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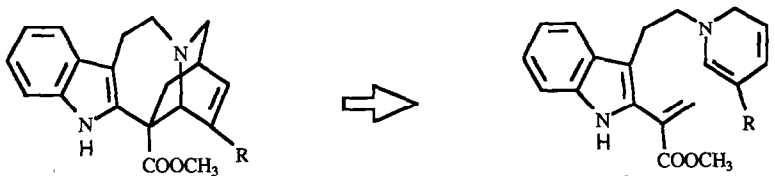
SYNTHESIS OF CHIRAL ISOQUINUCLIDINES AND DETERMINATION OF THEIR ABSOLUTE CONFIGURATION

M. Mehmandoust, C. Marazano*, R. Singh, B. Gillet, M. Cēsario, J.-L. Fourrey and B.C. Das

Institut de Chimie des Substances Naturelles, C.N.R.S.,
91198 Gif-sur-Yvette Cedex, France.

Summary: A route to 1,2-dihydropyridines N^1-substituted with chiral auxiliaries has been developed starting from commercially available chiral amines. Cycloaddition between these dihydropyridines and methyl acrylate gave, in moderate d.e., isoquinuclidines of good enantiomeric purity whose absolute configuration has been established.

The isoquinuclidine ring system, azabicyclo[2.2.2]octane, is common to *Iboga*-type indole alkaloids of which (+)-catharanthine (1, R = Et) is of special interest because of its eminent role as a biogenetic as well as a synthetic precursor of vinblastine and related antileukemic bisindole alkaloids (1).



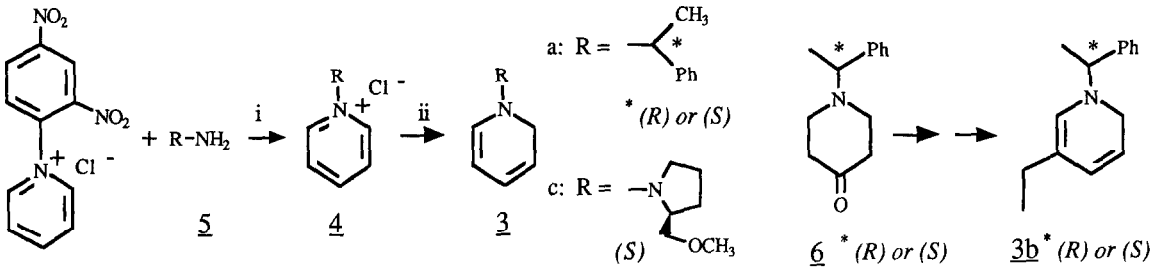
1 2

The key step in the biosynthesis of 1 presumably involves an asymmetric intramolecular Diels-Alder type cycloaddition of an elusive achiral intermediate, namely, dehydrosecodine (2, R = Et) (2). Several total syntheses of (±)-deethylcatharanthine (1, R = H) and (±)-catharanthine (1, R = Et), which mimic this process, are based on the cycloaddition between an appropriately substituted dihydropyridine (DHP) and acrylic esters (3). However, to date, there is no report on the synthesis of chiral isoquinuclidines by using this approach. With (+)-catharanthine as a synthetic target in mind, we therefore sought to explore conditions which should lead to enantiomerically pure isoquinuclidines by way of such cycloadditions. Optically pure isoquinuclidines were previously obtained through palladium-mediated intramolecular cyclization involving an amine and a vinyl epoxide function derived from a chiral precusor (4).

The control of the stereochemical outcome of the Diels-Alder reaction is a subject of rapidly growing interest (5) and recent ingenious solutions to this challenge make use of optically active acrylic ester dienophiles derived from secondary alcohols and Lewis acid catalysis. Since DHPs were found to be very unstable in the presence of Lewis acids, our attention was turned toward the possibility of inducing π-face stereoselection of 1,2-DHPs having different chiral N^1-substituents. We report here some preliminary results of our investigation in this area using (*R*)- and (*S*)-N^1-α-methylbenzyl-1,2-DHPs 3a, 3b and (*S*)-N^1-[2-(methoxymethyl)-pyrrolidinyl]-1,2-DHP 3c (Schemes 1 and 2). We also present evidence for the structure and absolute configuration of the isoquinuclidines obtained as diastereomeric mixtures in 20 to 68% overall yields, from the cycloaddition between these DHPs and methyl acrylate.

SYNTHESIS OF DHPs 3a-c

Since N^1-substituted 1,2-DHPs are readily accessible through sodium borohydride reduction of the corresponding pyridinium derivatives in alcaline medium, our synthesis commenced with the preparation of the salts 4a (*R*- or *S*-) and 4c (*S*-) by using commercially available chiral amines 5 namely, (*R*)-(+)- or (*S*)-(-)-α-methylbenzylamine 5a and (*S*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine 5c, respectively, according to Zincke's procedure starting from 2,4-dinitrophenylpyridinium chloride (6) (Scheme 1).



i. *n*-propanol, reflux overnight, yield 60-70%;
ii. $NaBH_4$, 5N NaOH-Et_2O, 15 min, N_2; yield: 3a *ca.* 50% and 3c 52%.

