JOC*Note*

Enantioselective Total Synthesis of (1*R*,3*S*,4*R*,5*R*)-1-Amino-4,5-dihydroxycyclopentane-1,3-dicarboxylic Acid. A Full-Aldol Access to Carbaketose Derivatives

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Abstract: The enantioselective synthesis of cyclopentanedicarboxylic amino acid **1**, a novel rigid and functionalized L-glutamic acid analogue, has been achieved in 15 linear steps from silyloxypyrrole **3**, utilizing L-glyceraldehyde **4** as the source of chirality. The key steps in the synthesis are three sequential aldol-based carbon−carbon bond-forming reactions: two crossed vinylogous aldol additions (**2** + **3** → **8** and **4** + **5** → **10** + **11**) and one intramolecular silylative aldolization (**6** → **7**). En passant, the short syntheses of (2*S*)-2-hydroxymethylglutamic acid (**16**) and its (2*R*)-enantiomer *ent*-**16**, a potent metabotropic glutamate receptor agonist, have been achieved.

The carbocyclic amino acid **1**, the synthetic object of this article, is a small yet intriguing molecular construct whose structure can be visualized under diverse perspectives. As shown in Figure 1, the integral molecule is in itself an oxidized form of an aminoated carba-ketofuranose (i.e., 5a-carba-β-D-fructofuranose[1]) that can be viewed either as a dihydroxylated analogue of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (*trans*-ACPDA), a selective metabotropic glutamate receptor agonist,[2] or as a constrained 2,4-disubstituted L-glutamic acid. Furthermore, within the structure of **1,** one can quickly identify the fragment of D-serine as well as the structural motif of (2*R*)-2-hydroxymethylglutamic acid (HMGA), a recently introduced selective metabotropic glutamate receptor agonist.[3]

From a synthetic perspective, **1** is a quite challenging target, for five consecutive functionalities and four stereocenters, including a quaternary one, converge into a small cyclopentane core unit. Retrosynthetically (Scheme 1), amino acid **1** could be disconnected along three strategic carbon−carbon bonds, as indicated, furnishing

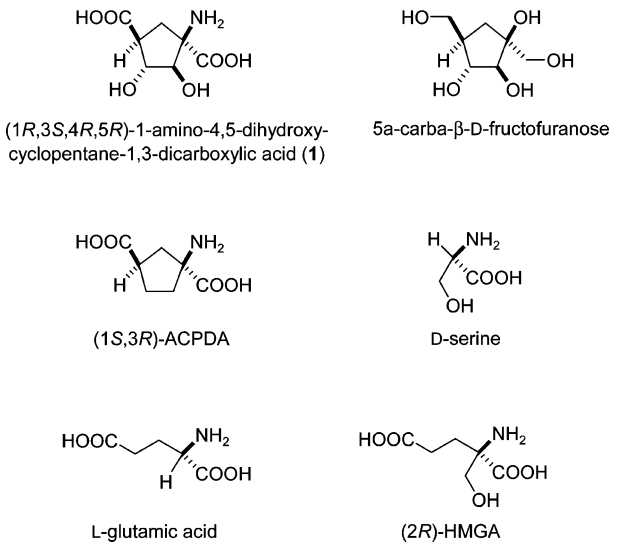
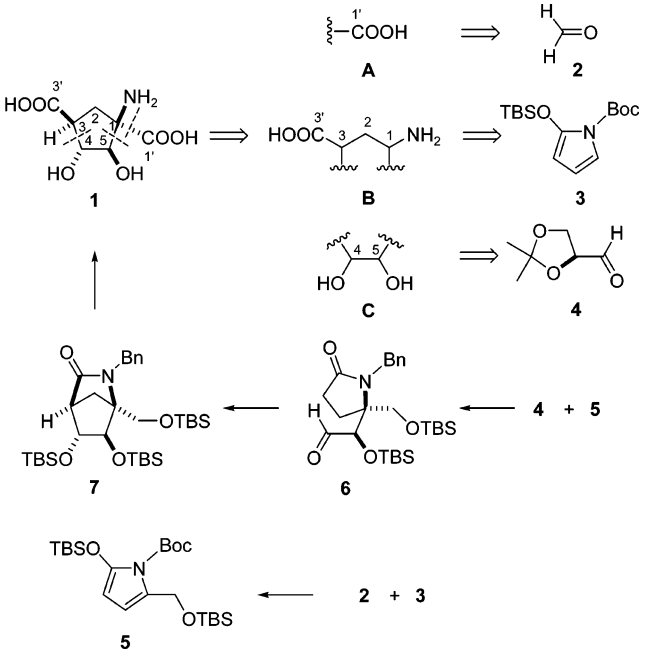


