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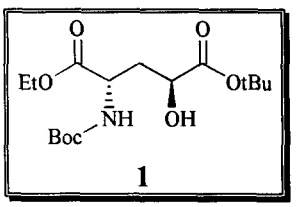
Asymmetric 1,3-Dipolar Cycloaddition: Synthesis of N-protected (4*S*)-4-Hydroxy L-Glutamic Acid Diester

Thierry Gefflaut, Udo Bauer, Karri Airola[a], Ari M.P. Koskinen*

*Department of Chemistry, University of Oulu, PO Box 333, FIN-90571 Oulu, Finland
[a]Department of Chemistry, University of Jyväskylä, PO Box 35, FIN-40351 Jyväskylä, Finland

Abstract: An asymmetric synthesis of N-protected (4*S*)-4-hydroxy L-glutamic acid diester is described. The key feature of the synthesis is the asymmetric 1,3-dipolar cycloaddition of nitrone **4** with **5**, which provides stereoselectively the isoxazolidine with the correct stereochemistry suitable for the synthesis of *N*-protected (4*S*)-4-hydroxy L-glutamic acid diester **1**.

γ-Hydroxy L-glutamic acids are naturally occurring amino acids which have been isolated from plants.[1] They are obviously interesting chiral synthetic intermediates for the generation of functionalized analogues of glutamic acid as well as structurally related amino acids.[2] The implication of these amino acids in memory processes and Alzheimer's disease and the potential of excitatory amino acid antagonists in anti-epileptic therapy and stroke prevention has initiated wide interest in the field.[2] Only a limited number of methods for the preparation of enantiopure γ-hydroxy L-glutamic acids have appeared in the literature, and they required enzymatic resolution of the racemate or resulted in an inseparable mixture of diastereomers.[3]



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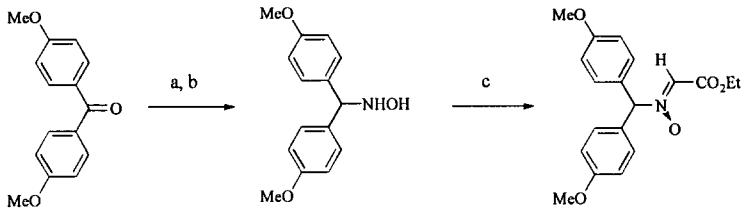
In connection with a program directed towards the development of novel prolyl 4-hydroxylase inhibitors we have developed an efficient method for the preparation of enantiopure N-protected γ-hydroxy L-glutamic acid diester **1**. The key feature of our approach is an asymmetric 1,3-dipolar cycloaddition of nitrone **4** with acrylamide **5** derived from Oppolzer's chiral sultam as a dipolarophile. Oppolzer's sultam has been extensively used as a chiral auxiliary and usually good to excellent π-face diastereoselectivities have been achieved in cycloaddition reactions.[4] Surprisingly, only a few examples are known, in which a camphor-derived chiral auxiliary has been used in cycloadditions involving the use of a nitrone as the dipole.[5] The efficacy of this chirality directing group has been attributed mainly to its rigid bicyclic framework which allows well-defined conformations and consequently effective stereofacial discrimination for the diastereotopic transition states.[6]

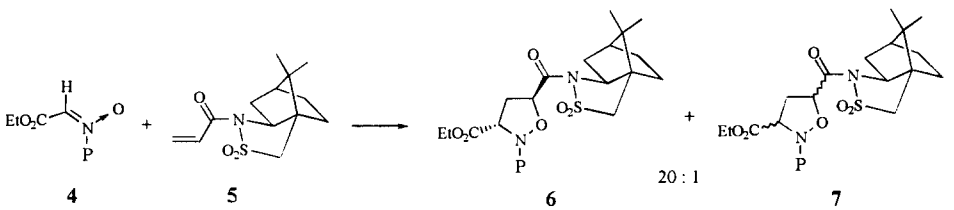
The nitrone **4** was readily available from 4,4'-dimethoxy-benzophenone **2** in 45% overall yield (Scheme I). Sequential treatment of **2** with hydroxylamine hydrochloride and pyridine-borane complex proceeded smoothly to give hydroxylamine **3**. Subsequent condensation of **3** with ethyl glyoxylate in benzene at 80°C for 30 min resulted in the formation of the nitrone **4**.[7]

The cycloaddition of *N*-acryloyl (2*S*)-bornane-10,2-sultam **5**, prepared by Kim's procedure,[5b] with nitrone **4** (existing as an *E*/*Z* equilibrium mixture) gave practically a single diastereomer **6** contaminated with less



