Pergamon

Tetrahedron Letters 39 (1998) 4143–4146

TETRAHEDRON LETTERS

Stereoselective Preparation of the ABCD Tetracycle of the 20-Methyl Analogue of Aspidospermidine and Related Alkaloids.

Anahí Urrutia and J. Gonzalo Rodríguez*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma, Cantoblanco 28049-Madrid, Spain

Received 24 February 1998; revised 25 March 1998; accepted 3 April 1998

Abstract: The natural *cis*[ABCD] tetracycle of the 20-methyl analogue of aspidospermidine has been synthesised, starting from the 4,4-ethylenedioxy-1-cyclohexanone. This, was transformed into 3-methyl-3-(3'-nitropropyl)-1,2,3,4-tetrahydrocarbazol-4-one. Two key synthetic steps permits the construction of the D ring: i) the one pot nickel boride catalyst to the imine tetracycle in excellent yield; and ii) the stereoselective reduction of this imine to the natural *cis* D ring junction in good yield.

Key Words: aspidospermidine, Henry reaction, indolisation, nickel boride.

The aspidosperma type indole alkaloids constitute a large group of alkaloids with important biological activity including the antitumor agents vincristine and vinblastine.[1] These compounds share as part of their structure, the ABCD tetracyclic indole ring also found in aspidospermidine **1**.

In the context of our work on 1,2,3,4-tetrahydrocarbazol-4-ones, we were attracted to the possibility of the transformation of the conjugated carbonyl group to synthesise analogues of aspidospermidine **1**.

The 1,2,3,4-tetrahydrocarbazole derivatives contain the ABC rings in the aspidospermidine structure and are important synthons for the construction of these indole alkaloids. One of those derivatives is the 1,2,3,4-tetrahydrocarbazol-4-one that has of an available carbonyl group apparently suitable for the preparation of the 4-amino derivatives of the 1,2,3,4-tetrahydrocarbazole that are intermediates for the synthesis of aspidosperma alkaloids, and also structural analogues with potential neuroactivity.

The carbonyl group in 1,2,3,4-tetrahydrocarbazol-4-one (NH, NMe or NTs derivatives) was inefficient for formation of C-C bonds with nucleophiles [2,3] or under the Wittig reaction conditions with stabilised ylides.[4]

0040-4039/98/$19.00
PII: S0040-4039(98)00710-2

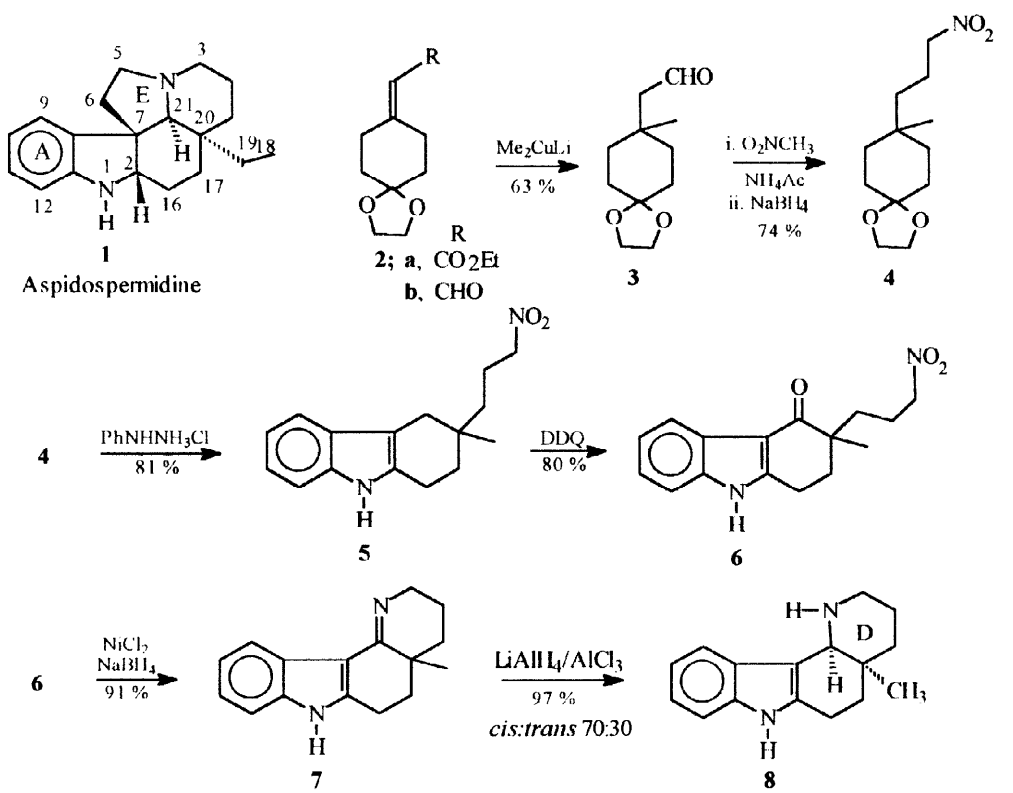
However, the reaction of 3-methyl-1-tosyl-1,2,3,4-tetrahydrocarbazol-4-one with a phenethylamine in presence of $TiCl_4$ has been reported.[5]

