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CHELATION CONTROL IN THE ADDITION OF HOMOPHTHALIC ANHYDRIDE TO α-ALKOXY IMINES. PANCRATISTATIN MODEL STUDIES.[1]

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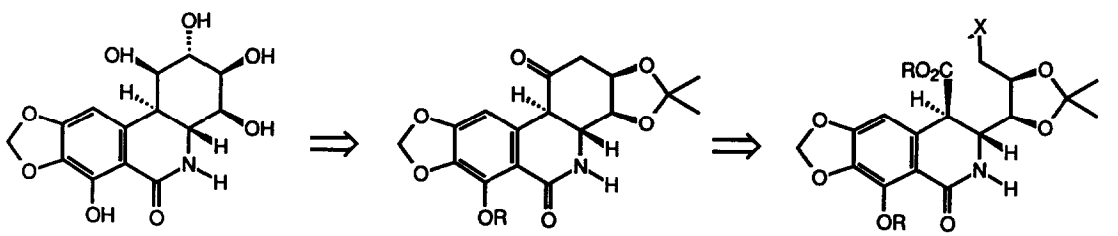
Summary: Diastereoselectivity in the addition of homophthalic anhydride to the α-alkoxy imine (S)-5 can be increased dramatically (to >90%) with addition of Lewis acids. This methodology has been applied to the synthesis of a model compound (12) which contains four asymmetric centers with the same relative stereochemistry as pancratistatin (1).

The phenanthridone alkaloid pancratistatin (1)[3,4] is of interest because of its antineoplastic activity[5] and synthetically challenging structure which includes a C-ring with six contiguous asymmetric centers. An imaginative total synthesis of racemic 1 was recently reported by Danishefsky and Lee.[6] Two syntheses of the related alkaloid lycoricidine have also been reported[7,8] including the remarkable, albeit non-stereoselective, preparation of (+)-lycoricidine from d-glucose. We now report model studies related to the synthesis of optically active 1 which demonstrate the utility of chelation control[9] in the addition of homophthalic anhydride to α-alkoxy imines.

