Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 3927-3930, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0705-3

A Simple Asymmetric Synthesis of 2-Substituted 2,3-Dihydro-4-Pyridones

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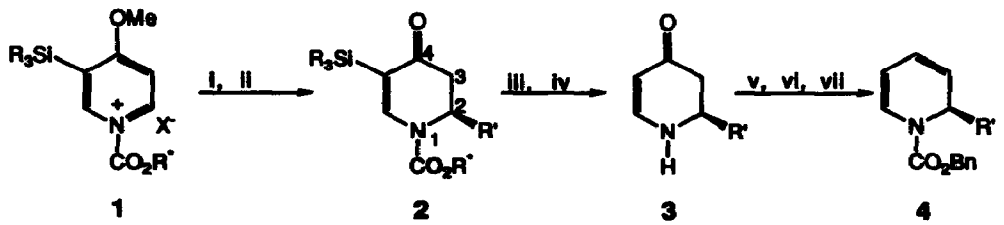
Summary. *- A pronounced asymmetric induction (d.e. = 95 %) was observed during methylation of pyridinium salt 7 with MeMgI which led ultimately to (2R) 2-methyl-2,3-dihydro-4-pyridone 9. This result is best explained by assuming chelate-control during the asymmetric alkylation step.*

2-Substituted 1-acyl-1,2-dihydropyridines **4** are useful intermediates for the preparation of natural products, such as piperidine,[1] indolizine,[2] quinolizidine,[3] or *cis*-decahydroquinoline[4] alkaloids ; also of piperidine carbohydrate derivatives.[5] Comins devised a general and useful methodology for the asymmetric synthesis of type **4** dihydropyridines : the chiral pyridinium salt **1** was prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)-pyridine and (-)-8-phenylmenthol chloroformate.[6,7] Reaction of **1** with RMgX gave dihydropyridone **2** in high yield and high *de*.[8] The chiral auxiliary and the trialkylsilyl group were removed from purified diastereomer **2** with sodium methoxide/methanol and oxalic acid to give enantiopure dihydropyridone **3**. N-protection with $ClCO_2Bn$ followed by reduction ($NaBH_4$, $CeCl_3$) of the carbonyl and dehydration (MsCl, DMAP) led to the enantiomerically pure dihydropyridines **4** in good yield (60-85%) (*Scheme 1*).[6]

Scheme 1



1 **2** **3** **4**

R = i-Pr or Me ; R* = (-)-8-phenylmenthyl ; R' = aryle or alkyle

I) R'MgX ; II) 10% HCl ; III) NaOH ; IV) oxalic acid ; V) $ClCO_2Bn$; VI) $NaBH_4$, $CeCl_3$; VII) MsCl, DMAP

We describe herein a simple alternative to Comin's procedure : replacement of the (-)-8-phenylmenthyl group by Seebach's less expensive chiral oxazolidine auxiliary (*2R,4S*) **5** did no longer require the bulky (and expensive) triisopropylsilyl group as a steric hindrance for the asymmetric C-alkylation step of pyridinium salt **7**.

Oxazolidine **5** was prepared from L-serine and pivalaldehyde as a diastereomeric mixture (ratio *ca.* 1:1) according to Seebach's procedure.[9-11] Reaction of **5** with phosgene led to two diastereomers (ratio *ca* 98:2) from which optically pure **6** was isolated in high yield (91%) after only one crystallization. ^{1}H-NMR nuclear Overhauser Effect measurements demonstrated that **6** appeared exclusively in the *cis* configuration, a result which had also been observed by Seebach with the N-formyl analogue of **6**.[11] Treatment of 4-methoxypyridine with **6** led to pyridinium salt **7** which when reacted with MeMgI, and finally with HCl, led to crude dihydropyridone **8** having a *de* of 95 % (according to HPLC). A single recrystallization led to **8** as a homogenous chiral compound in 74 % yield.