For the preparation of the 20-methyl analogue of aspidospermidine **1**, we undertook the synthesis of a 3,3-disubstituted tetrahydrocarbazol-4-one **6** to produce some sterical effect on the conjugated carbonyl group and also to force the stable envelope conformation of the cyclohexene ring in this molecule.[2]

To prepare the D ring of **1**, one of the substituents on position 3 should be a terminal propylamino chain, which should give the cyclic imino product **7** by condensation with a preformed C=O group at position 4.

In this way, (4,4-ethylenedioxy-1-cyclohexylidene)acetaldehyde **2**, was prepared starting of 4,4-ethylenedioxy-1-cyclohexanone by means of the Wittig reaction with the ethyl phosphonoacetate ylide to give ester **2a**, with control of temperature to avoid the double bond isomerisation. The ester **4** was reduced with DIBAL in dichloromethane to the allylic alcohol which was finally oxidised with chromium anhydride in dry pyridine to the aldehyde **2b** in good yield,[6] Scheme 1.

Scheme 1



The 1,4-addition of lithium dimethylcuprate to the aldehyde **2b** gave the acetaldehyde **3** in good yield. The aldehyde **3** was transformed in the nitro derivative **4** by condensation with nitromethane in presence of ammonium acetate,[7] in good yield which by selective reduction of the double bond with sodium borohydride in ethanol at -10° C, permited isolation of the saturated nitropropyl product **4** in good yield (77 %); the corresponding amine was also produced (10%).

The 3-methyl-3-(3'-nitropropyl)-1,2,3,4-tetrahydrocarbazol **5** was prepared by means of the Fischer reaction of the nitropropyl derivative **4** with phenylhydrazine hydrochloride in acetic acid (99 %). In this reaction, proton-catalysed acetal cleavage, formation of the phenylhydrazone, and cyclisation to the indole **5** all took place in one pot in good yield (81 %).

Before the reduction of the nitro group of compound **5**, the preparation of the 4-(1,2,3,4-tetrahydrocarbazol-4-one) derivative **6** was achieved by mild treatment of **5** with 2,3-dichloro-5,6-dicyano-1,4-p-benzoquinone in THF-H_2O (9:1), in good yield (85 %).

Finally, the reduction of the nitro to amino group in the ketone **6** was carried out with nickel boride as catalyst, which was prepared *in situ* by reduction of the nickel(II) chloride hexahydrate with sodium borohydride in ethanol,[8] using hydrazine hydrate as the hydrogen generator. During the reduction of the nitro group, an intramolecular condensation took place giving the imine and ring D, **7**. Thus, the double substitution in position 3 of the carbazol-4-one derivative **6** facilitates the intramolecular reaction of the recently formed terminal amino group with the carbonyl group, in one pot to give **7** in excellent yield (yellow solid, mp 128-9 °C, 91 %).