FIGURE 1. The multifacial structure of dicarboxylic amino acid **1**.

SCHEME 1. Retrosynthesis of Dicarboxylic Amino Acid 1



three simple building fragments, **A**, **B**, and **C**, that ultimately could be derived from formaldehyde (**2**), *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethyl)silyloxy]-pyrrole (**3**), and 2,3-*O*-isopropylidene-L-glyceraldehyde (**4**), respectively. In the synthetic direction, we planned first to attach formaldehyde (**2**) to **3**, forming the γ-substituted dienoxy pyrrole **5**, afterwhich **5** was to be coupled with **4** to give aldehyde **6**, which consequently was to be cyclized into bicycle **7**, and finally, the requisite amino and carboxy functionalities within **7** were to be unmasked, thus completing the construction of **1**.

Accordingly, our synthesis (Scheme 2) commenced with the gram-scale preparation of γ-substituted pyrrolinone

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(1) (a) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102−3104. (b) Gaudino, J. J.; Wilcox, C. S. *Carbohydr. Res.* **1990**, *206*, 233−250. (c) Seepersaud, M.; Al-Abed, Y. *Org. Lett.* **1999**, *1*, 1463−1465.

(2) (a) Knöpfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417−1426. (b) Schoepp, D. D.; True, R. A. *Neurosci. Lett.* **1992**, *145*, 100−104. (c) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365−402. (d) Palmer, E.; Monaghan, D. T.; Cotman, C. W. *Eur. J. Pharmacol.* **1989**, *166*, 585−587.

(3) (a) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555−7559. (b) Kozikowski, A. P. PCT Int. Appl. WO 02/22622 A2, 2002. (c) Kawasaki, M.; Namba, K.; Tsujishima, H.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2003**, *44*, 1235−1238.

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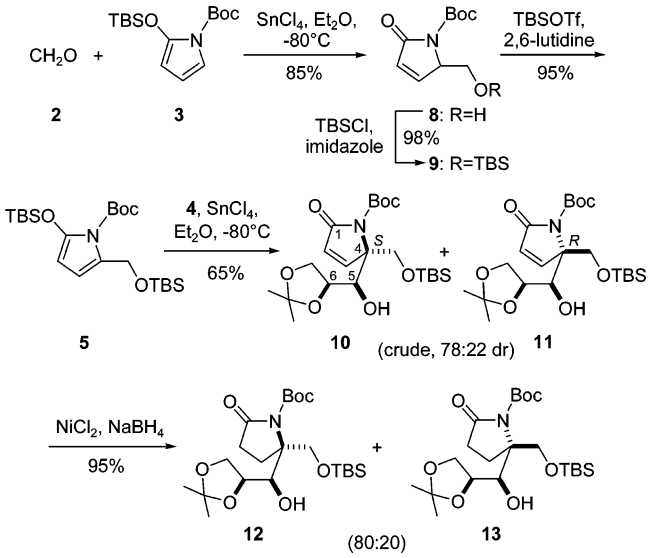
SCHEME 2. Preparation of Lactam Intermediates 12 and 13

