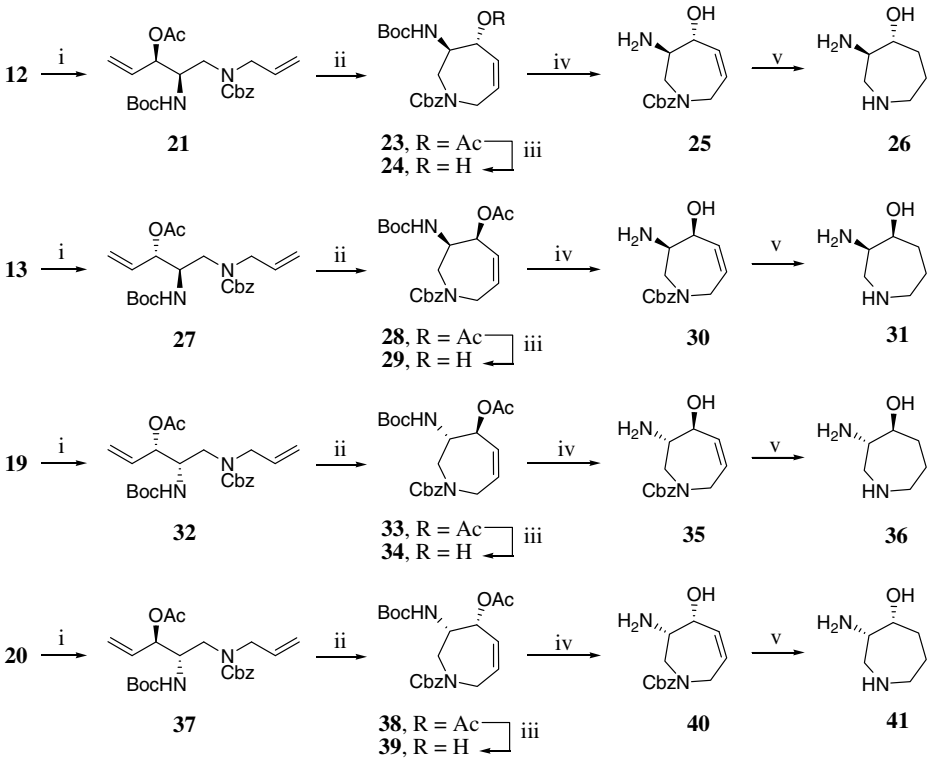


Scheme 1. Reagents and conditions: (i) allyl amine, molecular sieves 4 Å, CH_2Cl_2, 0 °C, 24 h; (ii) $NaBH_4$, THF, 0 °C to rt, 15 h; (iii) benzyl chloroformate, $NaHCO_3$, EtOAc, rt, 12 h, **10** (89%), **17** (87%); (iv) HCl (5%), MeOH, rt, 6 h, **11** (90%), **18** (92%); (v) oxalyl chloride, DMSO, *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, PPh_3, *p*-nitrobenzoic acid, THF, 0 °C to rt, 2 h, 89%; (vii) K_2CO_3, MeOH–H_2O, 1 h, 91%.

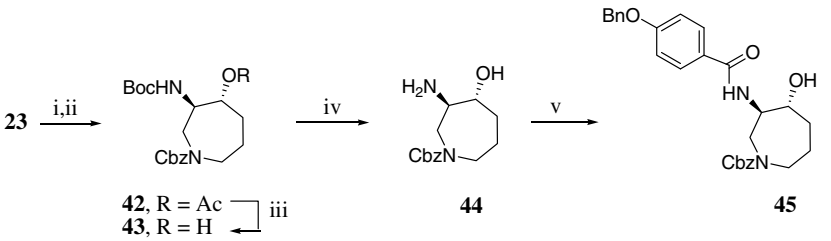
provided the protected amine **10** in an overall yield of 89% over three steps. Acid-catalysed deprotection of the oxazolidine unit in the latter followed by oxidation of the resulting alcohol **11** under modified Swern conditions[12] led to the corresponding chiral aldehyde which was used as such in the next step. Addition of this aldehyde to vinylmagnesium bromide in one-pot furnished the *syn*- and *anti*-allyl alcohols **12**, $[\alpha]_D$ −8 (*c* 1.5, $CHCl_3$), 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 studied[13] 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 inversion[14] 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, benzylidenebistricyclo-hexylphosphino-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)-ruthenium[16] (**22**), effected smooth ring closure and the desired cycloalkene **23**, $[\alpha]_D$ +12 (*c* 2.0, $CHCl_3$), 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**



Scheme 2. Reagents and conditions: (i) Ac_2O, DMAP, CH_2Cl_2, rt, 12 h, **21** (84%), **27** (92%), **32** (85%), **37** (84%); (ii) Grubbs' catalyst **22** (5 mol %), CH_2Cl_2, reflux, 6 h, **23** (89%), **28** (85%), **33** (84%), **38** (87%); (iii) K_2CO_3, MeOH, rt, 4 h, **24** (89%), **29** (92%) **34** (92%), **39** (91%); (iv) TFA–CH_2Cl_2 (1:1), 0 °C to rt, 2 h then $NaHCO_3$, **25** (76%), **30** (74%), **35** (72%), **40** (75%); (v) H_2, Pd–C (10%), MeOH, rt, 24 h, **26** (81%), **31** (79%), **36** (77%), **41** (71%).



