4. Chelate-Controlled Asymmetric Synthesis of 2-Substituted 2,3-Dihydropyridin-4(1*H*)-ones: Synthesis of D- and L-Aminodeoxyaltrose Derivatives

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Asymmetric methylation and phenylation of the chiral pyridinium salt **7**, as well as methylation of chiral pyridinium salt **18**, with *Grignard* reagents occurred in good yield and with good-to-excellent diastereoselectivities (*Schemes 2* and *3*, resp.). These results are best explained by assuming chelate control to govern the asymmetric alkylation/arylation process. The minimum-energy conformations of the out-of-plane twisted pyridinium salts **7** and **18**, as determined by the 'Molecular Simulations *Cerius-Dreiding* II' program, are in good agreement with the postulated asymmetric chelate-control mechanism.

Introduction. – Type-**4** 2-substituted 1-acyl-1,2-dihydropyridines (R^1 = alkyl or aryl; *Scheme 1*) are useful intermediates for the preparation of natural products, such as piperidine [1], indolizine [2], quinolizidine [3], or *cis*-decahydroquinoline [4] alkaloids, and also of piperidine-carbohydrate derivatives [5]. Despite the obvious utility of asymmetric induction for the construction of such target molecules, almost no reports have appeared on the enantioselective synthesis of 2-substituted 1,2-dihydropyridines **4** prior to the extensive and fruitful investigations of *Comins* and coworkers [6][1])[2]). These authors showed that a large sterically blocking group at C(3) of a chiral pyridinium salt **1b** is essential for high diastereoselectivity during alkylation of C(6) with a *Grignard* reagent, the chiral auxiliary being attached to the pyridinium N-atom. They choose in particular 4-methoxy-3-(triisopropylsilyl)pyridine, treated it with (−)-8-phenylmenthyl chloroformate, and reacted the resulting pyridinium salt **1b** with a *Grignard* reagent to obtain a series of 6-alkylated dihydropyridines and thence the corresponding dihydropyridin-4(1*H*)-ones **2b** in high yield and high d.e. [9] (*Scheme 1*). Easy removal of trialkylsilane and of the chiral auxiliary, followed by *N*-protection with benzyl chloroformate, gave the chiral 2,3-dihydropyridin-4(1*H*)-ones **3b**. Eventually, reduction of these latter *N*-protected enones to the corresponding allylic alcohols, mesylation, and 1,2-elimination gave the enantiomerically pure 2-substituted 1,2-dihydropyridine derivatives **4b** (R^1 = alkyl or aryl; *Scheme 1*) [9].

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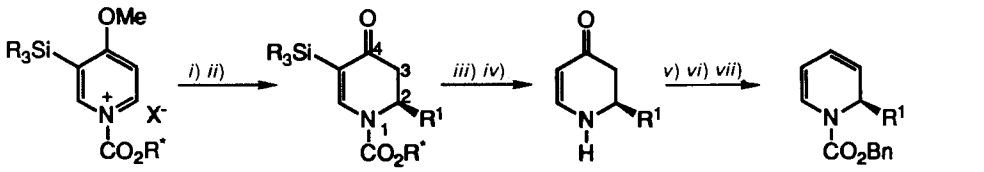
[1]) *Marazano et al.* reported the asymmetric cycloaddition of 2-unsubstituted 1,2-dihydropyridines which are *N*-substituted with a chiral auxiliary [7].

[2]) *Shono et al.* published an enantioselective synthesis of methyl 1,2-dihydropyridine-2-carboxylate from L-lysine [8].

Scheme 1



1a R = Me
b R = i-Pr

2a R = R¹ = Me
b R = i-Pr, R¹ = alkyl or aryl

3a R¹ = Me
b R¹ = alkyl or aryl

4a R¹ = Me
b R¹ = alkyl or aryl

R* = (1*R*,3*R*,4*S*)-8-phenylmenthyl

i) R^1MgX. *ii*) 10% HCl.
iii) NaOH. *iv*) Oxalic acid or CO_2. *v*) $ClCO_2Bn$. *vi*) $NaBH_4$, $CeCl_3$. *vii*) MsCl, DMAP.

In a previous publication, we reported the stereospecific synthesis of racemic 5-amino-1,5,6-trideoxyaltrose **15** from 2-methyl-1,2-dihydropyridine derivative (±)-**10** [5][3]). Since racemic azasugar **15** as well as some of its *N*-alkyl derivatives (*e.g.* R = Pr) proved to be potent α-fucosidase inhibitors[4]), it was of interest to prepare their D- and L-enantiomers for comparative α-fucosidase inhibitory assays.

We describe herein the asymmetric synthesis according to a *Comins* procedure [12], as well as a new chelate-controlled asymmetric synthesis, of (*R*)-2,3-dihydro-2-methylpyridin-4(1*H*)-one **9** and of *ent*-**9**. This latter procedure no longer required the bulky triisopropylsilyl group[5]); it led effectively to enantiomerically pure D-configurated **15** and **16**, as well as to their L-enantiomers, depending on the sense of chirality of the chiral auxiliary used, *i.e.*, L-serine or D-serine, respectively.

The *Comins* Approach to (*R*)-2,3-Dihydro-2-methylpyridin-4(1*H*)-one (9). – As depicted in *Scheme 1*, the advantage of *Comins'* method is threefold: *i*) the bulky triisopropylsilyl group at C(3) of **1b** prevents the *Grignard* reagent from approaching C(2) and forces it to attack specifically C(6); *ii*) the chiral auxiliary of **1b** – which in most cases is 8-phenylmenthyl – induces a highly diastereoselective alkylation at C(6); *iii*) the MeO group at C(4) is transformed after the alkylation process into a carbonyl group which permits removal of the chiral auxiliary (type-**2** compounds) without destruction of the newly created chiral center. Furthermore, the MeO group prevents alkylation from occurring at C(4).

To have reference compound **3a** at hand (*i.e.* **9**), we used *Comins'* approach with $SiMe_3$ instead of $Si(i\text{-}Pr)_3$ as a blocking handle. Thus, 4-methoxy-3-(trimethylsilyl)pyridine was treated [14] [15] with (−)-8-phenylmenthyl chloroformate in toluene and gave pyridinium salt **1a** which was not isolated. To this toluene solution kept at −78° was added MeMgI in a minimum amount of Et_2O. The reaction led in good yield and with

[3]) *Wong* and coworkers reported the synthesis of one of the enantiomers of **15** by a different route but without characterizing it [9] [10]. In a follow-up paper, where *Wong* discussed L-glucosidase inhibitors, compound **15** is missing [11].

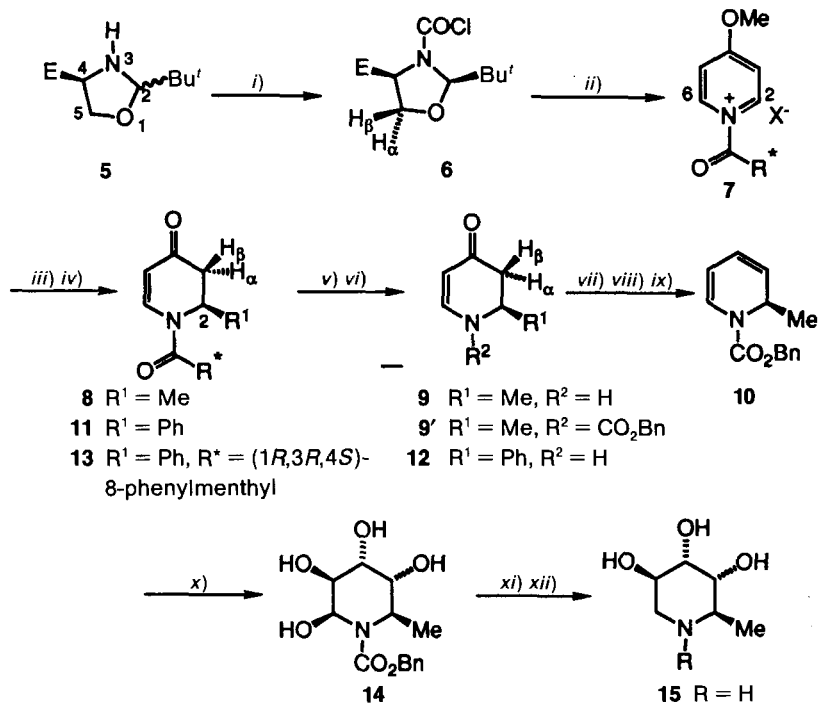
[4]) *B. Winchester*, Institute of Child Health, University of London: unpublished results concerning the percentage inhibition at 1 mM for human liver L-fucosidase, *i.e.*, for (±)-**15**·HCl 75% and for (±)-**16** 73%.

[5]) For a preliminary communication, see [13].

