Michael Additions to (*R*)-1-Acetyl-5-isopropoxy-3-pyrrolin-2-one and Subsequent *N*-Acyliminium Ion Generation: Synthesis of Enantiopure 1-Azabicycles and Preparation of an Intermediate for a Projected Synthesis of Roseophilin

Tim Luker, Wim-Jan Koot, Henk Hiemstra,* and W. Nico Speckamp*

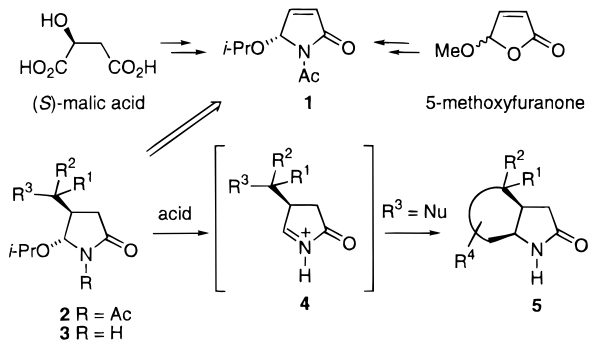
Laboratory of Organic Chemistry, Amsterdam Institute of Molecular Studies, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Received October 8, 1997

In 1992 we disclosed the synthesis of enantiopure (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one (**1**) from (*S*)-malic acid (Scheme 1).[1] More recently, Feringa and Kellogg have shown that larger quantities of similar building blocks are available in an efficient manner from elegant enzymatic resolutions of racemic lactams derived from 5-methoxyfuranone.[2] Importantly, both methods allow access to either antipode of **1**. It was hoped that **1** would be a powerful building block for organic synthesis by virtue of the fact that further functionalization should be possible at all of the ring atoms using well-established methodology.[3−5] As part of an ongoing research program committed to total synthesis via enantiopure iminium ion intermediates,[6] herein we wish to report that Michael additions to **1** proceed in essentially quantitative yields, affording building blocks **2** (Scheme 1). Further transformations indeed allow generation of enantiopure *N*-acyliminium ions **4**, which react intramolecularly with tethered nucleophiles to afford substituted azabicyles **5** in excellent yields. This flexible strategy toward such bicycles in enantiopure form should be particularly valuable considering its recent emergance as a structural unit in roseophilin, a natural product with promising anticancer properties.[7] Our efforts toward its first enantioselective total synthesis are also disclosed.

Michael additions to enantiopure 3-pyrrolin-2-ones have not been extensively studied. Previous attempts used metalated enolate anions.[8] We expected the presence of the *N*-acetyl group in **1** to enhance the electrophilicity of the double bond,[9] making it a good Michael acceptor and thus allowing additions to take place under milder conditions.

Scheme 1



First, the configurational stability of **1** under the conditions envisaged for the addition reactions was checked. After being stirred in DMF at rt in the presence of Et_3N for 72 h, the optical purity of **1** remained virtually unchanged (>96% ee). The Michael additions of a range of stabilized nucleophiles are summarized in Table 1. The reactions were generally performed in DMF containing Et_3N (1 equiv). The final entry shows addition of methyl phenylsulfonyl acetate. As this nucleophile was of identical polarity to the product **9**, only 1 equiv could be used. Thus, a large excess of the Et_3N base was used to achieve complete reaction. In all cases, only *trans*-products (**6**−**9**) were obtained, as deduced from the singlets for H5 of the pyrrolin-2-one moiety,[10] in excellent yields. The unsymmetrical nucleophiles afforded products **6** and **9** as 1:1 diastereomeric mixtures at the side chain stereocenter. With the more hindered methyl 2-(phenylsulfonyl)hexanoate, no significant addition had taken place after 30 h, thus precluding the use of nucleophiles "prealkylated" with π-electrophiles vide supra.

The active methine function in the lactam products could be further functionalized by alkylation. Such reactions permitted introduction of potential π-nucleophiles for use in later iminium ion cyclizations. These alkylation reactions are also summarized in Table 1. Anions were generated with NaH in DMF before addition of a suitable alkyl halide alkylating agent. With bromides and chlorides, LiI was used to accelerate the reactions and increase yields. A variety of unsaturated nucleophiles were introduced in good yield.[11]

With quantities of **10**−**13** in hand we were now in a position to examine cyclization reactions between the tethered π-nucleophile and the iminium ion generated by acid-induced loss of the isopropoxy group. Few examples of this type of intramolecular cyclization reaction exist,[3,12] but considering the constrained position of the nucleophile above the planar iminium ion, we were confident that the reaction would afford the desired *cis*-fused bicycles. The results are given in Table 2. The *N*-acyl group was first deprotected using excess dimethylamine in either CH_2Cl_2 or DMF[3a] (iminium ion generation is not possible when the nitrogen atom is flanked by two acyl groups).[6c] The products obtained were sensitive to hydrolysis at C5 and so were used immediately following solvent removal without further purification. The first two entries in Table 2 show cyclization of the isoprenyl nucleophile. The reaction proceeded in good yield with either formic acid or titanium tetrachloride. As expected, only the 5-*exo*-*trig* cyclization mode occurred (via

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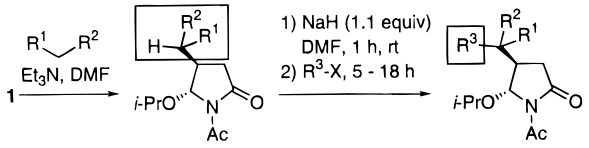
S0022-3263(97)01854-9 CCC: $15.00
Published on Web 01/06/1998

