Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 821–825

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of bicyclic α-amino acids by a Diels–Alder reaction to a new chiral α,β-didehydroalanine derivative

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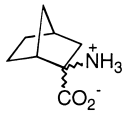
Received 19 January 1999; accepted 19 February 1999

Abstract

A new chiral cyclic α,β-didehydroalanine derivative, (6*S*)-6-isopropyl-3-methylene-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one, has been prepared by in situ aminomethylation–elimination of a chiral glycine-derived precursor. This oxazin-2-one acts as a reactive dienophile in highly diastereoselective Diels–Alder reactions with cyclopenta- and cyclohexadiene. The major cycloadducts have been isolated and hydrolyzed to afford enantiomerically pure (−)-*endo*-2-aminobicyclo[2.2.1]heptane-2-carboxylic and *exo*-2-aminobicyclo[2.2.2]octane-2-carboxylic acids.

1. Introduction

The synthesis of non-natural α-amino acids in an enantiomerically pure form is an important synthetic challenge nowadays due to their increasing role in chemistry and biology.[1] Among them, bicyclic amino acids have noticeable biological activities. For example, 2-aminobicyclo[2.2.1]heptane-2-carboxylic acids **1** inhibit the transport of nonpolar amino acids across cell membranes, act as an insulin-releasing factor and also inhibit the flavoprotein amino acid oxidases.[2] Furthermore, amino acids **1** and their homologues 2-aminobicyclo[2.2.2]octane-2-carboxylic acids **2** selectively perturb the levels of neutral amino acids in the cerebral cortex.[3]



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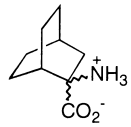

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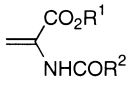
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00061-0

2. Results and discussion

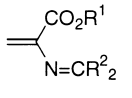
Preparation of these types of amino acids has been carried out by Strecker or Bucherer synthesis from the corresponding ketones[4] or, more frequently, by cycloaddition of α,β-didehydroamino acid (DDAA) derivatives with appropriate dienes. Thus, racemic amino acids **1** have been obtained via Diels–Alder reaction between cyclopentadiene and *N*-acyl-α,β-didehydroalanine derivative **3**,[5] *N*,*N*-diphenylmethylene-α,β-didehydroalaninate **4a**,[6a] *N*-bis(methylthio)methylene-α,β-didehydroalaninate **4b**[6b] or 2-isocyanatopropenoic acid **4c**.[6c] However, reports on the asymmetric version of these cycloaddition reactions are rather scarce. The reaction of *N*-acetyl-α,β-didehydroalaninate methyl ester **3a** with cyclopentadiene in the presence of a tartaric acid-derived titanium chiral Lewis acid mainly gave *exo*-**1** (*exo*:*endo* up to 79:21) in up to 70% ee.[7a] In addition, Lewis acid-catalyzed diastereoselective Diels–Alder reaction of chiral *N*-acetyl-α,β-didehydroalaninates **5** and cyclopentadiene, gave *endo*:*exo* ratios up to 18:82 when using a (−)-menthyl derivative (*exo*-**1** up to 78% ee; *endo*-**1** up to 76% ee), but *endo*:*exo* ratios up to 70:30 using a (−)-isobornyl derivative (*exo*-**1** up to 98% ee; *endo*-**1** up to 98% ee).[7] Moreover, methyleneoxazolidin-5-ones **6**[8,9] have been used in diastereoselective cycloaddition reactions with cyclopenta-[8a] and cyclohexadiene[8b,9] allowing the isolation of the free α-amino acids (+)-*exo*-**1**[8b] (45% ee starting from **6a** in 50% ee), (−)-*exo*-**1**[8b] (92% ee) and (−)-*exo*-**2**.[9]

Most of the starting α,β-didehydroamino acid derivatives mentioned presented a rather low reactivity towards Diels–Alder cycloadditions. For example, in the case of the chiral derivative **6**,[8] reaction times were in the order of days with the very reactive cyclopentadiene at room temperature, whereas derivative **5** proved unreactive under these conditions. Reaction rates may be increased by heating the reaction mixture or by adding a Lewis acid catalyst. Furthermore, all the above cited derivatives showed a tendency to give mainly carbonyl-*exo* cycloadducts, except the mentioned (−)-isobornyl ester derivative of **5**.[7a]

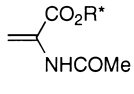
We have previously reported on the synthesis of a series of chiral DDAA derivatives by condensation of a new cyclic chiral glycine-derived oxazin-2-one **11** with aldehydes under phase-transfer-catalysis (PTC) conditions.[10] These compounds suffer diastereoselective cyclopropanation using Corey's ylide affording, after hydrolysis, 1-aminocyclopropane-1-carboxylic acids such as *allo*-coronamic and *allo*-norcoronamic acids.[10] We now report the preparation of the parent (6*S*)-6-isopropyl-3-methylene-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one **7** and its use as a reactive chiral dienophile in Diels–Alder reactions for the synthesis of enantiomerically pure bicyclic α-amino acids **1** and **2**.



