Lewis Acid Mediated Diastereoselective Allylation of 3-Menthyloxycarbonyl-5,6-dihydropyridin-4-ones

Sylvie Brocherieux-Lanoy, Hamid Dhimane, Corinne Vanucci-Bacqué, Gérard Lhommet*

Université Pierre et Marie Curie, Laboratoire de Chimie des Hétérocycles, UMR 7611, 4 Place Jussieu, F-75252 Paris Cedex 05, France
Fax 33 (0)1 44 27 30 56; E-mail: lhommet@ccr.jussieu.fr

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Abstract: Sakurai allylation of menthyl enoates **5a-c** afforded adducts **7a-c** with low to excellent facial selectivity, depending on the Lewis acid employed to promote this 1,4-nucleophilic addition of allyltrimethylsilane. A chelated model was assumed to explain the observed diastereoselectivity.

Key words: Sakurai allylation, dihydropyridone, stereoselective, Lewis acid, chiral auxiliaries

Along with our efforts towards the synthesis of enantiopure α-substituted piperidine moieties from naturally occurring amino acid,[1] we are currently investigating a new access to these structures by means of diastereoselective reactions using commercially available substrates and chiral auxiliaries. To this end, we selected conjugate 1,4-addition on 2,3-dihydro-4-pyridones **A** (Figure 1) bearing a menthyloxycarbonyl as the *N*-protecting group and the chiral auxiliary. A preliminary study of the Sakurai allylation of this substrate in the presence of various Lewis acids and solvents showed almost no facial selectivity,[2] as described recently by Kibayashi *et al*.[3] In order to improve this selectivity, these authors used more sophisticated chiral menthyl carbamates. In contrast to this approach, we decided to introduce the menthyloxycarbonyl group at the 3-position of the dihydropyridone structures and to investigate the effect of this substituent on the facial selectivity of the Sakurai allylation of such β-enamino-β-keto esters **B** (Figure 1). Moreover, in view of synthetic applications, the expected adducts thus obtained are more prone to regioselective functionalisation than the analogues obtained from dihydropyridone **A**.

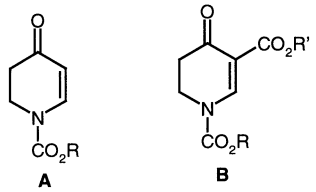
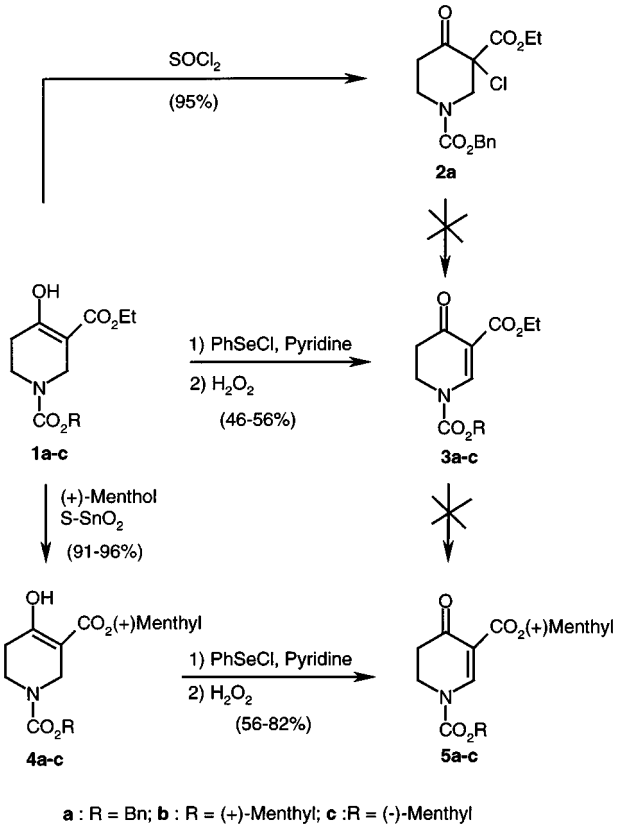


Figure 1

As a prelude to this study, we first synthesised the required dihydropyridones **3b** and **5a-c** bearing one or two menthyloxycarbonyl groups at the 1 and/or 3 positions (Scheme 1). Commercially available 3-carbethoxy-4-piperidone hydrochloride was readily converted to the corresponding benzyl, (+) and (-)-menthyl carbamates **1a-c**

