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Asymmetric Synthesis of 1-Substituted Tetrahydroisoquinolines by Nucleophilic Addition to Hydrazonium Ions. Application to the Enantioselective Syntheses of (+)- and (–)-Salsolidines and (–)-Cryptostyline II

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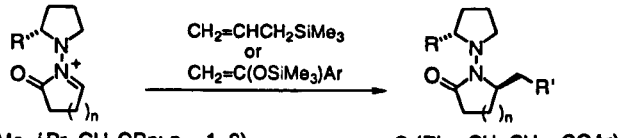
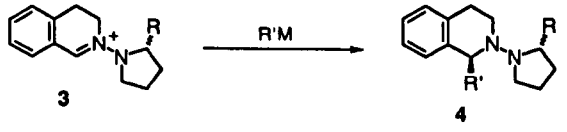
Abstract: Nucleophilic addition of carbon nucleophiles and metal hydride reagents to hydrazonium salts modified by optically active 2-substituted pyrrolidine auxiliaries leads to highly enantioselective synthesis of 1-substituted tetrahydroisoquinolines. This methodology was applied to asymmetric synthesis of the title isoquinoline alkaloids.

We have recently recognized[1] efficient asymmetric induction resulting from the addition of carbon nucleophiles to "*N*-acylhydrazonium ions" **1** (eq 1) which correspond to a new structural class of activated azomethines. In this methodology, the higher levels of diastereoselectivity are ascribed to steric control by the 2-substituted pyrrolidines as chiral auxiliaries and the methodology has been utilized for enantioselective preparation of alkaloid natural products.[2] As an extension of the asymmetric induction in this system, we envisioned that nucleophilic addition to "hydrazonium ions" **3** installed by some chiral 2-substituted pyrrolidine auxiliaries would result in the attainment of diastereoselective preparation of 1-substituted tetrahydroisoquinolines **4**[3] (eq 2) which allow for broad application to the construction of isoquinoline alkaloids, forming one of the largest families of natural bases, in an asymmetric manner.



1 (R = Me, *i*Pr, CH_2OBn; n = 1, 2) **2** (R' = $CH{=}CH_2$, COAr) (1)



3 **4** (2)

To this end, the phenethylamides **9** bearing various chiral pyrrolidine auxiliaries were subjected to Bischler–Napieralski reaction ($POCl_3$, benzene, reflux) as summarized in Scheme 1. After removal of the solvent in vacuo, the resulting hydrazonium salts **10** were immediately used in the subsequent reaction without purification. Thus, nucleophilic addition to **10** was carried out employing 1.5–3 equiv of organometallic reagents in THF. After work-up a chromatographically separable mixture of 1-substituted tetrahydroisoquinolines **11** and **12** was obtained. In all cases the reactions were found to proceed with high levels of diastereoselectivity in favor of the (1*S*)-isomers **11** (Table 1).

Scheme 1

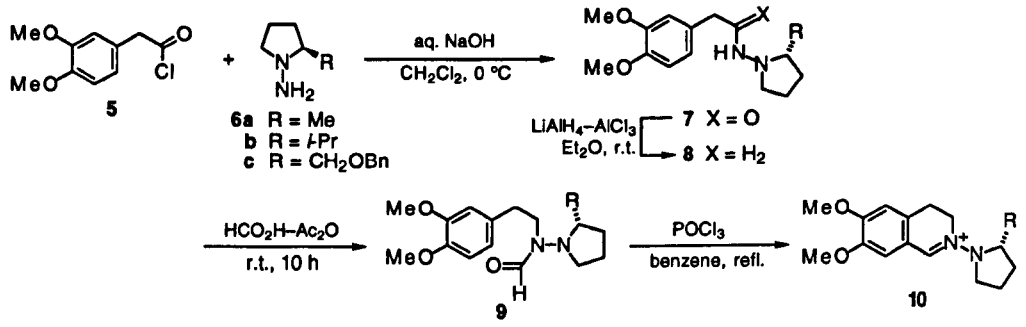
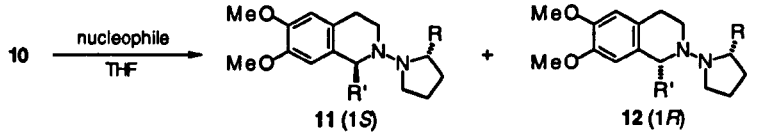


Table 1. Diastereoselective nucleophilic addition to hydrazonium ions 10.