3a, R^1=R^2=Me
3b, R^1=Et; R^2=Me
3c, R^1=Bn; R^2=Me
3d, R^1=Me; R^2=OMe



4a, R^1=Et; R^2=Ph
4b, R^1=Et; R^2=SMe
4c, R^1=Me; R^2= =O



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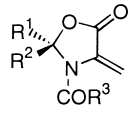
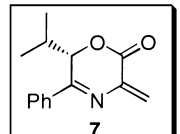


6a, R^1=Bu^t; R^2=H; R^3=Ph
6b, R^1=H; R^2=Ph; R^3=Ph
6c, R^1=H; R^2=Ph; R^3=Me



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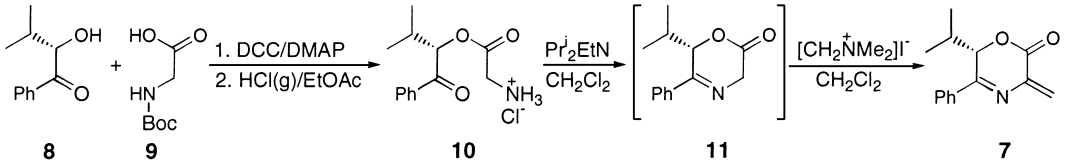
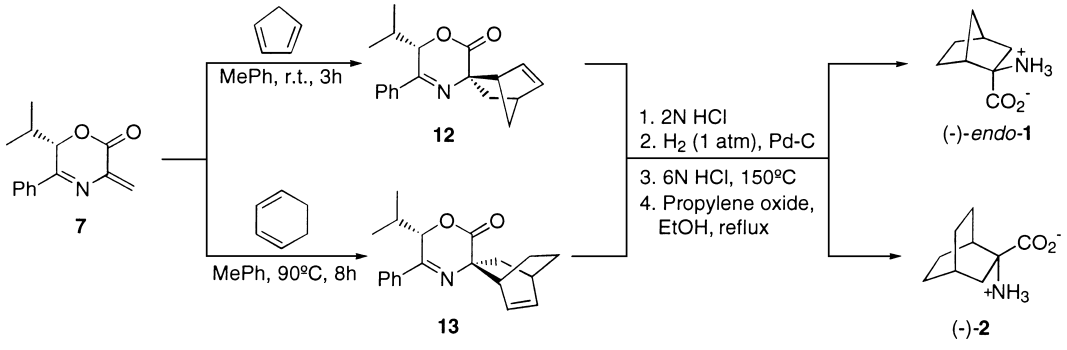
Starting oxazin-2-one **11** was obtained as reported:[10] esterification of Boc-protected glycine **9** with chiral hydroxyketone **8**, acid-mediated deprotection and final organic base-induced cyclization (Scheme 1). Attempted condensation of isolated **11** with aqueous or organic solutions of formaldehyde under different basic reaction conditions proved sluggish. However, when the hydrochloride precursor **10** was treated with diisopropylethylamine for 1 h followed by addition of *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt), the chiral α,β-didehydroalanine derivative **7** was obtained in 50% isolated yield after a one-pot cyclization–aminomethylation–elimination process. Purity of the crude **7** was high enough

for further synthetic uses (>90% by GLC and 300 MHz ^{1}H NMR), although analytical samples could be obtained after flash chromatography.[11,12]



Scheme 1.

When DDAA derivative **7** reacted with cyclopentadiene (20 equiv.) in toluene at room temperature, total consumption of the starting material was observed within 3 h (TLC). Analysis of the reaction crude (^{1}H NMR, 300 MHz) showed the presence of a major diastereomer **12** (85% **12**+15% other diastereomers) which was isolated in 55% yield after flash chromatography (Scheme 2). The stereochemistry of **12** was determined by X-ray diffraction analysis of a single crystal of racemic (±)-**12**[13] (Fig. 1), and obtained by a similar Diels–Alder reaction although using (±)-**7**.[14] It is remarkable that the reaction of this new DDAA derivative **7** with cyclopentadiene showed a 'normal' kinetic *endo*-selectivity with approximation of the diene by the less hindered, whereas it is reported that this reaction using other comparable DDAA derivatives such as **4a** or **6** showed opposite *exo*-selectivity. A lower steric hindrance close to the nitrogen atom in system **7** could account for the observed difference in stereoselectivity. In addition, the high reactivity of system **7** towards cyclopentadiene could be justified in terms of the rather low energy of its LUMO.[15]



Scheme 2.