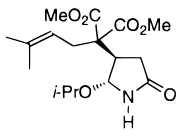
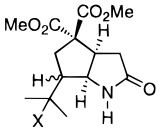
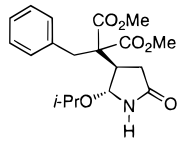
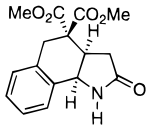
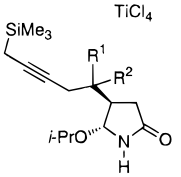
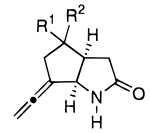
Table 1. Michael Additions of 1 and Alkylation of Adducts



R^1	R^2	nucleophile (equiv)	product (yield, %)	alkylating agent R^3X (equiv)	product (yield, %)
COMe	CO_2Me	1.1	**6** (99)	-	-
CO_2Me	CO_2Me	2.2	**7** (95)	$Me_2C{=}CHCH_2Br$ (2.4)[a]	**10** (50)
				$PhCH_2Cl$ (3.0)[a]	**11** (76)
CO_2Et	CO_2Et	2.2	**8** (90)	$TMSCH_2C{\equiv}CCH_2I$ (2.5)	**12** (77)
CO_2Me	SO_2Ph	1.0	**9** (100)	$TMSCH_2C{\equiv}CCH_2I$ (2.5)	**13** (80)

[a] LiI (3 equiv) added.

Table 2. Cyclization of *N*-Deprotected Alkylation Products 10−13

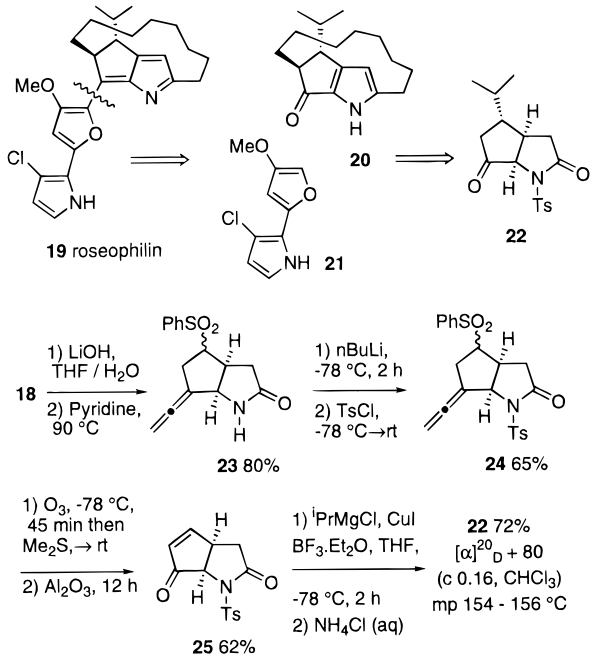
Precursor / Acid	Cyclization product(s) / yield[a]
	
HCO_2H, $TiCl_4$	**14** X = HCO_2, 57% (α-H), 16% (β-H) **15** X = Cl, 50% (α-H), 30% (β-H)
	
$TiCl_4$	**16** 79%
	
HCO_2H	**17** $R^1 = R^2 = CO_2Et$, 78% **18** $R^1 = CO_2Me$ $R^2 = SO_2Ph$, 80%[b]

[a] Yields (isolated) are for the two-step *N*-deprotection−cyclization protocol (**2** → **5**, Scheme 1). [b] 3:1 mixture of diastereomers.

a tertiary cation intermediate). No traces of the 6-*exo-trig* cyclization were detected (via a secondary cation). There was a preference for the isopropyl group on the concave face of the molecule. Similar stereoselectivities were obtained with either a Brönsted or Lewis acid. Fortunately, the crystals of **14α-H** were suitable for X-ray analysis, which allowed conclusive assignment of absolute stereochemistry. The benzyl group also proved an excellent nucleophile, affording **16** in good yield as a single diastereomer. We have previously obtained an analogous product to **16**, but devoid of the ester groups, by addition of a bis(phenylethyl)cuprate to **1** followed by a similar cyclization protocol.[3b] It was gratifying to note that this new methodology proceeded in similarly high yields. Finally, the tethered propargyl silanes allowed the synthesis of allenes **17** and **18** in excellent yields.

With relatively facile access to this range of enantiopure bicycles, we next considered synthetic applications. Roseophilin (**19**) is a complex synthetic target attracting much recent interest in view of both its unique structure and promising anticancer properties (Scheme 2).[7] Elegant work by Terishima established the viability of the retrosynthetic analysis shown and resulted in the synthesis of the heterobiaryl fragment **21**.[7b] Others have focused attention on the

Scheme 2



tricyclic core **20**, with both Fürstner[7c] and Fuchs[7d] achieving racemic syntheses. Our efforts toward enantiopure **20** are also given in Scheme 2. Allene **18** was transformed using standard procedures into enone **25**. Addition of a bis(isopropyl)magnesiocuprate occurred with complete stereocontrol in the presence of $BF_3{\cdot}Et_2O$ (no addition occurred in its absence), affording **22** as a single diastereomer. Work toward a completion of the total synthesis is in progress and will be reported in due course.

Acknowledgment. The European Union (TMR fellowship, T.L.) and The Netherlands Foundation for Chemical Research (in part) (SON, W.-J.K.) with financial aid from The Netherlands Organization for Scientific Research (NWO, W.-J.K.) are acknowledged for generous financial support. We thank M. P. Otero Cabredo (ERASMUS exchange from University of Santiago de la Compostela) for the synthesis of **1**, R. H. Balk for the preparation of propargyl silanes, and J. Fraanje and K. Goubitz (Crystallography Department, University of Amsterdam) for determining the X-ray crystal structure of **14α-H**.

Supporting Information Available: Experimental procedures and ^1H NMR spectra of all new compounds (27 pages).

JO971854D