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A Versatile Synthesis of ß-Amino Acids Using the Nicholas Reaction. I. Application to ß-Lactams of the Carbapenem Class

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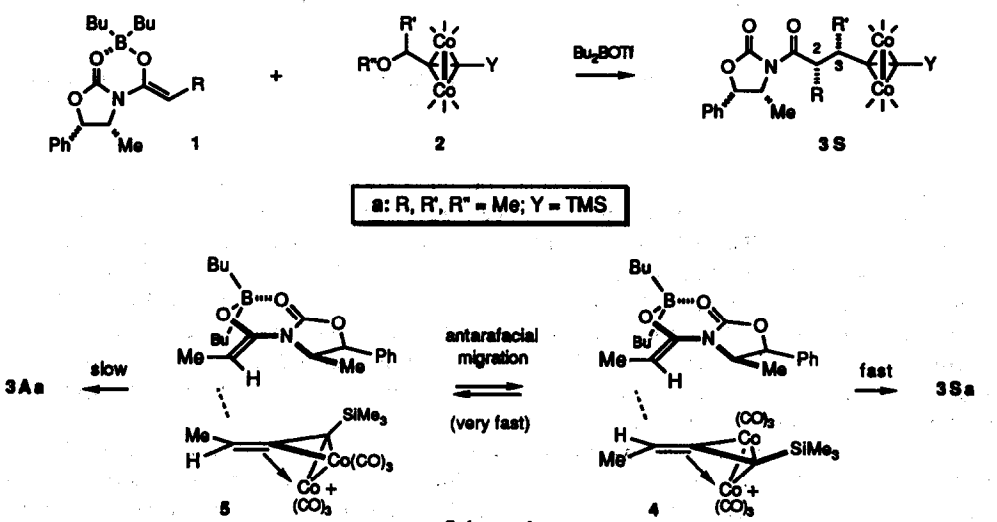
Key Words: Nicholas reaction; acetylenic acids; ß-amino acids; ß-lactam antibiotics; carbapenems.

Abstract: *Homochiral acetylenic acids of general structure 10, prepared using the Schreiber modification of the Nicholas reaction, have been converted to ß-amino acid derivatives of type 11 by a two step sequence involving Curtius rearrangement followed by oxidative cleavage of the acetylenic bond. Amino acid derivatives 11 are excellent precursors for ß-lactams of the carbapenem class.*

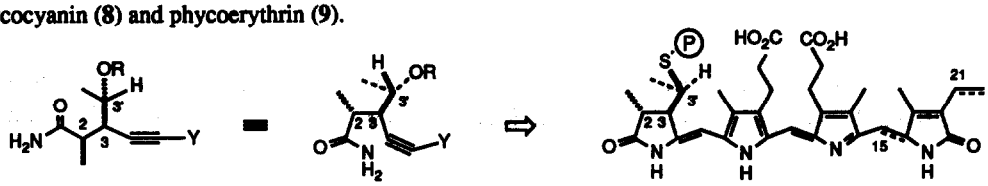
The Nicholas reaction takes advantage of the fact that acetylenic cobalt complexes of the type illustrated in **2** greatly facilitate the heterolytic cleavage of adjacent alcohols or ethers, which upon HBF_4 or Lewis acid catalysis afford cobalt stabilized carbonium ions that are readily captured by nucleophiles (Scheme 1).[1] The