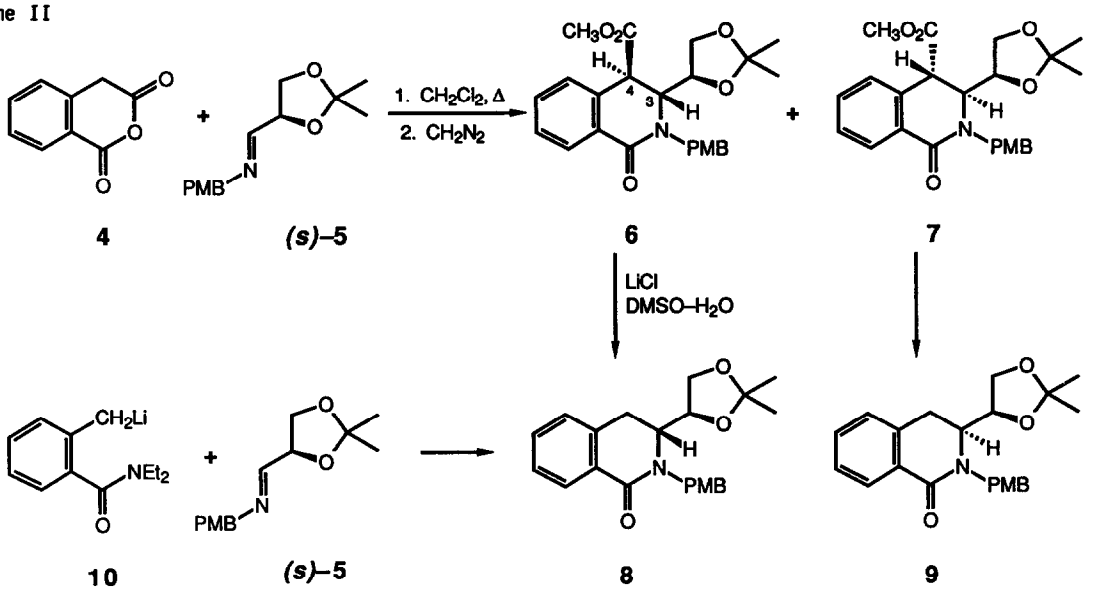
Scheme I



1 2 3

Retrosynthetic analysis (Scheme I) suggested that 1 could be prepared from ketone 2 which in turn might be available, by a key carbon-carbon bond formation, from a seco derivative 3. We anticipated that 3 would be accessible in optically active form by cyclo-condensation[10,11] of a suitably functionalized homophthalic anhydride and a chiral imine provided the stereochemistry of such a process could be controlled. To answer this key stereochemical question, the model reaction of homophthalic anhydride (4) with the chiral p-methoxybenzyl (PMB) imine (S)-5[12] was studied (Scheme II).

Scheme II



Condensation of 4 and (S)-5 in dichloromethane at reflux afforded a ca. 1:1 mixture of adducts 6[13] and 7[14] after esterification of the crude product with diazomethane. These products were easily separable by chromatography. The 3,4-trans stereochemistry of 6 and 7 was assigned based on the small $J_{H\text{-}3,H\text{-}4}$ (1.3-1.4 Hz) which is characteristic of trans 3,4-disubstituted dihydroisoquinolones.[10,15] Further evidence for trans stereochemistry was that 6 and 7 were recovered unchanged after either base (NaOMe, MeOH, reflux) or acid (p-TsOH, toluene, reflux) treatment. Relative (and absolute) stereochemistries were determined by hydrolysis-decarboxylation[16] which afforded diastereomers 8 and 9. Compound 8 had been prepared previously in enantiomerically pure form by condensation of lithio species 10 with (S)-5 and its stereochemistry was established by degradation and correlation with material of known absolute configuration.[12]

Since product 8 was the result of an apparently chelation controlled[9] addition of 10 to (S)-5,[12] we felt the stereoselectivity in the formation of the desired diastereomer 6 could be enhanced by Lewis acid complexation between the nitrogen and α-alkoxy group of the imine.[17] The results of condensation of 4 and (S)-5 in the presence of several Lewis acids are presented in the Table. It can be noted that addition of Lewis acids, particulary magnesium iodide and trimethylaluminum, increased the stereoselectivity in the formation of the chelation product 6 to a synthetically useful range (> 90:10 ratio 6:7). The temperature at which the cyclocondensation occurred was also dramatically lowered in the presence of these Lewis acids. The use of trimethylaluminum in dichloromethane was especially convenient as the resulting reaction mixture was homogeneous. Under this protocol, 6 was isolated in yields of > 60%.[18]

Table. Results of Condensation of 4 and (S)-5 in the Presence of Lewis Acids.

Lewis Acid[a]	Solvent	Temperature	Time	Ratio 6:7[c]
none	CH_2Cl_2	reflux	10 min	50:50
LiI	THF	reflux	10 min	60:40
$ZnCl_2$	CH_3CN	rt	2 h	82:18
MgI_2	THF	0°C	2 h	70:30
MgI_2	THF	-50 to 0°C	2 h[b]	80:20
MgI_2	CH_3CN	0°C	2 h	83:17
MgI_2	CH_3CN	-30 to 0°C	24 h[b]	93:7
$AlMe_3$[d]	CH_2Cl_2	-78 to 0°C	5 h[b]	91:9

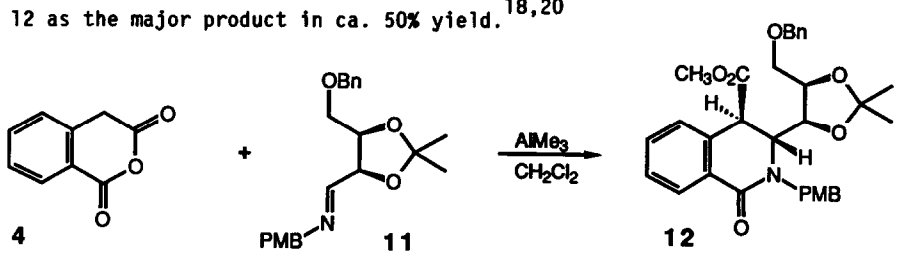
[a] One equiv of the imine was added to a mixture of one equiv of 4 and one equiv of Lewis-acid.