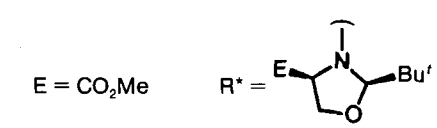
moderate diastereoisomeric excess (d.e. *ca.* 58% according to ^{1}H-NMR) to **2a** as the major diastereoisomer whose absolute configuration (2*R*) was ascertained by X-ray analysis (see below). Sequential reaction of **2a** with NaOH in MeOH, then with CO_2, gave dihydropyridinone **3a** which appeared as a single peak in a HPLC analysis using a chiral column (see *Exper. Part*).

Chelate-Controlled Asymmetric Synthesis of 5-Amino-1,5,6-trideoxy-D-altrose 15 Using a *Seebach* Oxazolidine Chiral Auxiliary[5]). – To circumvent the attachment – and subsequent removal – of a trialkylsilyl blocking group, we devised a chelate-controlled asymmetric alkylation of a chiral 4-methoxypyridinium salt, as follows. Oxazolidine **5** was prepared from L-serine and pivaldehyde as a diastereoisomer mixture (ratio *ca.* 1:1) according to *Seebach*'s procedure [16–18]. Reaction of **5** with phosgene led to two diastereoisomers (ratio *ca.* 98:2) from which optically pure **6** was isolated in high yield (91%) after a single crystallization. ^{1}H-NMR Nuclear *Overhauser* effect measurements demonstrated that **6** was the *cis*-compound, a result which had also been observed by *Seebach* with the *N*-formyl analogue of **6** [18]. Treatment of 4-methoxypyridine with **6** led

Scheme 2



i) $COCl_2$, toluene, recrystallization. *ii*) 4-Methoxypyridine, NaI, toluene. *iii*) MeMgI, toluene. *iv*) 10% HCl, recrystallization. *v*) 50% HCl, H_2O. *vi*) NaOH, H_2O. *vii*) BuLi, $ClCO_2Bn$, THF. *viii*) $NaBH_4$, $CeCl_3$, MeOH. *ix*) MsCl, DMAP, CH_2Cl_2. *x*) OsO_4, NMO, acetone/H_2O 9:1. *xi*) H_2, Pd/C, MeOH. *xii*) H_2, Pd/C, $MeCH_2CHO$, MeOH.



to pyridinium salt **7** which when treated with MeMgI, then with HCl, gave crude dihydropyridinone **8** having a d.e. of 95% (according to HPLC). A single recrystallization afforded enantiomerically pure **8** in 74% yield. Acid hydrolysis of **8** led to removal of pivaldehyde. At pH 11, the resulting intermediate, which was not isolated, underwent intramolecular cleavage of the urea functionality leading thereby to enantiomerically pure dihydropyridone **9** (*Scheme 2*). This latter compound was identical with **3a** as obtained according to the *Comins* procedure (see above), *i.e.* **9** had (2*R*)-configuration.

Reaction of **9** with BuLi, then with benzyl chloroformate, followed by reduction ($NaBH_4/CeCl_3$) to the allylic alcohols, mesylation, and elimination (MsCl, 4-(dimethylamino)pyridine (DMAP)), led to enantiomerically pure 1,2-dihydropyridine **10** in 71% overall yield. Catalytic double osmylation of **10** in the presence of *N*-methylmorpholine *N*-oxide (NMO) as described previously [5] gave, with total stereoselection, the D-piperidinose derivative **14** in good yield. Hydrogenolysis (H_2, Pd/C) of this aminoaltrose derivative led in excellent yield to the corresponding piperidine-triol **15**. *Fleet et al.* having observed a marked enhancement of the glycosidase inhibitory effect when DNJ was *N*-alkylated [19], we prepared the *N*-propyl derivative **16** using a one-pot procedure (propanal, H_2, Pd/C, traces of acid) as performed with **14**.

A second series of 'mirror-image' experiments were performed with D-serine as the chiral auxiliary. They led to *ent*-**9**, *ent*-**14**, and eventually to *ent*-**15** and *ent*-**16** (see *Exper. Part*).

When **7** was treated with PhMgBr, α-phenylation occurred in moderate yield (69%), but again with high d.e. as determined for dihydropyridinone **11** (*ca.* 92%, according to ^{1}H-NMR). This result again points to chelate control during the arylation step of pyridinium salt **7**. Enantiomerically pure **11** was obtained by recrystallization but was not amenable to X-ray diffraction analysis. Therefore, the chiral oxazolidine auxiliary was removed and replaced by 8-phenylmenthyl *via* reaction of **9** with phenylmenthyl chloroformate. X-Ray analysis of the resulting chiral and crystalline compound **13** permitted to assign the (2*S*)-configuration to it, as indicated in *Scheme 2* (see below)[6]).

X-Ray Structure Analyses of 2a and 13. – The absolute configuration of the major adducts **8** and **11** was determined by X-ray analysis of the corresponding 8-phenylmenthyl derivatives **2a** and **13**, respectively. The structures of **2a** and **13** as obtained by X-ray analysis are shown in *Fig. 1*. Crystal data and parameters of the data collection are compiled in the *Table*.

Unit-cell parameters were determined by accurate centering of 25 strong independent reflections by the least-squares method. Reflection intensities were collected at room temperature on a four-cycle diffractometer *Enraf-Nonius CAD4* equipped with a graphite monochromator and using CuK_α radiation. Three standard reflections monitored every h during data collection showed no intensity loss. The usual corrections were applied. Diffraction absorption correction was determined by ψ scans. The structures were solved by direct-method strategies using the program SIR92 [20]. Anisotropic least-squares full-matrix refinement was carried out on all non-H-atoms using the program CRYSTALS [21]. Scattering factors were taken from 'International Tables of Crystallography, Vol. VI.' Fractional coordinates are deposited in the *Cambridge Crystallographic Data Base*.

Chelate Control and Molecular Mechanics. – In one instance, *Comins* and coworkers had also proposed a chelate-control mechanism [6a]. During the reaction of (triphenylsilyl)magnesium bromide with a type-7 4-methoxypyridinium salt (R* = (1*R*,3*R*,4*S*)-

[6]) Albeit the *Cahn-Ingold-Prelog* notation is (2*R*) for **8** (R^1 = Me) and (2*S*) for **11** (R^1 = Ph), the overall topology is the same, since these two products result both from a *re*-attack.

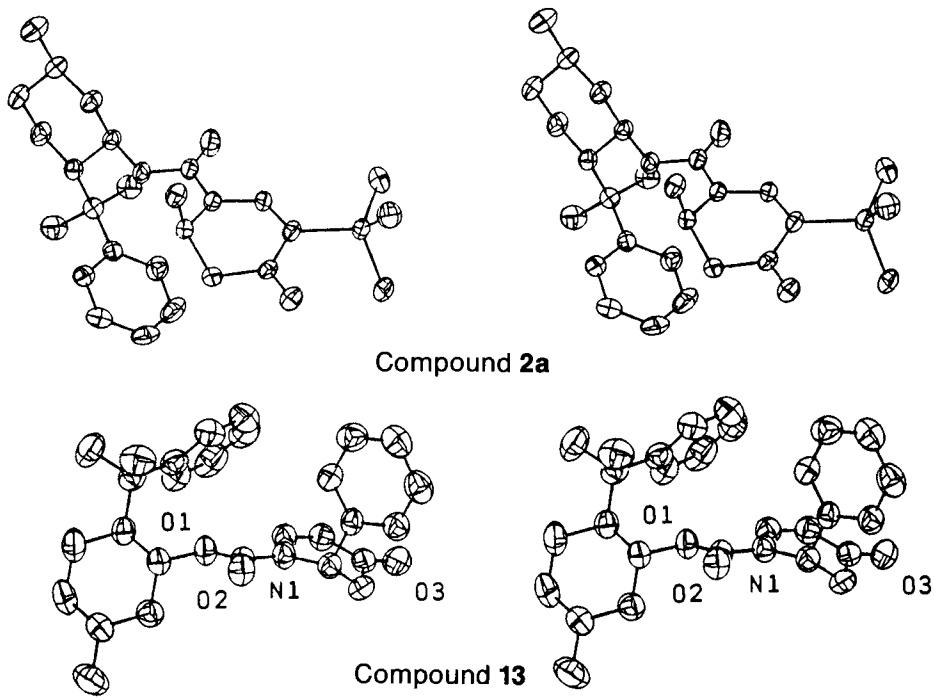


Fig. 1. *Stereoviews of compounds* **2a** *and* **13**. C–H Bonds not represented.