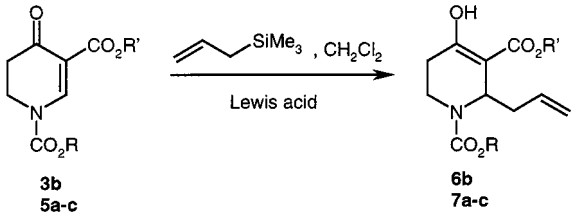


Scheme 1

respectively (84-97% yield). Attempts to prepare the dihydropyridone **3a** by *anti* elimination starting from α-chlorinated β-keto ester **2a** failed under various conditions,[4] probably due to an equatorial orientation of the chlorine atom. The carbon-carbon double bond introduction was then performed on β-keto esters **1a-c** following the selenation-oxidative elimination sequence to lead to compounds **3a-c** (46-56% yield). Unfortunately, neither the use of DMAP[5] nor of $Ti(OiPr)_4$[6] as catalysts could promote the transesterification of ethyl enoates **3a-c** to the corresponding menthyl esters **5a-c**. We then envisioned to obtain **5a-c** by a reverse sequence *i.e.* transesterification of **1a-c** prior to carbon-carbon double bond formation. The transesterification step proved once again difficult with the catalysts[5, 6] mentioned above which led to **4a-c** in only low yield (30%). However, this reaction proceeded efficiently (91-96% yield) following the S. Chavan[7] con-

ditions using the super acid species $S.SnO_2$ as a catalyst (0.1 eq w/w). Finally, compounds **5a-c** were obtained by selenation/oxidative elimination of **4a-c** in 56-82% yield (Scheme 1).

We next examined the diastereoselectivity of allylations of substrates **3b** and **5a-c** in the presence of various Lewis acids (Scheme 2). Use of $SnCl_4$ resulted in 1,2-addition of allyltrimethylsilane leading to an unseparable diastereomeric mixture[8] of homoallylic alcohols, whereas $BF_3•Et_2O$ and $TiCl_4$ promoted the desired 1,4-addition in good yield[9] with complete regioselectivity (Table 1). With such Lewis acids, allylation of ethyl enoate **3b**, protected as a menthyl carbamate showed, as expected, no improvement in the facial selectivity (d.e.≤14%, entry a), consistently with the result obtained by using the corresponding simple dihydropyridone **A**. However, when the menthyloxycarbonyl group was located only at the 3-position, as in benzyl carbamate **5a**, we noticed a marked enhancement of the diastereoselectivity (50≤d.e.≤60%, entries b-c). We then examined the combined effect of two (+)-menthyloxycarbonyl groups located both at the 1 and 3 positions. When reacted in the presence of $BF_3•Et_2O$, substrate **5b** did not lead to noticeable improvement in the diastereoselectivity, which is comparable with the one observed in the case of compound **5a** (entry d). Noteworthy was the remarkable facial selectivity, which reached 92% d.e. in the presence of 4 eq of $TiCl_4$ (entry e) in the case of the Sakurai allylation of dihydropyridone **5b**. Moreover, when the substrate beared two menthyl groups of opposite configuration (**5c**) a significant drop in diastereoselectivity was observed either with $BF_3•Et_2O$ (entries d, g) or $TiCl_4$ (entries e, h).



3b **5a-c** **6b** **7a-c**

Scheme 2

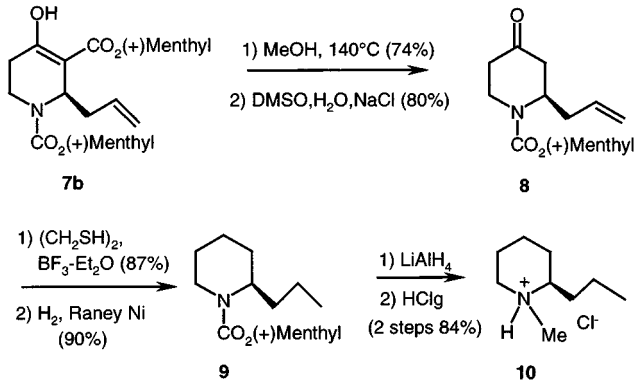
In order to be able to rationalise these results, we had first to ascertain the absolute configuration of the major adducts **6** and **7** resulting from the allylation of compounds **3** and **5** in the presence of $TiCl_4$ (4 eq). To this end, we first decided to convert compound **7b** in five steps to the known alkaloid: *N*-methylconiine, as depicted in Scheme 3. Transesterification and subsequent decarbomethoxylation gave the piperidin-4-one derivative **8** in 59% overall yield. Treatment of the latter with ethanedithiol in the presence of $BF_3•Et_2O$ led to the corresponding dithioketal (87% yield) which was readily converted to 2-*n*-propylpiperidine **9** under a hydrogen atmosphere in the presence of Raney nickel (90% yield). Reduction of the carbamate moiety with $LiAlH_4$ afforded the corresponding *N*-methylpiperidine which was isolated as its hydrochloride salt **10** (84% yield from **9**). The physical properties of the latter (mp = 191-192°C, $[\alpha]_D^{22}$ = - 29.5 (c 0.39, EtOH)) were in good agreement with those reported for the (-)-(*R*)-*N*-methylconiine hydrochloride.[3,10] Accordingly, the major adduct **7b** was proved to have an (*R*) configuration for the new generated chiral centre α to the nitrogen atom.

