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Improved Synthesis of C4α- and C4β-Methyl Analogues of 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylate

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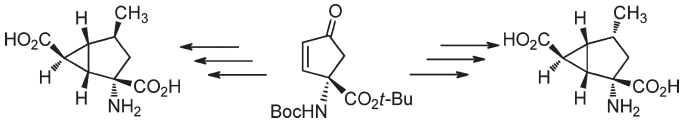
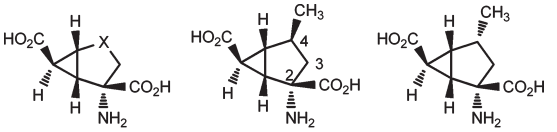
ABSTRACT



An efficient and divergent synthesis of C4α- and C4β-methyl-substituted analogues of 2-aminobicyclo[3.1.0]hexane 2,6-dicarboxylate, which are important tools in the study of metabotropic glutamate receptor function, has been achieved. By taking advantage of an unanticipated facial selectivity of the bicyclo[3.1.0]hexane ring system, either the C4α- or C4β-methyl substituent was introduced in a highly stereoselective and high-yielding manner.

The metabotropic glutamate (mGlu) receptors are promising targets for the treatment of CNS disorders.[1] Our laboratory has focused on the design and synthesis of orthosteric (glutamate-site) agonists targeting metabotropic glutamate receptors 2 and 3 (mGlu2/3 receptors). These investigations have resulted in the identification of several conformationally constrained glutamate analogues (**1**–**3**, Figure 1), which exhibit high potency and excellent selectivity for mGlu2/3 receptors over other mGlu and ionotropic glutamate receptors but which do not pharmacologically differentiate between mGlu2 and mGlu3 receptor subtypes.[2]

To investigate the effects of ring substitution of **1** on mGlu receptor function and selectivity, we prepared (±)-**4** and (+)-**5**.[3] Evaluation of the functional effects of these molecules in cells expressing human mGlu2 or mGlu3 receptors revealed that C4β-methyl analogue (±)-**4**, like compounds **1**–**3**, acted as a full agonist at both mGlu2 and mGlu3 receptors (EC_{50} = 45 and 34 nM, respectively), whereas the C4α-methyl derivative (+)-**5** (LY541850) exhibited an unexpected mixed mGlu2 agonist/mGlu3 antagonist pharmacological profile (mGlu2 EC_{50} = 161 nM, mGlu3 IC_{50} = 1050 nM). Despite their interesting pharmacologic properties, several issues associated with the originally



1, X = CH_2
2, X = O
3, X = SO_2

(±)-**4**

(+)-**5**

Figure 1. mGlu2/3 receptor agonists.

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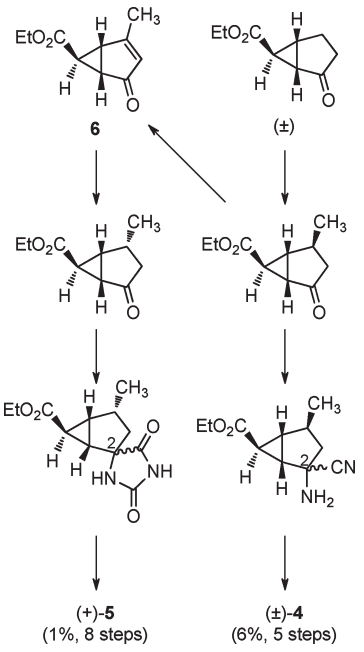
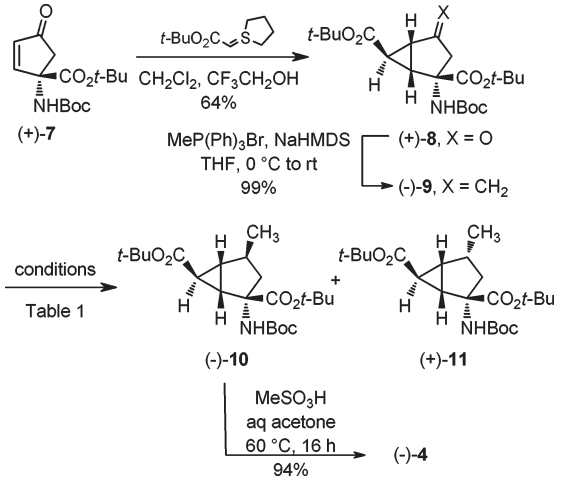
reported synthesis of (±)-**4** and (+)-**5** severely limited our access to these molecules, precluding our ability to assess their effects in vivo. First, the original synthesis as outlined in Scheme 1 utilized conventional Strecker or Bucherer–Bergs methodology to install amino acid functionality at the C2 center. These were low-yielding transformations and required a selective crystallization approach to obtain the desired C2 diastereomer. Second, the synthesis of (+)-**5** was particularly lengthy owing to a cumbersome inversion of C4β-methyl intermediate in order to obtain the desired C4α stereochemistry. Third, the approach was based on a racemic precursor necessitating chiral chromatography in order to separate the mGlu receptor active and inactive enantiomers. These synthetic issues resulted in extremely low overall yields of (±)-**4** (6%) and (+)-**5** (1%).