Table. *Crystal Data and Parameters of the Data Collection for* **2a** *and* **13**

	2a	**13**
Molecular formula	$C_{26}H_{39}NO_3Si$	$C_{28}H_{33}NO_3$
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a [Å]	10.314(1)	7.976(1)
b [Å]	9.698(1)	14.477(1)
c [Å]	13.820(1)	21.045(2)
α [°]	90	90
β [°]	109.503(6)	90
γ [°]	90	90
V [Å^3]	1303.01(17)	2430.05(50)
Z	2	4
Crystal dimensions [mm]	0.30·0.54·0.58	0.34·0.44·0.44
Temperature [K]	293	293
Θ_{max}	74.33	74.33
Radiation	CuK_α, λ = 1.54178 Å	CuK_α, λ = 1.54178 Å
Scan type	$\omega/2\Theta$	$\omega/2\Theta$
No. of independent refl.	2822	2813
No. of refl. in refinement	2698	2559
No. of variables	280	289
Final R	3.17	3.24
Final R_w	3.85	4.19
Weighting scheme	weight·[1-($\Delta F/6\sigma F$)^2]^2	weight·[1-($\Delta F/6\sigma F$)^2]^2

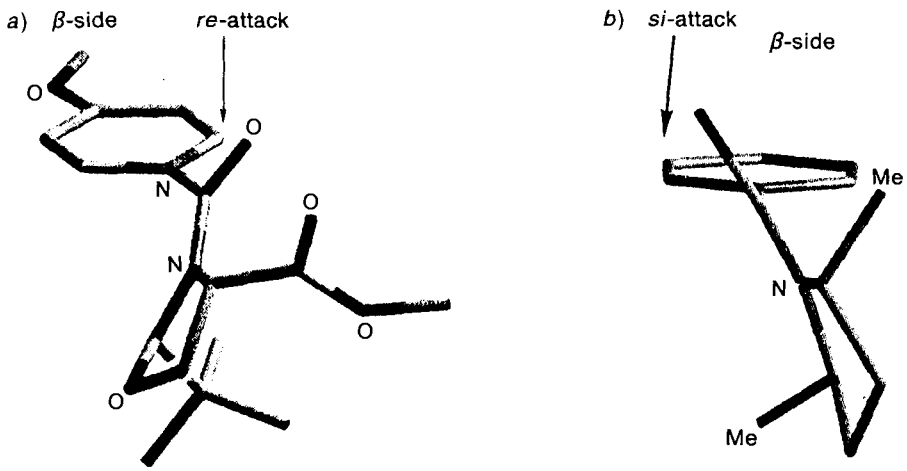


Fig. 2. *Minimum-energy conformations:* a) *of pyridinium salt* **7** *and* b) *of pyridinium salt* **18**, *according to the 'Molecular Simultations* Cerius-Dreiding *II' program.* C–H Bonds not represented.

8-phenylmenthyl), *i.e.*, with a pyridinium salt which was devoid of the trialkylsilyl group, they observed a pronounced d.e. (96%). As a working model for this 'peculiar mechanism', *Comins* and *Killpack* proposed chelate control which they derived from molecular mechanics (MMX) [6a].

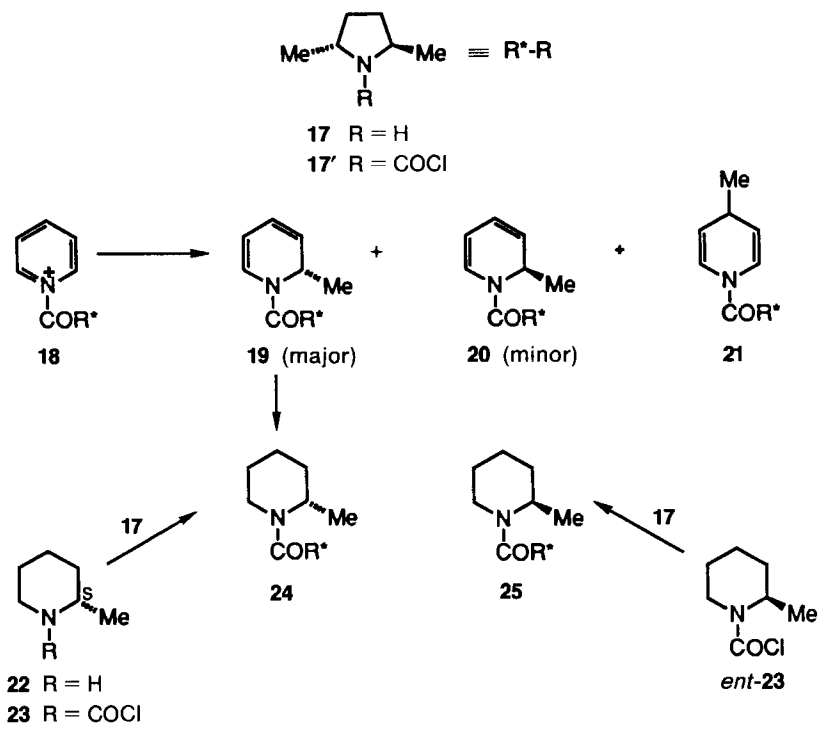
In our opinion, the pronounced diastereoselective methylation and phenylation which we observed in the absence of any trialkylsilyl group can only be explained by postulating asymmetric chelate control. The *Grignard* reagent MeMgI (or PhMgBr) is chelated – by the carbonyl group of the urea moiety of pyridinium salt **7** – so that methylation (or phenylation) occurs according to a *re*-attack, leading thereby to **8** or to **11**. This obviously requires a proper orientation of the chiral auxiliary, as achieved by chelation.

Whether asymmetric chelate-controlled alkylation (arylation) of type-**7** pyridinium salts is a general phenomenon remains an open question: to the best of our knowledge, scope and limitations of such asymmetric syntheses have not been studied so far, with the exception of the above cited example [6a]. We tend to believe that the urea carbonyl group of type-**7** pyridinium salts is a better ligand than the urethane carbonyl group of type-**1a** pyridinium salts (R* = (1*R*,3*R*,4*S*)-8-phenylmenthyl).

Molecular modeling of pyridinium salt **7** using the 'Molecular Simulations *Cerius-Dreiding* II' program led to the minimum-energy conformation as indicated in *Fig. 2a*, the dihedral angle between the urea carbonyl group and the pyridinium ring being *ca.* 60°. If we assume chelation control to operate, the urea carbonyl group tethering MeMgI (or PhMgBr), then *re*-alkylation from the β-side takes place at C(2) leading thereby to the (2*R*)-configuration for methylation ((2*S*) for phenylation!).

A Further Example of Asymmetric Chelate-Controlled α-Methylation. – It seemed worthwhile to investigate whether asymmetric chelate control would still be operating in the absence of any substituent at C(4) of the pyridinium ring, and whether there would be any competition between α- and γ-methylation of this latter one. For that reason,

Scheme 3



(2*R*,5*R*)-2,5-dimethylpyrrolidine (**17**) [22] was treated with phosgene (→**17'**) and then with pyridine in the presence of NaI, whereby pyridinium salt **18** was formed in good yield but was not isolated. A suspension of **18** in anhydrous Et_2O was treated with MeMgI which led to a mixture of the two α-methyl-substituted dihydropyridine derivatives **19** and **20** in a ratio of *ca.* 99:1 (^{1}H-NMR) and in 75% overall yield, as well as to the γ-adduct **21** in 3% yield. Clearly, α-methylation outweights γ-methylation by a factor of 25:1. These results again are in excellent agreement with the above postulated asymmetric chelate-controlled methylation mechanism.

The absolute configuration of **19** was shown to be (2*S*) by chemical correlation with (+)-α-pipecoline (**22**) which is known to be (2*S*) [23]. Exhaustive catalytic hydrogenation of the major adduct **19** gave α-pipecoline derivative **24**. This same compound **24** was also obtained by reacting pyrrolidine **17** with the *N*-chloroformyl derivative **23** of **22**. Furthermore, the ^{1}H-NMR spectra of **24** – as obtained by both methods, *i.e.*, either from **19** or from **22** – were identical (see *Exper. Part*). The minor adduct **20** which was formed in trace amounts could not be obtained pure so that a similar chemical correlation with *ent*-**22** *via* **25** could not be achieved. The ^{1}H-NMR spectrum of product **25**, as obtained from *ent*-**22** *via ent*-**23**, was different from that of **24**. Most important: the ^{1}H-NMR spectrum of minor adduct **20** is different from that of the major isomer **19**.

The 'Molecular Simulations *Cerius-Dreiding* II' program, as applied to the chiral salt **18** led to the minimum-energy conformation as indicated in *Fig. 2b*. Assuming chelate

control to operate, then *si*-methylation takes place from the β-face and leads to a (2*S*)-configuration, *i.e.*, to compound **19**.

