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An enantioselective synthesis of isoquinuclidines from 3-substituted chiral pyridinium salts

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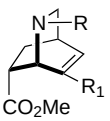
Abstract—A new enantioselective approach to chiral isoquinuclidines, such as **15**, **18** and **21**, is reported. The key step of these syntheses is a cycloaddition between chiral dihydropyridines **14** or **20**, now readily available from tetrahydropyridinium salts **6** or **11**, and achiral dienophiles. The reaction proceeds with a very good *endo*-selectivity and moderate d.e. © 2001 Published by Elsevier Science Ltd.

Isoquinuclidine derivatives, such as **1** and related compounds, are valuable intermediates in alkaloid synthesis, especially *Iboga*-type indole alkaloids of which (+)-catharantine **2** is of special interest because of its role as biogenetic and synthetic precursors of vinblastine and related antitumoral bisindole alkaloids.[1] Despite the progress in the synthesis of those alkaloids, no total asymmetric synthesis was reported hitherto,[2] and few methods for the asymmetric synthesis of functionalized isoquinuclidines have been reported.[3] This paper presents a convenient enantioselective access to derivatives **1**.



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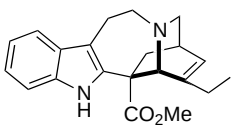
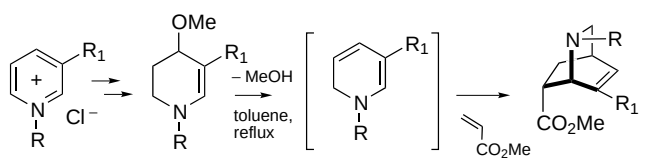


(+)-**2**

This approach takes advantage of the recently reported[4] synthesis of tetrahydropyridines **3** (Scheme 1) from the corresponding pyridinium salts **4**, and the observation that these intermediates are excellent precursors of 3-alkyl 1,6-dihydropyridines **5** which are difficult to obtain with good regioselectivity.[3] These dihydropyridines were too unstable to be isolated, but could be trapped with common dienophiles, affording isoquinuclidine derivatives **1** via a cycloaddition reaction. With (+)-catharantine **2** as a synthetic target in mind, we therefore sought to explore conditions which should lead to enantiomerically pure isoquinuclidines by way of such cycloadditions. Using different chiral *N*-substituents (R = chiral groups), our intention was to induce a π-facial stereoselectivity during the reaction between the in situ formed chiral dihydropyridine **5** and the achiral dienophile. We now report the preparation of these reactive intermediates from chiral pyridinium salts **4** and their reaction with dienophiles like methylacrylate to furnish chiral isoquinuclidine system **1**, in few steps.

The chiral pyridinium salt **6** (Scheme 2), obtained from the corresponding Zincke salt,[5] was reduced by treatment with $NaBH_4$ in a mixture of methanol/water (90:10) to provide the tetrahydropyridine **7** in 70% yield. Oxidation with *m*-CPBA furnished diastereomeric *N*-oxides **8** which were filtered over alumina and treated immediately with trifluoroacetic anhy-



4 **3** **5** (+/–)–**1**

Scheme 1.

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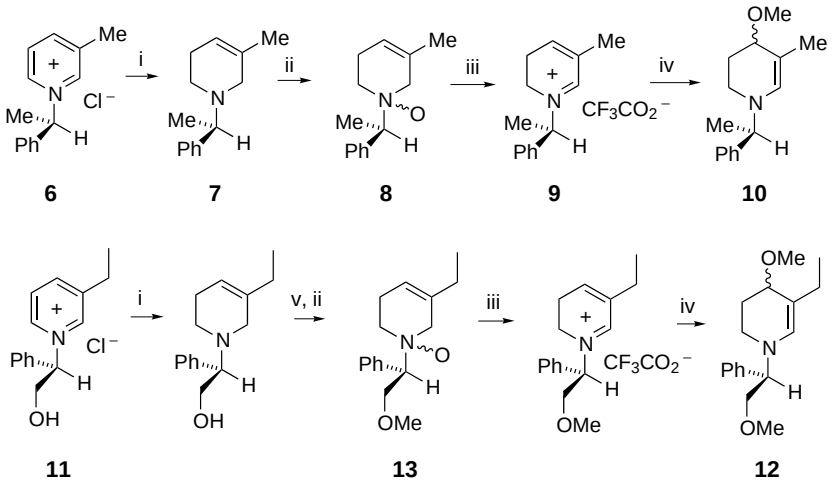