Scheme 1. Published Synthetic Approach to (±)-**4** and (+)-**5**



To improve upon this route, we envisioned beginning with a nonracemic precursor already possessing the C2 amino acid functionality. If successful, this would eliminate the loss of material during separation of both diastereomeric and enantiomeric mixtures. It was originally considered that (+)-**5** might be prepared by reduction of exocyclic olefin intermediate (−)-**9**, with the hydrogenation catalyst envisioned to approach the double bond from the convex face of the bicyclo[3.1.0]hexane ring system as was observed during reduction of the endocyclic olefin **6** in the original route. As shown in Scheme 2, bicyclic ketone (+)-**8** was prepared in high yield and excellent diastereomeric purity from previously reported enone (+)-**7**[4] via carboxy cyclopropanation in the presence of trifluoroethanol. Addition of trifluoroethanol or other proton sources with a similar pK_a is essential to achieve high selectivity for the desired diastereomer. Under the conditions described (10 equiv of trifluoroethanol), the desired cyclopropanation product is formed as a 95:5 mixture of the desired (+)-**8** and the undesired diastereomer with inverted configuration at C-6 ("*endo*-ester"). In the absence of an appropriate proton source the product ratio is reversed; the *endo*-ester diastereomer is the dominant (>85%) stereoisomer in the reaction mixture.[5] Subsequent reaction of (+)-**8** with methyltriphenylphosphonium ylide provided (−)-**9** in 99% yield.

Scheme 2. Synthesis of C4β-Methyl Analogue (−)-**4**



When (−)-**9** was subjected to hydrogenation using Pd/C as the catalyst, we observed a mixture consisting of C4β-methyl (−)-**10** and C4α-methyl (+)-**11** derivatives in a ratio of 97:3 as judged by the integration of the individual C4 methyl doublets in the ^{1}H NMR of the crude reaction mixture. Stereochemical assignment of the individual isomers could be determined based on the splitting pattern of the C4 hydrogens in (−)-**10** and (+)-**11**. Specifically, the C4 hydrogen oriented on the α-face of the bicyclic system, as is the case with (−)-**10**, is nearly orthogonal to both C5-H and C3β-H resulting in coupling constants that approach 0 Hz. Hence, C4α-H shows coupling to only the C3α-H and the hydrogens on the attached C4-methyl substituent leading to an observed pentet, Figure 2. In contrast, the C4 hydrogen oriented on the β-face of the bicyclic system, as with (+)-**11**, is coupled to C5-H (dihedral angle ≈ 40°, $J \approx 7$ Hz), C3β-H (dihedral angle ≈ 15°, $J \approx 5$ Hz), C3α-H, and the methyl

(4) Enone (+)-**7** was prepared on a kilogram scale in eight steps with an overall yield of 23% as described in the following publication: Varie, D. L.; Beck, C. B.; Borders, S. K.; Brady, M. D.; Cronin, J. S.; Ditsworth, T. K.; Hay, D. A.; Hoard, D. W.; Hoying, R. C.; Linder, R. J.; Miller, R. D.; Moher, E. D.; Remacle, J. R.; Rieck, J. A., III. *Org. Process Res. Dev.* **2007**, *11*, 546–559.

(5) The role of the proton source in controlling cyclopropanation stereoselectivity has not been definitively established. The diastereomeric esters do not interconvert under the reaction conditions. The pK_a and quantity of the proton source, the nature of the alkyl substituent on the ylide ester, and to a lesser extent, solvent all impact the stereoselectivity of the reaction. A full account of the investigation of factors controlling the stereochemical outcome of this reaction will be published in a separate report.

hydrogens leading to a much more complex, unresolved multiplet.

