

HANTZSCH 1,2,3,4-TETRAHYDROPYRIDINES RELATED TO CALCIUM ANTAGONISTS.  
TWO SYNTHETIC APPROACHES.

David A. Claremon\* and Steven D. Young\*  
Merck Sharp & Dohme Research Laboratories  
West Point, Pennsylvania 19486

**ABSTRACT:** Two stereoselective routes to tetrahydropyridines related to calcium entry antagonists are described.

1,2,3,4-Tetrahydropyridine derivatives related to the calcium entry antagonist nifedipine are unavailable by direct heterogeneous catalytic reduction of the respective pyridine or 1,4-dihydropyridine.<sup>1</sup> Recently, Rosentreter<sup>2</sup> reported the preparation of all trans 1,2,3,4-tetrahydropyridines by triethylsilane reduction of 1,4-dihydropyridines. We wish to report two methods for preparing two of the four diastereomers stereoselectively, which complement the triethylsilane reduction of 1,4-dihydropyridines, along with the synthesis of fused lactones of this class.

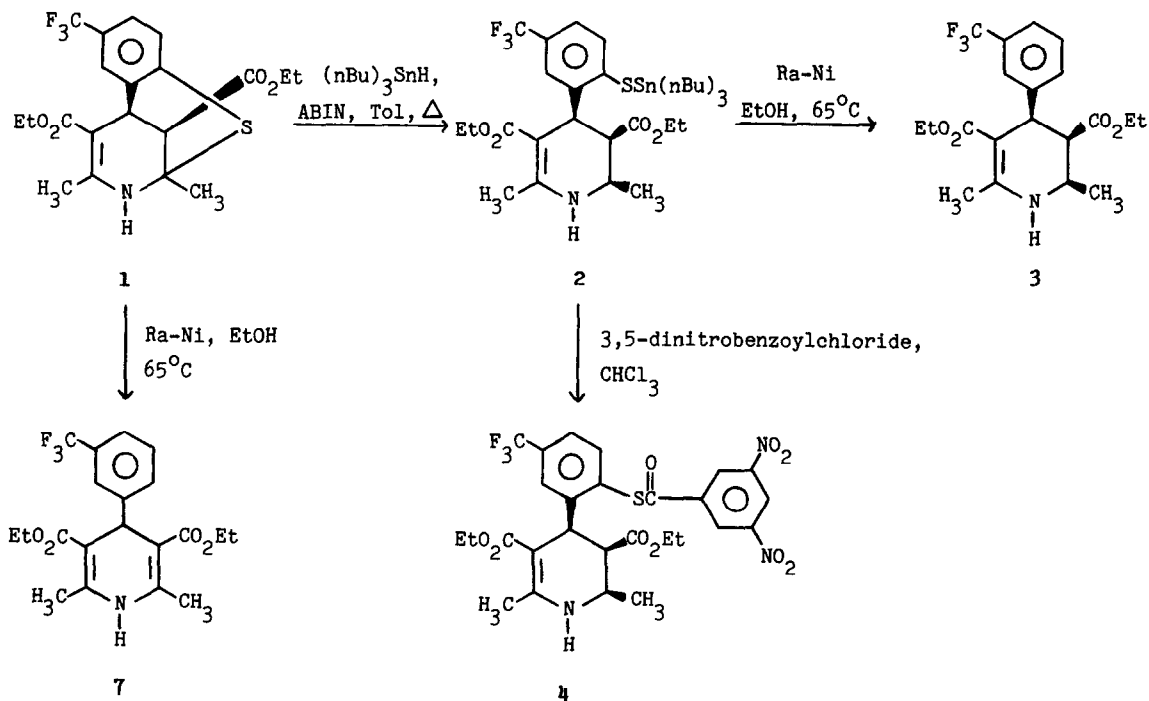
Our first approach to the tetrahydropyridines was via reductive cleavage of benzothiazocine 1<sup>3</sup> with tributyltin hydride<sup>4</sup> in refluxing toluene (3.0 equiv., cat. ABIN) followed by concentration at reduced pressure to give a crude tin-sulfide intermediate 2 which was further reductively cleaved with Raney-Nickel in ethanol (excess Ra-Ni, 65°C). Filtration and flash chromatography provided a 60% overall yield of a single diastereomer 3.<sup>5</sup> We were unable to prepare crystals of 3 suitable for X-ray analysis. However, crude 2 was treated with 3,5-dinitrophenylbenzoylchloride in chloroform<sup>6</sup> at 25°C for 15 min to provide, after flash chromatography, the crystalline thio-benzoate 4. X-ray analysis<sup>7</sup> conclusively supported the proposed assignment based on 360 MHz <sup>1</sup>H NMR coupling constants. Similarly, the diastereomeric benzothiazocine 5 when exposed to the above sequence supplied the diastereomeric tetrahydropyridine 6<sup>5</sup> in comparable yield. The stereochemistry of 6 was assigned based on coupling constants in agreement with the oxidation product II (vide infra). Attempted direct reduction of 1 or 5 with various activities of Raney-Nickel gave only the 1,4-dihydropyridine 7. We suggest that the observed stereochemistry of 2 or 6 is a result of hydrogen atom capture by the pyridine radical intermediate's more sterically accessible face.

