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SYNTHETIC STUDIES DIRECTED TOWARD AVERMECTINS DEVELOPMENT OF AN ASYMMETRIC DARZENS TYPE CONDENSATION.

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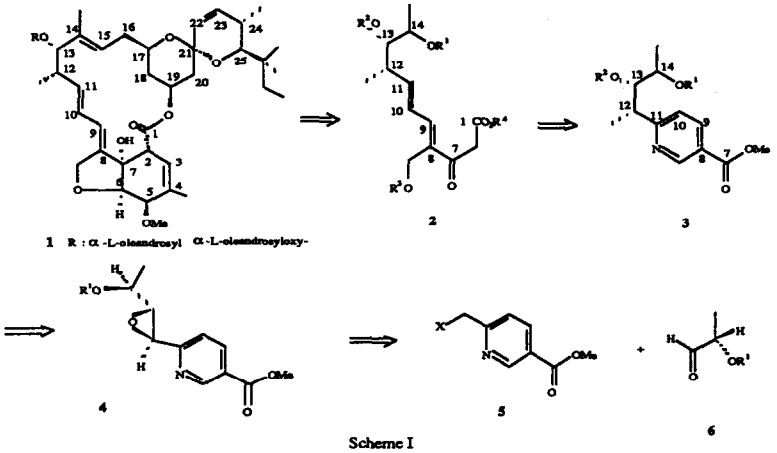
Abstract : The stereocontrol of two asymmetric centers in an Avermectin synthon has been secured by a two step Darzens type condensation.

As part of a program[1] directed toward the total synthesis[2] of insecticidal avermectins[3] (e.g. avermectin A_1a **1**), we anticipated that a substituted pyridine such as **3** could be a precursor[4] of the "west" part of these antibiotics. The control of the absolute configurations at C-12 and C-13 (avermectin numbering) could also be secured by the use of a condensation reaction between pyridine derivative **5** and enantiomerically pure protected lactaldehyde **6** following the retrosynthetic scheme I :



Scheme I

We report in the present communication our preliminary results leading to the stereocontrol of the asymmetric centers at C-12 and C-13.

Selective oxidation[5] of 5-ethyl-2-methyl pyridine **7** afforded after esterification 3-methoxycarbonyl-6-methyl pyridine **8** (Scheme II). Numerous attempts to deprotonate the C-6 methyl in order to introduce a trialkylsilyl group were unsuccessful. These negative results ruled out the possibility of using a Peterson olefination followed by a Sharpless epoxidation.

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The Darzens reaction which constitues an other possibility of introducing an epoxide moiety was studied next.

Thus radical halogenation[6] of the pyridine derivative **8** with N-chloro or N-bromosuccinimide afforded the corresponding halogeno pyridine esters **9a** (55%) and **9b** (45%)[7]. In contrast with 2-halogenomethyl pyridines themselves, pyridines **9a** and **9b** were quite stable. The presence of a methoxycarbonyl group decreased the basicity of nitrogen and precluded intermolecular N-alkylation. Deprotonation of the pyridine esters **9a** and **9b** with lithium hexamethyl disilylamide followed by condensation with (S)-2-*ter*butyldimethylsilyloxypropanal **10** afforded a mixture of diastereomeric halohydrins **11a, 12a** and **11b, 12b** with a good diastereoselectivity albeit in modest yields (Table). The best result was obtained with chloromethylpyridine **9a** affording chlorhydrins **11a** and **12a** (entry 1) (Scheme II).

The absolute configurations of the asymmetric carbons were established after two chemical transformations. Thus, the mixture of chlorhydrins **11a** + **12a** after treatment with potassium *ter*butylate in THF-HMPA afforded trans epoxides **13a** and **13b**[8] (entry 1). The same products could be obtained directly without isolation of the chlorhydrin intermediates after additional treatment with potassium *ter*butylate and HMPA (entry 3) or by the use of lithium isopropyl cyclohexylamide as a single base (entry 4).

On the other hand, the mixture of chlorhydrins **11a** and **12a** after deprotection with hydrogen fluoride in acetonitrile-water and ketalization with 2,2-dimethoxy propane furnished ketals **14a** and **15a** (Scheme II). The absolute configuration of C-2' was in turn deduced from a study of the nuclear Overhauser effect on these acetonides[8].

The stereochemical control observed during the formation of chlorhydrins **11a** and **12a** could be rationalized as nucleophilic attack of the pyridine anion on the aldehyde **10** in a Felkin-Ahn conformation[9]. This peculiar stereochemical outcome[10] could be the result of several factors such as the presence of a bulky protective group on alcohol [10,11] which disfavored a chelated conformation and the presence of a nitrogen in the nucleophile which can act as an additional chelating center [12].

Despite good stereoselectivity of these asymmetric Darzens reactions[13], the low overall yield precluded their use in synthesis. However the presence at a stabilizing group on the pyridine side chain, such as selenoether, could overcome the polycondensation which probably occured during the previous experiments.