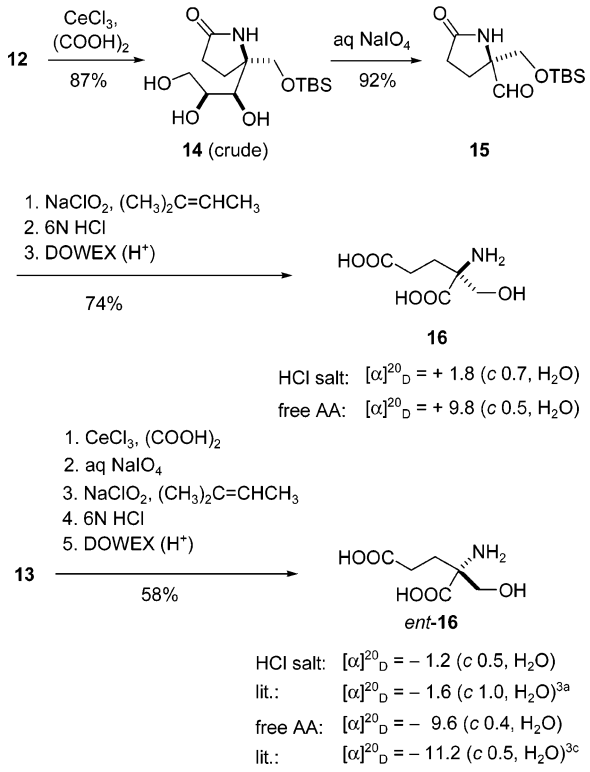


8 via $SnCl_4$-assisted vinylogous hydroxyalkylation of pyrrole-derived dienoxysilane **3** with anhydrous formaldehyde (**2**) (85% yield).[4] After silylation to **9**, TBSOTf-lutidine treatment then led to substituted dienoxy pyrrole **5** (93% yield, two steps), which was coupled to 2,3-*O*-isopropylidene-L-glyceraldehyde (**4**) under the guidance of $SnCl_4$ in diethyl ether. A mixture of two unsaturated adducts, **10** and **11** (65% combined yield), was obtained, where the (4*S*)-configured isomer **10** strongly predominated (78:22 dr, by ^{1}H NMR).[5] Isolation of the individual components in the unsaturated adduct mixture proved indeed difficult; so we opted to move ahead with the reduction of the lactam double bond within **10** and **11** ($NiCl_2$, $NaBH_4$), arriving at stable γ,γ-disubstituted pyrrolinone **12** in an acceptable 50% yield over two steps. During the separation workup a minor, crystalline isomer (12% yield, two steps) was also isolated, to which structure **13** was tentatively assigned.[6]

To fix, at least, the absolute configuration at the quaternary carbon C4 in both isomers **12** and **13**, chemical correlations of these compounds to known (2*S*)-2-hydroxymethylglutamic acid (**16**)[7] and (2*R*)-2-hydroxymethylglutamic acid (*ent*-**16**),[3] a novel, remarkable selective agonist of group II metabotropic glutamate receptors, were executed (Scheme 3). Thus, removal of both the *N*-Boc and isopropylidene protections within the major isomer **12** cleanly afforded a triol intermediate **14**, which was first fragmented to aldehyde **15** and then oxidized and hydrolyzed to (2*S*)-configured amino acid **16** (59% yield from **12**).

In a parallel fashion, minor isomer **13** was elaborated into (2*R*)-configured amino acid *ent*-**16** in a 58% overall yield. The values we obtained for the optical rotation of both the free amino acid *ent*-**16** ($[\alpha]^{20}_D = -9.6$) and its HCl salt ($[\alpha]^{20}_D = -1.2$) nicely matched the values