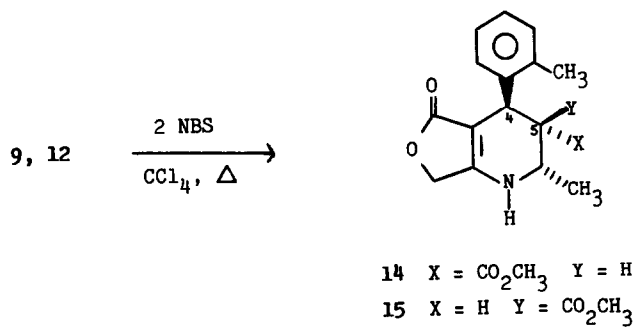
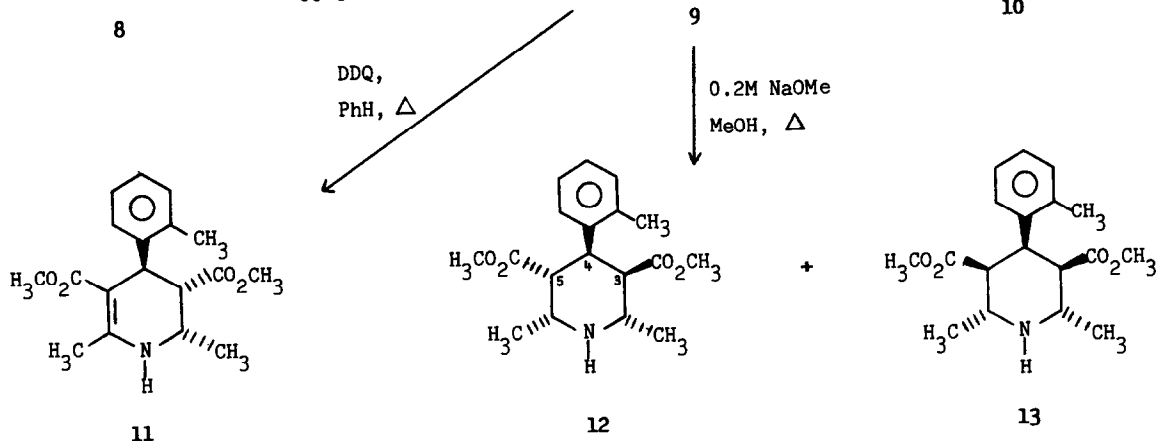
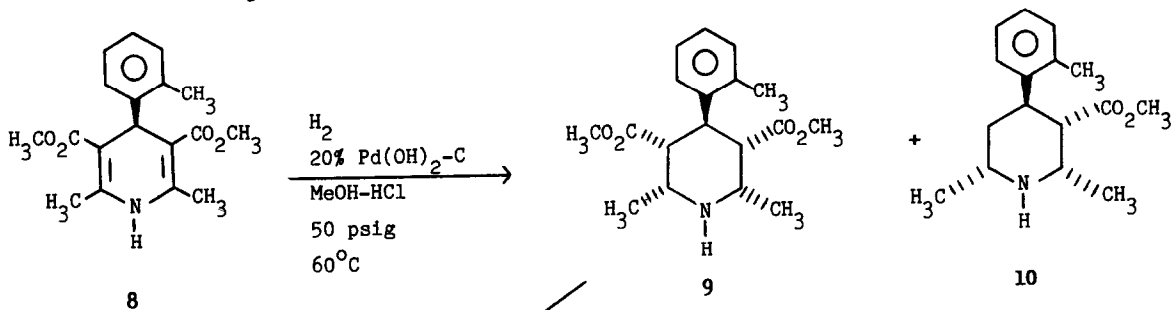
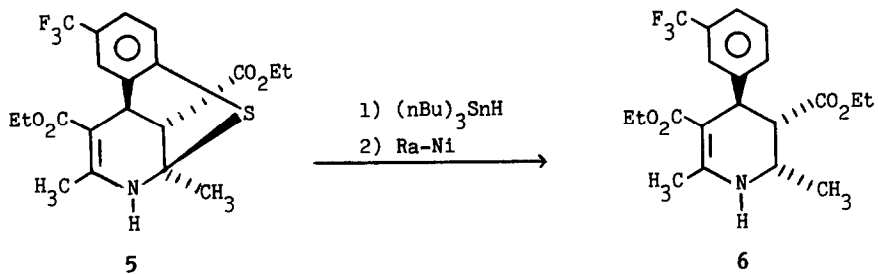
The second approach to preparing 1,2,3,4-tetrahydropyridines was based on catalytic reduction of the dihydropyridine ring to the piperidine, followed by selective reoxidation. This scheme also lends itself to the preparation of the corresponding fused lactones (1,2,3,4,5,7-hexahydrofuro[3,4-b]pyridines).

