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ASYMMETRIC SYNTHESIS OF TOPOGRAPHICALLY CONSTRAINED AMINO ACIDS: SYNTHESIS OF THE OPTICALLY PURE ISOMERS OF α,β-DIMETHYL-PHENYLALANINE AND α,β-DIMETHYL-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACID

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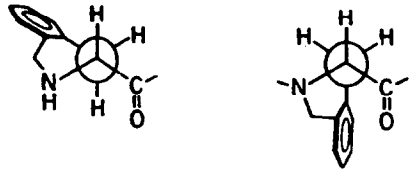
Abstract: All four isomers of α,β-dimethylphenylalanine and α,β-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid have been synthesized in high optical purity for use in the design of topographically constrained peptides.

Recently we have proposed a new approach for the design of bioactive peptides using the concept of topographical constraints.[1] As an example of this approach, we have utilized 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic, Figure 1) as a replacement of phenylalanine and tyrosine into somatostatin derived mu

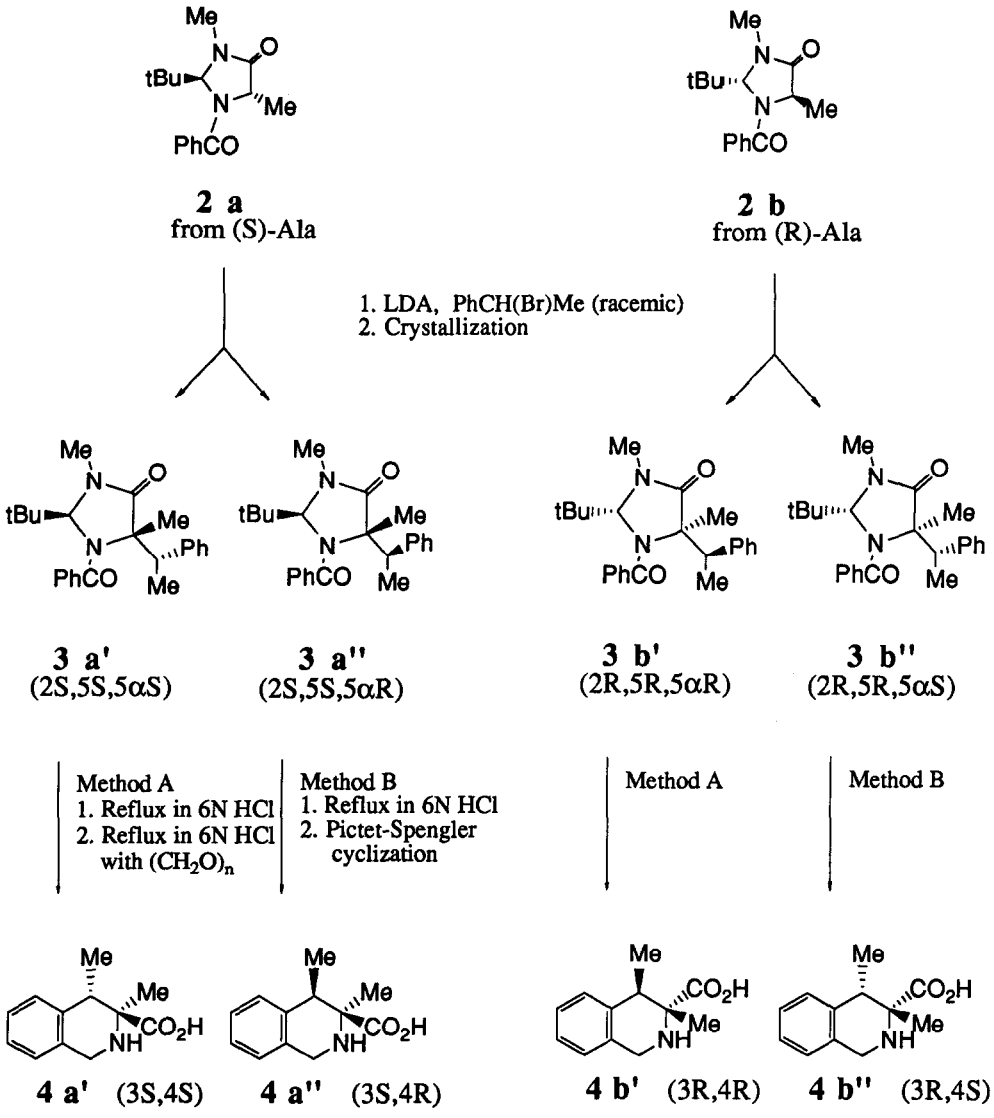


opioid antagonists. This led to one of the most mu opioid receptor potent and selective peptides known to date, D-Tic-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2.[2] Utilizing both NMR[1a,1c] and theoretical calculations,[3] we found that an N-terminal D-Tic residue has a gauche(-) side chain conformation (χ_1 = +60°), while an acylated Tic residue has a guache(+) side chain conformation (χ_1 = -60°) (Figure 1) owing to pseudoallylic strains.[1a,4] In order to obtain access to amino acids with complementary conformational behavior of their side chain moieties (e.g. g(-) when acylated and g(+) when on an N-terminal position), there is a need for a general method for the asymmetric synthesis of the four individual isomers of α,β-dimethylphenylalanine (**4a′**, **4a″**, **4b′**, **4b″** on Scheme 1), with the idea of stabilizing the pipecolic acid ring conformation by two bulky (e.g. methyl) substituents. We have tested this idea by molecular mechanics calculations (SYBYL, version 5.3) and, indeed, found a strong stabilization of the gauche(-) conformation for N-acylated α,β-dimethylated Tic derivatives.

