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STEREOSELECTIVE METHYLATIONS OF BICYCLIC LACTAMS DERIVED FROM PYROGLUTAMIC ACID

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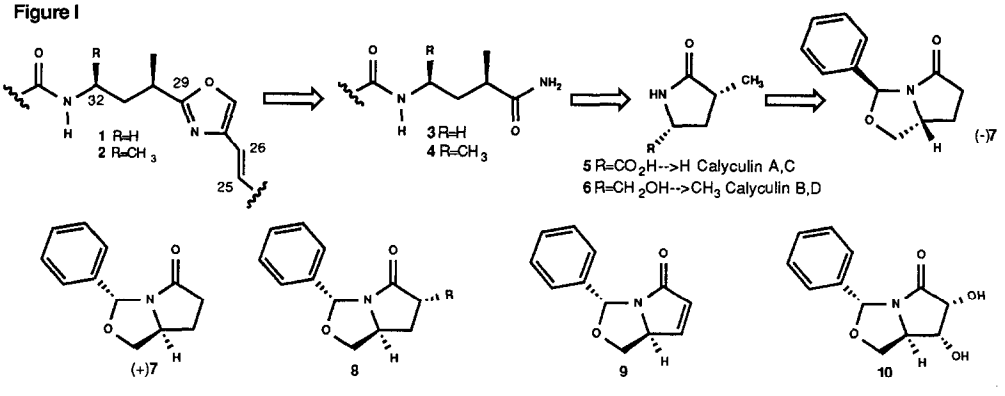
Abstract: *Reaction of the lithium enolate of (-)7 with iodomethane provides a stereoselective synthesis of (2R,4S)-4-amino-2-methylpentanamide derivatives.*

In the course of our studies on the calyculin series of antibiotics,[1] the *trans* olefin at C25/C26 was identified as a key disconnection for condensation of two highly functionalized fragments at a late stage in the synthesis. We recently utilized the method of Blumlein and Lewry to synthesize 4-chlorooxazoles which could be converted to their phosphonium salts (or phosphonates).[2] Deprotonation and condensation with a variety of aldehydes resulted in good yields (50-95%) and high stereoselectivity (<5:>95% Z/E) of the resulting trans-4-alkenyl oxazoles. We wish to report on the further elaboration of the C2 substituent of the oxazole.

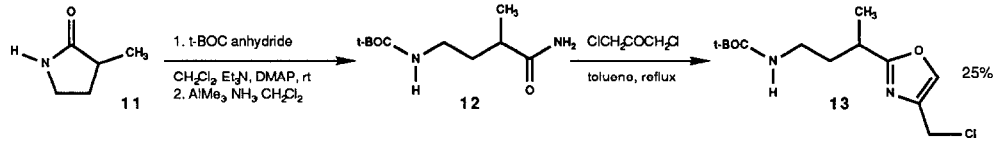
Figure I



The C29/C32 fragment of the calyculins differ by a methyl substituent at C32 (**1**,**2** Figure I). Since the oxazole synthesis involves condensation of primary amides such as **3** or **4** with 1,3-dichloroacetone, disconnection of the C32 amide led us to identify lactams **5** and **6** as suitable precursors for stereoselective introduction of alkyl substituents. Following the elegant work of the Squibb group in the synthesis of 4-alkyl-substituted prolines,[3] we chose to investigate the use of the bicyclic O,N-acetal (-)7 derived from D-pyroglutamic

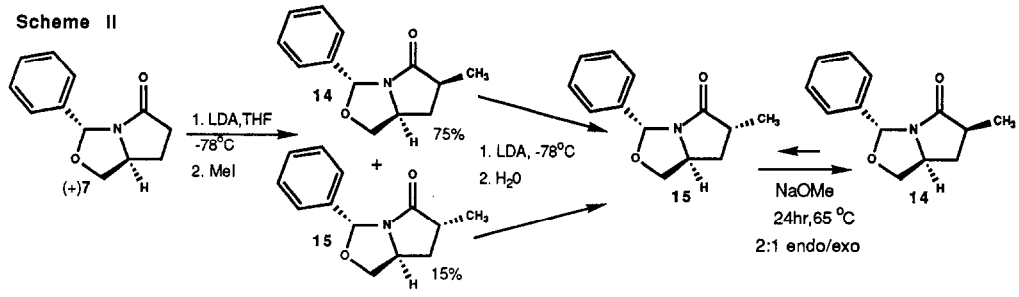
acid. This substrate appeared ideal since radical decarboxylation of the methylated pyroglutamic acid **5** should afford the fragment found in calyculins A and C. Likewise, radical deoxygenation of lactam **6** affords entry into the synthesis of calyculins B and D. Conversion of racemic 3-methylpyrrolidinone **11** to a suitably functionalized oxazole **13** in only three steps prompted us to pursue this route.