Scheme 1

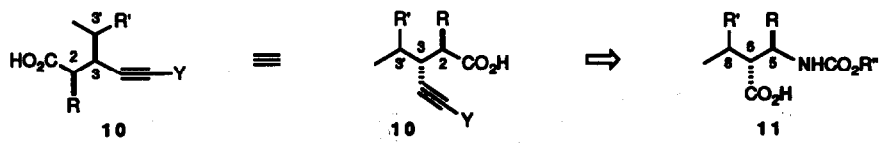
parent acetylenes can then be regenerated under mild oxidative conditions.[1c] In a noteworthy variant of this reaction, Schreiber *et al.* demonstrated that homochiral imide enolate **1a** readily combined with cobalt complex **2a** under conditions of Bu_2BOTf catalysis, affording Nicholas adduct **3Sa** in 80% yield and with syn-selectivity on the order of 12:1 (S = syn, A = anti).[1d] This selectivity was elegantly rationalized by postulating a novel double stereodifferentiating process, in which cations **4** and **5** interconvert *via* enantiomerization at a rate which is fast relative to alkylation (kinetic resolution). Reaction of **1** with the "matched" cation **4**, affording syn-adduct **3Sa**, was predicted to occur at a faster rate than with the "mismatched", enantiomeric cation **5**, which would give anti-adduct **3Aa** (inversion of configuration at C_3). Recently, we have expanded upon this methodology to prepare homochiral acetylenic amides of type **6** (R = Me, Bn; Y = H, TMS, 2-pyrrolo),[2] which

are attractive intermediates for the synthesis of biologically important tetrapyrroles such as phytochrome (**7**), phycocyanin (**8**) and phycoerythrin (**9**).



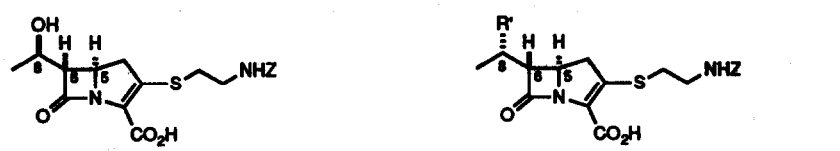
6 **6** **7** (Δ-15, Δ-21); **8** (Δ-15); **9** (Δ-21)

As part of our continuing studies in this area, we have been investigating the possibility that acetylenic acids of type **10** might serve as convenient precursors for amino acid derivatives of general structure **11**, which in turn are versatile intermediates for the synthesis of ß-lactam antibiotics of the carbapenem class (Scheme 2).[3]



10 **10** **11**

a: R' = H; **b**: R' = Me; **c**: R' = *S*-OP; **d**: R' = *R*-OP



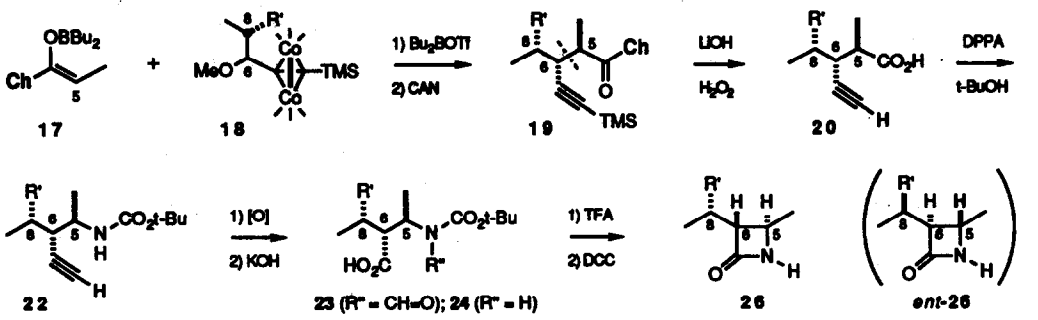
12 (Z = H); **13** (Z = CH=NH) **14** (R' = OH; Z = H); **15** (R' = H; Z = Ac); **16** (R' = Me; Z = Ac)

