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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6113–6116

A stereodivergent route to epimeric 2-piperidinylglycines: application to the synthesis of carbocyclic β-lactam derivatives

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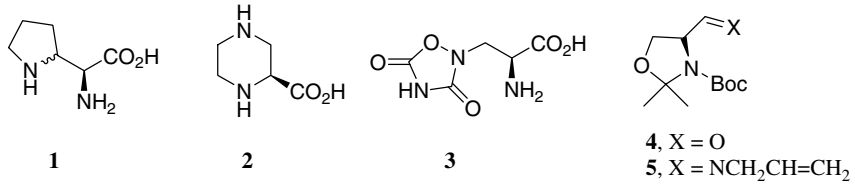
Received 24 May 2007; revised 17 June 2007; accepted 27 June 2007
Available online 4 July 2007

Abstract—A route to two epimeric hitherto unknown 2-piperidinylglycine derivatives, as precursors of carbocyclic β-lactam derivatives, has been developed, which features diastereoselective addition of allyl metal reagents to an *N*-allylimine derivative of Garner's aldehyde and ring-closing metathesis as key steps.

α,β-Diamino acids constitute an important class of compounds of chemical and biological significance, which has generated interest in their synthesis. In particular, derivatives in which one or both of the nitrogen atoms constitutes a heterocyclic ring are important as conformationally constrained amino acids, chiral auxiliaries/building blocks and are present in several natural products.[1,2] Compounds **1**–**3** (Fig. 1) are good examples.[3] Moreover, the synthesis and biological evaluation of heterocycle-substituted non-proteinogenic α-amino acids are subjects of continuing interest.[4] Although the 2-piperidinylglycine ring-system is present in the antitumour antibiotic DKP 593A,[5] it is otherwise less known. We report herein a stereodivergent route to two epimeric 2-piperidinylglycine derivatives as possible candidates for applications in chemistry and biology.

Garner's aldehyde[6] (**4**, Fig. 1) has emerged as a valuable reagent, amongst other amino acid derived building blocks,[7] for the asymmetric synthesis of α-amino acids and related compounds of biological interest. However, imine derivatives of **4** have seen fewer applications.[8] We anticipated that the piperidinylglycine ring-system could possibly be constructed by ring-closing metathesis of an appropriate N-tethered diene obtainable from addition of a suitable allyl metal species to the *N*-allylimine derivative **5**. Allylation of imines has been extensively studied[9] as a route for the preparation of homoallylic amines. Although excellent catalytic[10] and auxiliary based methodologies[11] have been developed for the synthesis of chiral amines, the use of chiral-pool derived imines is of obvious advantages. A range of allylmetal reagents (wherein the metal component is either boron, magnesium, zinc, copper, tin, silicon, indium or aluminium) have been shown to be effective in specific instances. However, allylmagnesium or allylzinc reagents have found most applications as they can be used without any additive.

Thus, compound **4**, prepared following an improved procedure,[12] on dehydrative condensation with allylamine smoothly led to the corresponding imine **5** (Scheme



1 **2** **3**

4, X = O
5, X = $NCH_2CH{=}CH_2$

Figure 1.

Keywords: Imine; Amino acids; Allylation; Ring-closing metathesis; β-Lactam.
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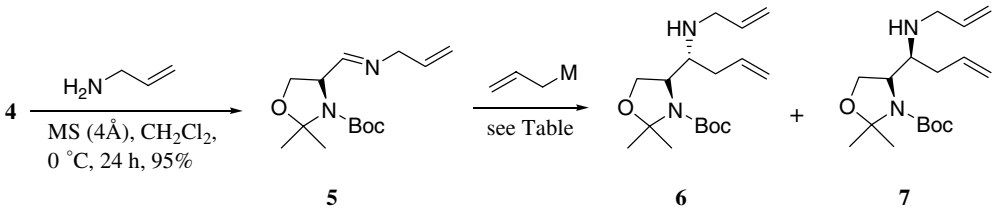
doi:10.1016/j.tetlet.2007.06.148



Scheme 1.