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Experimental Part

General. Flash chromatography (FC): silica gel (*Merck 60*, 230–400 mesh). TLC: Al sheets silica gel (*Merck 60*, F_{254}); detection by UV or by spraying with a 5% $H_3[P(Mo_3O_{10})_4]$ soln. in EtOH followed by heating, or with a soln. of $KMnO_4$ (2 g) and Na_2CO_3 (4 g) in H_2O (100 ml) followed by heating. M.p.: *Kofler* hot bench or *Büchi-SMP-20* apparatus; corrected. $[\alpha]_D$ Values: *Schmidt-Haensch-Polartronic-Universal* polarimeter. IR Spectra (cm^{-1}): *Nicolet 205FT*. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AC-F250*, using double-irradiation techniques; $SiMe_4$ (^{1}H-NMR) and MeOH, $CDCl_3$ or C_6D_6 (δ = 49.0, 77.0, or resp. 128.0 ppm rel. to $SiMe_4$; ^{13}C-NMR) as internal references; δ in ppm and J in Hz; T 300K (if not specified otherwise). High-resolution (HR) MS: *MAT-311* spectrometer; measured at the University of Rennes. Microanalyses were carried out by the 'Service Central de Microanalyses' of the CNRS at Vernaison.

Glycolisation Catalyst. It was prepared according to [24] from OsO_4 (1 g) and *t*-BuOOH (1 ml) in *t*-BuOH (200 ml). This soln. contained *ca.* 0.02 mmol per ml.

(2R,1'R,2'S,5'R)-5'-Methyl-2'-(1-methyl-1-phenylethyl)cyclohexyl 1,2,3,4-Tetrahydro-2-methyl-4-oxo-5-(trimethylsilyl)pyridine-1-carboxylate (**2a**). To a stirred soln. of 4-methoxy-3-(trimethylsilyl)pyridine [16] (1.50 g, 8.27 mmol) in anh. toluene (30 ml) was added dropwise at −35° a soln. of phenylmenthyl chloroformate (2.41 g, 8.18 mmol) in toluene (15 ml). After 30 min, the stirred mixture was cooled to −78° and 2M MeMgI (5 ml, 10 mmol) in Et_2O was added dropwise. After 1 h, the temp. was raised to −20°, and 10% HCl soln. (50 ml) was added. The resulting mixture was extracted with Et_2O, and the org. extracts were washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The crude mixture of **2a** and its diastereoisomer (d.e. *ca.* 56% according to ^{1}H-NMR) was separated by FC (AcOEt/cyclohexane 1:15). Recrystallization gave **2a** as colorless crystals. M.p. 99–100.5° (MeOH). IR (KBr): 2967, 2954, 2920, 1728, 1653, 1579, 1321, 1302, 1249, 1222, 1110, 842. ^{1}H-NMR (C_6D_6, 333 K): 7.72 (br., H–C(6)); 7.20–6.80 (*m*, Ph); 4.98 (*td*, J = 10.8, 4.5, H–C(1')); 3.30 (br., H–C(2)); 2.40 (*dd*, J = 15.9, 6.7, H_α–C(3)); 1.96 (*dd*, J = 15.9, 1.6, H_β–C(3)); 2.10–0.70 (*m*, 17 H); 0.81 (*d*, J = 6.6, Me–C(2)); 0.31 (*s*, Me_3Si). ^{13}C-NMR ($CDCl_3$, 333 K): 196.0 (C(4)); 152.2 (C=O); 152.0, 128.2, 125.2, 125.2 (C of Ph); 145.3 (C(6)); 114.6 (C(5)); 48.3 (C(2)); 42.5 (C(3)); 16.9 (Me–C(2)); −1.3 (Me_3Si); 77.5, 50.9, 42.1, 39.6, 34.7, 31.5, 29.9, 26.6, 23.0, 21.7 (C of phenylmenthyl). Anal. calc. for $C_{26}H_{39}NO_3Si$ (441.68): C 70.70, H 8.90, N 3.17; found: C 70.5, H 8.9, N 3.2.

For the structure determination of **2a** by X-ray diffraction, see *General Part*.

(2R)-2,3-Dihydro-2-methylpyridin-4(1H)-one (**3a**, *i.e.* **9**). To a stirred soln. of **2a** (1.815 g, 4.12 mmol) in MeOH (50 ml) was added powdered NaOH (1.20 g, 30 mmol). After 30 min, the soln. was neutralized with dry ice (10 g). After another 30 min, some Et_2O was added, the suspension filtered, and the filtrate evaporated. The residue was taken up in Et_2O, filtered, and evaporated: (446 mg, 97%), optically pure (HPLC). Pale yellow oil. HPLC (*Daicel-Chiracel-OD* column, hexane/i-Pr_2O 95:5, detection at 300 nm): t_R of a 1:1 mixture 51.6 and 55.9 min. $[\alpha]_D^{20}$ = +462 (c = 1.4, $CHCl_3$). IR ($CHCl_3$): 3444, 3004, 1636, 1600, 1585, 1336, 1234, 1218, 669. ^{1}H-NMR ($CDCl_3$): 7.15 (*dd*, J = 7.4, 7.0, H–C(6)); 5.02 (*d*, J = 7.4, H–C(5)); 4.92 (br. *s*, NH); 3.80 (*dqd*, J = 12.4, 6.5, 5.8, H–C(2)); 2.44 (*dd*, J = 16.1, 5.8, H_α–C(3)); 2.34 (*dd*, J = 16.1, 12.4, H_β–C(3)); 1.31 (*d*, J = 6.5, Me–C(2)). ^{13}C-NMR ($CDCl_3$): 193.1 (C(4)); 151.1 (C(6)); 99.0 (C(5)); 49.2 (C(2)); 44.0 (C(3)); 20.2 (Me–C(2)).

*Methyl (2R,4S)-2-(*tert*-Butyl)-3-(chlorocarbonyl)-1,3-oxazolidine-4-carboxylate* (**6**). To a stirred soln. of oxazolidine **5** (17.36 g, 92.7 mmol; obtained from L-serine [18]) in CH_2Cl_2 (350 ml) kept at −15° was added dropwise 1.93M $COCl_2$ in toluene (72 ml, 139 mmol). Et_3N (16.8 ml, 120 mmol) was added dropwise and the mixture left to warm up to r.t. After 2 h, N_2 was bubbled through the mixture to remove excess $COCl_2$. The solvents were evaporated, and the residue was filtred through a silica-gel column (AcOEt/cyclohexane 3:7) whereby **6** was eluted (22.11 g; d.e. *ca.* 96% according to ^{1}H-NMR). After recrystallization in pentane, **6** was isolated as a single product (21.1 g, 91%). M.p. 76.5–77.5. $[\alpha]_D^{20}$ = −32 (c = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 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, H_β–C(5)); 4.21 (*dd*, J = 8.8, 8.1, H_α–C(5)); 3.81 (*s*, CO_2Me); 0.97 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 169.0 (CO_2Me); 149.2 (NCOCl); 99.4 (C(2)); 68.2 (C(5)); 62.1 (C(4)); 52.8 (CO_2Me); 38.0 (Me_3C); 25.6 (Me_3C). Anal. calc. for $C_{10}H_{16}ClNO_4$ (249.69): C 48.10, H 6.46, Cl 14.20, N 5.61; found: C 48.4, H 6.5, Cl 14.3, N 5.7.

ent-**6** was prepared in a similar way as **6**, starting from *ent*-**5** (11.47 g, 61.2 mmol; as obtained from D-serine). Recrystallization in pentane gave 12.45 g (81%). M.p. 77–78°. $[\alpha]_D^{20} = +32$ (c = 1.0, $CHCl_3$). ^{1}H- and ^{13}C-NMR: identical to those of **6**.

*Methyl (2*R,*2*′R,*4*S*)-3-(*tert-*Butyl)-3-[(1′,2′,3′,4′-tetrahydro-2′-methyl-4′-oxopyridin-1′-yl)carbonyl]-1,3-oxazolidine-4-carboxylate* (**8**). To a stirred soln. of **6** (7.50 g, 30 mmol) and anh. NaI (9.0 g, 60 mmol) as a suspension in anh. toluene (120 ml), 4-methoxypyridine (3.28 g, 30 mmol) was added under Ar and the mixture left to react for 5 d at r.t. The resulting soln. was diluted with anh. toluene (380 ml) and cooled to 0°. To this slightly heterogeneous soln. was added dropwise 2M MeMgI in anh. Et_2O until complete disappearance of salt **7** (as monitored by NMR). After 1 h, the mixture was left to warm up to r.t. After another 30 min, 10% HCl soln. (120 ml) was added and the aq. phase extracted with Et_2O (3 × 100 ml). The combined org. phase was washed with sat. NaCl soln. (2 × 50 ml), dried ($MgSO_4$), and evaporated. HPLC (*Daicel-Chiracel-OD* column, hexane/i-PrOH 9:1, detection at 300 nm): ratio of the specially prepared 1:1 diastereoisomer mixture, 845:869; t_R 17.3 (**8**) and 20.4 (minor stereoisomer) min; d.e. 95%. Recrystallization from i-Pr_2O led to pure **8**. The mother liquors were purified by FC (AcOEt/cyclohexane 1:1) and recrystallized (i-Pr_2O) to give a 2nd crop of **8**. Total yield: 7.20 g (74%). M.p. 157.5–159°. $[\alpha]_D^{20} = -364$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 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 (*qd*, J = 6.6, 6.2, H–C(2′)); 4.47 (*d*, J = 8.9, H_β–C(5)); 4.26 (*d*, J = 6.0, H–C(4)); 3.88 (*dd*, J = 8.9, 6.0, H_α–C(5)); 3.79 (*s*, CO_2Me); 2.79 (*dd*, J = 16.7, 6.2, H_α–C(3′)); 2.35 (*ddd*, J = 16.7, 1.5, 1.1, H_β–C(3′)); 1.33 (*d*, J = 6.6, Me–C(2′)); 0.94 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 193.5 (C(4′)); 170.0 (CO_2Me); 159.8 (NCON); 143.1 (C(6′)); 106.7 (C(5′)); 98.2 (C(2)); 69.9 (C(5)); 63.4 (C(4)); 52.9 (CO_2Me); 51.0 (C(2′)); 43.0 (C(3′)); 35.5 (Me_3C); 25.4 (Me_3C); 15.7 (Me–C(2′)). 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.