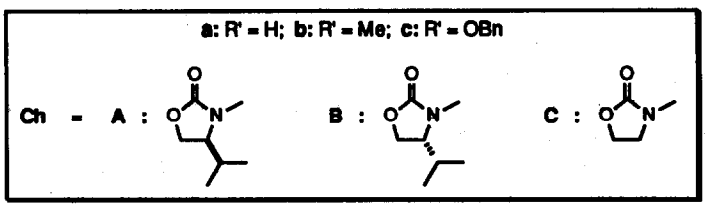
Scheme 2

For example, we expected that Curtius rearrangement of **10d** (R'= *R*-OP),[4a] followed by oxidative cleavage of the acetylenic bond,[3e,5] would afford amino acid derivatives **11d** of a type which have been efficiently converted to thienamycin (**12**) and imipenem (**13**).[3a-f] In analogous fashion, **10c** (R'= *S*-OP) would provide access to members of the olivanic acid class of antibiotics, such as MM-22381 (**14**), which differ from the thienamycins primarily in having the *S*-configuration at C_8.[3h] Finally, acetylenic acids **10a** (R'= H) and **10b** (R'= Me) appeared to be viable precursors to the important des-hydroxy derivatives PS-5 (**15**) and PS-6 (**16**), respectively.[3a-c,i,j] In this paper we provide preliminary results which demonstrate the feasibility of this strategy for the synthesis of **14-16**, and in the accompanying note we describe a formal total synthesis of the most important member of this class, thienamycin (**12**).

Our initial efforts were directed toward the preparation of ß-lactams **26a-c** and *ent*-**26a-c**,[3k] which we expected would provide a suitable test for the transformation **10** --> **11** (*vide supra*), and also serve as a model study for the synthesis of ß-lactams **14-16** (Scheme 3, following page; *ent* = mirror image of parent structure shown). Cobalt derivatives **18a-c** and *ent*-**18c** (8*R*-configuration) were readily obtained by condensation of lithiotrimethylsilylacetylene with aldehydes R'CHMeCHO (R'= H, Me, *S*-OBn, *R*-OBn),[2] followed by *in situ* methylation (DMS) and complexation of the resulting methylpropargyl ethers with $Co_2(CO)_8$.[1] Imide enolates **17A-C** (Ch = A-C) were prepared following the general procedure of Schreiber *et al.*,[1d] employing 1.0 equivalents each of $(i\text{-}C_3H_7)_2NEt$ and Bu_2BOTf at 0 °C in CH_2Cl_2. The resulting enolate solutions were then cooled to -78 °C, treated with an additional 0.5-1.0 eq of Bu_2BOTf, followed by an equimolar quantity of **18** (based on *excess* Bu_2BOTf), and warmed to 0 °C to afford the desired adducts **19** and *ent*-**19** after oxidative

cleavage with ceric ammonium nitrate (CAN) (Table 1). In general, yields for this reaction were excellent (85-98%) utilizing a ratio of **17:18** = 2:1 (entries 1 and 4), and only slightly less satisfactory (75-85%) employing a ratio of **17:18** = 1:1 (entries 2 and 5). Not surprisingly, however, **19b(A)** [R'= Me, Ch = A] was obtained in considerably lower yield (19%, entry 3), presumably due to steric hindrance and competing elimination reactions in the stabilized carbonium ion derived from **18b**.[1]





Scheme 3

Diastereo- and enantioselectivities were also generally excellent, with *syn:anti* ratios of >98:2 employing chiral enolates **17A** and **17B** with achiral cobalt complexes **18a,b** (entries 1 and 2; somewhat lower selectivity [~12:1] was observed with chiral enolate **1a**,[1d] *vide supra*). These results are in full accord with the transition state model proposed by Schreiber *et al.* (Scheme 1).[1d] Equally impressive ratios (>98:2) were obtained with the "matched" chiral substrates **17A** + **18c** --> **19c(A)** and **17B** + *ent*-**18c** --> *ent*-**19c(B)** (entries 4 and 5; the case of "mis-matched" substrates will be discussed in the following paper). Interestingly, 5*R*,6*R*-diastereoselectivity of >98:2 was also realized in the condensation of **18c** with the achiral enolate **17C**, as judged by conversion of the derived adduct **19c(C)** to the identical homochiral acetylenic acid **20c** derived from chiral

Table 1

Entry	Compd (Ch)	Yield[a]	$[\alpha]^{25}_D$ (c)[d]	Compd	Yield[a]	$[\alpha]^{25}_D$ (c)[d]	Compd	Yield[a]	$[\alpha]^{25}_D$ (c)[d]
1	**19a (A)**	94[b]	+28.7 (12.4)	**20a**	95	+11.7 (27.8)	**22a**	82	+61.1 (24.8)
2	*ent*-**19a (B)**	81[c]	-26.0 (30.6)	*ent*-**20a**	91	-11.5 (60.7)	*ent*-**22a**	74	-64.0 (20.1)
3	**19b (A)**	19[b]	+15.9 (4.5)	**20b**	34	-1.3 (45.8)	**22b**	62	+55.2 (20.4)
4	**19c (A)**	93[b]	-33.1 (6.4)	**20c**	85	-31.6 (7.8)	**22c**	83	+34.9 (19.8)
5	*ent*-**19c (B)**	75[c]	+37.4 (14.7)	*ent*-**20c**	77	+30.2 (19.5)	*ent*-**22c**	82	-34.4 (4.7)

