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A Versatile Synthesis of ß-Amino Acids Using the Nicholas Reaction. II. Formal Total Synthesis of Thienamycin.

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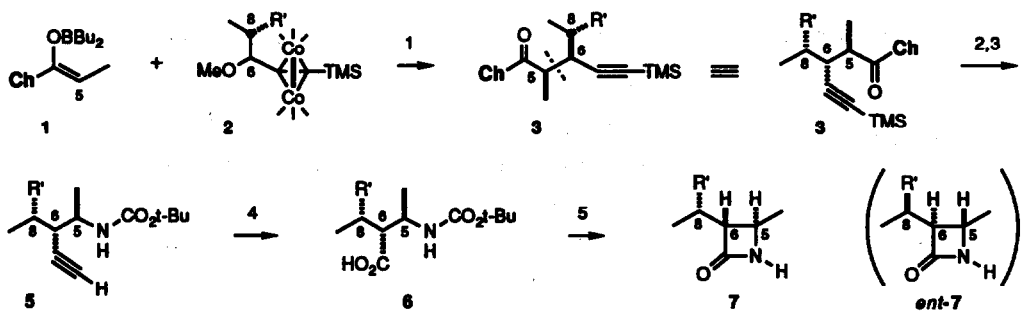
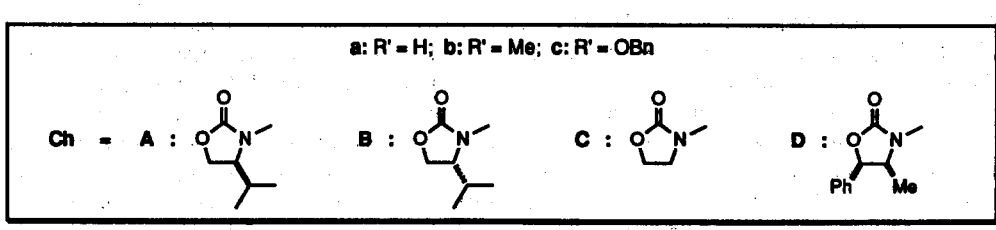
Key Words: Nicholas reaction; acetylenic acids; ß-amino acids; ß-lactam antibiotics; thienamycin.

Abstract: *Homochiral acetylenic acid 26, prepared using the Schreiber modification of the Nicholas reaction, has been converted to ß-amino acid derivative 28 by a two step sequence involving Curtius rearrangement followed by oxidative cleavage of the acetylenic bond. Amino acid derivative 28 was then converted to thienamycin (12) precursor 30 by cyclization with DCC followed by epimerization.*

In the preceeding paper in this series we reported that Nicholas adducts of general structure **3** serve as convenient precursors to ß-amino acid derivatives of type **6**,[1] *via* a three step sequence consisting of (1) imide hydrolysis with concomitant TMS group removal;[2a] (2) Curtius rearrangement of the resulting carboxylic acids **4** to afford *tert*-butylcarbamates **5**;[3] and (3) oxidative cleavage of the acetylenic triple bond (Scheme 1).[4,5b]



1. Bu_2BOTf, i-Pr_2NEt; CAN. 2. LiOOH. 3. DPPA, t-BuOH (Curtius). 4. $KMnO_4/NaIO_4$ (or $OsO_4/NaIO_4$). 5. TFA; DCC.



Scheme 1

Deprotection of **6** (TFA) followed by cyclization (DCC) then provided an efficient route to ß-lactams **7**.[5a] In identical fashion, Nicholas adducts *ent*-**3** were cleanly converted to the enantiomeric ß-lactams *ent*-**7** with virtually 100% stereoselectivity (*ent* = mirror image of parent structure shown). Yields throughout this sequence were generally high, except for the sterically hindered example **3b**(A) (R'= Me, Ch = A).[1]

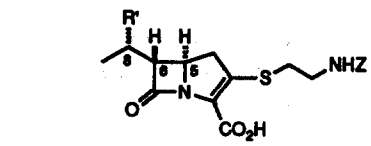
In each case the Nicholas reaction of chiral enolates **1A,B** took place with >98:2 syn-selectivity (C_5-C_6, carbapenem numbering),[1] and for achiral substrates **2a,b**, with a stereochemical outcome in accordance with the kinetic resolution model proposed by Schreiber *et al.* (see also Scheme 1, preceeding paper).[6] These results are summarized in Table 1 (upper case letters refer to auxiliaries Ch; lower case letters refer to substituents a-c). In