The method of Seebach and co-workers[5] seemed to be particularly suitable for controlling the stereochemistry at both α- and β-carbon atoms on the same step in the reaction scheme, though other approaches could conceivably be used.[6]

Both L- and D-alanine were converted to their N-methyl amides, condensed with pivaloyl aldehyde and the resulting imines were cyclized to the substituted imidazolidin-4-ones **2a** and **2b** (Scheme 1) respectively,

SCHEME 1


2 a
from (S)-Ala
2 b
from (R)-Ala
1. LDA, PhCH(Br)Me (racemic)
2. Crystallization
3 a'
(2S,5S,5αS)
3 a''
(2S,5S,5αR)
3 b'
(2R,5R,5αR)
3 b''
(2R,5R,5αS)
Method A
1. Reflux in 6N HCl
2. Reflux in 6N HCl with (CH2O)n
Method B
1. Reflux in 6N HCl
2. Pictet-Spengler cyclization
Method A
Method B
4 a' (3S,4S)
4 a'' (3S,4R)
4 b' (3R,4R)
4 b'' (3R,4S)

in high yield and optical purity.[5] Two series of experiments were then performed on **2a** and **2b**. In the first, an equivalent amount of racemic (1-bromo)ethylbenzene was added to the LDA generated anion of **2a** and **2b** to give exhaustive alkylation of position 5 by both enantiomers of (1-bromo)ethylbenzene with moderate yields of both diastereomers derived from **2a** (**3a′** and **3a″**)[7] and **2b** (**3b′** and **3b″**) that could be separated by crystallization[8] (Method I, Table 1). In the second approach, a three fold excess of (1-bromo)ethylbenzene was used resulting in high yields of the diastereomers **3a″** and **3b″**, and only negligible amounts of **3a′** and **3b′** (Method II, Table 1). Each of the four diastereoisomers of 1-benzoyl-2-tert-butyl-3-methyl-5-(α-methylbenzyl)-

Table 1. Ratio of racemic (1-bromo)ethylbenzene to **2a** and **2b** versus observed diastereoselectivity of **3a′, 3a″, 3b′**, and **3b″** (kinetic resolution)

METHOD	3a′	3a″	3b′	3b″
I (1:1)	28%	72%	25%	75%
II(3:1)	7.7%	92.3%	3%	97%

imidazolin-4-one (**3a′**, **3a″**, **3b′** and **3b″**, Scheme 1) were hydrolyzed with hot 6N aqueous HCl, and the hydrochloride salts were converted to the free α,β-dimethylphenylalanine amino acid isomers by ion exchange chromatography on Dowex 50X8-100. Next they were subjected to a Pictet-Spengler type cyclization followed by ion exchange chromatography resulting in **N-Me-4a′**, **4a″**, **N-Me-4b′**, **4b″** in high yields and high optical purities. Use of the classical Pictet-Spengler conditions[9a] (HCHO and aqueous HCl, reflux) led to the expected 3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids **4a″** and **4b″**. The remaining diastereomers **4a′** and **4b′** were initially obtained as N-methyl amino acids, probably due to a faster (competing side reaction) reduction of an iminium cation intermediate to the N-methyl by the formic acid, and then subsequent cyclization to the tetrahydroisoquinoline skeleton via a subsequently formed iminium cation. Due to different steric hindrance in **4a″** and **4b″** (as compared to **4a′** and **4b′**) the cyclization reaction is much faster than the competing reduction of the iminium cation, and classical Picter-Spengler reaction takes place.

To circumvent these problems, we have modified the reaction conditions by use of paraformaldehyde $(CH_2O)_n$ and thorough deoxygenation of the reaction media in a sealed tube. Using this improved methodology followed by ion exchange chromatography, we obtained pure **4a′** and **4b′**. Currently, we are investigating the conformational properties of **4a′**, **4a″**, **4b′** and **4b″**[10] in simple tripeptide derivatives by both NMR and X-ray crystallography.

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6. For recent developments in the asymmetric synthesis of amino acids, see Williams, R.M. In "Synthesis of Optically Active α-Amino Acids," Pergamon Press, 1989.
7. The absolute configuration of **3a′** (SSS) was determined by the X-ray crystallography (Dr. Zofia Urbanczyk-Lipkowska, Stevens Institute of Technology, Hoboken, N.J.). **3a′** and **3b′** have identical ^{1}H and ^{13}C NMR spectra, thus **3b′** has the RRR configuration. The same reasoning establishes the absolute configuration of **3a″** (SSR) and **3b″** (RRS) on the basis of identical spectral and opposite optical properties. The structure has been submitted to the Cambridge Data Centre.
8. The C_2-H chemical shift for the **3a′** and **3b′** proton is at δ=5.76 ppm. For **3a″** and **3b″**, there are minor and major conformers probably due to the presence of a tertiary amide N^1 and restricted rotation of the benzoyl group around the C-N bond. Minor C_2-H δ=4.86 ppm, major C_2-H δ=4.80 ppm. All spectra are in $CDCl_3$, 250 MHz. These observations allow us to determine the optical purity of **3a′**, **3a″**, **3b′**, **3b″** as > 96%.
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10. Spectroscopic (EI or CI/MS, ^{1}H and ^{13}C NMR), optical rotation (OR), X-ray (for **3a′**), and elemental analyses data support the structures and purities for all of the compounds shown.

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