Entry (cont'd)	Compd	Yield[a]	$[\alpha]^{25}_D$ (c)[d]	Compd	Yield[a]	$[\alpha]^{25}_D$ (c)[e]
1	**24a**	93	+12.7 (2.7)	**25a**	68	+19.8 (10.3)
2	*ent*-**24a**	92	-13.8 (7.2)	*ent*-**25a**	78	-18.3 (19.5)
3	**24b**	97	+23.8 (15.1)	**25b**	82	+11.3 (23.0)
4	**24c**	64	+62.4 (16.3)	**25c**	73	+35.5 (19.8)
5	*ent*-**24c**	68	-64.7(12.8)	*ent*-**25c**	79	-36.5 (10.5)

a) Average yield for several runs. b) Yield employing 2 eq **17**. c) Yield employing 1 eq **17**. d) Measured in MeOH (c = mg/ml). e) Measured in CH_2Cl_2 (c = mg/ml).

enolate **17A** (*vide infra*). This example provides some indication of the powerful directing influence which chiral substituents can exert on the Nicholas reaction.[6]

Once in hand, oxazolidinones **19** were readily converted to the corresponding acetylenic acids **20** by hydrolysis with excess lithium hydroperoxide (4-8 eq, 3:1 THF/H_2O, 0º --> RT),[7] which effected concomitant cleavage of the TMS group. As indicated, yields for this step were excellent (80-98%), except for the special case where R'= Me (entry 3, *vide supra*). Curtius rearrangement of **20** to **22** was then conveniently carried out with diphenylphosphoryl azide (DPPA, 80-100 ºC, benzene or toluene),[4a] followed by HCl catalyzed capture of the resulting isocyanate **21** (not isolated) with *tert*-butanol.[4b] Within the limits of detection, this last step occurred with complete retention of stereochemistry, as determined by NMR analysis and comparison of the specific rotations for **22a,c** and ***ent*-22a,c** (entries 1, 2, 4, and 5).

We experienced some initial difficulties in effecting the oxidative cleavage of acetylenic carbamates **22** to the corresponding carboxylic acids **24**. For **22a,b** and ***ent*-22a**, this transformation was best accomplished with $KMnO_4/NaIO_4$,[3e] which afforded ~50:50 mixtures of the corresponding acids **24a,b** and ***ent*-24a** together with the N-formyl derivatives **23a,b** and ***ent*-23a**. These mixtures were usually not separated, but rather were directly hydrolyzed (KOH) to afford pure **24a,b** and ***ent*-24a** in >90% overall yield (entries 1-3). With **22c** and ***ent*-22c**, however, $KMnO_4/NaIO_4$ caused extensive decomposition due to oxidation of the benzyl protecting group to produce benzoic acid. This difficulty was eventually circumvented with the finding that $OsO_4/NaIO_4$ provided the desired chemoselectivity,[5] leading exclusively to the N-formyl derivatives **23c** and ***ent*-23c**. As with **23a,b** and ***ent*-23a**, above, these last materials were readily cleaved with KOH to afford the desired carboxylic acids **24c** and ***ent*-24c** (entries 4,5). The utility of these amino acid derivatives for the synthesis of ß-lactams was then convincingly demonstrated by their facile conversion to **26** and ***ent*-26** following standard literature procedures (DCC).[3e]

The appeal of this strategy derives from its highly convergent nature, and the fact that in principle both relative and absolute stereochemistry at C_5-C_8 can be rigorously controlled. However, as described in the accompanying paper, syn-selectivity in Nicholas reactions employing chiral imide enolates is strongly dependent upon the nature of chiral substituents in acetylenic cobalt complexes of type **2**.[8]

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