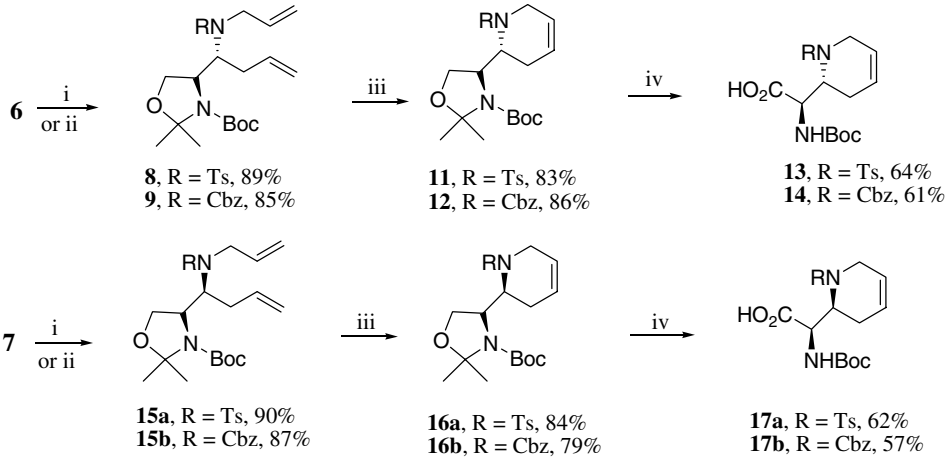
Table 1. Reaction conditions for the allylation of **5**

Entry	Reagent	Conditions	Yield (%)	**6**:**7**
1	CH_2=$CHCH_2MgBr$	Ether–THF (9:1), −30 °C, 12 h	67	99:1
2	CH_2=$CHCH_2MgBr$+$ZnBr_2$	Ether–THF (9:1), −30 °C, 12 h	63	77:23
3	CH_2=$CHCH_2ZnBr$	THF, 0 °C to rt, 18 h	59	18:82
4	CH_2=$CHCH_2Br$, In	DMF, rt, 24 h	74	34:66

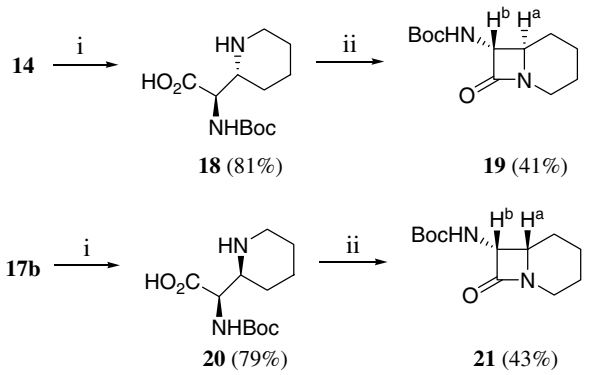
1, Table 1) in good yield. Addition of this imine to allylmagnesium bromide in ether solution proceeded well at −30 °C and the corresponding homoallyl amine **6** was obtained under optimised conditions in moderate yield but almost exclusively as one stereoisomer. We then considered addition of other allyl metals to **5** and the results are tabulated. In an attempt to affect *syn*-selective allylation through chelation, imine **5** was treated with allylmagnesium bromide in the presence of anhydrous zinc bromide. However, the diastereoselectivity in favour of the desired *syn*-isomer **7** increased only to 23% (HPLC). On the other hand, use of allylzinc bromide (prepared in situ from allyl bromide and zinc powder) under optimised conditions, led to the formation of *syn*-isomer **7** as the major product (*syn*:*anti* 82:18) in moderate yield. Indium has been shown[13] to facilitate nucleophilic addition to C=N bonds. Accordingly, allylation of **5** with indium and allyl bromide was studied under a range of conditions. The reaction proceeded best in *N*,*N*-dimethylformamide at room temperature to provide a separable mixture of isomeric homoallylic amines **6** and **7** in a slightly better yield but with lower selectivity in favour of **7**.

The diastereomeric excess of the amines was measured by HPLC analysis. The stereochemical assignment of the products was based on Cram's open chain and chelate models with further support from synthetic work described later in this Letter. It is interesting to note that only *syn*-selectivity was observed[14] during allylation of the *N*-benzyl nitrone derivative of **4**. The complementary mode of the present allylation reactions is therefore of advantage.