Scheme 2. *Reagents*: (i) $NaBH_4$; (ii) *m*-CPBA, CH_2Cl_2; (iii) $(CF_3CO)_2O$, CH_2Cl_2; (iv) MeONa, MeOH; (v) NaH, MeI.

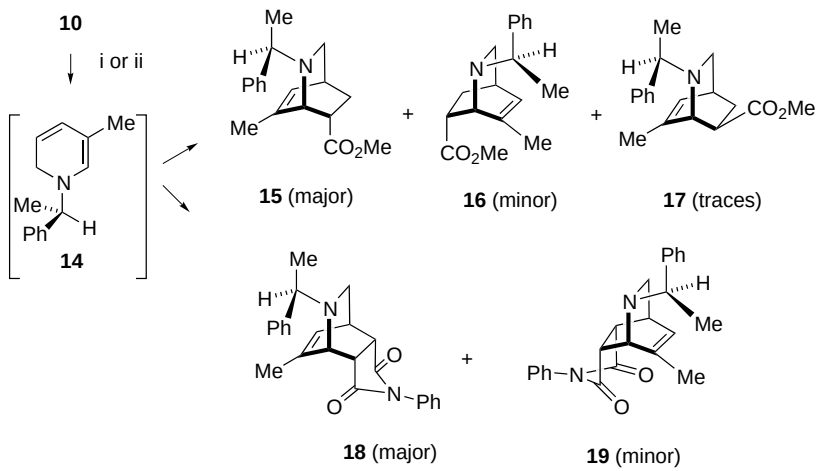
dride to afford quantitatively the 5,6-dihydropydinium salt **9**, using conditions of the Polonovski–Potier reaction.[6] The reaction of salt **9** with sodium methoxide in methanol gave the tetrahydropyridine **10** as a diastereomeric mixture and with a good yield (78%, 55% overall from **6**). The same sequence, applied to salt **11**, gave the corresponding diastereomeric tetrahydropyridines **12** in 45–50% overall yield. In that case the protection of the primary alcohol function as a methyl ether was done in order to prevent the reactivity of the hydroxyl group during the next steps. Care must also be taken due to the instability of *N*-oxides **13** which are sensitive to Cope elimination and, thus, must be used without further purification.

Heating of tetrahydropyridine **10** (Scheme 3) with methylacrylate (10 equiv.) in refluxing toluene overnight produced, via unstable dihydropyridine **14**, the chiral diastereomeric isoquinuclidines **15**[7] and **16** in 55% yield. These diastereomers, as for other chiral isoquinuclidine derivatives (vide infra), were easily separated by flash chromatography and recovered in 35 and 20% yield, respectively. A small amount of the *exo*-adduct **17** was also detected.

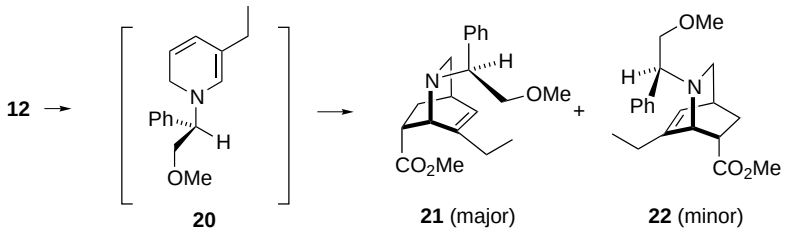
The ratio **15**:**16**:**17** was found by GC to be 58:35:7, respectively, thus showing a modest d.e. for **15** (26%), but an excellent *endo*-selectivity. Reaction of tetrahydropyridine **10** with *N*-phenylmaleimide (1.1 equiv.) in refluxing toluene for 2 h gave the adducts **18**[8] and **19** in 77% isolated yield and a 60:40 ratio, respectively (20% d.e.). No *exo*-adduct was detected in this case.