ent-**8** was prepared in a similar way as **8**, starting from *ent*-**6** (4.00 g, 16.0 mmol). Recrystallization in i-Pr_2O: 1.95 g (40%). Colorless compound. M.p. 158–159°: $[\alpha]_D^{20} = +352$ (c = 1.0, $CHCl_3$). ^{1}H- and ^{13}C-NMR: identical to those of **8**.

*(2*R*)-2,3-Dihydro-2-methylpyridin-4(1*H*)-one* (**9**, *i.e.* **3a**). A suspension of **8** (5.49 g, 16.9 mmol) in 50% HCl soln. (60 ml) was stirred overnight at r.t. (→homogeneous soln.). After evaporation of HCl and H_2O *i.v.*, H_2O (30 ml) and some pellets of NaOH were added until pH 12 was reached. After 2 h, the mixture was neutralized with conc. HCl soln. and extracted with CH_2Cl_2 (6 × 50 ml). The org. phase was dried ($MgSO_4$) and evaporated: **9** (1.85 g, 98%). Yellow oil. $[\alpha]_D^{20} = +495$ (c = 1.4, $CHCl_3$). IR and ^{1}H- and ^{13}C-NMR: identical to those of **3a**.

ent-**9** was prepared in a similar way as **9**, starting from *ent*-**8** (3.00 g, 9.25 mmol): 960 mg (93%). Yellow oil $[\alpha]_D^{20} = -487$ (c = 1.3, $CHCl_3$). ^{1}H- and ^{13}C-NMR: identical to those of **9**.

*(2*R*)-Benzyl 1,2,3,4-Tetrahydro-2-methyl-4-oxopyridine-1-carboxylate* (**9′**). To a stirred soln. of **9** (446 mg, 4.01 mmol) in anh. THF (20 ml) kept at −78° was added a soln. of BuLi in hexane (3.0 ml, 4.8 mmol). After 15 min, benzyl chloroformate (0.73 ml, 5.2 mmol) was added and the mixture left to warm up to r.t. After addition of H_2O (20 ml), the mixture was extracted with Et_2O, and the org. phases were washed with brine, dried ($MgSO_4$), and evaporated: **9′** (920 mg, 93%). Oil. $[\alpha]_D^{20} = -104$ (c = 1.65, $CHCl_3$). IR ($CHCl_3$): 3011, 1725, 1667, 1605, 1334, 1321, 1271, 1234, 1220, 1195, 1064, 753, 732, 668. ^{1}H-NMR ($CDCl_3$): 7.74 (*d*, J = 7.9, H–C(6)); 7.39 (*m*, Ph); 5.33 (*dd*, J = 7.9, 1.3, H–C(5)); 5.31, 5.25 (*AB*, J = 10.7, PhCH_2); 4.73 (*quint. d*, J = 6.7, 1.4, H–C(2)); 2.85 (*dd*, J = 16.4, 6.7, H_β–C(3)); 2.32 (*ddd*, J = 16.4, 1.4, 1.3, H_α–C(3)); 1.26 (*d*, J = 6.7, Me–C(2)). ^{13}C-NMR ($CDCl_3$): 192.8 (C(4)); 152.2 (C=O); 141.1 (C(6)); 134.9, 128.8, 128.7, 128.4 (C of Ph); 106.7 (C(5)); 68.9 (Ph CH_2); 49.2 (C(2)); 41.7 (C(3)); 16.6 (Me–C(2)). Anal. calc. for $C_{14}H_{15}NO_3$ (245.28): C 68.55, H 6.17, N 5.71; found: C 68.4, H 6.4, N 5.5.

ent-**9′** was prepared in a similar way as **9′**, starting from *ent*-**9** (1.021 g, 9.18 mmol): 1.75 g (78%). Oil. $[\alpha]_D^{20} = +103$ (c = 1.6, $CHCl_3$). ^{1}H- and ^{13}C-NMR: identical to those of **9′**.

*(2*R*)-Benzyl 1,2-Dihydro-2-methylpyridine-1-carboxylate* (**10**). To a stirred soln. of **9′** (920 mg, 3.76 mmol) in MeOH (30 ml) kept at 0° was added $CeCl_3 \cdot 7\,H_2O$ (1.49 g, 4.01 mmol). After 30 min, $NaBH_4$ (230 mg, 6.0 mmol) was added portionwise and the mixture left to warm up to r.t. After 1 h, H_2O was added (20 ml), the soln. extracted with Et_2O, and the org. layer dried ($MgSO_4$) and evaporated. The crude residue was purified by FC (AcOEt/cyclohexane 3:7): oily mixture of the allylic alcohols (701 mg, 75%) which was not characterized. To a stirred soln. of these alcohols (681 mg, 2.83 mmol) in anh. CH_2Cl_2 (30 ml) kept at 0° were added 5 ml of *Furukawas'* reagent (MsCl, (1.15 g, 10 mmol), DMAP (610 mg, 5 mmol), H_2O (72 mg, 4 mmol) in CH_2Cl_2 (13 ml)) [25]. The mixture was left to warm up to r.t. After 1 h, aq. Na_2CO_3 soln. was added, the mixture extracted twice with Et_2O, the org. phase dried

($MgSO_4$) and evaporated and the residue purified by FC (AcOEt/cyclohexane 2:8): **10** (473 mg, 73%). Yellow oil. $[\alpha]_D^{20} = -546$ ($c = 0.61$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 330 K): 7.38–7.33 (*m*, Ph); 6.69 (*d*, $J = 7.6$, H–C(6)); 5.84 (*dd*, $J = 9.6, 5.4$, H–C(4)); 5.52 (*dd*, $J = 9.6, 5.6$, H–C(3)); 5.21 (*AB*, PhCH_2); 5.17 (*dd*, $J = 7.6, 5.4$, H–C(5)); 4.85 (*qd*, $J = 6.6, 5.6$, H–C(2)); 1.16 (*d*, $J = 6.6$, Me–C(2)). ^{13}C-NMR ($CDCl_3$, 330 K): 153.5 (C=O); 136.3, 128.6, 128.2, 128.0 (C of Ph); 124.6 (C(6)); 124.0 (C(5)); 120.6 (C(3)); 105.3 (C(4)); 67.7 (CH_2); 48.7 (C(2); 19.1 (*Me*–C(2)).

ent-**10** was prepared in a similar way as **10**, starting from *ent*-**9′** (730 mg, 2.97 mmol): 375 mg (55%). Yellow oil. $[\alpha]_D^{20} = +588$ ($c = 0.6$, $CHCl_3$). ^{1}H- and ^{13}C-NMR: identical to those of **10**.

*(2*R*,2′*R*,4*S*)-Methyl 2-(*tert*-Butyl)-3′-[(1′,2′,3′,4′-tetrahydro-4′-oxo-2′-phenylpyridin-1′-yl)carbonyl]-1,3-oxazolidine-4-carboxylate* (**11**). As described for **8**, with **6** (287 mg, 1.15 mmol), NaI (345 mg, 2.3 mmol), 4-methoxypyridine (125 mg, 1.15 mmol), and 0.9M PhMgBr in Et_2O (1.55 ml, 1.38 mmol). ^{1}H-NMR: 92% d.e. FC (AcOEt/cyclohexane 5:5) and recrystallization in i-Pr_2O gave **11** (305 mg, 69%). Colorless crystals. M.p. 153–154.5°. $[\alpha]_D^{20} = -289$ ($c = 1.0$, $CHCl_3$). IR (KBr): 1749, 1675, 1661, 1594, 1365, 1345, 1298, 1199. ^{1}H-NMR ($CDCl_3$): 8.21 (*dd*, $J = 8.2$, 1.6, H–C(6′)); 7.30–7.17 (*m*, Ph); 5.64 (*ddd*, $J = 6.2$, 2.1, 1.6, H–C(2′)); 5.44 (*s*, H–C(2)); 5.32 (*dd*, $J = 8.2$, 1.3, H–C(5′)); 4.48 (*d*, $J = 9.0$, H_β–C(5)); 4.30 (*d*, $J = 6.1$, H–C(4)); 3.89 (*dd*, $J = 9.0, 6.1$, H_α–C(5)); 3.77 (*s*, CO_2Me); 3.04 (*dd*, $J = 16.8, 6.2$, H_α–C(3′)); 2.94 (*ddd*, $J = 16.8, 2.2, 1.3$, H_β–C(3′)); 0.93 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 192.2 (C(4′)); 170.4 (CO_2Me); 160.0 (NCON); 143.6 (C(6′)); 137.0, 128.7, 127.7, 126.2 (C of Ph); 108.7 (C(5′)); 98.5 (C(2)); 70.1 (C(5)); 63.4 (C(4)); 57.0 (C(2′)); 52.9 (COO*Me*); 42.8 (C(3′)); 35.5 (Me_3C); 25.5 (Me_3C). Anal. calc. for $C_{21}H_{26}N_2O_5$ (386.45): C 65.27, H 6.78, N 7.25; found: C 65.4, H 6.8, N 7.1.

