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# Racemization of (-)-Vincadifformine Using Microwave Oven

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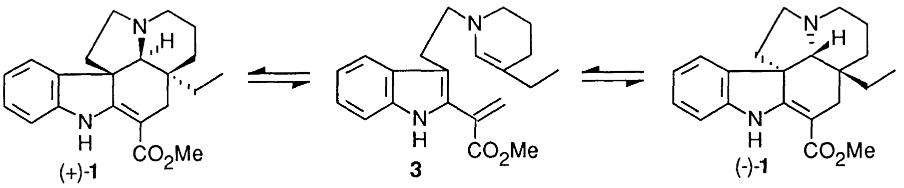
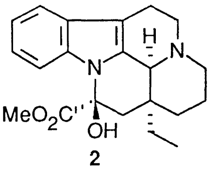
Thermolysis of (-)-vincamine in DMF using a microwave oven has brought about total racemization via concurrent Diels-Alder cycloreversion and cycloaddition.

Vincadifformine (**1**), a representative member of the Aspidosperma indole alkaloids, occurs naturally in both enantiomeric forms.[1)] Although both enantiomers of vincadifformine (**1**) possess no significant biological activities, the (+)-enantiomer ((+)-**1**) serves as the synthetic precursor[2)] of the Eburnane alkaloid, (+)-vincamine (**2**), which has been found to be useful remedy in the treatment of cerebral insufficiency in man.[3)] Inversion or racemization of the unnecessary (-)-enantiomer ((-)-**1**), therefore, is very critical for the production of the medici-





**2**

Table 1. Racemization of (-)-vincadifformine ((-)-**1**)[a)] using a microwave oven

| Entry | Solvent[b)] | Time/min | $[\alpha]_D^{24\pm2}$/° (c, $CHCl_3$) | Yield / % |
|---|---|---|---|---|
| 1 | $H_2O$ | 10 | -536.42 (0.95) | 62.7 |
| 2 | N,N-dimethylaniline | 10 | -645.56 (0.79) | 82.1 |
| 3 | MeOH | 10 | -591.12 (0.71) | 96.9 |
| 4 | DMF[c)] | 10 | -314.06 (1.28) | 78.5 |
| 5 | DMF | 15 | -39.26 (0.87) | 76.3 |
| 6 | DMF | 20 | -5.43 (1.55) | 92.2 [e)] |
| 7 | DMA[d)] | 5 | -491.80 (1.0) | 67.3 |
| 8 | DMA | 10 | -246.54 (0.55) | 36.3 |
| 9 | DMA | 15 | -123.07 (0.99) | 48.7 |

a) $[\alpha]_D^{27}$ -646.06° (c 0.60, $CHCl_3$). b) All solvents were degassed and used under argon. c) N,N-Dimethylformamide. d) N,N-Dimethylacetamide. e) Optimized yield.

nally important alkaloid (**2**) which is not sufficiently obtained naturally. We report here an efficient method which brought about total racemization of (-)-vincadifformine ((-)-**1**) in a single step in an excellent yield. The reaction could be simply carried out by heating briefly a DMF solution of ((-)-**1**) in a glass sealed tube using a microwave oven. Although the racemization was also observed when ((-)-**1**) was refluxed longer time in a high boiling solvent such as o-dichlorobenzene, it was accompanied by a considerable amount of uncharacterizable by-products.

Thus, a degassed solution of (-)-vincadifformine[4) ((-)-**1**), $[\alpha]_D^{27}$ -646.06° (c 0.60, $CHCl_3$), (203 mg, 0.6 mmol) in N,N-dimethylformamide (DMF) (2 ml) in a glass-sealed tube (10 ml) under argon was heated for 20 min using a commercial microwave oven[5,6) (500 W, microwave frequency 2450 MHz). After cooling, the mixture was evaporated under reduced pressure and the residue was purified on a silica gel column to give racemic vincadifformine ((±)-**1**), $[\alpha]_D^{24}$ -5.43° (c 1.55, $CHCl_3$), in 92% (188 mg) yield (entry 6). As appeared in Table 1 solvent choice was found to be the most important in this process though other critical factors such as temperature and pressure effects have yet to be investigated.

The present result clearly indicated that the optically active alkaloid ((-)-**1**) racemized through the intervention of the secodine intermediate (**3**) by concurrent Diels-Alder cycloreversion and cycloaddition. Intervention of the secodine intermediate (**3**) in the biogenetic formation of vincadifformine (**1**) and its congeners has been proposed[7) and has been synthetically mimicked,[8) however, unambiguous evidence of its in vitro regeneration has not so far been clearly exemplified though suggestive reports have appeared.[7,9)

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