Having access to stereoisomerically pure *anti* and *syn* homoallylic amines **6** and **7** (separated by silica gel chromatography), we next focused on their conversion to the corresponding piperidine derivatives by ring-closing metathesis of the N-tethered diene unit. To this end, the N-protected dienes **8** and **9** were prepared from the *anti*-diamine **6** under conventional conditions (Scheme 2). Ring-closing metathesis of each of these dienes separately with Grubbs' first generation catalyst, (benzylidene bistricyclohexyl-phosphinoruthenium(IV) dichloride[15] **10**), proceeded well[16] under optimised conditions to provide the dehydropiperidine derivatives **11** and **12** in very good yields. One-pot deprotection–oxidation of



Scheme 2. Reagents and conditions: (i) 4-toluenesulphonyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 18 h; (ii) CbzCl, $NaHCO_3$, H_2O–EtOAc, rt, 12 h; (iii) Grubbs' catalyst **10** (5 mol %), CH_2Cl_2, rt, 0.5–2 h; (iv) Jones' reagent, acetone, 0 °C to rt, 5–6 h.



Scheme 3. Reagents and conditions: (i) H_2, Pd–C (10%), MeOH, rt, 12 h; (ii) 2-chloro-1-methylpyridinium iodide, DIPEA, MeCN, 70 °C to rt, 20 h.

the oxazolidine unit with Jones' reagent led to the piperidinylglycine derivatives **13**, $[\alpha]_D$ +9 (*c* 0.11, $CHCl_3$) and **14**, $[\alpha]_D$ −11 (*c* 2.5, $CHCl_3$). The same sequence of reactions on the N-protected dienes **15a**,**b**, prepared from the *syn*-homoallylic amine **7**, ultimately led to the isomeric unsaturated piperidinylglycine derivatives **17a**, $[\alpha]_D$ −6 (*c* 0.08, $CHCl_3$) and **17b**, $[\alpha]_D$ −29 (*c* 0.15, $CHCl_3$) in good overall yields.

Bacterial resistance to β-lactam antibiotics has motivated growing interest in the preparation and biological evaluation of new types of β-lactams.[17] The carbon analogues of penicillins and cephalosporins, namely, carbapenems and carbacephems, have thus emerged as a new generation of β-lactams. We considered the synthesis of carbacepham derivatives from the isomeric piperidinylglycine derivatives **14** and **17b** through lactamisation involving the ring nitrogen and the side chain carboxyl function. Thus, concomitant hydrogenation of the double bond and hydrogenolysis of the *N*-Cbz group in **14** were achieved in one step using Pd–C in methanol to provide the piperidinylglycine derivative **18** (Scheme 3) in good yield. The latter underwent cyclisation with Mukaiyama's reagent,[18] 2-chloro-1-methylpyridinium iodide to provide the β-lactam derivative **19** as a colourless solid in moderate yield. Similarly, the β-lactam derivative **21** was prepared from **17b**. Compounds **19** and **21** proved to be diastereomerically pure (NMR, HPLC) indicating that no racemisation took place during their formation. The *anti*-orientation of the protons H^a and H^b in compound **19** followed from analysis of the coupling constants.[19] Thus, in the ^1H NMR spectrum of **19**, H^b appeared as a doublet ($J = 7.0$ Hz), coupling with H^a not being observed. On the other hand, H^b in **21** appeared as a triplet ($J = 4.5$ Hz) with almost equal coupling with H^a and –N*H*Boc. These, in turn, corroborated the *anti*- and *syn*-configurations of homoallylic amines **6** and **7**, respectively.

In summary, we have developed a brief synthesis of two hitherto unknown epimeric N-protected 2-piperidinylglycine derivatives in which one of the stereogenic centres of the system is derived from the starting material and the second is created in a stereodivergent fashion. The prepared title compounds were demonstrated as precursors of carbocyclic β-lactams of current relevance. The bicyclo[4,2,0]octane ring-system has been prepared by an unusual synthetic route, which first involves formation of the six-membered ring, followed by construction of the β-lactam ring. The compounds prepared may find use in chemistry and biology.

Acknowledgement

We are thankful to DST, Government of India (Grant No. SR/S1/OC-51/2005) for financial support and UGC, CSIR, and University of Kalyani, for fellowships.