*(2*R*)-2,3-Dihydro-2-phenylpyridin-4(1*H*)-one* (**12**). As described for **9**, with **11** (201.8 mg, 0.522 mmol): **12** (87.4 mg, 96%). Yellow oil. ^{1}H-NMR ($CDCl_3$): 7.40–7.27 (*m*, Ph); 7.27 (*dd*, $J = 7.4, 5.8$, H–C(6)); 5.30 (br. NH); 5.10 (*d*, $J = 7.4$, H–C(5)); 4.73 (*dd*, $J = 14.6, 5.0$, H–C(2)); 2.73 (*dd*, $J = 16.3, 14.6$, H_α–C(3)); 2.50 (*dd*, $J = 16.3, 5.0$, H_β–C(3)). ^{13}C-NMR ($CDCl_3$): 192.4 (C(4)); 151.2 (C(6)); 140.0, 129.1, 128.5, 126.6 (C of Ph); 99.8 (C(5)); 58.5 (C(2)); 44.6 (C(3)).

*(2*R*,1′R,2′S,5′R)-5′-Methyl-2′-(1-methyl-1-phenylethyl)cyclohexyl 1,2,3,4-Tetrahydro-4-oxo-2-phenylpyridine-1-carboxylate* (**13**). As described for **9′**, with **12** (72.3 mg, 0.42 mmol), THF (4 ml), BuLi (0.32 ml, 0.44 mmol), and 8-phenylmenthyl chloroformate (129 mg, 0.44 mmol). Recrystallization in i-Pr_2O gave **13** (138 mg, 76%). Colorless crystals. M.p. 181–182°. ^{1}H-NMR ((D_6)DMSO, 360 K): 7.40–7.15 (*m*, Ph); 7.03 (*dd*, $J = 8.3$, 1.5, H–C(6)); 5.07 (*dd*, $J = 8.3$, 1.3, H–C(5)); 4.72 (*td*, $J = 10.8, 4.3$, H–C(1′)); 4.55 (br., H–C(2)); 2.82 (*dd*, $J = 16.5, 7.7$, H_α–C(3)); 2.48 (*ddd*, $J = 16.5, 1.7, 1.3$, H_β–C(3)); 2.20–0.60 (*m*, 17 H). ^{13}C-NMR ($CDCl_3$, 333 K): 191.7 (C(4)); 152.0 (C=O); 152.8, 139.4, 128.6, 128.3, 127.8, 126.0, 125.2, 125.1 (C of Ph); 142.7 (C(6)); 107.1 (C(5)); 55.3 (C(2)); 41.9 (C(3)); 78.1, 50.7, 41.4, 39.4, 34.6, 31.4, 30.9, 26.4, 21.7, 21.6 (C from phenylmenthyl). For the structure determination of **13** by X-ray diffraction, see *General Part*.

*5-[(Benzyloxycarbonyl)amino]-5,6-dideoxy-β-*D*-altropyranose* (**14**). To a stirred soln. of **10** (450 mg, 1.96 mmol) in acetone/H_2O 9:1 (10 ml) kept at 0° were added sequentially NMO (582 mg, 4.32 mmol) and a catalytic OsO_4 soln. (1.5 ml). After 1 h at 0° and 20 h at r.t., the solvents were evaporated, and the residue was purified by FC (AcOEt, then AcOEt/MeOH 8:2): **14** (504 mg, 86%). Viscous oil. $[\alpha]_D^{20} = -36$ ($c = 5$, MeOH). IR ($CHCl_3$): 3547, 3457, 3290, 1693, 1399, 1335, 1315, 1098, 1038, 972, 788, 753, 699. ^{1}H-NMR (CD_3OD): 7.36–7.31 (*m*, Ph); 5.80 (*d*, $J = 4.1$, H–C(1)); 5.19, 5.09 (*AB*, $J = 12.4$, PhCH_2); 4.32 (*qd*, $J = 7.2, 2.0$, H–C(5)); 3.99 (*dd*, $J = 10.1, 3.0$, H–C(3)); 3.82 (*dd*, $J = 3.0, 2.0$, H–C(4)); 3.77 (*dd*, $J = 10.1, 4.1$, H–C(2)); 1.31 (*d*, $J = 7.2$, Me–C(5)). ^{13}C-NMR (CD_3OD): 157.8 (C=O); 137.9, 129.5, 129.1, 128.9 (C of Ph); 79.6 (C(1)); 74.2 (C(2)); 69.7 (C(4)); 68.6 (PhCH_2); 67.8 (C(3)); 55.7 (C(5)); 19.2 (C(6)). Anal. calc. for $C_{14}H_{19}NO_6$ (297.30): C 56.56, H 6.44, N 4.71; found: C 56.3, H 6.4, N 4.7.

ent-**14** was prepared in a similar way as **14**, starting from *ent*-**10** (740 mg, 3.92 mmol): 830 mg (86%). Yellow oil. $[\alpha]_D^{20} = +35$ ($c = 5$, MeOH). ^{1}H- and ^{13}C-NMR identical to those of **14**.

*(2*R*,3*R*,4*S*,5*R*)-2-Methylpiperidine-3,4,5-triol* (**15**). A stirred soln. of **14** (62 mg, 0.21 mmol) in EtOH (3 ml) containing 5% Pd/C (20 mg) was put under H_2 (1 atm) at r.t. After 1 h, the suspension was filtered over *Celite* and the solvent evaporated: **15** (30 mg, quant.). Oil. $[\alpha]_D^{20} = +2$ ($c = 1.1$, MeOH). **15**·HCl: ^{1}H-NMR (D_2O): 4.43 (*ddd*, $J = 4.8, 3.6, 2.3$, H–C(5)); 4.29 (*ddd*, $J = 4.8, 3.0, 0.9$, H–C(4)); 4.15 (*dd*, $J = 9.6, 3.0$, H–C(3)); 3.71 (*dq*, $J = 9.6, 6.7$, H–C(2)); 3.64 (*dd*, $J = 13.5, 2.3$, H_{ax}–C(6)); 3.47 (*ddd*, $J = 13.5, 3.6, 0.9$, H_{eq}–C(6)); 1.69 (*d*, $J = 6.7$, Me–C(2)). ^{13}C-NMR (CD_3OD): 70.4 (C(4)); 69.5 (C(3)); 68.0 (C(5)); 52.4 (C(2)); 45.8 (C(6)); 15.4 (*Me*–C(2)). HR-MS: 147.0898 ($C_6H_{13}NO_3^+$, calc. 147.08954).

ent-**15** was prepared in a similar way as **15**, starting from *ent*-**14** (250 mg, 0.84 mmol): 92 mg (75%). Oil. $[\alpha]_D^{20} = -2$ ($c = 1.1$, MeOH). ^{1}H- and ^{13}C-NMR: identical to those of **15**.