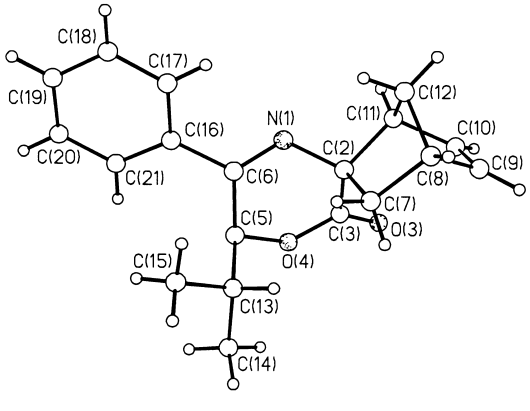


Figure 1. X-Ray crystal structure of (±)-**12**

The cycloaddition reaction was also carried out using cyclohexa-1,3-diene (20 equiv.), but then heating at 90°C during 8 h was necessary to get complete reaction (TLC). Analysis of the crude (^{1}H NMR, 300 MHz) showed again a major diastereomer **13** (88% **13**+12% other diastereomers) which was isolated by flash chromatography in 49% yield (Scheme 2). The stereochemistry of this major compound **13** was determined from the final amino acid (see below) as a thermodynamic *exo* cycloadduct derived from the diene following again the less hindered face of the double bond in derivative **7**.

Cycloadducts **12** and **13**[16] were subjected to the same hydrolytic protocol in order to achieve the desired final bicyclic amino acids (Scheme 2). Thus, acid hydrolysis of the imine moiety with 2 N HCl in THF, followed by catalytic hydrogenation at normal pressure of the double bond and subsequent hydrolysis of the ester function with 6 N HCl at 150°C (pressure tube) yielded amino acid hydrochlorides. Final treatment with propylene oxide in refluxing ethanol allowed the isolation of the free enantiomerically pure (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid[17] (−)-*endo*-**1** and (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.2]octane-2-carboxylic acid[17] (−)-**2** in 85% and 75% overall yields, respectively. The NMR and specific rotation data of amino acid (−)-**2** confirmed the proposed stereochemistry for adduct **13**.

3. Conclusion

In conclusion, we have found that chiral cyclic DDAA derivative **7** is an appropriate reactive dienophile for achieving highly diastereoselective Diels–Alder cycloaddition reactions for the synthesis of enantiomerically pure bicyclic α-amino acids (−)-*endo*-**1** and **2**. Further studies on the synthetic uses of these new DDAA derivatives in other cycloaddition reactions are now underway.

Acknowledgements

We thank the Dirección General de Investigación Científica y Técnica (DGICYT) of the Spanish Ministerio de Educación y Cultura (MEC) (PB94-1515 and PB95-0792) for financial support. N. G. thanks MEC for a grant.

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11. All the compounds reported gave consistent spectroscopic data (^{1}H and ^{13}C NMR, IR, MS)
12. Specific rotation of **7**: $[\alpha]_D^{25}$ −360 (*c*, 2; CH_2Cl_2).
13. Crystal data for compound (±)-**12**: $C_{19}H_{20}NO_2$, *M* 294.4. Crystal size 0.79×0.27×0.22 mm. *T*=298(2) K. Crystal system: monoclinic, space group P2(1)/n, *a*=12.9886(16) Å, *b*=7.3729(8) Å, *c*=17.672(2) Å. *V*=1598.1(3) Å^3; D_c=1.223 g/cm^3. Full structural details have been deposited with the Cambridge Crystallographic Data Centre.
14. Prepared from racemic hydrochloride **10**, which was obtained in 85% yield by reaction of α-bromoisovalerophenone with the potassium salt of *N*-Boc-protected glycine in DMF, followed by HCl(g)/AcOEt deprotection.
15. AM1 calculated frontier orbital energies of compound **7**: E_{HOMO}=−9.46 eV, E_{LUMO}=−0.94 eV. For example, for compound **6a**: E_{HOMO}=−9.60 eV, E_{LUMO}=−0.33 eV (Hyperchem 5.0 from Hypercube Inc.).
16. Specific rotations: **12**, $[\alpha]_D^{25}$ −60.0 (*c*, 1.4; CH_2Cl_2). **13**, $[\alpha]_D^{25}$ −45.1 (*c*, 1.3; CH_2Cl_2).
17. Specific rotations: (−)-*endo*-**1**, $[\alpha]_D^{25}$ −61.0 (*c*, 1; H_2O), lit.[2] $[\alpha]_D^{25}$ −61.4 (*c*, 1; H_2O). (−)-**2**·HCl, $[\alpha]_D^{25}$ −12.8 (*c*, 0.5; H_2O), lit.[9] (2*S*-enantiomer) $[\alpha]_D^{25}$ +12.4 (*c*, 0.5; H_2O).