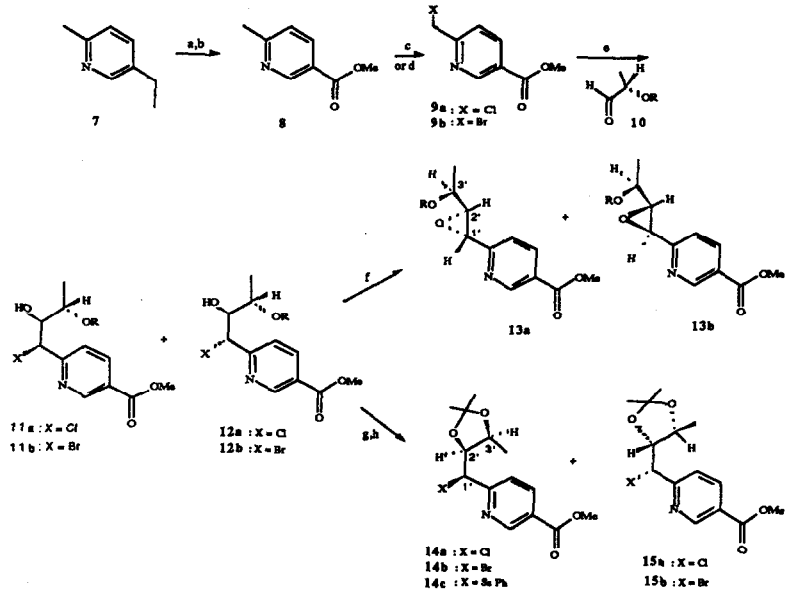
Thus, bromomethylpyridine **9b** afforded seleno ether **16** (84%) after treatment with sodium phenyl selenolate[14] (Scheme III). Deprotonation of this compound and condensation with aldehyde **10** gave rise to a diastereomeric mixtures of three hydroxy selenides **17** and **18a** + **18b** in 78% yield (ratio **17** : (**18a** + **18b**) = 84:16).

The configuration on carbon C-2' in the major hydroxy selenide **17** has been established as previously by sequential treatment with HF and 2,2 dimethoxypropane and nOe study on the acetonide **14c** (Scheme II).

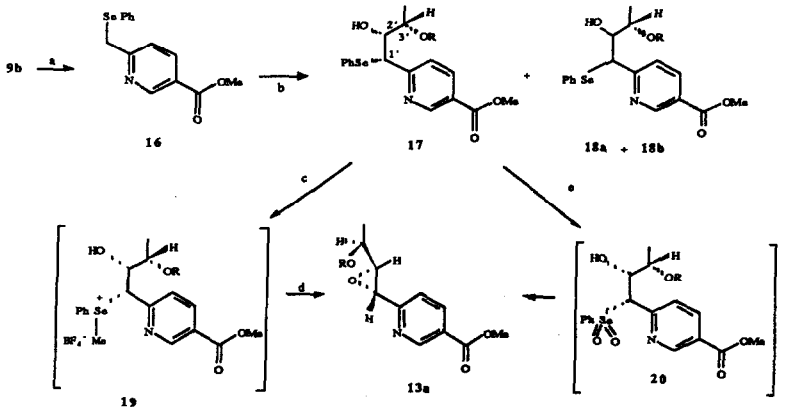
Two possible routes were then explored in order to convert hydroxy selenide **17** into an epoxide[15] (Scheme III). In the first one, compound **17** was alkylated with trimethoxy tetrafluoroborate and the selenonium salt intermediate **19** after treatment with K_2CO_3 afforded the trans epoxyde **13a** (23%). The low yield of this process in probably due to a simultaneous alkylation at nitrogen. On the other hand, treatment of hydroxyselenide **17** with 2.5 equivalents of MCPBA in the presence of K_2CO_3 afforded the same epoxide **13a** through a hydroxy selenone **20** which was not isolated (45% overall yield).

Entry	Starting material	Reagent (-78°C -50°C) [3h]	Halohydrins (Ratio) [Yield %]	Reagent (-50°C +20°C) [20h]	Epoxide (Ratio) [Yield %]
1	9a	LiHMDS	11a + 12a (88 : 12) [91]	tBuOK THF - HMPA	13a + 13b (88 : 12) [46]
2	9b	LiHMDS	11b + 12b (91 : 9) [18]	–	–
3	9a	LiHMDS	–	tBuOK THF - HMPA	13a + 13b [21]
4	9a	LiICA	–	THF - HMPA	13a + 13b [19]

TABLE : Condensation of pyridine derivatives **9a** and **9b** with aldehyde **10**.



Scheme II : R = SitBuMe$_2$. a : $KMnO_4$ (3.7 eq.), H_2O, 35°C, 2h ; b : SO_2H_2, MeOH, Rflx,5h ; c or d : NCS (1.2 eq.) or NBS (1.2 eq.), CCl_4, Rflx, e and f : see table ; g : HF, H_2O (40%), MeCN, 20°C, 2h ; h : $Me_2C(OMe)_2$, TsOH (2.4 eq.), M.S. 4 Å, THF, 20°C, 20h.



Scheme III : R = SitBuMe$_2$. a : PhSeSePh (0.5 eq.), $NaBH_4$ (1 eq.), EtOH, 20°C, 20h ; b : LiHMDS, 10, THF, - 78°C, 2h, NH_4Cl,H_2O, - 50°C ; c : MeO_3BF_4 (1.2 eq.), CH_3CN, 20°C, 2h ; d : CO_3K_2 (10 eq.), 20°C, 20h ; e : MCPBA (2.5 eq.), CO_3K_2 (10 eq.), CH_2Cl_2, 20°C, 20h.

This sequence of reactions allowed the stereochemical control of the anticipated C-12 and C-13 of avermectins as well as the synthesis of a C7-C14 unit. Reverse absolute configurations can be obtained from (R)-2-hydroxy propanal[16]. Opening of epoxide **13a** in order to introduce a methyl group at C-12 is under investigation.

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