Scheme I



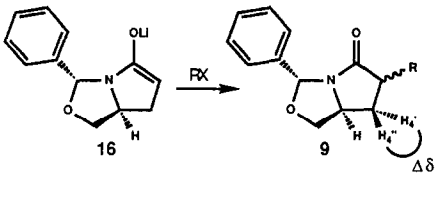
Alkylation of lithium enolates of (+)**7** (derived from L-pyroglutamic acid) have been recently studied.[3,4] Predominant formation of anti substituted products (Figure I, **8**) has been observed resulting from addition of the electrophile to the exo (convex) face of the bicyclic lactam. The ratios have been reported to range from 1.8:1 trans/cis (R=benzyl) to 100:1 trans/cis (R=*p*-NO_2-benzyl). Exo addition was also favored in the osmylation (**10**) and conjugate addition[4] to the unsaturated lactam **9**. Interestingly, diol **10**, which has been utilized in the total synthesis of the gastroprotective substance AI-77-B,[5] is a superb candidate for elaboration of the C33/C37 fragment of the calyculins. Because the R stereochemistry is desired at C30, D-pyroglutamic acid was utilized to generate the bicyclic lactam (-)**7**. In addition, the syn relationship of the two methyl substituents at C30 and C32 requires endo alkylation. The observation that endo alkylation is the predominant product in related bicyclic lactams[6] (see below) and the possibility of equilibration at the α-carbon led us to investigate this alkylation more closely.

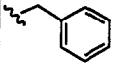
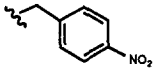
Scheme II



Generation of the lithium enolate of (+)**7** at -78°C with LDA followed by addition of iodomethane resulted in formation of a 5:1 ratio of diastereomers in 90% yield (Scheme II, 10% recovered **7**). Analysis using ^{1}H NMR nuclear Overhauser enhancement lead us to conclude that the major diastereomer was the desired endo addition product (**14**). When either diastereomer **14** or **15** was submitted to enolate formation (2 equivalents LDA, THF, -78°C) followed by an aqueous quench, only exo product **15** was obtained in near quantitative yield. Equilibration of either **14** or **15** with sodium methylate in methanol for 24hr at 65°C resulted in formation of a 2:1 ratio favoring the endo diastereomer **14**. Since these observations are not in accord with previous reports,[4a] several other electrophiles were condensed under similar conditions (1.0-1.1 equivalents LDA, THF, -78°C, 30min). As shown in table I, benzyl bromide afforded a 2:1 ratio of diastereomers favoring the exo product. Similar results were obtained with *p*-NO_2-benzyl bromide (2:1 exo/endo). Allyl bromide afforded a 1:1 mixture in low yield (27%).

Table I

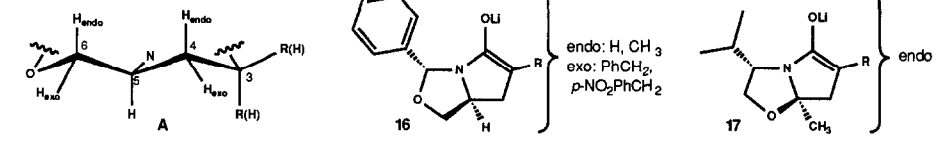


R	endo/exo[b]	yield	Δδ $H_{4'}$,$H_{4''}$ (PPM)[a] endo	exo
CH_3	5:1	90%	1.06	0.19
	1:2	80%	0.78	0.12
	1:2	60%	0.86	0.0
	1:1	27%	0.91	0.0

a. For clarity, H4" in **9** refers to $H4_{endo}$, while H4' refers to $H4_{exo}$. The terms endo and exo in the table reflect the relationship of R to C6 in **9**. b. All ratios were determined from isolated yields of diastereomers except for p-nitrophenyl derivative, where yields were extrapolated after hydrolysis of anti product.[7]

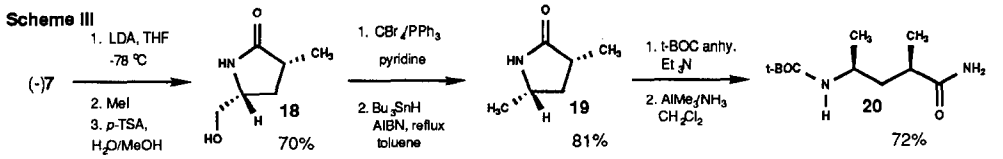
The stereochemistry in the products was assigned by NOE difference spectroscopy. In all cases except the *p*-nitrobenzyl exo derivative,[7] NOE experiments were carried out on both diastereomers. Relationships which are common to all products result from the close proximity of the $H4_{endo}/H6_{endo}$ and $H4_{exo}/H5$ hydrogens, and the respective NOE's observed between H4's and the corresponding H or R groups at C3 (Figure II, **A**). Analysis of the shift dependence on structure was also useful. For all eight diastereomers shown in Table I, the difference in chemical shift between the H4 hydrogens is consistently large (0.78-1.06) for the endo products and small (0.0-0.19) for the exo derivatives. The syn relationship of $H6_{endo}$ and the R substituent at C3 in the endo products of the rigid bicyclic lactams should result in steric compression at C4 and may account for these observations. This relationship does not exist in the anti derivatives. Confirmation of the stereochemistry of the major isomer **14** was obtained by analysis of the X-ray structure of a derivative.[8]