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19. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **11**: $[\alpha]_D$ −18 (*c* 0.08, $CHCl_3$). IR ($CHCl_3$): 2979, 1695, 1598, 1377, 1162, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (2H, d, $J = 8.0$), 7.21 (2H, d, $J = 8.0$), 5.58 (2H, br s), 4.21–4.19 (3H, m), 4.05–4.01 (1H, m), 3.81 (2H, dd, $J = 9.0$, 5.0), 2.39 (3H, s), 1.87–1.80 (1H, m), 1.72–1.69 (1H, m), 1.61 (3H, s), 1.50 (3H, s), 1.44 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2 (s), 143.2 (s), 137.8 (s), 129.6 (d), 127.0 (d), 124.7 (d), 121.6 (d), 94.6 (s), 80.4 (s), 64.8 (t), 57.0 (d), 51.4 (d), 41.0 (t), 29.7 (t), 28.3 (q), 27.1 (q), 26.8 (q), 21.5 (q). Elemental Anal. Calcd for $C_{22}H_{32}N_2O_5S$: C, 60.53; H, 7.39; N, 6.42. Found: C, 60.78; H, 7.56; N, 6.59. Mass (TOF MS ES+): *m*/*z* 459 (M+Na). Compound **16a**: $[\alpha]_D$ −76 (*c* 0.1, $CHCl_3$). IR ($CHCl_3$): 2925, 1694, 1366, 1260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.66 (2H, m), 7.24–7.22 (2H, m), 5.58–5.59 (1H, m), 5.48 (1H, br s), 4.42–4.37 (1H, m), 4.18–4.12 (2H, m), 3.89 (2H, dd, $J = 7.0$, 3.5), 3.79–3.77 (1H, m), 2.38 (3H, s), 2.08–2.03 (1H, m), 1.86–1.83 (1H, m), 1.55 (9H, s), 1.44 (6H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6 (s), 142.7 (s), 138.0 (s), 129.5 (d), 127.0 (d), 124.3 (d), 121.3 (d), 94.6 (s), 80.3 (s), 65.5 (t), 57.5 (d), 52.3 (d), 41.9 (t), 29.6 (t), 28.3 (q), 27.1 (q), 24.6 (q), 21.4 (q). Mass (TOF MS ES+): *m*/*z* 459 (M+Na). Compound **19**: $[\alpha]_D$ −9 (*c* 1.06, $CHCl_3$). IR (KBr) 3321, 1751, 1713, 1528, 1166 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 5.12 (1H, d, $J = 6.0$), 4.39 (1H, d, $J = 7.0$), 3.83 (1H, dd, $J = 13.0$, 4.0), 3.32 (1H, dd, $J = 11.0$, 4.0), 2.80–2.77 (1H, m), 2.14 (1H, br d, $J = 12.0$), 1.91–1.88 (1H, m), 1.69–1.64 (1H, m), 1.44 (9H, s), 1.41–1.37 (2H, m), 1.33–1.27 (1H, m) ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9 (s), 154.9 (s), 80.2 (s), 65.1 (d), 58.0 (d), 39.0 (t), 28.9 (t), 28.2 (q), 24.3 (t), 22.0 (t). HRMS (TOF MS ES+): obsd 263.1384 (M+Na); calcd 263.1372 ($C_{12}H_{20}N_2O_3$+Na). Compound **21**: $[\alpha]_D$ −61 (*c* 1.45, $CHCl_3$). IR (KBr): 3317, 1750, 1716, 1533, 1168 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 5.08 (1H, d, $J = 5.0$), 4.94 (1H, t, $J = 4.5$), 3.81 (1H, dd, $J = 13.5$, 5.0), 3.56 (1H, td, $J = 11.5$, 4.0), 2.71 (1H, dt, $J = 12.5$, 4.0), 1.91 (1H, d, $J = 13.0$), 1.81 (1H, d, $J = 13.0$), 1.67–1.63 (1H, m), 1.47–1.45 (1H, m), 1.43 (9H, s), 1.41–1.39 (1H, m), 1.36 (1H, ddd, $J = 12.5$, 5.5, 3.0). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9 (s), 155.1 (s), 80.2 (s), 60.3 (d), 53.7 (d), 38.7 (t), 28.2 (q), 24.9 (t), 24.6 (t), 21.3 (t). Mass (TOF MS ES+): *m*/*z* 263 (M+Na).