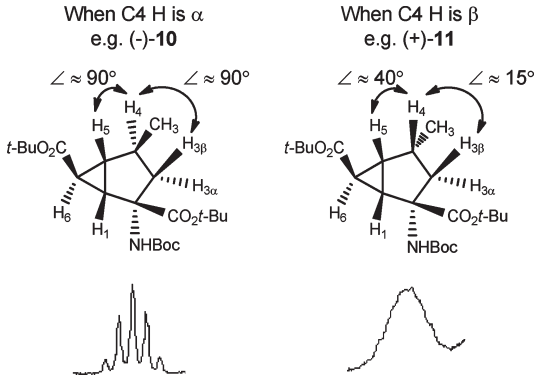


Figure 2. ^{1}H NMR splitting patterns of the C4 proton.

The facial selectivity observed in the Pd/C-catalyzed reduction of (−)-**9** clearly indicated that hydrogenation under these conditions occurred preferentially from the concave face of the bicyclohexane ring system. In order to further explore this finding, a variety of alternative hydrogenation catalysts were surveyed. All reactions were screened in both methanol and ethyl acetate (0.06 M of **9**) at 40 °C with an initial pressure of 100 psi of H_2. No effect of solvent was observed on the resultant diastereomeric ratios, and therefore, only results from reactions conducted in methanol are reported (Table 1). As can be seen, each of the catalysts investigated, including those employing chiral ligands, (entries 8 and 9), provided diastereomeric mixtures of (−)-**10** and (+)-**11** strongly favoring the former, though none provided superior selectivity over what was originally achieved with Pd/C.[6] In this case, the isomeric mixture was separated on silica resulting in diastereomerically pure (−)-**10** in 74% yield. Deprotection with methanesulfonic acid followed by cation exchange chromatography afforded (−)-**4** in 69% overall yield from (+)-**8**.

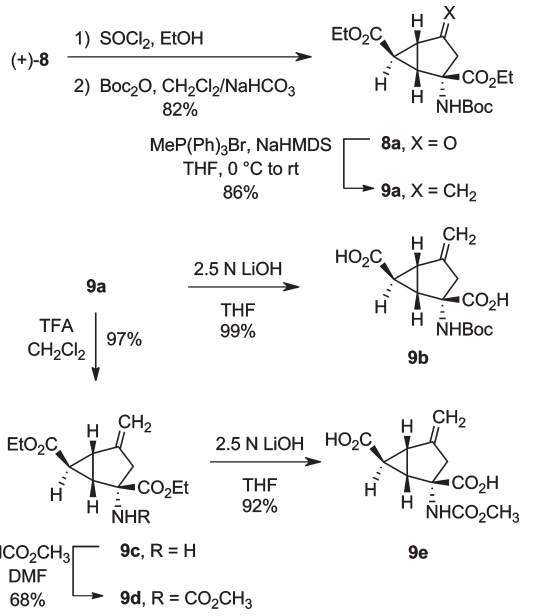
Table 1. Catalyst Effect on Ratio of **10** to **11**

entry	catalyst	(−)-**10**/(+)-**11**
1	Pd/C 5%	97/3
2	$Pd(OH)_2$	88/12
3	PtO_2	95/5
4	Raney Ni	94/6
5	$(PCy_3)Ir(cod)py-PF_6$	83/17
6	$RhCl(PPh_3)_3$	90/10
7	$(dippf)Rh(cod)-BF_4$	79/21
8	(R,R)-(Et-DuPhos)$Rh(cod)-BF_4$	74/26
9	(S,S)-(Et-DuPhos)$Rh(cod)-BF_4$	75/25

(6) In some instances during the reduction with Pd/C, varying amounts of a byproduct believed to result from reductive opening of the cyclopropane ring have been observed. In contrast, Wilkinson's catalyst showed no evidence of byproduct under all conditions explored. Factors that lead to the ring-opened product are not yet fully understood.

Given the facial selectivity observed during hydrogenation of (−)-**9**, we surmised that the *tert*-butyl ester functionality at the C2-position of this molecule, not present in enone **6**, might be exerting a strong 1,3-steric influence over the approach of reagents to the C4-position. To further explore this hypothesis, a series of analogues was prepared in which the size of the carboxylic acid and amine protecting groups were varied, Scheme 3.