Table 1

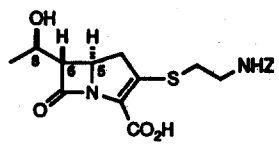
1.	1A + 2a --> 3a(A)	:	2.	1B + 2a --> *ent*-3a(B)
3.	1A + 2b --> 3b(A)	:	4.	1B + 2b --> *ent*-3b(B)
5.	1A + 2c --> 3c(A)	:	6.	1B + *ent*-2c --> *ent*-3c(B)
7.	1C + 2c --> 3c(C)	:	8.	1C + *ent*-2c --> *ent*-3c(C)

addition to achiral substrates **2a,b** (entries 1-3), chiral substrates **2c** (8*S*) and ***ent*-2c** (8*R*) reacted in a "matched" fashion with chiral enolates **1A** and **1B**, respectively, providing adducts **3c(A)** and ***ent*-3c(B)** with virtually 100% stereocontrol (entries 5, 6). Interestingly, **2c** and ***ent*-2c** also reacted with achiral enolate **1C** to provide homochiral adducts **3c(C)** and ***ent*-3c(C)** with >98% stereoselectivity (entries 7, 8). The structure of **3c(C)** was confirmed by hydrolysis to the identical carboxylic acid **4c** derived from **3c(A)**, whose structure was established by X-ray analysis.[7a] This last result serves to illustrate the powerful directing influence which chiral substituents can exert on the Nicholas reaction.

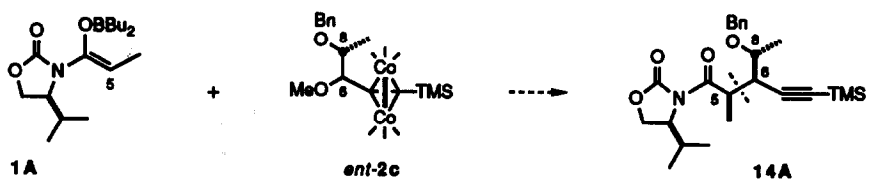
ß-Lactams **7a** (R'= H) and **7b** (R'= Me) have a substitution pattern which is characteristic of the important antibiotics PS-5 (**10**) and PS-6 (**11**), respectively (5*R*,6*R*-stereochemistry), and **7c** (R'= OBn) is directly related to olivanic acids of the type exemplified by MM-22381 (**9**) (5*R*,6*S*,8*S*-stereochemistry) (Scheme 2).[5]



9 (R' = OH; Z = H); **10** (R' = H; Z = Ac); **11** (R' = Me; Z = Ac)



12 (Z = H); **13** (Z = CH=NH)