Scheme I. **Reagents and conditions**: **a)** $NH_2OH{\cdot}HCl$, EtOH, 80°C, 3 h; **b)** borane-pyridine, HCl, EtOH, -5°C; *c*) ethyl glyoxylate, C_6H_6, reflux, 30 min. 45 % overall from **2.**

than 4% of unidentified isomer **7** (Scheme II). The major diastereomer **6** (mp. 95-96 °C; $[\alpha]_D$ = +101.6 (*c*= 0.9, $CHCl_3$)). was separated from **7** by flash chromatography and was isolated in 82% yield. The absolute stereochemistry of **6** was established from single crystal X-ray diffraction analysis and the newly generated C-3 and C-5 stereogenic centers of the isoxazolidine were both determined as *S* (Fig. 1).[8]



Scheme II. **Reagents and conditions**: toluene, 25°C, 36 h, P = di(p-methoxyphenyl)methyl.

The predominant *trans* stereochemical outcome observed in this cycloaddition is consistent with a reaction pathway involving *endo* addition of the *Z*-nitrone as well as *exo* addition of the *E*-nitrone (Fig. 2). The excellent π-face stereoselectivity seen in this cycloaddition reaction may result mainly from face shielding due to Coulombic interaction (repulsion) between the dipolar oxygen and the sultam oxygen, as recently suggested by Kim *et al.*[6a]

The major isomer **6** was converted to the *N*-protected (4*S*)-4-hydroxy L-glutamic acid diester **1** as outlined in Scheme III. Basic cleavage with LiOH in 1:1 THF:water turned out to be completely unselective, leading to cleavage of both the ester and the sultam groups. However, treatment of **6** with a milder base $LiOH/H_2O_2$ at -15°C cleanly gave the acid **8** ($[\alpha]_D$ = +5.1 (*c*= 2.4, $CHCl_3$), 95% yield) along with recovered sultam. The *tert*-butyl ester **9** was efficiently prepared in 87 % yield by reacting **8** with 3 equiv. of *O-tert*-butyl-*N,N'*-diisopropylisourea and a catalytic amount of CuCl at 25°C for 16 h. Subsequent catalytic hydrogenation of **9** over Pd/C in the presence of di-*tert*-butyl dicarbonate afforded the enantiopure diester **1** in 82% yield.

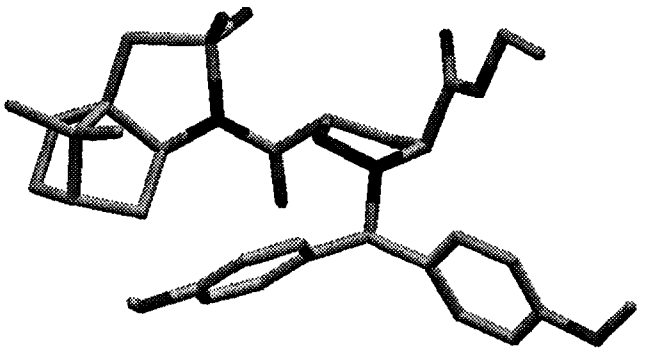


Fig. 1. X-ray structure of 6 (MacroModel Plot)

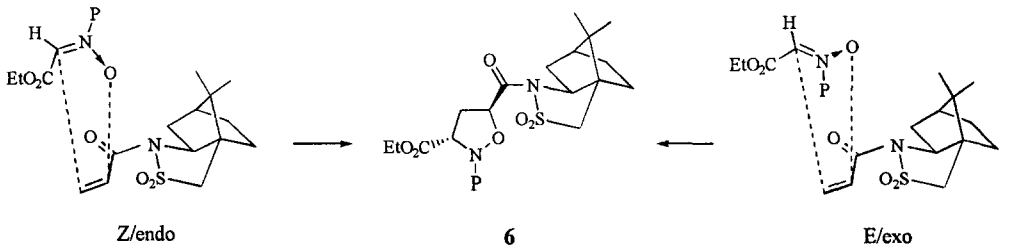
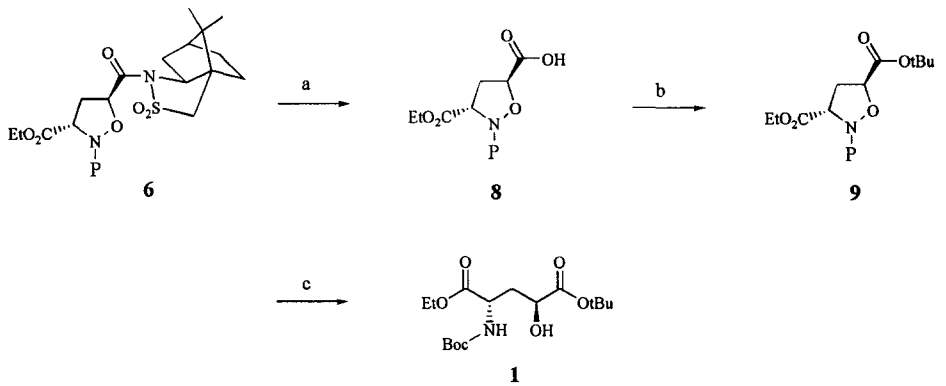