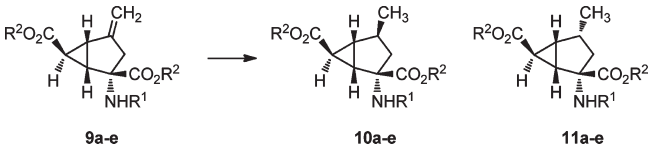
Scheme 3. Preparation of Alternatively Protected **9**



Olefins **9a**−**e** were exposed to Wilkinson's catalyst under 1 atm of hydrogen. The results of these studies are detailed in Table 2. Decreasing the size of either CO_2R (R = *t*-Bu, Et, H; entries 1−3) or NHR (R = *t*-BuO_2C, MeO_2C, H) substituents had little impact on the ratio of methyl-substituted products **10** and **11**. This suggests that in each case the C2-CO_2R substituent likely resides in a pseudoaxial orientation on the β-face of the bicyclic ring system. This particular conformation may be preferred over the alternative (pseudoequatorial C2-CO_2R, pseudoaxial NHR) owing to a likely negative steric interaction between the C6 hydrogen and C2-NHR substituent. Further supporting this hypothesis, it is interesting to note that the crystal structures of both **1** and a sulfoxide variant of **3** have been solved and each appears to possess conformations in which the amine and carboxylic acid functionalities reside in a pseudoequatorial and pseudoaxial orientation respectively.[2a,c]

Based on these data, we hypothesized that approach of a hydride donor or other nucleophiles to the C4 carbonyl carbon of (+)-**8** might also occur preferentially from the side opposite to the C2-ester (i.e., from the concave face) and that we might be able take advantage of this bias for the preparation of (+)-**5**. In this respect, we were gratified to find that reaction of ketone (+)-**8** in THF at −5 °C with L-Selectride provided C4β-carbinol (−)-**12** with excellent

Table 2. Protecting Group Effect on Ratio of **10** to **11**

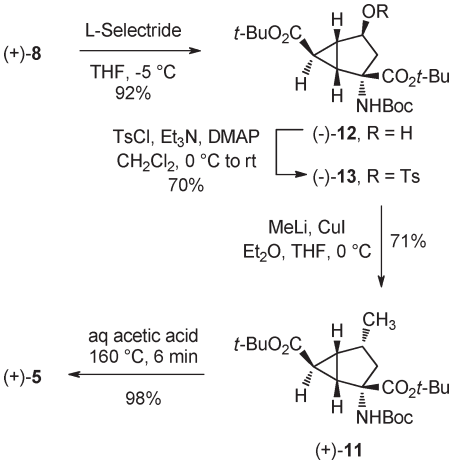


entry	**9**	R^1	R^2	**10/11**
1	**9**	CO_2-*t*-Bu	*t*-Bu	86/14
2	**9a**	CO_2-*t*-Bu	Et	82/18
3	**9b**	CO_2-*t*-Bu	H	77/23
4	**9d**	CO_2CH_3	Et	84/16
5	**9e**	CO_2CH_3	H	85/15
6	**9c**	H	Et	80/20

diastereomeric excess (>98%) and in high isolated yield (92%, Scheme 4). Alcohol (−)-**12** was smoothly converted to tosylate (−)-**13** (89%) under standard conditions, and the tosylate subsequently underwent S_N2-mediated displacement with freshly prepared lithium dimethyl cuprate[7] to provide C4α-methyl intermediate (+)-**11** in 71% isolated yield. Simultaneous deprotection of the carboxy amino protecting groups with aqueous acetic acid[8] afforded zwitterion (+)-**5** in 45% overall yield from (+)-**8**.

New synthetic approaches to pharmacologically interesting bicyclic amino acids from nonracemic precursor (+)-**7** have been established. The current methodology takes advantage of an unanticipated facial bias that allows

Scheme 4. Synthesis of C4α-Methyl Analogue (+)-**5**



for excellent stereochemical control of the approach of reagents to either C4-ketone or C4-exocyclic methylene functionalities. In addition, this methodology obviates the need for chiral chromatography and avoids the low-yielding introduction of the C2-amino acid functionality as described in the original route.[5] Hence, the synthetic routes described in this account resulted in a significant improvement in overall yield and throughput of (−)-**4** and (+)-**5**. Notably, access to the latter has enabled both in vitro and in vivo studies designed to elucidate the individual roles of mGlu2 and mGlu3 receptors within the central nervous system.[9] Finally, the approach described herein also highlights the value of intermediate (+)-**8**, which, owing to the presence of the C4-ketone functionality, should enable additional structure−activity relationship studies to be pursued. Results of these investigations will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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