Scheme 1

Reduction of 4a with $NaBH_4$ in a two-phase system (NaOH-H_2O/Et_2O) afforded unstable 3a which, after quick filtration over alumina under nitrogen, was immediately used for the cycloaddition reaction with methyl acrylate. The DHP 3c, obtained under the same conditions, was found to be much more stable and could be isolated pure after chromatography over alumina.

As $NaBH_4$ reduction of 3-alkyl substituted pyridinium salts is known (7) to give the regioisomeric 1,2-dihydro compounds and not the 3-alkyl-1,6-dihydro derivatives, the requisite 3-ethyl DHPs 3b were prepared according to our previously reported procedure (3d) starting from the 4-piperidone derivatives 6 which could be conveniently obtained by reacting the chiral α-methylbenzylamines 5a with methyl acrylate in the presence of BF_3-Et_2O followed by Dieckmann cyclization (NaH-PhMe, 1h at 20°C, then 120°C for 24h) and subsequent decarboxylation (H_3O^+, 100°C, 5h) (8).

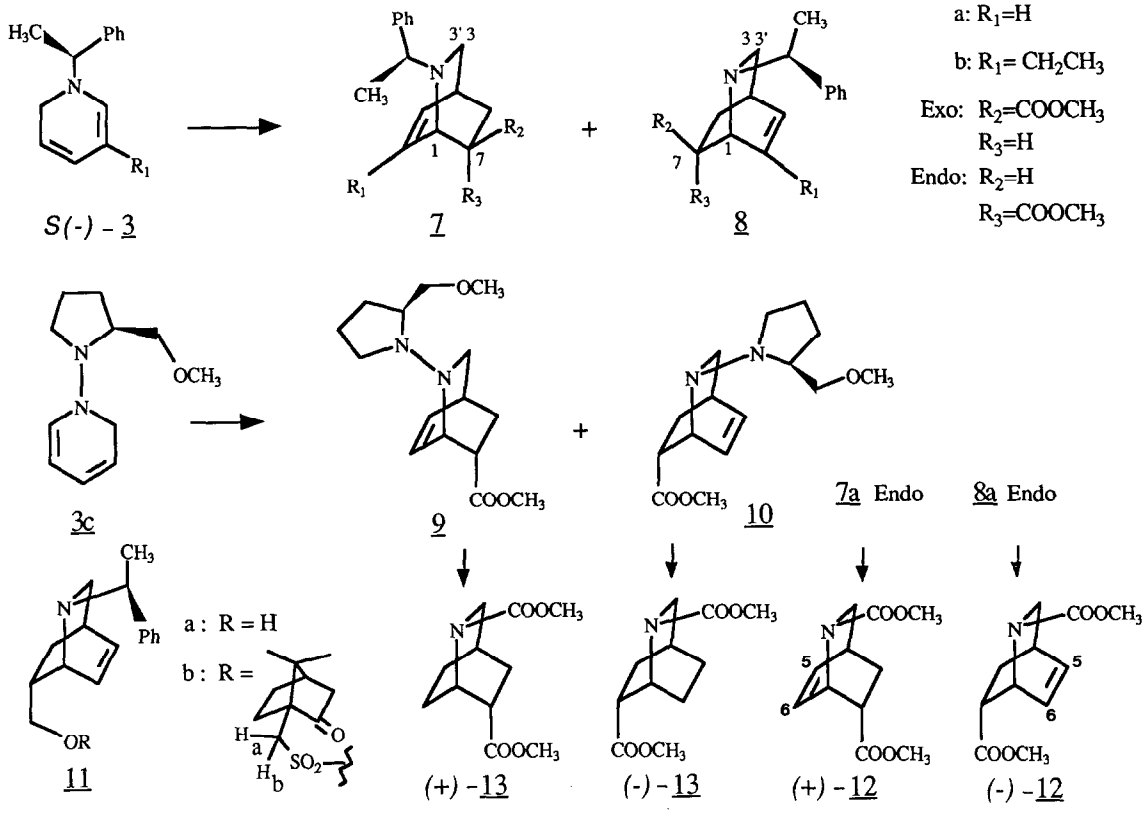
ADDITIONS OF DHPs 3a-c TO METHYL ACRYLATE

Each DHP (having a chiral auxiliary on the nitrogen) was dissolved in methyl acrylate and the resulting solution was refluxed overnight under nitrogen. Diastereomeric isoquinuclidines* (Scheme 2) formed were separated by chromatography over alumina. The results summarized in Table 1 show modest diastereomeric excess (d.e.) of *endo* 8a, 8b and 10 in the corresponding mixtures of adducts (9). Whereas a good *endo*-selectivity could be noticed for DHPs 3b (*R* or *S*) and 3c, a better overall yield was obtained with the DHP 3c which might be attributed to its higher stability.