Finally, heating of tetrahydropyridine **12** in refluxing toluene with methylacrylate in the conditions used for **10**, gave adducts **21** and **22** in 60% yield and a 65:35 ratio, respectively (Scheme 4). Only traces of the *exo*-adduct were detected.

The configurations of all isoquinuclidines were unambiguously established by comparison with analogous derivatives.[3b] Despite the low facial selectivity observed (d.e. = 20–30%), this methodology is very practical to produce functionalized optically active isoquinuclidines with very good *endo*-selectivity and good yields. In particular the present method considerably shortens the previously reported approach[3b] which makes use of a tedious multistep synthesis of 3-alkyl 5,6-dihydropyridines.



Scheme 3. *Reagents and conditions*: (i) Methylacrylate, toluene, reflux, overnight; (ii) *N*-phenylmaleimide, toluene, reflux, 2 h.



Scheme 4.

Acknowledgements

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7. The structure was established by comparison with an authentic sample, see Ref. 3b. Selected data for **15**: $[\alpha]_D = +10$ (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3031, 2968, 2950, 2875, 2850, 1737, 1656, 1600, 1494, 1450, 1431; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (3H, d, $J=6.4$ Hz), 1.63 (3H, d, $J=1.7$ Hz), 1.60–1.85 (2H, m), 2.06 (1H, dt, $J=9.3$ Hz, 2.5 Hz), 2.53 (1H, m), 2.98 (1H, dd, $J=9.3$ Hz, 2.5 Hz), 3.00 (1H, ddd, $J=9.6$ Hz, 4.5 Hz, 3.2 Hz), 3.23 (1H, q, $J=6.4$ Hz), 3.48 (1H, dd, $J=3.2$ Hz, 1.8 Hz), 3.52 (3H, s), 6.03 (1H, ddd, $J=6.7$ Hz, 1.8 Hz, 1.7 Hz), 7.20–7.45 (5H, m); ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 21.14, 23.06, 26.58, 30.99, 44.26, 51.40, 53.53, 55.67, 64.89, 126.90, 127.21, 128.54, 137.87, 146.18, 174.47; HRMS calcd for $C_{18}H_{23}NO_2$: 285.1729; found: 285.1725.
8. Selected data for **18**: $[\alpha]_D = +16$ (*c* 1.62, $CHCl_3$); IR (cm^{-1}) 3031, 2968, 2937, 1769, 1712, 1693, 1431, 1400, 1343, 1168; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (3H, d, $J=6.4$ Hz), 1.34 (3H, d, $J=1.5$ Hz), 2.12 (1H, dd, $J=9.6$ Hz, 2.4 Hz), 2.86 (1H, dd, $J=7.8$ Hz, 3 Hz), 3.05 (1H, m), 3.09 (1H, dd, $J=9.6$ Hz, 2 Hz), 3.18 (1H, dd, $J=7.8$ Hz, 4 Hz), 3.18 (1H, q, $J=6.4$ Hz), 3.55 (1H, dd, $J=4$ Hz, 1.5 Hz), 4.44 (1H, d, $J=14$ Hz), 4.52 (1H, d, $J=14$ Hz), 5.70 (1H, m), 7.20–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 20.89, 22.93, 33.92, 41.47, 42.15, 45.96, 52.13, 54.90, 64.93, 123.48, 127.14, 127.37, 127.73, 128.39, 128.61, 128.82, 135.90, 139.41, 145.20, 176.77, 178.62; HRMS calcd for $C_{25}H_{27}N_2O_2$: 387.2073; found: 387.2071.