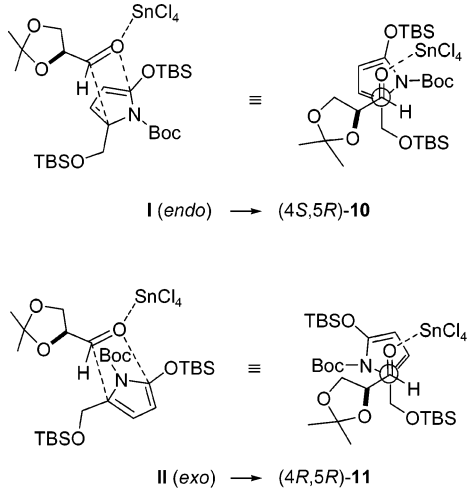
SCHEME 3. Chemical Correlations of 12 and 13 to α-Substituted Glutamic Acids 16 and *ent*-16



present in the literature for the same compound (lit. free amino acid $[\alpha]^{20}_D = -11.2$;[3c] HCl salt $[\alpha]^{20}_D = -1.6$[3a]). As expected, enantiomeric amino acid **16** displayed almost equal optical rotation as its enantiomer *ent*-**16**, but of opposite sign ($[\alpha]^{20}_D = +9.8$). Thus, having established

(4) For recent reviews dealing with the silyloxy diene chemistry, see: (a) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford; 1998; Vol. 3, pp 113−189. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, 109−118. (d) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.

(5) Presumably, the reaction proceeds via the Diels−Alder-like *endo* transition structure **I**, featuring a Felkin-type facial diastereoselectivity (addition of the aldehyde from the *re*-face). The transition state **I** then collapses to afford the major 4*S*,5*R*-configured adduct **10**. Formation of the minor 4*R*,5*R* isomer **11**, in contrast, would require a high-energy *exo* transition state **II** possessing an unfavorable orientation of the aldehyde dioxolanyl substituent.

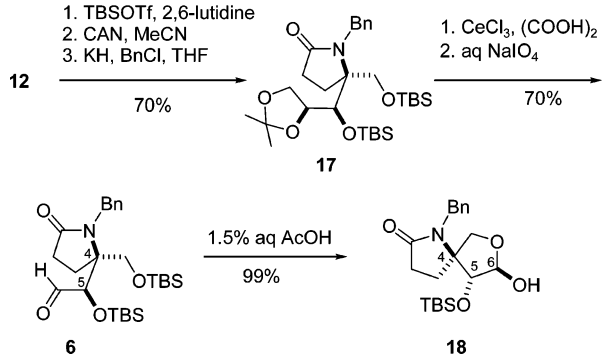


For a recent theoretical study of the mechanisms of related Lewis acid assisted reactions involving five-membered heterocyclic dienes, see: Yu, Z.-X.; Wu, Y.-D. *J. Org. Chem.* **2003**, *68*, 421−432.

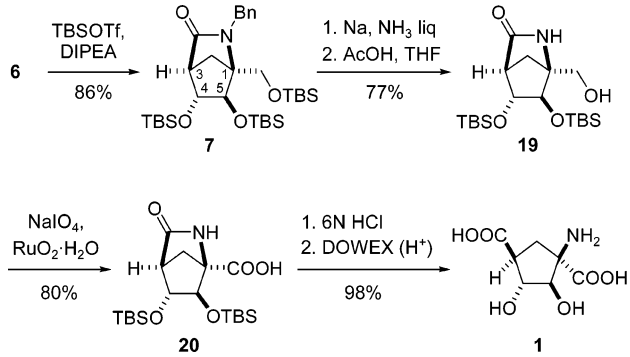
(6) For this minor isomer, the absolute configuration at C5 could not be firmly assigned.

(7) Choudhury, P. K.; Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 463−464.

SCHEME 4. Preparation of Aldehyde 6



SCHEME 5. Completion of Amino Acid 1



the absolute configuration at the quaternary carbons of **12** and **13** as 2*S* and 2*R*, respectively, we proceeded along our synthesis with the elaboration of the more abundant isomer **12** into aldehyde **6**, as shown in Scheme 4.

After silylation of the secondary hydroxyl of **12**, the *N*-Boc protective function was switched to *N*-Bn by a deprotection-reprotection protocol consisting of cerium ammonium nitrate treatment, followed by benzylation. Orthogonally protected lactam **17** was thus obtained in a 70% yield for the three-step sequence. Exposure of **17** to cerium trichloride in the presence of catalytic oxalic acid[8] selectively delivered a terminal diol intermediate (not shown), which was oxidatively shortened by one carbon atom ($NaIO_4$) to give aldehyde **6** in a 70% global yield.