Scheme 3. Reagents and conditions: (i) Pd–C (10%), MeOH, H_2, rt, 12 h, 80%; (ii) Cbz-Cl, $NaHCO_3$, EtOAc–H_2O, rt, 7 h, 90%; (iii) K_2CO_3, MeOH, rt, 4 h, 89%; (iv) TFA–CH_2Cl_2 (1:1), 0 °C to rt, 2 h; (v) Et_3N, 4-benzyloxybenzoyl chloride, CH_2Cl_2, rt, 4 h, 72% over two steps.

was converted to the corresponding azepane derivatives **31**, **36** and **41**, respectively, following the same sequence of events detailed for the conversion **12**→**26**. The azepane derivatives thus prepared showed spectroscopic properties consistent with their structures.[17]

Whilst the configuration of the major product in each of the vinylation reactions has been assigned *syn* based on the assumption that chelation control had predominated during addition, further support came from the following synthetic work (Scheme 3). Cycloalkene **23** was converted into the corresponding saturated compound **42** via a two-step sequence involving hydrogenation and re-introduction of the Cbz-protecting group lost concomitantly during saturation. Deacetylation of compound **42** then led smoothly to the corresponding alcohol **43** which on treatment with trifluoroacetic acid provided the amine **44** in readiness for amide bond formation with 4-benzyloxybenzoyl chloride to provide compound **45** as a colourless solid, mp 123 °C, $[\alpha]_D$ −72 (*c* 2.0, $CHCl_3$). The latter was found to display optical and spectroscopic properties in close agreement with those of (3*R*,4*R*)-benzyl 3-(4-(benzyloxy)benzamido)-4-hydroxy-azepane-1-carboxylate reported[3g] by Nicolaou et al.

In conclusion, we have developed a stereocontrolled route to the azepane core of two important natural products, balanol and ophiocordin, using inexpensive L-serine as starting material and inexpensive reagents. The stereoisomeric intermediates prepared may provide access to some of their analogues. The methodology developed may complement those existing in the literature and may also find application in the synthesis of other azepane derivatives of interest.

Acknowledgements

We are thankful to DST, Government of India (Grant No. SR/S1/OC-51/2005), for financial assistance and UGC (New Delhi) for a fellowship to one of us (S.P.R.).

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17. Data for selected compounds. **26**: $[\alpha]_D$ +19 (*c* 2.2, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 4.18 (1H, td, *J* = 2.7, 5.8), 3.60 (1H, td, *J* = 2.8, 9.5), 3.42 (1H, dd, *J* = 13.9, 9.6), 3.31–3.23 (2H, m), 3.12 (1H, ddd, *J* = 13.5, 9.8, 3.6), 2.01–1.90 (2H, m), 1.80–1.67 (2H, m). ^{13}C NMR (75 MHz, D_2O+MeOD): δ 69.2, 52.5, 47.8, 43.6, 31.8, 19.3. MS (TOF MS ES+): *m/z* 131 (M+H). **31**: $[\alpha]_D$ −18 (*c* 2.0, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 3.52 (1H, dt, *J* = 3.8, 8.5), 3.12 (1H, dd, *J* = 2.7, 13.9), 3.04–3.00 (2H, m), 2.98 (1H, dd, *J* = 2.6, 8.5), 2.89 (1H, dd, *J* = 9.1, 13.9), 1.99–1.94 (1H, m), 1.87–1.81 (1H, m), 1.70–1.61 (2H, m). ^{13}C NMR (75 MHz, D_2O+MeOD): δ 75.4, 56.2, 47.3, 46.9, 32.6, 20.9. MS (TOF MS ES+): *m/z* 131 (M^++H). **36**: $[\alpha]_D$ −18 (*c* 2.8, MeOH). ^{1}H NMR (600 MHz, D_2O): δ 4.07 (1H, td, *J* = 2.4, 7.2), 3.35 (1H, td, *J* = 2.5, 7.5), 3.25–3.19 (2H, m), 3.16 (1H, dd, *J* = 4.2, 8.4), 3.12 (1H, dd, *J* = 3.0, 13.8), 1.99–1.88 (2H, m), 1.82–1.72 (m, 2H). ^{13}C NMR (75 MHz, D_2O+MeOD): δ 71.8, 52.4, 46.7, 45.7, 30.4, 19.9. MS (TOF MS ES+): *m/z* 131 (M^++H). **41**: $[\alpha]_D$ +19 (*c* 2.0, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 3.45 (1H, dt, *J* = 3.5, 8.3), 3.01 (1H, dd, *J* = 2.8, 14.0), 2.94–2.92 (2H, m), 2.88 (1H, dt, *J* = 2.8, 8.8), 2.76 (1H, dd, *J* = 8.9, 14.0), 1.94–1.88 (1H, m), 1.80 (1H, dt, *J* = 5.2, 13.2), 1.63–1.58 (2H, m). ^{13}C NMR (75 MHz, D_2O+MeOD): δ 76.3, 57.2, 47.9, 46.7, 32.0, 21.8. MS (TOF MS ES+): *m/z* 131 (M^++H).