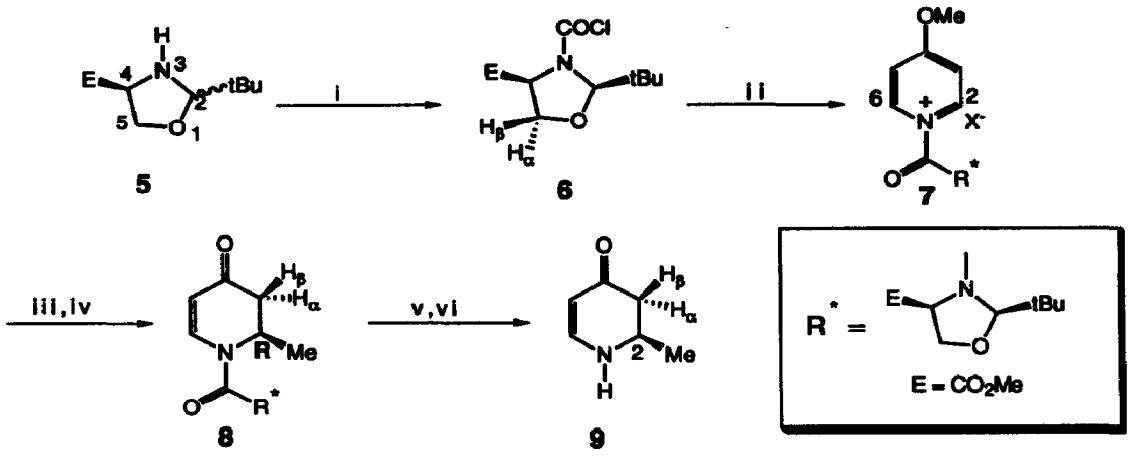
Methyl (2*R*,4*S*)-2-(*t*-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate 6. - To a stirred soln. of oxazolidine **5** (17.36 g, 92.7 mmol) in CH_2Cl_2 (350 ml) kept at -15°C was added dropwise a 1.93 M soln. of $COCl_2$ in toluene (72 ml ; 139 mmol). Et_3N (16.8 ml, 120 mmol) was added dropwise and the reaction mixture left to warm up to rt. After 2 h N_2 was bubbled through the reaction mixture in order to remove excess of $COCl_2$. The solvents were evaporated and the residue was purified on a silica gel column (AcOEt/cyclohexane 3:7) whereby **6** was eluted (22.11 g ; *de* = *ca.* 96 % according to ^{1}H-NMR). After recrystallisation in n-pentane **6** was isolated as a single product (21.1 g ; 91 %), m.p. = 76.5-77.5°C ; $[\alpha]^{20}_D$ = - 32 (c = 1.0 ; $CHCl_3$).[12]

Methyl (2*R*,2'*R*,4'*S*)-3'-[2-methyl-4-oxo-1,2,3,4-tetrahydro-1-pyridinyl] carbonyl-2'-*t*-butyl-(1,3) oxazolidine-4-carboxylate 8. - To a stirred soln. of **6** (7.50 g , 30 mmol) and of anhyd. NaI (9,0 g, 60 mmol) as a suspension in anhyd. toluene (120 ml) 4-methoxypyridine (3.28 g, 30 mmol) was added under Ar and the reaction mixture left to react for 5 d at rt. The resulting soln. was diluted with 380 ml anhyd. toluene and cooled to 0°C. To this slightly heterogenous soln. was added dropwise a 2 M soln. of MeMgI in anhyd. ether (49 mmol). After 1 h the reaction mixture was left to warm up to rt ; after another 30 min 10 % HCl (120 ml) was added and the aq. phase was extracted with Et_2O (3 x 100 ml). The combined organic phases were washed with sat. NaCl soln. (2 x 50 ml), dried over $MgSO_4$, and the solvents evaporated. According to HPLC (DAICEL CHIRACEL OD column ; n-hexane/iPrOH 90:10 ; 300nm UV detector ; ratio of the specially prepared diastereoisomeric 1:1 mixture : 845:869 ; 17.3 (8) and 20.4 (minor stereoisomer) min) the reaction mixture had a *de* of 95 %. It was recrystallised from i-Pr_2O to yield **8** ; the mother liquors were purified by flash chromatography (AcOEt/cyclohexane 1:1) and recrystallised (iPr_2O) to yield a second crop of **8**. Combined yield of **8** : 7.20 g (74 %) ; m.p. 157.5-159°C.[12]