The complete stereostructure of **6** (and hence that of its predecessors) awaited decisive confirmation, and this was simply established from that of its spirocyclic derivative **18**, which was quantitatively obtained by desilylation of the primary hydroxyl group within **6**, followed by spontaneous ring-closing hemiacetalization.[9] Examination of the interproton NOE correlations within **18** (Supporting Information) unambiguously provided clear-cut evidence of the *erythro* relationship between the lactam nitrogen and the hydroxyl C5 substituent, as well as the *trans* orientation of the protons H5 and H6. Thus, having already established the absolute configuration of the quaternary C4 center (vide supra), the stereochemistry of both **17** and **6** was assigned as 4*S*,5*R*, as shown.

The third aldol maneuver connecting the C2 nucleophilic carbon of **6** to its terminal aldehyde group (C6) was the key step in our synthesis (Scheme 5).

This operation, which completed the cyclopentane ring of **1**, was executed as previously described[10] by exposure of aldehyde **6** to an equimolar mixture of TBSOTf and DIPEA in CH_2Cl_2 at room temperature. Under these performing silylative conditions, cycloadduct **7** was cleanly obtained as a predominant isomer in a gratifying 86% isolated yield (>90% dr).[11] The stereochemical confirmation of the silylated aldol **7** was obtained by 2D NOESY experiments (Supporting Information) that substantiated the *trans* relationship between the substituents at C4 and C5, as well as the *erythro* disposition of the C5 hydroxyl and the lactam nitrogen (target numbering), thus confirming the stereochemistry of the precursor aldehyde **6**.

Unmasking of the latent C1 carboxyl moiety of **1** was effected by oxidation of the hydroxymethyl group in the adduct **7**. Thus, the *N*-benzyl protection was first cleaved (Na, liquid NH_3) and the hydroxymethyl function was selectively deprotected (AcOH) to deliver free alcohol **19** (77% yield, two steps), which was directly exposed to $NaIO_4$ in the presence of catalytic RuO_2. In the event, bicyclic carboxylic acid **20** was isolated in a 80% yield. The fragmentation of the lactam ring of **20**, which liberated both the amino group at C1 and carboxylic function at C3, was realized with concomitant desilylation, via exposure to 6 N aqueous HCl at 110 °C, followed by DOWEX (H^+ form) treatment, to finally obtain the targeted cyclopentane-1,3-dicarboxylic amino acid **1** in a 98% isolated yield.

In summary, we have established a viable, stereoselective synthetic route to L-glutamic acid related amino acid **1** that can provide a foundation for the search of novel metabotropic glutamate receptor probes, as well as relevant densely functionalized carba-ketose constructs. The synthesis was completed within 15 individual steps with a 8% global yield, in a sequence featuring three highly productive aldol-based, carbon−carbon bond junctions accompanied by the rational execution of suitable functional group transformations and selective protection-deprotection protocols. As a corollary, routine elaboration of two intermediary compounds, lactams **12** and **13**, resulted, respectively, in the short chemical syntheses of (2*S*)-2-hydroxymethylglutamic acid (**16**) and (2*R*)-2-hydroxymethylglutamic acid (*ent*-**16**), a recently introduced selective metabotropic glutamate receptor agonist.

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Supporting Information Available: Experimental details and characterization data for all synthesized compounds, ^1H NMR resonances, coupling constants and $^1H-^1H$ NOE correlations for **1**, **7**, and **18**, (Tables S1−S3), as well as copies of ^1H NMR spectra for compounds **1**, **6**, **7**, **18**, and **20** and $^1H-^1H$ NOESY spectra for compounds **1**, **7**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Xiao, X.; Bai, D. *Synlett* **2001**, 535−537.

(9) On standing, this material equilibrated into a 60:40 anomeric mixture.

(10) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881−5885 and references therein.

(11) A minor 4,5-*cis*-configured isomer was also isolated and fully characterized (Supporting Information).