*(2*R*,3*R*,4*S*,5*R*)-2-Methyl-1-propylpiperidine-3,4,5-triol* (**16**). A stirred mixture of **14** (92 mg, 0.31 mmol), propanal (0.46 ml, 0.62 mmol) in MeOH (1 ml), and AcOH (1 drop) containing some 5% Pd/C catalyst (20 mg) was put under H_2 (1 atm). After 30 min, the suspension was filtered over *Celite* and the solvent evaporated. The residue

was separated by prep. TLC ($CHCl_3$/MeOH/28% NH_4OH soln. 8:2:0.2): **16** (38 mg, 66%). Viscous oil. $[\alpha]_D^{20} = -41$ ($c = 0.63$, MeOH). ^{1}H-NMR (CD_3OD): 3.77 (*td*, $J = 6.4$, 3.8, H–C(5)); 3.61 (*dd*, $J = 6.4$, 3.3, H–C(4)); 3.57 (*dd*, $J = 6.0$, 3.3, H–C(3)); 2.86 (*qd*, $J = 6.6$, 6.0, H–C(2)); 2.75 (*dd*, $J = 12.0$, 3.6, H_{eq}–C(6)); 2.51 (*m*, $MeCH_2CH_2$); 2.50 (*dd*, $J = 12.0$, 6.4, H_{ax}–C(6)); 1.50 (*m*, $MeCH_2CH_2$); 1.07 (*d*, $J = 6.6$, Me–C(2)); 0.89 (*t*, $J = 7.4$, $MeCH_2CH_2$). ^{13}C-NMR (CD_3OD): 70.3 (C(5)); 70.2 (C(3)); 67.8 (C(4)); 59.4 ($MeCH_2CH_2$); 55.6 (C(2)); 52.9 (C(6)); 17.8 (*Me*–C(2)); 12.0 ($MeCH_2CH_2$); 11.3 ($MeCH_2CH_2$). HR-MS: 189.1361 ($C_9H_{18}NO_3^+$, calc. 189.13648).

ent-**16** was prepared in a similar way as **16**, starting from *ent*-**14** (200 mg, 0.67 mmol): 80 mg (63%). Oil $[\alpha]_D^{20} = +35$ ($c = 0.72$, MeOH). ^{1}H- and ^{13}C-NMR: identical to those of **16**.

(2R,5R)-2,5-Dimethylpyrrolidine-1-carbonyl Chloride (**17′**). To a stirred soln. of **17** (423 mg, 3.12 mmol) [16] and ethyldiisopropylamine (1.1 ml, 2.2 equiv.) in CH_2Cl_2 (10 ml) kept at −20° was added dropwise the phosgene soln. in toluene (3.9 ml, 2.2 equiv.). The mixture was stirred for 2 d under Ar at r.t. Then N_2 was blown through to remove excess $COCl_2$. The soln. was evaporated, the residue taken up in AcOEt/cyclohexane 1:1 (100 ml), and the resulting soln. filtered over a short silica-gel column. Evaporation of the solvents led to **17′** (460 mg, 91%). The colorless oil was used as such for the coupling reaction with pyridine (see below). ^{1}H-NMR ($CDCl_3$): 4.15 (*m*, H–C(2), H–C(5)); 2.22 (*m*, H–C(3), H–C(4)); 1.62 (*m*, H–C(3), H–C(4)); 1.30 (*d*, $J = 6.4$, Me); 1.24 (*d*, $J = 6.4$, Me). ^{13}C-NMR ($CDCl_3$): 145.8, 57.6, 56.2, 29.9, 29.6, 20.6, 18.6.

1-[(2R,5R)-2,5-Dimethylpyrrolidine-1-carbonyl]pyridinium Halide (**18**·Hal$^-$). A soln. of **17′** (460 mg, 2.85 mmol) and NaI (427 mg, 1 equiv.) in pyridine (1 ml, 4.3 equiv.) was stirred at 0° for 1 d under Ar. Excess pyridine was evaporated. The residue contained **18**·Hal$^-$ (*ca.* 92%) and some unreacted **17′** (*ca.* 8%) according to ^{1}H-NMR. ^{1}H-NMR (CD_3OD) of **18**: 9.41 (*m*, 2 H_o of py); 8.87 (*m*, H_p of py); 8.31 (*m*, 2 H_m of py); 4.41, 4.09 (2 br. *s*, H–C(2), H–C(5)); 2.36, 1.73 (2 br. *s*, H–C(3), H–C(4)); 1.41, 0.80 (2 br. *s*, Me–C(2), Me–C(5)).

(2S,2′R,5′R)- and (2R,2′R,5′R)-1-(2′,5′-Dimethylpyrrolidine-1′-carbonyl)-1,2-dihydro-2-methylpyridine (**19** and **20**, resp.) *and (2′R,5′R)-(2′,5′-Dimethylpyrrolidine-1′-carbonyl)-1,4-dihydro-4-methylpyridine* (**21**). To a stirred suspension of **18**·Hal (*ca.* 420 mg; see above) in anh. Et_2O (2 ml) kept at 0° under Ar was added dropwise 3.14M MeMgI in Et_2O (1.4 ml, 1.5 equiv.). After 1 h at r.t., the mixture was washed with brine, extracted with AcOEt, and the combined org. phase dried ($MgSO_4$) and evaporated. ^{1}H-NMR of the residue: **19**/**20** *ca.* 99:1 and **21** (*ca.* 3%). FC (AcOEt/cyclohexane 5:95) led to **21** (20 mg, 3%) and to **19**/**20** (470 mg, 75%). A 2nd FC (AcOEt/cyclohexane 3:97) gave pure **19**. Very viscous oil. $[\alpha]_D^{20} = +995$ ($c = 0.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 6.24 (*dq*, $J = 7.4$, 1.1, H–C(6)); 5.88 (br. *dd*, $J = 9.4$, 5.2, H–C(4)); 5.59 (*ddt*, $J = 9.4$, 6.2, 1.1, H–C(3)); 5.30 (*ddd*, $J = 7.4$, 5.2, 1.2, H–C(5)); 4.58 (*quint. d*, $J = 6.4$, 1.1, H–C(2)); 4.02 (*sext. m*, $J = 6.2$, H–C(2′), H–C(5′)); 2.06 (*m*, H–C(3′), H–C(4′)); 1.46 (*m*, H–C(3′), H–C(4′)); 1.19 (*d*, $J = 6.4$, Me–C(2)); 1.08 (*d*, $J = 6.2$, Me–C(2′), Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 157.5 (C=O); 126.9 (C(6)); 124.3 (C(3)); 121.2 (C(4)); 105.1 (C(5)); 55.2 (C(2′), C(5′)); 48.3 (C(2)); 32.2 (C(3′), C(4′)); 20.0 (*Me*–C(2′), Me–C(5′)); 18.0 (*Me*–C(2)). MS: 220 (12, M^+), 205 (20), 126 (100, $C_7H_{12}NO^+$), 83 (82). HR-MS: 220.1572 ($C_{13}H_{20}N_2O^+$, $M^{+\cdot}$, calc. 220.15755).

The minor adduct **20** was obtained enriched but could not be totally separated from **19**. **20**: ^{1}H-NMR ($CDCl_3$): 6.50 (*dm*, $J = 7.8$, H–C(6)); 5.79 (*ddt*, $J = 9.5$, 5.4, 1.1, H–C(4)); 5.36 (*ddt*, $J = 9.5$, 4.7, 1.2, H–C(3)); 4.97 (*ddd*, $J = 7.8$, 5.4, 1.3, H–C(5)); 4.93 (*qdd*, $J = 6.3$, 4.8, 1.4, H–C(2)); 4.02 (*m*, H–C(2′), H–C(5′)); 2.06 (*m*, H–C(3′), H–C(4′)); 1.46 (*m*, H–C(3′), H–C(4′)); 1.22 (*d*, $J = 6.3$, Me–C(2)); 1.19 (*d*, $J = 6.2$, Me–C(2′), Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 128.1 (C(6)); 123.1 (C(3)); 121.0 (C(4)); 100.8 (C(5)); 55.3 (C(2′), C(5′)); 49.6 (C(2)); 32.4 (C(3′), C(4′)); 20.9 (*Me*–C(2)); 20.2 (*Me*–C(2′), *Me*–C(5′)).

The 1,4-adduct **21** could not be obtained in a pure form either. ^{1}H-NMR: 6.47 (*dd*, H–C(2), H–C(6)); 4.74 (*m*, H–C(3), H–C(5)); 3.03 (*m*, H–C(4)); 1.13 (*d*, $J = 6.2$, Me–C(2′), Me–C(5′)); 1.09 (*d*, $J = 7.0$, Me–C(4)).

(2S,2′R,5′R)-1-(2′,5′-Dimethylpyrrolidine-1′-carbonyl)-2-methylpiperidine (**24**) *from* **19**. A stirred soln. of **19** (50 mg, 0.23 mmol) in 96% EtOH (3 ml) containing some 5% Pd/C (20 mg) was put under H_2 (1 atm) at r.t. After 5 h, the suspension was filtered over *Celite* and the solvent evaporated: **24** (48 mg, 95%). Colorless oil. $[\alpha]_D^{20} = +90$ ($c = 0.97$, $CHCl_3$). IR ($CHCl_3$): 1605, 1464, 1442, 1419, 1373. ^{1}H-NMR ($CDCl_3$): 4.04–3.88 (2*m*, H–C(2), H–C(2′), H–C(5′)); 3.61 (*dm*, $J = 14.1$, H–C(6)); 2.91 (*ddd*, $J = 14.1$, 9.3, 6.8, H–C(6)); 2.07 (*m*, H–C(3′), H–C(4′)); 1.65–1.40 (2*m*, H–C(3′), H–C(4′), 2 H–C(3), 2 H–C(4), 2 H–C(5)); 1.26 (*d*, $J = 6.9$, Me–C(2)); 1.08 (*d*, $J = 6.1$, Me–C(2′), Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 162.0 (C=O); 54.1 (C(2′), C(5′)); 49.0 (C(2)); 41.2 (C(6)); 31.3 (C(3′), C(4′)); 31.0 (C(3)); 25.4 (C(5)); 20.2 (*Me*–C(2′), *Me*–C(5′)); 19.7 (C(4)); 15.3 (*Me*–C(2)). MS: 224 (15, $M^{+\cdot}$), 126 (72), 98 (100). HR-MS: 224.1882 ($C_{13}H_{24}N_2O^+$, $M^{+\cdot}$, calc. 224.18885).