Acid hydrolysis of **8** led to the removal of pivalaldehyde. At pH=11 the resulting primary alcohol, which was not isolated, induced intramolecular cleavage of the urea functionality leading thereby to enantiopure dihydropyridone **9**, $[\alpha]^{20}_D$ = + 495 (*Scheme 2*). This very enantiomer **9**, $[\alpha]^{20}_D$ = + 462, has also been obtained by using Comins' method, *i.e.* via methylation of **1** (R=Me)(overall yield from **1**=74%), and proved to have the (*2R*) configuration by X-ray analysis of the crystalline intermediate **2** (R=R'=Me).[13]

(2*R*)-2-Methyl-2,3-dihydro-1H-4-pyridone 9. - A suspension of **8** (5.49 g, 16.9 mmol) in 50 % HCl (60 ml) was stirred overnight at rt whereby a homogenous soln. resulted. After evaporation of HCl and H_2O *i. vac.*, H_2O (30 ml) and some pellets of NaOH were added until pH=11. After 2 h the reaction mixture was neutralised with conc. HCl, and extracted with CH_2Cl_2 (6 x 50 ml). The organic phases were dried over $MgSO_4$ and evaporated to dryness yielding **9** (1.85 g, 98 %) as a yellow oil. $[\alpha]^{20}_D$ = +495 (c=1.4, $CHCl_3$).[12]

Scheme 2



i) $COCl_2$, recrystallization ; ii) p-MeO-pyridine, NaI; iii) MeMgI ;
iv) 10% HCl, recrystallization ; v) 50% HCl ; vi) NaOH

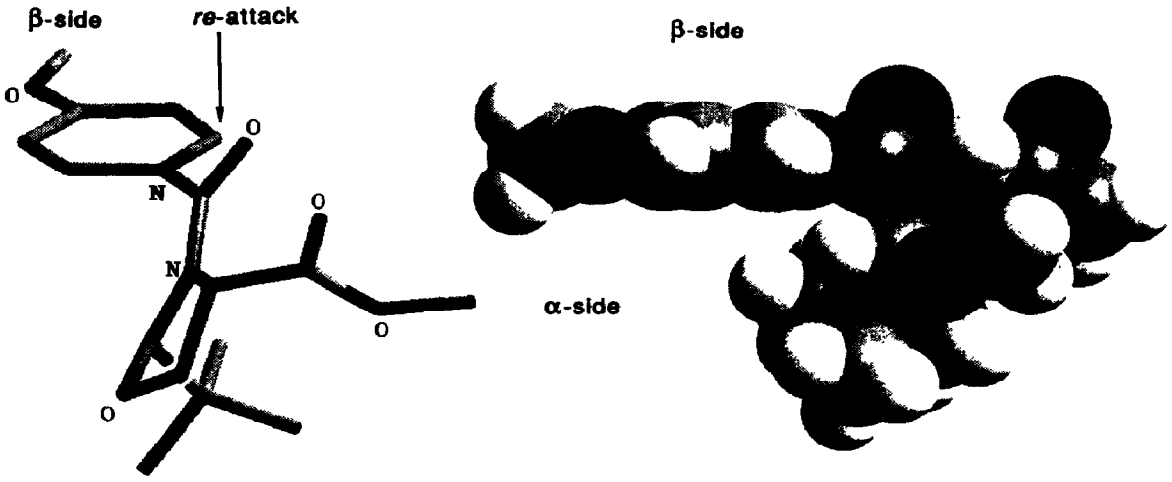


Figure 1. Minimun energy conformation of pyridinium salt 7 according to the Molecular Simulations Cerius-Dreiding II program.

