

**A CONVENIENT SYNTHESIS OF DIASTEREOMERIC SYNTHONS:
ETHYL 3-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE-1-ACETATES
BY DIRECT AND REVERSE SUBSTITUENT INTRODUCTIONS**

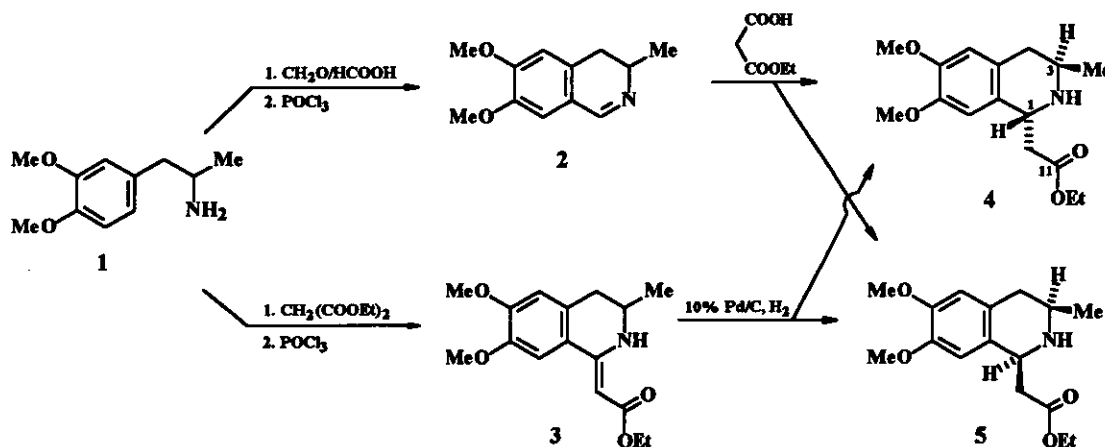
Ferenc Fülöp*, János Tari, Gábor Bernáth*, and Pál Sohár*

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University,
H-6701 Szeged, POB 121, Hungary; *Department of General and Inorganic Chemistry,
Loránd Eötvös University, H-1518 Budapest, POB 112, Hungary

Abstract- The two diastereomers of ethyl 3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetate (**4** and **5**) were synthesized from 1-(3',4'-dimethoxyphenyl)isopropylamine (**1**) by direct and reverse substituent introductions. The cause of the diastereoselectivity is rationalized.

Although 1,2,3,4-tetrahydroisoquinoline-1-acetates are β -amino acid synthons for the preparation of different kinds of isoquinoline-fused heterocycles¹⁻⁵ and modified peptides of potential pharmacological interest,^{2,3} few methods are known for their syntheses.⁵⁻⁷ Interestingly, no method is available for the synthesis of such derivatives containing two chiral carbons.

When 1-(3',4'-dimethoxyphenyl)isopropylamine (**1**) reacted with formaldehyde and was cyclized with a standard Bischler-Napieralski method, compound (**2**) was formed.⁸⁻¹⁰ The similar procedure involving the reaction of **1** with diethyl malonate and subsequent ring closure resulted in compound (**3**) (mp 89-91 °C, ether)¹¹ in an overall yield of 42%. The reaction of **2** for 1 h at 120 °C with an equivalent amount of malonic acid half ester, with carbon dioxide elimination, furnished a diastereomeric mixture of **4** and **5** in a 4:1 ratio with an excellent conversion. After fractional crystallization from diisopropyl ether, diastereomerically pure **4** was obtained with the (1*R**,3*R**)-configuration (mp 92-94 °C).¹²



Hydrogenation of **3** in acetic acid over Pd/C catalyst (10% Pd) under normal conditions furnished a mixture of **4** and **5** in a 1:19 ratio, with almost quantitative conversion. Recrystallization of the crude product from *n*-hexane resulted in the diastereomerically pure **5** with the (1*S**,3*R**)-configuration (mp 63-65 °C).¹³ As concerns the nmr data^{12,13} on the diastereomeric pair (**4** and **5**); the most characteristic difference is observed in the chemical shifts of the H-3 and C-3 signals, in accordance with expectations. In **4**, the bulky side-chain is *quasi-equatorial*, and consequently the methyl group is *axial*, while in its diastereomer (**5**), the 3-methyl group can also be *equatorial*.

Formation of the products (4 and 5) in different ratios can be rationalized by the structures of the intermediates (2)¹⁰ and (3).¹¹ Compound (3), with an *exo* double bond and *Z* configuration, is stabilized by chelation. In both cases, the 3-methyl group is *quasi-equatorial*, and the reactants attack from the sterically less hindered side, opposite to the methyl direction, resulting in diastereomers (4 and 5), respectively, as main products.

The above direct and reverse substituent introduction is a convenient method for the synthesis of diastereomers (4 and 5). Further applications of the above method are in progress.