Fig. 2. Transition state

In summary, we have demonstrated the utility of an asymmetric 1,3-dipolar cycloaddition for the practical synthesis of optically pure differentially protected γ-hydroxy L-glutamic acid esters.



Scheme III. **Reagents and conditions**: **a)** LiOH, THF/H_2O_2, -15 to 0°C, 95 %; **b)** *O-tert*-butyl-*N,N'*-diisopropylisourea, cat. CuCl, 25°C, 16 h; **c)** H_2, 10% Pd/C, Boc_2O, MeOH, 8 h, 82 %. P = di(p-methoxyphenyl)methyl.

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References and notes:

1. a) Adams, E.; Goldstone, A. *J. Biol. Chem.* **1960**, *235*, 3504. b) Virtanen, A.I.; Hietala, P.K. *Acta Chim. Scand.* **1955**, 9, 175.
2. Dinsmore, A.; Doyle, P.M.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 7503 and references cited therein.
3. a) Benoiton, L.; Winitz, M.; Birnbaum, S.M.; Greenstein, J.P. *J. Am. Chem. Soc.* **1957**, *79*, 6192.b) Kusumi, T.; Kakisawa, H.; Suzuki, S.; Harada, K.; Kashima, C. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1261. c) Kirstensen, E.P.; Larsen, L. M.; Olsen, O.; Sorensen, H. *Acta Chim. Scand.* **1980**, *34*, 497. d) Passerat, N.; Bolte, J. *Tetrahedron* **1987**, *28*, 1277. e) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401.
4. Kim, B.H.; Curran, D.P. *Tetrahedron* **1993**, *49*, 293 and references cited therein.
5. a) Kim, B.H.; Lee, J.Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27. b) Kim, B.H.; Lee, J.Y.; *Tetrahedron: Asymmetry* **1991**, *2*, 1359.
6. a) Kim, K.S.; Kim, B.H.; Park, W.M.; Cho, S.J; Mhin, B.J. *J. Am. Chem. Soc.* **1993**, *115*, 7472. b) Curran, D.P.; Kim, B.H.; Daugherty, J.; Heffner, T.A. *Tetrahedron Lett.* **1988**, *29*, 3555.
7. All new compounds are fully characterized by their spectroscopic and analytical data.
   Selected spectroscopic data for compound **1**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, J = 6.9 Hz, 3H, CH_2-$\underline{CH_3}$); 1.43, 1.47 (2s, 18 H, C-$\underline{CH_3}$); 2.07 (m, 2H, CH_2); 3.10 (bs, 1H, OH); 4.10 (dd, J = 3.8, 8.9 Hz, 1H, CH); 4.20 (q, J = 6.9 Hz, 2H, OCH_2); 4.47 (m, 1H, CH); 5.46 (bd, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.10 (CH_2-$\underline{CH_3}$); 27.99, 28.28 (6C-$\underline{CH_3}$); 36.88 (CH_2); 51.27 (NCH); 61.43 (OCH_2); 68.05 (OCH); 80.15, 82.75 (2$\underline{C}$-CH_3); 155.78 (CON); 172.24, 173.13 (2C=O).
8. $C_{32}H_{40}N_2O_8S$ (612.72): orthorhombic, $P2_12_12_1$, a = 7.741 (4), b = 16.882 (11), c = 24.210(11) Å, V = 3164 Å^3, Z = 4, d_{calc} = 1.286 g cm^{-3}, λ (CuK_α) 1.5418 Å, μ = 13.47 cm^{-1}, T = 293 K, 3790 collected reflections, 3253 independent reflections, [I >2σ(I), R = 0.0693, R_w = 0.1334]. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre.

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