When **7** was reacted with PhMgBr α-phenylation occurred in moderate yield (69 %) but with high *d.e.* (*ca.* 92 % according to ^{1}H-NMR). The reason why such pronounced diastereoselections are obtained in the absence of any trialkylsilyl group may have to do with chelate control. Molecular modeling of pyridinium salt **7**, using the Molecular Simulations Cerius-Dreiding II program led to the minimum energy conformation as indicated in *Figure 1*, the dihedral angle between the urea carbonyl and the pyridinium ring being *ca.* 60°. If we assume chelation control to operate, the urea carbonyl tethering MeMgI or PhMgBr, then (2*R*) configuration

follows as indicated in **8** for the methylated product. Comins had proposed a similar interpretation in one instance : reaction of (triphenylsilyl) magnesium bromide with a type **7** 4-methoxypyridinium salt (R* = (-)-8-phenylmenthyl) - *i.e.* a pyridinium salt which was devoid of the trialkylsilyl group - led to a pronounced *d.e.* (96 %) too. As a working model for this "peculiar mechanism" Comins proposed chelate control which he derived from molecular mechanics (MMX).[14] Let us be more explicit about the postulated *chelate control* : in the absence of a bulky SiR_3 group both C(2) and C(6) carbon atoms of **7** are prone to get alkylated from the least hindered β-side (*Figure 1*). If the alkylating agent becomes chelated to the urea carbonyl - which is obviously a better ligand than a urethane carbonyl - then it sits on top of carbon atom C(2), and adds to it according to a *re*-approach, leading thereby to **8**. Albeit the absolute configuration of the major phenyl-derivative is not known yet, we believe it is also formed according to the above described chelate-controled *re*-approach mechanism.[15]

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12. **Compound 6.** - ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) : 5.18 (s, H-C(2)) ; 4.89 (dd, J=8.1, 4.5, H-C(4)) ; 4.40 (dd, J=8.8, 4.5, Hβ-C(5)) ; 4.21 (dd, J=8.8, 8.1, Hα-C(5)) ; 3.81 (s, CO_2Me) ; 0.97 (s, $C(CH_3)_3$). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, 300 K) 169.0 ($C\,O_2CH_3$) ; 149.2 (NCOCl) ; 99.4 (C(2)) ; 68.2 (C(5)) ; 62.1 (C(4)) ; 52.8 (CO_2CH_3) ; 38.0 ($C(CH_3)_3$) ; 25.6 ($C(CH_3)_3$). Anal. calc. for $C_{10}H_{16}ClNO_4$ (249.69) : C 48.10, H 6.46, N 5.61, Cl 14.20 ; found : C 48.4, H 6.5, N 5.7, Cl 14.3.
Compound 8. - ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) : 7.99 (dd, J=8.1, 1.5, H-C(6)) ; 5.40 (s, H-C(2')) ; 5.30 (dd, J=8.1, 1.1, H-C(5)) ; 4.50 (m, H-C(2)) ; 4.47 (d, J=8.9, Hβ-C(5')) ; 4.26 (d, J=6.0, H-C(4')) ; 3.88 (dd, J=8.9, 6.0, Hα-C(5')) ; 3.79 (s, CO_2CH_3)) ; 2.79 (dd, J=16.7, 6.2, Hα-C(3)) ; 2.35 (ddd, J=16.7, 1.5, 1.1, Hβ-C(3)) ; 1.33 (d, J=6.6, CH_3-C(2)) ; 0.94 (s, $C(CH_3)_3$). Anal. calc. for $C_{16}H_{24}N_2O_5$ (324.38) : C 59.24, H 7.46, N 8.64 ; found : C 59.5, H 7.5, N 8.6.
Compound 9. - ^{1}H-NMR ($CDCl_3$, 250 MHz, 300K) : 7.15 (dd, J=7.4, 7.0, H-C(6)) ; 5.02 (d, J=7.4, H-C(5)) ; 4.92 (sbr, N-*H*) ; 3.80 (m, H-C(2)) ; 2.44 (dd, J=16.1, 5.8, Hβ-C(3)) ; 2.34 (dd, J=16.1, 12.4, Hα-C(3)) ; 1.31 (d, J=6.5, CH_3-C(2)). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, 300 K) : 193.1 (C(4)) ; 151.1 (C(6)) ; 99.0 (C(5)) ; 49.2 (C(2)) ; 44.0 (C(3)) ; 20.2 (CH_3-C(2)).
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15. This preliminary communication has been presented by one of us as part of a poster at the *Spring Meeting* of the *Royal Society of Chemistry Carbohydrate Group*, Exeter April 21, **1994**.

(*Received in France* 25 *March* 1994; *accepted* 8 *April* 1994)