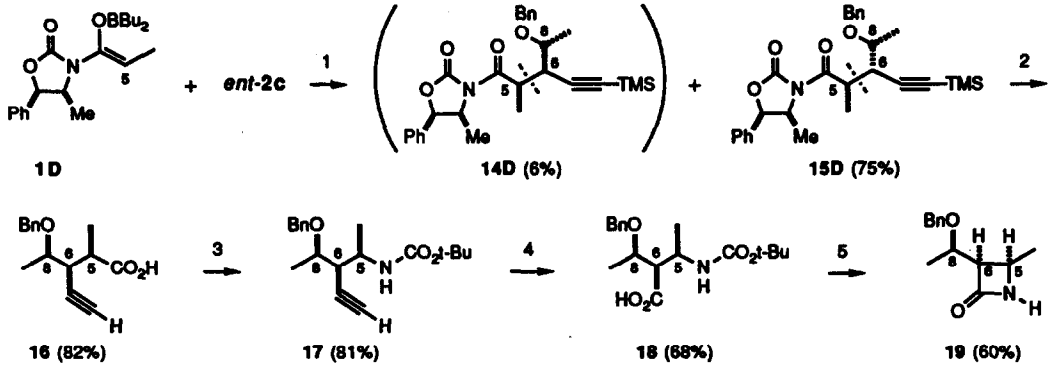
1A + ***ent*-2c** ----> **14A**

Scheme 2

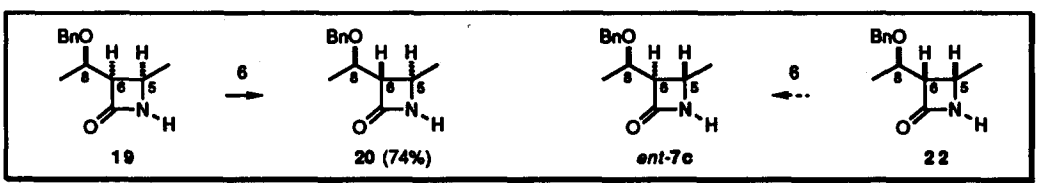
On the basis of these results, it seemed likely that the Nicholas-Schreiber methodology might be extended to the preparation of analogs having the 5*R*,6*S*,8*R*-configuration found in thienamycin (**12**) and imipenem (**13**).[1,5] In principle, this substitution pattern was available by "mis-matched" condensation of chiral enolate **1A** with cobalt complex ***ent*-2c** (Scheme 2), which would afford adduct **14A** if transition state interactions were dominated by chiral auxiliary A (*cf.* Scheme 1). However, all attempts in this direction provided only complex mixtures of products, which contained at least three isomeric adducts in a ratio of ~7:3:1 (29% combined yield).

In contrast to the case with **1A**, chiral enolate **1D** underwent clean condensation with ***ent*-2c** to provide a 12.5:1 mixture of two isomeric acetylenic acid derivatives. These were subsequently identified as syn-adduct **14D** and anti-isomer **15D** (Scheme 3, following page). Interestingly, however, the major isomer proved to be the undesired **15D**. Thus, **15D** was cleanly converted to the carboxylic acid **16**,[2a] which upon Curtius rearrangement,[3] followed by oxidative cleavage,[4] afforded amino acid derivative **18** in exact analogy to our earlier studies with **6** (*cf.* Scheme 1). Up to this point it was impossible to distinguish between syn- and anti-isomers on the basis of spectral data alone. However, upon cyclization of **18** to **19** the cis-relationship between

H_5-H_6 was immediately apparent from their relatively large coupling constant ($J_{5,6}$ = 6.0 Hz), which for trans-ß-lactams is typically <3 Hz.[8] The question of absolute stereochemistry at C_5-C_6 was then resolved by epimerization studies (see box). As expected, **19** was readily epimerized to the desired trans-isomer **20** ($J_{5,6}$ = 1.8 Hz),[9] which proved to be identical to the material obtained directly from syn-adduct **14D**. As indicated, if **19** had been of opposite absolute configuration at C_5-C_6 (*i.e.* **22**), epimerization would have afforded the known ß-lactam *ent*-**7c** (*cf.* Scheme 1).

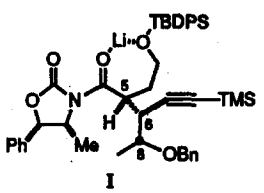


1. Bu_2BOTf, i-Pr_2NEt; CAN. 2. LiOOH. 3. DPPA, t-BuOH (Curtius). 4. $OsO_4/NaIO_4$. 5. TFA; DCC. 6. TMSTf, NEt_3; H_3O^+



Scheme 3

Finally, these observations were readily extended to a formal total synthesis of thienamycin (**12**),[5] although not without an unexpected diversion. Thus, condensation of chiral enolate **23** with *ent*-**2c** provided a 79% yield of the Nicholas adduct **24**,[6] which was obtained with ~17:1 anti-selectivity (Scheme 4, following page). Interestingly, however, hydrolysis of **24** under the usual conditions (LiOOH, 3:1 THF/H_2O) afforded a complex mixture of products,[2a] from which *endo*-ring opened product **25** could be isolated in 30% yield. No trace of the desired product **26** derived from *exo*-nucleophilic attack could be detected. This unexpected reaction pathway might be due to complexation of Li cation between the *exo*-carbonyl functionality and the -OTBDPS group (*cf.* I, below), since the related *n*-propyl derivative (OTBDPS = Me) underwent normal hydrolysis.[7b] In