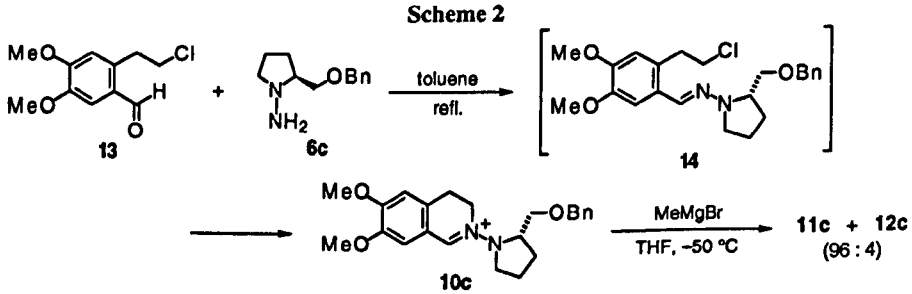


Entry	Compound 10		Nucleophile	Temp, °C	Products 11 and 12			
		R				R'	11 : 12[a]	Yield, %[b]
1	a	Me	MeLi	−50	a	Me	95 : 5	71
2	b	*i*-Pr	MeMgBr	−50	b	Me	94 : 6	85
3	c	CH_2OBn	MeMgBr	−50	c	Me	96 : 4	89
4	c	CH_2OBn	MeMgBr	−90	c	Me	97 : 3	84
5	c	CH_2OBn	Me_3Al	−50	c	Me	95 : 5	24
6	c	CH_2OBn	CH_2=$CHCH_2MgBr$	−50	d	CH_2CH=CH_2	92 : 8	77
7	c	CH_2OBn	PhMgBr	−50	e	Ph	96 : 4	70

[a]Determined by HPLC analysis. [b]Isolated yield of the diastereomeric mixture from **9**.

The hydrazonium ion **10c** was alternatively generated via the hydrazone **14** by treatment of the formyl chloride **13** with the chiral 1-aminopyrrolidine **6c** in refluxing toluene and, without purification, subjected to nucleophilic addition of MeMgBr to yield a 96:4 ratio of the products (68% yield from **13**) favoring the (1*S*)-isomer **11c** (Scheme 2).

Scheme 2



The efficiency of this methodology prompted us to undertake a further investigation of the enantioselective approach to 1-substituted tetrahydroisoquinolines by means of hydride addition to hydrazonium

ions. The required hydrazonium ions, i.e., 1-substituted dihydroisoquinolinium salts **16** modified by the chiral pyrrolidine auxiliaries, were easily available by Bischler–Napieralski reaction of the corresponding phenethylamides **15** (Scheme 3). Hydride addition to **16** was carried out employing various metal hydride reagents and the results are summarized in Table 2. As can be seen in the Table, the (1*R*)-isomers **12** were preferentially formed in all cases in high to excellent diastereoselection.

Scheme 3

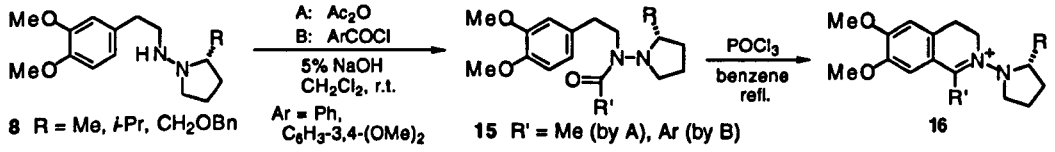
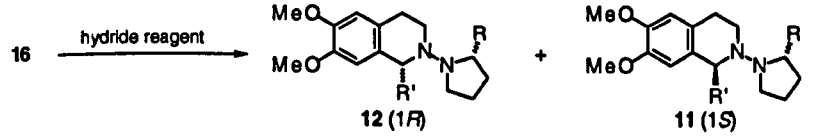


Table 2. Diastereoselective hydride reduction of hydrazonium ions 16.



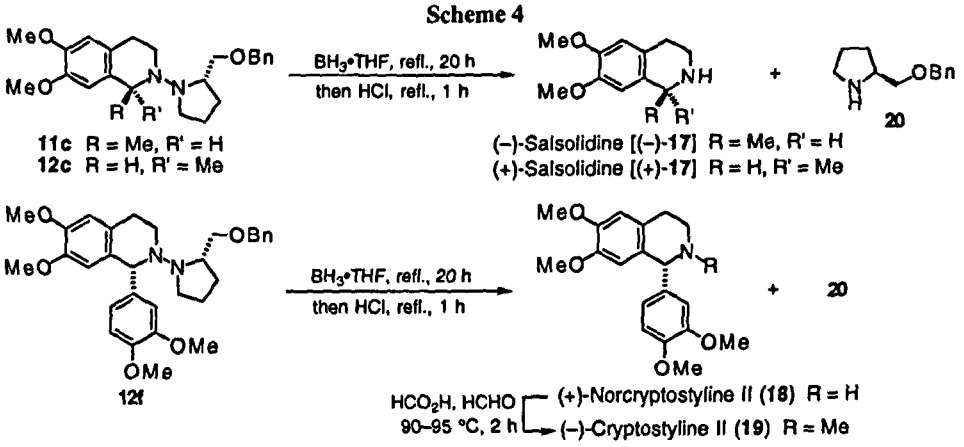
Entry	Compound 16	R	R'	Hydride reagent	Solvent	Temp, °C	Products 12 and 11	12 : 11[a]	Yield, %[b]
1	a	Me	Me	$NaBH_4$	MeOH	−50	a	92 : 8	73
2	b	*i*-Pr	Me	$NaBH_4$	MeOH	−50	b	93 : 7	71
3	c	CH_2OBn	Me	$NaBH_4$	MeOH	−10	c	95 : 5	88
4	c	CH_2OBn	Me	$NaBH_4$	MeOH	−50	c	96 : 4	84
5	c	CH_2OBn	Me	$NaBH_4$	MeOH	−90	c	97 : 3	81
6	c	CH_2OBn	Me	$LiB(Et)_3H$	THF	−50	c	96 : 4	68
7	c	CH_2OBn	Me	Vitride	THF	−50	c	96 : 4	63
8	c	CH_2OBn	Me	DIBAL-H	THF	−50	c	96 : 4	42
9	c	CH_2OBn	Me	K-Selectride	THF	−50	c	98 : 2	44
10	d	CH_2OBn	Ph	$NaBH_4$	MeOH	−50	e	97 : 3	75
11	e	CH_2OBn	Ar[c]	$NaBH_4$	MeOH	−50	f	95 : 5	70