Likewise, a similar sequence of reactions, starting from adduct **7c,** allowed an (*R*) absolute configuration to be assigned to the 2-position of the major diastereoisomer **7c**.

Table 1 : Diastereoselectivity of Sakurai allylations of **3b** and **5a-c**.

Entry	Substrates	R	R'	Lewis acid (eq)	Products (%)[a)]	d.e. (%)[b)]
a	**3b**	(+)-menthyl	ethyl	$TiCl_4$ (4)	**6b** (79)	14
b	**5a**	benzyl	(+)-menthyl	$BF_3•Et_2O$ (4)	**7a** (87)	50
c	**5a**	benzyl	(+)-menthyl	$TiCl_4$ (4)	**7a** (93)	60
d	**5b**	(+)-menthyl	(+)-menthyl	$BF_3•Et_2O$ (4)	**7b** (89)	60
e	**5b**	(+)-menthyl	(+)-menthyl	$TiCl_4$ (4)	**7b** (92)	92
f	**5b**	(+)-menthyl	(+)-menthyl	$TiCl_4$ (1)	**7b** (18)	30
g	**5c**	(-)-menthyl	(+)-menthyl	$BF_3•Et_2O$ (4)	**7c** (90)	40
h	**5c**	(-)-menthyl	(+)-menthyl	$TiCl_4$ (4)	**7c** (95)	72

a) Yields of isolated product.
b) Determined by ^1H NMR analysis of the crude products in toluene-d_8 at 373 K. The presence of two rotamers of the carbamate moiety at r.t. did not allow the d.e. estimation.



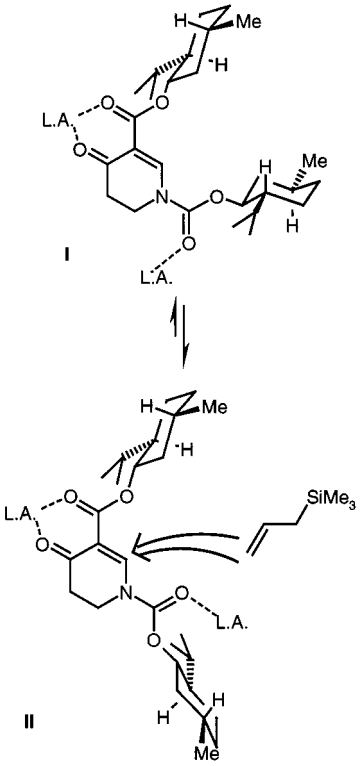
Scheme 3

On the other hand, decarbethoxylation of compound **6b** (DMSO, H_2O, NaCl) led to a mixture of piperidin-4-ones, in which the major isomer was epimer **8**. Finally, major isomer of **7a** was also shown[11] to have an (*R*) configuration for the new chiral centre.