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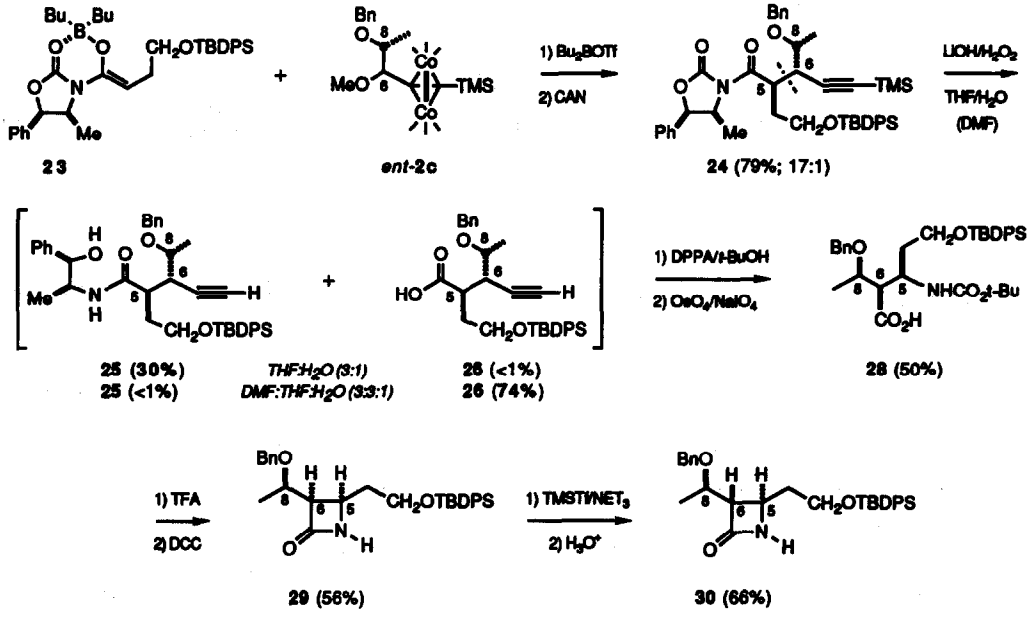
any event, addition of DMF to the hydrolysis reaction completely reversed the regioselectivity (3:3:1 DMF/THF/H_2O), and afforded a 74% yield of the desired acetylenic acid **26**.[2b] As described above for **16**

(Scheme 3), **26** was then converted in two steps (71%, 71%) to the homochiral amino acid derivative **28**, which upon deprotection and cyclization with DCC afforded the cis-β-lactam **29** (56%, unoptimized). Finally, epimerization of **29** according to the procedure of Nakai *et al.* afforded the known thienamycin (**12**) precursor **30**,[9,5b] which had identical spectral data as that reported by Grieco *et al.* for the racemic material (66% yield, viscous pale yellow oil, $[\alpha]^{25}_D$ = -1.9° [c = 6.3, CH_2Cl_2]).[5b,c,10]



Scheme 4

References and Notes

1. Jacobi, P. A.; Zheng, W., preceeding article in this journal.
2. (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (b) This result is in qualitative agreement with the suggestion of Evans *et al.* that the rate determining step in HOO- hydrolyses is collapse of the initially formed tetrahedral intermediates (Ref. 2a). Interestingly, DMF had no effect on the regioselectivity of HO- hydrolysis (steric control), which in both cases was exclusively endocyclic.
3. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Benalil, A.; Roby, P.; Carboni, B.; Vaultier, M. *Synthesis*, **1991**, 787.
4. Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
5. (a) For recent reviews on the synthesis and chemistry of thienamycin (**12**) and related materials, see footnote 3 in Ref. 1. (b) Grieco, P. A.; Flynn, D. L.; Zelle, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 6414. (c) We are grateful to Professor Paul Grieco, of Indiana University, for providing nmr spectral data for (±)-**30**. Satisfactory analytical and spectral data were obtained for all new compounds reported. Rotation values for **14D-30**, $[\alpha]^{25}_D$: **14D** = +1.9° (13.3, CH_2Cl_2); **15D** = -27.6° (3.5, MeOH); **16** = +4.1° (25.8, MeOH); **17** = +12.8° (15.0, MeOH); **18** = +14.7° (19.8, MeOH); **19** = -56.8° (11.4, CH_2Cl_2); **20** = -26.4° (7.7, CH_2Cl_2); **24** = 0.00° (68.3, CH_2Cl_2); **26** = +9.6° (25.7, CH_2Cl_2); **27** = +20.8° (6.8, CH_2Cl_2); **28** = -1.3° (17.4, CH_2Cl_2); **29** = -24.6° (12.2, CH_2Cl_2); **30** = -1.9° (6.3, CH_2Cl_2).
6. Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.
7. (a) We are grateful to Ms. Gayle Schulte, of Yale University, for carrying out the X-ray analysis of acetylenic acid **4c**. (b) We are grateful to Dr. Shaun Murphree for carrying out this experiment, and for his contributions to the early stages of this project.
8. Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Yoshioka, K. *Tetrahedron Lett.* **1989**, *30*, 1253.
9. Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647.

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