[b] Reaction mixture was maintained at low temperature for this time and then allowed to warm to 0°C. Diazomethane was added and the crude product was obtained after filtration and evaporation.

[c] Determined by ^1H NMR analysis of crude product.

[d] Added as a 2 M solution in hexane.

Similar stereoselectivity was observed in the trimethylaluminum mediated condensation of homophthalic anhydride and the more highly functionalized (racemic) imine 11[19] which furnished 12 as the major product in ca. 50% yield.[18,20]



These results indicate that Lewis acid induced chelation control can be effectively utilized to control stereoselectivity in the addition of homophthalic anhydride to α-alkoxy imines. Additional applications to other imine addition processes and to the preparation of more advanced pancratistatin precursors are under investigation.

References and Notes:

1. Contribution No. 799 from the Institute of Organic Chemistry.
2. Syntex Research Post-Doctoral Fellow, 1988-1989.
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13. Compound 6: ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, s), 1.50 (3H, s), 3.25 (3H, s), 3.44 (1H, d, J = 1.3 Hz), 3.56 (1H, dd, J = 7, 8.3 Hz), 3.78 (3H, s), 3.86 (1H, dd, J = 6, 8.3 Hz), 4.02 (1H, dd, J = 1.3, 8.5 Hz), 4.05 (1H, m), 4.12 (1H, d, J = 14.4 Hz), 5.63 (1H, d, J =14.4 Hz) 6.84 (2H, d, J = 9 Hz) 7.12 (1H, m) 7.24 (2H, d, J = 9 Hz), 7.46 (2H, m), 8.16 (1H, m); $[\alpha]_D^{25}$ -76 ° (c 1, $CHCl_3$).
14. Compound 7: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, s), 1.38 (3H, s), 3.30 (3H, s), 3.65 (1H, dd, J = 6, 8.8 Hz), 3.72 (1H, dd, J = 4.2, 8.8 Hz), 3.78 (3H, s), 3.86 (1H, m), 4.02 (1H, d, J = 1.4 Hz), 4.05 (1H, d, J = 14.5 Hz), 4.10 (1H, dd, J = 1.4, 7.7 Hz), 5.40 (1H, d, J = 14.5 Hz), 6.85 (2H, d, J = 8.7 Hz), 7.20 (1H, m), 7.26 (2H, d, J = 8.7, Hz), 7.40-7.54 (2H, m), 8.12 (1H, dd, J = 1.5, 7 Hz); $[\alpha]_D^{25}$ + 65° (c 1, $CHCl_3$).
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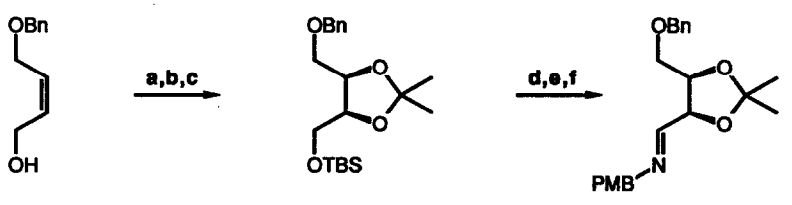
17. Chelation control has been demonstrated in the addition of allylic organometallic reagents to α-alkoxyimines: Yamamoto, Y.; Komatsu, T.; Maruyama, K. J. Chem. Soc., Chem. Commun. 1985, 814.
18. Yields have not yet been optimized.
19. Racemic imine 11 was prepared according to the following sequence:



13 14 11

(a) TBS-Cl, DMF, Imidazole, 88%; (b) NMO-OsO_4,98%; (c) Dimethoxypropane, TsOH, 94%; (d) Bu_4NF, THF, 85%; (e) DMSO-$COCl_2$, 80-90%; (f) p-Methoxybenzylamine, molecular sieves, 90-95%.

20. The assignment of the stereochemistry of 12 was based on the similarity of the ^{1}H NMR spectrum with that of compound 6.

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