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10. Spectral data on 2.HCl: Ir (KBr, cm⁻¹) 1643 (C=N), ~2750 (N⁺H); ¹H-nmr (500 MHz, CDCl₃, δ ppm *J* in Hz) 1.60 (3H, *d*, *J*=6.8, 3-CH₃), 2.91, 3.98 (2x1H, 2x*dd*, *J*=16.9, 10.0 and 16.9, 6.7, respectively, 4-CH₂), 3.97, 4.01 (2x3H, 2x*s*, OCH₃), 4.26 (1H, *m*, 3-H), 6.80 (1H, *s*, 5-H), 7.29 (1H, *s*, 8-H); 9.08 (1H, *s*, NH); ¹³C-nmr (125 MHz, CDCl₃, δ ppm) 18.8 (3-CH₃), 32.8 (4-C), 49.4 (3-C), 57.0 (6,7-OCH₃), 111.5 (5-C), 115.8 (8-C), 116.9 (8a-C), 132.5 (4a-C), 149.4 (7-C), 157.6 (6-C), 163.4 (1-C).
11. Spectral data on 3: Ir (KBr, cm⁻¹) 1644 (C=O, chelate, br); ¹H-nmr (500 MHz, CDCl₃, δ ppm *J* in Hz) 1.31, (3H, *t*, *J*=7.1, CH₂CH₃), 1.34 (3H, *d*, *J*=6.4, 3-CH₃), 2.63, 2.75 (2x1H, 2x*dd*, *J*=15.0, 11.2 and 15.0, 3.8, respectively, 4-CH₂), 3.60 (1H, *m*, 3-H), 3.89, 3.90 (2x3H, 2x*s*, OCH₃), 4.17 (2H, *qa*, OCH₂), 5.05 (1H, *s*, 1'-H), 6.63 (1H, *s*, 5-H), 7.13 (1H, *s*, 8-H); ~8.9 (1H, *br s*, NH); ¹³C-nmr (125 MHz, CDCl₃, δ ppm) 14.7 (CH₂CH₃), 21.1 (3-CH₃), 36.4 (4-C), 45.5 (3-C), 56.0, 56.1 (6,7-OCH₃), 58.6 (OCH₂), 108.0, 110.5, 110.7 (5,8,1'-C), 121.3 (8a-C), 129.6 (4a-C), 147.8 (7-C), 151.1 (6-C), 156.4 (1-C), 171.2 (C=O).
12. Spectral data on 4: Ir (KBr, cm⁻¹) 1722 (C=O), 3310 (NH); ¹H-nmr (250.14 MHz, CDCl₃, δ ppm *J* in Hz) 1.20 (3H, *d*, *J*=6.3, 3-CH₃) ~2.0 (1H, *br*, NH), 2.41 (1H, *dd*, *J*=16.0, 10.3, 1'-CH₂), ~2.65, (2H, coalesced signals of one H each of methylene groups in pos. 1' and 4), 2.83 (1H, *dd*, *J*=15.4, 10.3, 4-H), 3.20 (1H, *m*, 3-H), 3.83, 3.84 (2x3H, 2x*s*, OCH₃), 4.46 (1H, *dd*, *J*=10.2, 3.7, 1-H), 6.55 (1H, *s*, 5-H), 6.57 (1H, *s*, 8-H); ¹³C-nmr (63 MHz, CDCl₃, δ ppm) 14.0 (CH₂CH₃), 22.0 (3-CH₃), 36.8 (4-C), 41.4 (1'-C), 42.4 (3-C), 52.6 (1-C), 55.6, 55.8 (6,7-OCH₃), 60.3 (OCH₂), 109.3 (8-C), 111.5 (5-C), 127.0 (8a-C), 129.2 (4a-C), 147.3, 147.7 (6,7-C), 172.3 (C=O).
13. Spectral data on 5: Ir (KBr, cm⁻¹) 1725 (C=O), 3420 (NH); ¹H-nmr (250.14 MHz, CDCl₃, δ ppm *J* in Hz) 1.23 (3H, *d*, *J*=6.2, 3-CH₃) 2.27 (1H, *br*, NH), 2.6, 3.0 (2+2+1H, coalesced signals of 1'-CH₂, 4-CH₂ and 3-H), 3.84, 3.85 (2x3H, 2x*s*, OCH₃), 4.43 (1H, ~*d*, *J*=7.0, 1-H), 6.57 (1H, *s*, 5-H), 6.60 (1H, *s*, 8-H); ¹³C-nmr (63 MHz, CDCl₃, δ ppm) 13.9 (CH₂CH₃), 22.2 (3-CH₃), 37.5 (4-C), 41.4 (1'-C), 48.5 (3-C), 53.1 (1-C), 55.6, 55.8 (6,7-OCH₃), 60.3 (OCH₂), 108.1 (8-C), 111.6 (5-C), 128.1, 129.2 (4a,8a-C), 147.2, 147.5 (6,7-C), 172.5 (C=O).