Hydrogenation of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylate 8<sup>8</sup> with 20% palladium hydroxide on carbon in methanol containing one equivalent of HCl at 50 psig and 60°C gave piperidine 9 (mp: 257-259°C,

HCl salt) in 87% yield, and the decarbomethoxylation product **10**, in 5% yield. The stereochemistry of piperidine **9**<sup>5</sup> was established by single crystal X-ray analysis.<sup>7</sup> Selective oxidation of piperidine **9** with 1.05 equivalents of DDQ in refluxing benzene for 1 h gave tetrahydropyridine **11**<sup>5</sup> (40% yield, mp: 135-141°C); the stereochemistry was confirmed by an observed H5-H6 coupling constant of 3.7 Hz and H4-H5 coupling constant of 1.2 Hz. When piperidine **9** was subjected to refluxing 0.2M sodium methoxide in methanol for 7 days, equilibration of the ester(s) occurred to give a 2:1 mixture of trans-cis compound **12**<sup>5</sup> and cis-cis compound **13**<sup>5</sup>. These compounds were readily separable by column chromatography on silica gel using 2.5% methanol in chloroform as eluant (**12**: R<sub>f</sub> = 0.25, mp: 238-239°C (HCl salt); **13**: R<sub>f</sub> = 0.20, mp: 235-240°C (HCl salt)). The stereochemistry of the C-3 and C-5 ester and C-4 aryl groups was established on the basis of <sup>1</sup>H NMR spectroscopy, which revealed the unsymmetrical and symmetrical nature of piperidines **12** and **13**, respectively (**12**: J<sub>3,4</sub> = 6.8 Hz, J<sub>4,5</sub> = 2.5 Hz; **13**: J<sub>3,4</sub> = 6.8 Hz). Neither of the two equilibrated piperidines could be successfully oxidized with DDQ. Treatment of **9** and **12** with two equivalents of N-bromosuccinimide in refluxing carbon tetrachloride gave α,β-unsaturated lactones **14**<sup>5</sup> (J<sub>4,5</sub> = 1.5 Hz, mp: 180-185°C) and **15**<sup>5</sup> (J<sub>4,5</sub> = 5.8 Hz, mp: 207-209°C) in 35% and 20% yield, respectively. We believe that the NBS serves first to oxidize one ester to the vinylogous carbamate which is further brominated on the C-2 methyl group and this bromomethyl-α,β-unsaturated ester cyclizes to the lactone. This probably occurs in a manner similar to that reported for the 1,4-dihydropyridine-3,5-dicarboxylate parent compounds themselves.<sup>9</sup>

This methodology now provides a stereoselective route to several diastereomers of an important class of biologically interesting compounds.