Taking into account all these results, we suggest a model susceptible to rationalising the observed facial selectivities (Scheme 4). Both the nature and the amount of Lewis acid are crucial for the conversion and the diastereoselectivity (Table 1). As depicted in Scheme 4, more than one equivalent of Lewis acid is indeed required to coordinate both the carbamate and the β-keto ester moieties (entry f). On the other hand, the use of a bidentate Lewis acid ($TiCl_4$) noticeably increases the diastereoselectivity compared with that obtained with monodentate BF_3•Et_2O.[12]

Moreover, we assume an *s-cis* conformation for both menthyloxycarbonyl groups. In conformer **II** which is favoured due to the steric hindrance between these groups,[13] the *N*-chiral auxiliary is moved away from the reactive centre. Therefore, in the case of menthyl enoates **5b-c**, the main chiral induction is due to the 3-menthyloxycarbonyl moiety. Indeed, the allytrimethylsilane approach takes place preferentially *anti* to the isopropyl substituent of the menthyl ester (Scheme 4). Such a directing role of the menthyloxycarbonyl group at the 1-position is also effective, but to a lesser extend due to its remoteness from the electrophilic centre (entry a). However, when both 1,3-menthyloxycarbonyl groups of the same configuration are present, a synergy was observed leading to allylation compounds with a high facial selectivity (entry e).

In conclusion, we have devised a dihydropyridone Michael acceptor **5b** bearing simple chiral auxiliaries, which undergoes Sakurai allylation with modest to excellent diastereoselectivity, depending on the Lewis acid used as the catalyst. Further efforts towards the application of these results to the total synthesis of naturally occurring alkaloids are currently under investigation in our Laboratory.



Scheme 4

References and notes

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(4) Treatment of **2a** by *N,N*-dimethylaniline, pyridine or DBU did not affect the starting material.
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(8) The diastereoselectivity of the obtained adducts is not yet ascertained.
(9) *Typical procedure for Sakurai allylations* : *Preparation of* ***7b***. Compound **5b** (1.65g, 3.57 mmol) and allyltrimethylsilane (2.3 mL, 14.47 mmol) were dissolved in CH_2Cl_2 (50 mL) at – 78°C under argon atmosphere. Titanium tetrachloride (1.57 mL, 14.3 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to warm to – 10°C over 3 hours, then quenched with an aqueous suspension of $NaHCO_3$ (10 g, 119 mmol in 10 mL of H_2O). After warming to room temperature, water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water (50 mL) and dried over Na_2SO_4. Evaporation under vacuum gave a yellow oil which was purified by column chromatography using AcOEt-Cyclohexane (1:4) as eluent giving pure diastereomeric mixture **7b** as a colourless oil (1.65 g, 92%); IR (neat) 1710, 1680 cm^{-1} ; ^1H NMR (To-

luene-d_8, 250 MHz, 373 K) δ (ppm) : 0.8-1.1 (m, 26H), 1.25-1.7 (m, 7H), 1.9-2.2 (m, 4H), 2.25-2.55 (m, 2H), 2.55-2.7 (m, 1H), 2.92-3.1 (m, 1H), 4.1-4.25 (m, 1H), 4.78 (td, J = 10.7 and 4.4 Hz, 1H), 4.91 (td, J = 10.7 and 4.4 Hz, 1H), 4.95-5.15 (m, 2H), 5.2-5.35 (m, 1H), 5.85-6.05 (m, 1H), 12.74 and 12.83 (2s, 1H); ^{13}C NMR (Toluene-d_8, 62.5 MHz, 373 K) δ (ppm) : 17.05, 17.61, 20.95, 21.13, 22.15, 22.30, 24.59, 25.07, 27.24, 27.74, 28.93, 32.93, 34.93, 35.26, 36.21, 39.55, 41.74, 42.34, 48.25, 48.62, 50.14, 75.49, 75.75, 101.61, 116.50, 136.28, 155.16, 170.93, 171.91; Analysis calcd. for $C_{30}H_{49}NO_5$; C 71.53, H 9.80, N 2.78 ; found C 71.66, H 9.91, N 2.73.

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(11) When the reaction mixture of **7a** (entry c) was quenched at r.t. with water, debenzyloxycarbonylation took easily place leading to the corresponding free amine. The latter was then converted to the (+)-menthyl carbamate **7b**, thus allowing the correlation with compound obtained from substrate **5b**.

(12) However, Maruaka and coworkers reported recently some examples of pentacoordinate chelates of boron Lewis acid ($B(C_6F_5)_3$). Ooi, T.; Uragushi, D.; Kagoshima, N.; Maruaka, K. *J. Am. Chem. Soc.* **1998**, *120*, 5727.

(13) Similar conformation for the carbamate moiety has been assumed in the case of 1-(8-phenylmenthyl)oxycarbonyl-3-triisopropylsilylpyridinium salts derivatives by D. Comins *et al*: Comins, D. L.; Joseph, S. P.; Goehring, R. R. J. *Am. Chem. Soc*. **1994**, *116*, 4719.