Figure II



Kinetic endo selectivity in the alkylation of **16** is preferred in cases where the steric demand of the electrophile is small. Endo addition with very high diastereoselectivity has also been observed in the elegant work of Meyers on bicyclic lactam **17** and related systems (Figure II).[6] For **17**, endo addition does not appear to be modulated in a dramatic fashion by the nature of the electrophile. This is especially true in the second alkylation of an α-substituted lactam. Theoretical aspects of the selectivity resulting from addition of the electrophile anti to the pseudopyramidal nitrogen lone pair have been addressed.[9] In the case of lactam **16**, the kinetic endo selectivity appears more sensitive to steric demands and a more substantial switch to exo addition (vs. **17**) occurs with larger electrophiles. Subtle conformational differences might attenuate the observed difference in **16** and **17**.

Synthesis of amide **20** was accomplished as shown in Scheme III. Alkylation of the O,N acetal derived from D-pyroglutamic acid followed by hydrolysis afforded alcohol **18** in 70% yield from **7**(-). Conversion to the bromide derivative followed by reduction afforded lactam **19** in 81% yield. Conversion to the t-Boc derivative[10] and ring opening in the prescence of $NH_3/Al(Me)_3$[11,12] provided **20** in 72% yield.



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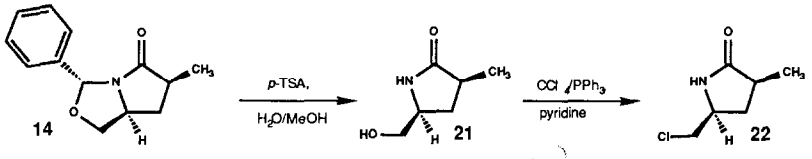
References:

1. Structure: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930; Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780; Activity: Ishihara, K.; Martin, B.L.; Brautigan, D.L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, H.; Uemura, K.; Hartshorne, K.J. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871; Synthesis: Duplantier, A.J.; Nantz, M.H.; Roberts, J.C.; Short, R.P. Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357; Evans, D.A.; Gage, J.R. *Tetrahedron Lett.* **1990**, *31*, 6129; Hara, O.; Hamada, Y.; Shiroi, T. *Syn. Lett.* **1991**, 283; Hara, O.; Hamada, Y.; Shiroiri, T. *Syn. Lett.* **1991**, 285.
2. Zhao, Z.; Scarlato, G.R.; Armstrong, R.W. *Tetrahedron Lett.*, **1991**, *32*, 1609.
3. Thottathil, J.K.; Moniot, J.L.; Mueller, R.H.; Wong, M.K.Y.; Kissich, T.P. *J. Org. Chem.* **1986**, *51*, 3140.
4. a)Baldwin, J.E.; Moloney, M.G.; Shim, S.B. *Tetrahedron Lett.* **1991**, *32*, 1379 and references therein; b) For related alkylations of L-pyroglutamic acid, see: Baldwin, J.E.; Miranda, T.; Moloney, M. *Tetrahedron* **1989**, *45*, 7459.
5. Hamada, Y.; Kawai, A.; Khono, Y.; Hara, O.; Shioiri, T. J. *Am. Chem. Soc.* **1989**, *111*, 1524.
6. Meyers, A.I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146; Meyers, A.I.; Lefker, B.A.; Wanner, K.T.; Aitken, R.A. *J. Org. Chem.* **1986**, *51*, 1936.
7. In all cases, the behavior on thin layer chromatography (silica gel, hexanes/EtOAc) is consistent with the endo product having a larger Rf value. The separation of both diastereomers is straightforward from one another and from starting material. The one exception is the exo *p*-nitrobenzyl derivative, which co-elutes with starting material in all solvents investigated. Characterization of this material was accomplished following hydrolysis of the O,N acetal.
8. The X-ray structure of **22** confirmed the syn relationship of the lactam substituents:



9. Durkinb, K.A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162; Meyers, A.I.; Wallace, R.H. *J. Org. Chem.* **1989**, *54*, 2509.
10. Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, *48*, 2424.
11. Schoenfelder, A.; Mann, A. *Synthetic Comm.* **1990**, *20*, 2585.
12. Basha, A.; Lipton, M.; Weinreb, S.M. *Tetrahedron Lett.* **1977**, *18*, 4171.

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