The stereoselective reduction of the imine **7** to prepare the natural *cis* C/D ring junction isomer was examined with different hydride complexes, Table 1. The reaction of the imine **7** with sodium borohydride, or sodium borohydride-boron trifluoride, in ethanol, isopropanol or THF, and lithium aluminium hydride in diethyl ether, gave only the *trans* fused C/D rings isomer (**8**), Table 1.

Table 1

Stereoreduction of the imine **7** by hydride complexes.

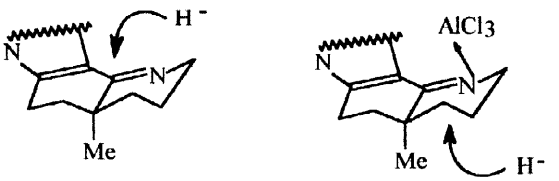
Reagent	Solvent	cis:trans	Reagent	Solvent	cis:trans
$NaBH_4$	^{i}PrOH	0:100	$NaBH_4$-BF_3	THF	0:100
DIBAL	THF	5:95	DIBAL	CH_2Cl_2	10:90
$LiAlH_4$	Et_2O	0:100	$LiAlH_4$	Et_2O	0:100
$LiAlH_4$	THF	20:80	$LiAlH_4$-$AlCl_3$	Et_2O	0:100
$LiAlH_4$-$AlCl_3$	toluene:THF 4:1	45:55	$LiAlH_4$-$AlCl_3$	toluene:THF 9:1	50:50
$LiAlH_4$-$AlCl_3$	toluene:THF 20:1	65:35	$LiAlH_4$-$AlCl_3$	toluene:THF 30:1	70:30

However, treatment of the imine **7** with lithium aluminium hydride in the presence of aluminium trichloride, in THF or mixtures with toluene, afforded both *cis* and *trans* isomers, in variable relative amounts depending of

the solvent employed, Table 1. Thus, in toluene:THF 30:1, the *cis:trans* ratio was 70:30 respectively and both isomers were isolated by silica gel column chromatography.[6]

On the other hand, the *trans* diequatorial type C/D rings junction in **8** is the more stable (crystal structure molecular models) with both rings in a chair and a half chair conformation respectively, that permits an aproach of hydride attack. Thus, the coordination of the aluminium trichloride to the imine nitrogen by the sterically more accessible face, allows the hydride ion attack on the more hindered side, Scheme 2. The solvent competes with the imine nitrogen in the coordination to the aluminium trichloride which produces increasing percentages in the *trans*-isomer.

Scheme 2



trans *cis*

The reduction of the imine **7** with the $LiAlH_4/AlCl_3$ in toluene results unsuccessful, however we found that addition of a little THF rendered the reaction mixture homogeneous, which favoured the N-aluminium trichloride coordination and hence the selectivity to the *cis*-isomer **8**. [9]

References

1. Saxton, J. E. *Nat. Prod. Rep.*, **1994**, *11*, 493.
2. Rodríguez, J. G.; Temprano, F.; Esteban-Calderón, C.; Martinez-Ripoll, M. *J. Chem. Soc. Perkin Trans.* 1, **1989**, 2117.
3. Rodríguez, J. G.; del Valle, C.; Esteban-Calderón, C.; Martinez-Ripoll, M. *J. Chem. Cryst.* **1995**, *25*, 249.
4. Wadsworth, W.S.; Emmons, W.D.E. *J. Am. Chem. Soc*, **1961**, *83*, 1733.
5. Weingarten, H.; Chupp, J.P.; White, W.A. *J. Org. Chem.*, **1967**, *32*, 3246.
6. *cis*-isomer, white solid, mp 185-7 °C; m/z, 240 (M^+, 100), Rodríguez, J. G. to be published.
7. Canoira, L.; Rodríguez, J. G.; Subirats, J. *Eur. J. Med. Chem.* **1989**, *24*, 39.
8. Han, D. H.; Shin, D. H.; Cho, S. Y. *Tetrahedron Lett.*, **1985**, *50*, 6233.; Lloyd, D. H.; Nichols, D. E. *J. Org. Chem.*, **1986**, *51*, 4292.
9. All the compounds exhibited satisfactory elemental analysis, spectral, and mass data.