STRUCTURE AND ABSOLUTE CONFIGURATION OF THE ISOQUINUCLIDINES 7-13

The nitrogen substituent of unsaturated isoquinuclidines is known to lie preferentially in a *syn* relationship with respect to the double bond (4, 10). Bearing in mind this important conformational feature of these molecules, the structure and absolute configuration of all the adducts 7 and 8 could be established unambiguously on the basis of their complete ^1H chemical shift assignments through 400 MHz n.m.r. COSY experiments. For adducts 7a and 8a, *endo*- vs. *exo*- isomer [in a given *R* or *S* series] was recognized from the chemical shift value of the H-7

proton which is downfield for the *exo*-isomer compared to the corresponding *endo*-isomer (11). The absolute configuration could then be deduced from a comparison of the chemical shift values of H-1, H-3 and H-3' within each diastereomeric pair. Thus, while the H-1 proton was deshielded ($\Delta\delta$ + 0.35 ppm) in going from *endo* 8a to *endo* 7a, the H-3 and H-3' protons were significantly shielded ($\Delta\delta$ - 0.33 and - 0.19 ppm, respectively). Similar differences were also observed in the *exo* 7a/*exo* 8a series. These shielding effects may be attributed to the influence of the neighbouring phenyl ring. Also, nuclear Overhauser proximity effects were displayed between H-1 and the benzylic methyl group for *endo* 7a and between H-3' and the benzylic methyl group in the case of *endo* 8a. By analogous ^{1}H n.m.r. assignments, the structure and



Scheme 2

the absolute configuration of the isoquinuclidine diastereoisomers *endo* 7b/*endo* 8b, depicted in Scheme 2 could be established with certainty. Furthermore, X-ray crystallography of the crystalline alcohol 11a, obtained by LAH reduction of *endo* 8a confirmed the assigned structure.

Adducts *endo* 7a and *endo* 8a, when heated with methyl chloroformate, afforded the carbamates (+)-12 {$[\alpha]_D$ = + 109°} and (-)-12 {$[\alpha]_D$ = - 110°}, respectively. On the other hand, Raney nickel reduction followed by methyl chloroformate treatment of 9 and 10 gave products (+)-13 and (-)-13, respectively, which could be correlated with 5,6-dihydro (+)-12 and (-)-12, thereby confirming the absolute configuration of the adducts 9 and 10. Finally, the extent of optical purity of these isoquinuclidines was checked in the following manner. For example, the alcohols (+)-11a and (-)-11a were separately reacted with (+)-10-camphor sulphonylchloride to give the corresponding esters 11b which are diastereomers. The diastereomeric ratio 95:5 in each of these esters was evaluated on the basis of the integration of the H-a and H-b signals in the ^{1}H

n.m.r. (400 MHz) spectra showing 90% e.e. for adducts (+)-8a or (-)-8a. These data indicate that little racemization occurred during the preparation of the salts 4 by Zincke's procedure.

TABLE 1

DHP	Conditions	cycloadducts (yield %)[c]	Total yield	*exo/endo* ratio	d.e. (*endo*) (%)
3a	a)	*exo* 7a (traces); *exo* 8a (6) *endo* 7a (11); *endo* 8a (18)	35%	20:80	24
3a	b)	*exo* 7a (traces); *exo* 8a (4) *endo* 7a (5); *endo* 8a (10)	20%	23:77	33
3b	a)	*endo* 7b (11); *endo* 8b (17)	28%	0:100	20
3c	a)	*endo* 9 (23); *endo* 10 (45)	68%	3:97	33

a) Methyl acrylate, Δ, 15h; b) methyl acrylate, 20°C, 48h; c) yield of isolated isoquinuclidines after chromatography over alumina. The ratio of isoquinuclidines formed was also checked by 400 MHz n.m.r. of the crude reaction mixture and parallels the isolated yield.

In conclusion, the present approach provides a quick access to chiral isoquinuclidines of defined configurations albeit in moderate yields. We are currently exploring conditions to improve the yield as well as the stereoselectivity of this cycloaddition strategy.

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9. a) $[\alpha]_D$ in $CHCl_3$ (*c* 1) of isoquinuclidines; obtained from *R*-(+)-methylbenzylamine/obtained from *S*-(-)-methylbenzylamine: *exo* 7a, - 20°/+ 21°; *endo* 7a: - 51°/+ 48°; *exo* 8a: + 64°/- 62°; *endo* 8a: + 100°/- 97°; *endo* 7b: - 15°/+ 11°; *endo* 8b: + 67°/- 67°; b) compound 9 $[\alpha]_D$ = - 41° (*c* 1; $CHCl_3$), compound 10 $[\alpha]_D$ = - 240° (*c* 1; $CHCl_3$).
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