[a]Determined by HPLC analysis. [b]Isolated yield of the diastereomeric mixture from **15**. [c]C_6H_3-3,4-$(OMe)_2$.

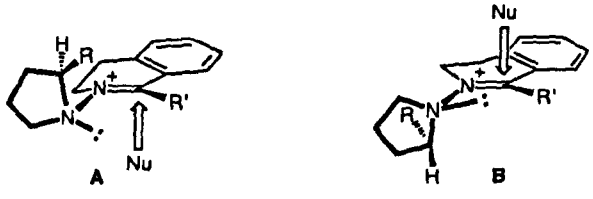
The resulting adducts **11** and **12** can be easily converted to the optically active 1-substituted tetrahydroisoquinolines via reductive cleavage of the N–N bond. Accordingly, preparations of the natural alkaloids (−)- and (+)-salsolidines (**17**) and (−)-cryptostyline II (**19**) were attained using **11c**, **12c**, and **12f**, respectively, as outlined in Scheme 4, which allowed the absolute configurations of the newly induced asymmetric centers of the (1*S*)- and (1*R*)-diastereomers, **11** and **12**, to be confirmed and demonstrated the usefulness of the present asymmetric induction on the chiral hydrazonium salts. Thus, from **11c** was obtained (−)-salsolidine [(−)-**17**], $[\alpha]^{29}_D$ −58.5° (*c* 1.07, EtOH) [lit.[4] $[\alpha]^{22}_D$ −59.5° ±0.5° (*c* 4.39, EtOH)], in 77% yield along with the chiral auxiliary **20** recovered (65%). Application of the same procedure to **12c** gave (+)-salsolidine [(+)-**17**], $[\alpha]^{29}_D$ +58.9° (*c* 1.18, EtOH) [lit.[5] $[\alpha]^{16}_D$ +59.9° (*c* 25, EtOH)]. In a similar manner, **12f** was subjected to the reductive cleavage to provide (+)-norcryptostyline II (**18**) (71%), mp 116.5–117.5 °C;

$[\alpha]^{30}_D$ +34.7° (*c* 0.51, $CHCl_3$) [lit.[6] mp 114–115 °C; $[\alpha]_D$ –33.5° ($CHCl_3$)], and **20** (66%), the former of which was further subjected to Eschweiler–Clarke N-methylation to form (–)-cryptostyline II (**19**) (73%), mp 116–117 °C; $[\alpha]^{29}_D$ –58.2° (c 0.55, $CHCl_3$) [lit.[7] mp 116–117 °C; $[\alpha]^{22}_D$ –58° (*c* 0.4, $CHCl_3$)].

Scheme 4



The preferential formation of the (1*S*)- and (1*R*)-diastereomers, **11** and **12**, in the addition of carbon nucleophiles and metal hydride reagents, respectively, can be rationalized on the basis of our previous study[1] in nucleophilic addition in the *N*-acylhydrazonium ions (eq 1), wherein facial selectivity arises from the pyramidal stability of the trivalent nitrogen in the auxiliary pyrrolidine ring constituting an asymmetry inducing chiral center. Thus, the perpendicular approach of the carbon nucleophile (when R' = H) or hydride ion (when R' = alkyl, aryl) to the azomethine group should preferably occur from the sterically less shielded bottom face of the energetically favored conformer **A** leading to the (1*S*)-isomer **11** or (1*R*)-isomer **12**, respectively. The alternative conformer **B**, which allows a perpendicular approach of the nucleophile, leading to the opposite sense of asymmetric induction is disfavored because of steric repulsion between the α oriented 2-substituent (R) in the pyrrolidine ring and the C-3 methylene group in the dihydroisoquinoline.



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