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

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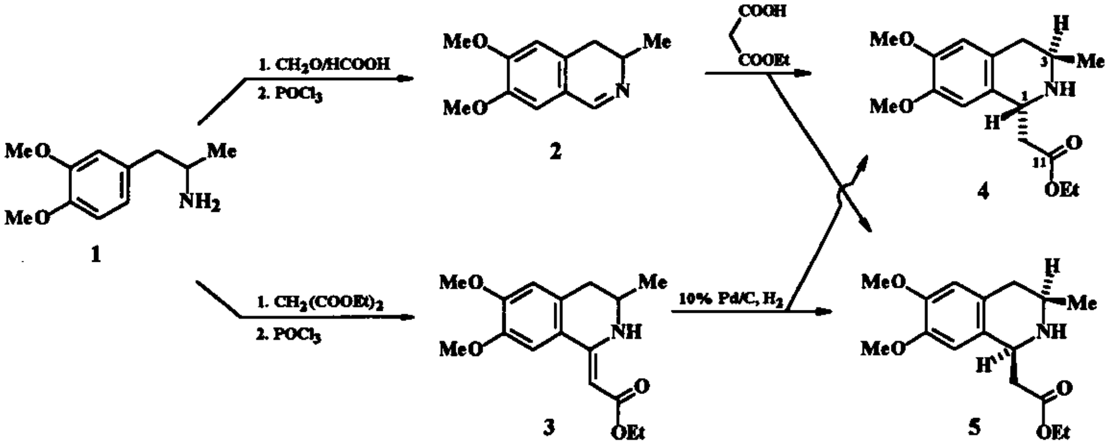
***Abstract***- The two diastereomers of ethyl 3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetate (**4** and **5**) were synthesized from 1-(3',4'-dimethoxyphenyl)isopropylamine (**1**) by direct and reverse substituent introductions. The cause of the diastereostereoselectivity is rationalized.

Although 1,2,3,4-tetrahydroisoquinoline-1-acetates are β-amino acid synthons for the preparation of different kinds of isoquinoline-fused heterocycles[1-5] 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 diasteromeric 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 $(1R^*,3R^*)$-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 $(1S^*,3R^*)$-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 ($N^+H$); $^1$H-nmr (500 MHz, $CDCl_3$, δ ppm *J* in Hz) 1.60 (3H, *d*, *J*=6.8, 3-$CH_3$), 2.91, 3.98 (2x1H, 2x*dd*, *J*=16.9, 10.0 and 16.9, 6.7, respectively, 4-$CH_2$), 3.97, 4.01 (2x3H, 2x*s*, $OCH_3$), 4.26 (1H, *m*, 3-H), 6.80 (1H, *s*, 5-H), 7.29 (1H, *s*, 8-H); 9.08 (1H, *s*, NH); $^{13}$C-nmr (125 MHz, $CDCl_3$, δ ppm) 18.8 (3-$CH_3$), 32.8 (4-C), 49.4 (3-C), 57.0 (6,7-$OCH_3$), 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); $^1$H-nmr (500 MHz, $CDCl_3$, δ ppm *J* in Hz) 1.31, (3H, *t*, *J*=7.1, $CH_2\mathit{CH}_3$), 1.34 (3H, *d*, *J*=6.4, 3-$CH_3$), 2.63, 2.75 (2x1H, 2x*dd*, *J*=15.0, 11.2 and 15.0, 3.8, respectively, 4-$CH_2$), 3.60 (1H, *m*, 3-H), 3.89, 3.90 (2x3H, 2x*s*, $OCH_3$), 4.17 (2H, *qa*, $OCH_2$), 5.05 (1H, *s*, 1'-H), 6.63 (1H, *s*, 5-H), 7.13 (1H, *s*, 8-H); ~8.9 (1H, *br s*, NH); $^{13}$C-nmr (125 MHz, $CDCl_3$, δ ppm) 14.7 $CH_2\mathit{CH}_3$), 21.1 (3-$CH_3$), 36.4 (4-C), 45.5 (3-C), 56.0, 56.1 (6,7-$OCH_3$), 58.6 ($OCH_2$), 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); $^1$H-nmr (250.14 MHz, $CDCl_3$, δ ppm *J* in Hz) 1.20 (3H, *d*, *J*=6.3, 3-$CH_3$) ~2.0 (1H, *br*, NH), 2.41 (1H, *dd*, *J*=16.0, 10.3, 1'-$CH_2$), ~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*, $OCH_3$), 4.46 (1H, *dd*, *J*=10.2, 3.7, 1-H), 6.55 (1H, *s*, 5-H), 6.57 (1H, *s*, 8-H); $^{13}$C-nmr (63 MHz, $CDCl_3$, δ ppm) 14.0 ($CH_2\mathit{CH}_3$), 22.0 (3-$CH_3$), 36.8 (4-C), 41.4 (1'-C), 42.4 (3-C), 52.6 (1-C), 55.6, 55.8 (6,7-$OCH_3$), 60.3 ($OCH_2$), 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); $^1$H-nmr (250.14 MHz, $CDCl_3$, δ ppm *J* in Hz) 1.23 (3H, *d*, *J*=6.2, 3-$CH_3$) 2.27 (1H, *br*, NH), 2.6, 3.0 (2+2+1H, coalesced signals of 1'-$CH_2$, 4-$CH_2$ and 3-H), 3.84, 3.85 (2x3H, 2x*s*, $OCH_3$), 4.43 (1H, ~*d*, *J*=7.0, 1-H), 6.57 (1H, *s*, 5-H), 6.60 (1H, *s*, 8-H); $^{13}$C-nmr (63 MHz, $CDCl_3$, δ ppm) 13.9 ($CH_2\mathit{CH}_3$), 22.2 (3-$CH_3$), 37.5 (4-C), 41.4 (1'-C), 48.5 (3-C), 53.1 (1-C), 55.6, 55.8 (6,7-$OCH_3$), 60.3 ($OCH_2$), 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).

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