(2S)-2-Methylpiperidine-1-carbonyl Chloride (**23**). To a stirred soln. of (+)-(2*S*)-pipecoline (**22**) [26] (119 µl, 1 mmol) and Et_3N (145 µl, 1 mmol) in CH_2Cl_2 (7 ml) kept at −20° was added 1.9M phosgene in toluene (1 ml, 1.9 mmol) under Ar. After 20 h at r.t., N_2 was passed through the soln. to remove excess $COCl_2$, the mixture evaporated, the residue dissolved in AcOEt/cyclohexane 1:1 (100 ml), and the resulting soln. filtered over a silica-

gel column. Evaporation gave **23** (113 mg, 70%). Oil. ^{1}H-NMR ($CDCl_3$): 4.62 (*m*, H–C(2)); 4.17 (*dm*, H–C(6)); 3.07 (br. *s*, H–C(6)); 1.59 (*m*, H–C(3), H–C(4), H–C(5)); 1.25 (*d*, J = 7.0, Me–C(2)). ^{13}C-NMR ($CDCl_3$): 51.1 (C(2)); 43.0 (C(6)); 30.1 (C(3)); 25.5 (C(5)); 18.5 (C(4)); 16.0 (*Me*–C(2)).

ent-**23** was prepared in a similar way from (–)-(2*R*)-pipecoline (*ent*-**22**). ^{1}H- and ^{13}C-NMR: identical to those of **23**.

24 *from* **23**. To a stirred soln. of **17**·HCl (50 mg, 0.37 mmol) and 1,8-diazabicyclo[2.2.2]octane (DBU; 110 µl, 0.74 mmol) in CH_2Cl_2 (2 ml) under Ar at r.t., a soln. of **23** (54 mg, 0.37 mmol) and NaI (55 mg, 0.37 mmol) in CH_2Cl_2 (2 ml) was added dropwise. After 2 d, the soln. was evaporated and the residue purified by FC (AcOEt/cyclohexane 8:2): **24** (20 mg, 60%). Colorless oil. $[\alpha]_D^{20} = +88$ (c = 0.66, $CHCl_3$). IR, ^{1}H- and ^{13}C-NMR: identical with those of **24** obtained from **19**.

*(2*R*,2′*R*,5′*R*)-1-(2′,5′-Dimethylpyrrolidine-1-carbonyl)-2-methylpiperidine* (**25**). Same procedure as above using **17**·HCl (50 mg, 0.37 mmol) and *ent*-**23** (55 mg, 0.37 mmol): **25** (42 mg, 50%). $[\alpha]_D^{20} = +23$ (c = 0.6, $CHCl_3$). IR ($CHCl_3$): 1602, 1417, 1373, 1278. ^{1}H-NMR ($CDCl_3$): 4.11 (*m*, H–C(2)); 3.92 (*m*, H–C(2′), H–C(5′)); 3.42 (*dm*, J = 12.8, H–C(6)); 3.0 (*dt*, J = 12.8, 3.0, H–C(6)); 2.04 (*m*, H–C(3′), H–C(4′)); 1.75–1.40 (*m*, H–C(3′), H–C(4′), 2 H–C(3), 2 H–C(4), 2 H–C(5)); 1.12 (*d*, J = 6.8, Me–C(2)); 1.11 (*d*, J = 6.1, Me–C(2′), Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 54.5 (C(2′), C(5′)); 48.0 (C(2)); 41.8 (C(6)); 32.0 (C(3′), C(4′)); 30.5 (C(3)); 26.2 (C(5)); 20.2 (*Me*–C(2′), *Me*–C(5′)); 19.5 (C(4)); 16.4 (*Me*–C(2)). MS: 224 (13, M^+), 126 (76), 98 (100). HR-MS: 224.1882 ($C_{13}H_{24}N_2O^+$, M^+, calc. 224.18885).

REFERENCES

[1] M. Natsume, I. Utsunomiya, K. Yamaguchi, S. Sakai, *Tetrahedron* **1985,** *41,* 2115, and ref. cit. therein; D.L. Comins, M.A. Weglarz, *J. Org. Chem.* **1991,** *56,* 2506.

[2] D.L. Comins, H. Hong, *J. Am. Chem. Soc.* **1991,** *113,* 6672.

[3] J.D. Brown, M.A. Foley, D.L. Comins, *J. Am. Chem. Soc.* **1988,** *110,* 7445.

[4] D.L. Comins, A. Dehghani, *Tetrahedron Lett.* **1991,** *32,* 5697.

[5] Th. Tschamber, F. Backenstrass, M. Neuburger, M. Zehnder, J. Streith, *Tetrahedron* **1994,** *50,* 1135.

[6] a) D.L. Comins, M.O. Killpack, *J. Am. Chem. Soc.* **1992,** *114,* 10972, and ref. cit. therein; b) D.L. Comins, S.P. Joseph, R.R. Goehring, *ibid.* **1994,** *116,* 4719.

[7] C. Marazano, S. Yannic, Y. Genisson, M. Mehmandoust, B.C. Das, *Tetrahedron Lett.* **1990,** *31,* 1995, and ref. cit. therein.

[8] T. Shono, Y. Matsumura, O. Onomura, Y. Yamaha, *Tetrahedron Lett.* **1987,** *28,* 4073.

[9] K.K.-C. Liu, T. Kajimoto, L. Chen, Z. Zhong, Y. Ichikawa, C.-H. Wong, *J. Org. Chem.* **1991,** *56,* 6280.

[10] T. Kajimoto, L. Chen, K.K.-C. Liu, C.-H. Wong, *J. Am. Chem. Soc.* **1991,** *113,* 6678.

[11] D.P. Dumas, T. Kajimoto, K.K.-C. Liu, C.-H. Wong, D.B. Berkowitz, S.J. Danishefsky, *Bioorg. Med. Chem. Lett.* **1992,** *2,* 33.

[12] D.L. Comins, H. Hong, J.M. Salvador, *J. Org. Chem.* **1991,** *56,* 7197.

[13] J. Streith, A. Boiron, T. Sifferlen, Ch. Strehler, Th. Tschamber, *Tetrahedron Lett.* **1994,** *35,* 3927.

[14] D.L. Comins, D.H. La Munyon, *Tetrahedron Lett.* **1988,** *29,* 773.

[15] D.L. Comins, R.R. Goehring, S.P. Joseph, S. O'Connor, *J. Org. Chem.* **1990,** *55,* 2574.

[16] D. Seebach, J.D. Aebi, *Tetrahedron Lett.* **1984,** *25,* 2545.

[17] D. Seebach, J.D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* **1987,** *70,* 1194.

[18] D. Seebach, G. Stucki, P. Renaud, *Chimia* **1988,** *42,* 176.

[19] G.W.J. Fleet, A. Karpas, R.A. Dwek, L.E. Fellows, A.S. Tyms, S. Peturson, S.K. Namgoong, N.G. Ramsden, P.W. Smith, J. Chan Son, F. Wilson, D.R. Witty, G.S. Jacob, Th.W. Rademacher, *FEBS Lett.* **1988,** *237,* 128.

[20] SIR92: A. Altomare, M.C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, G. Polidori, submitted to *J. Appl. Crystallogr.*

[21] 'CRYSTALS, Issue 9', D. Watkin, Chemical Crystallography Laboratory, Oxford, 1990.

[22] R.P. Short, R.M. Kennedy, S. Masamune, *J. Org. Chem.* **1989,** *54,* 1755.

[23] J.C. Craig, A.R. Pinder, *J. Org. Chem.* **1971,** *23,* 3648; H. Ripperger, K. Schreiber, *Tetrahedron* **1965,** *21,* 1485.

[24] K. Akashi, R.E. Palermo, K.B. Sharpless, *J. Org. Chem.* **1978,** *43,* 2063.

[25] J. Furukawa, N. Morisaki, H. Kobayashi, S. Iwasaki, S. Nozoi, S. Okuda, *Chem. Pharm. Bull.* **1985,** *33,* 440.

[26] J. Cymerman Craig, A.R. Pinter, *J. Org. Chem.* **1971,** *23,* 3648; H. Ripperger, K. Schreiber, *Tetrahedron* **1965,** *21,* 1485.