## REFERENCES AND NOTES

- (1) O. Mumm, O. Roder and H. Ludwig, Ber., 57, 865 (1924).
- (2) U. Rosentreter, Synthesis, 210 (1985).
- (3) D. A. Claremon, J. Hirshfield, P. K. Lumma, D. E. McClure and J. P. Springer, Synthesis, in press.
- (4) Photochemical reaction with tributyl allyltin gave the expected allyl substituted pyridine of undetermined stereochemistry.
- (5)  $^1\text{H}$  NMR spectral data (360 MHz,  $\text{CDCl}_3$ ) **4**:  $\delta$  0.69 (t, J = 7.5, 3 H), 0.91 (t, J = 7.5, 3 H), 1.20 (d, J = 7.0, 3 H), 2.38 (s, 3 H), 3.05 (dd, J = 3.0, 7.5, 1 H), 3.65-3.88 (m, 5 H), 4.11 (br s, 1 H), 4.33 (d, J = 7.5, 1 H), 7.28-7.45 (m, 4 H); **7**:  $\delta$  0.96 (t, J = 7.5, 3 H), 1.24 (d, J = 7.0, 3 H), 1.27 (t, J = 7.5, 3 H), 2.41 (s, 3 H), 2.60 (m, 1 H, collapsing to dd (J = 1.7, 3.7) upon irradiation at 4.12 (NH)), 3.28 (m, 1 H, collapsing to dq (J = 3.7, 7.0) upon irradiation at 4.12 (NH)), 3.89 (dq, J = 7.5, 12.0, 1 H), 3.97 (dq, J = 7.5, 12.0, 1 H), 4.12 (br s, 1 H), 4.17 (q, J = 7.5, 2 H), 4.40 (br d, J = 1.7, 1 H), 7.35-7.48 (m, 4 H); **9**:  $\delta$  1.18 (d, J = 6.2, 6 H), 2.45 (s, 3 H), 2.95 (dd, J = 6.6, 9.0, 2 H), 3.49 (m, 2 H), 3.51 (s, 6 H), 3.82 (t, J = 9.0, 1 H), 7.05-7.20 (m, 4 H); **11**:  $\delta$  1.20 (d, J = 6.8, 3 H), 2.44 (dd, J = 1.2, 3.7, 1 H), 2.46 (s, 3 H), 2.47 (s, 3 H), 3.35 (ddq, J = 1.5, 3.8, 6.9, 1 H), 3.46 (s, 3 H), 3.71 (s, 3 H), 4.09 (br s, 1 H (N-H)), 4.45 (m, 1 H), 7.00-7.40 (m, 4 H); **12**:  $\delta$  1.06 (d, J = 6.7, 3 H), 1.29 (d, J = 6.2, 3 H), 2.34 (s, 3 H), 2.53 (dd, J = 2.9, 3.9, 1 H), 2.89 (d, J = 6.9, 10.5, 1 H), 3.25 (dq, J = 3.9, 6.7, 1 H), 3.33 (s, 3 H), 3.70 (dq, J = 10.5, 6.1, 1 H), 3.73 (s, 3 H), 3.94 (dd, J = 6.8, 2.5, 1 H), 7.10-7.40 (m, 4 H); **13**:  $\delta$  1.40 (d, J = 6.0, 6 H), 2.27 (s, 3 H), 2.57 (dd, J = 6.9, 11.2, 2 H), 3.28 (s, 6 H), 3.64 (dq, J = 11.4, 5.9, 2 H), 4.27 (t, J = 6.8, 1 H), 7.10-7.40 (m, 4 H); **14**:  $\delta$  1.24 (d, J = 7.0, 3 H), 2.41 (s, 3 H), 2.58 (dd, J = 1.0, 1.5, 1 H), 3.45 (m, 1 H), 3.70 (s, 3 H), 4.22 (d, J = 1.5, 1 H), 4.72 (m, 2 H), 5.24 (br s, 1 H (N-H)), 6.90-7.30 (m, 4 H); **15**:  $\delta$  1.26 (d, J = 6.5, 3 H), 2.40 (s, 3 H), 2.66 (dd, J = 5.8, 11.0, 1 H), 3.45 (s, 3 H), 3.93 (dq, J = 11.0, 6.0, 1 H), 4.49 (d, J = 5.6, 1 H), 4.69 (m, 2 H), 4.92 (br s, 1 H (N-H)), 6.90-7.30 (m, 4 H).
- (6) Y. Ueno, M. Nozomi and M. Okawara, Chem. Lett. 1199 (1982).
- (7) J. P. Springer and J. Hirshfield, unpublished results.
- (8) B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi and E. Macko, J. Med. Chem., 17, 956 (1974).
- (9) S. D. Young, Synthesis, 617 (1984).

(Received in USA 13 August 1985)