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Enantioselective Syntheses of (+)- and (-)-Phaseolinic Acid

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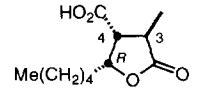
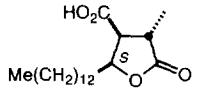
Abstract: (+)- and (-)-Phaseolinic acid (**1**) have been prepared in an enantioselective fashion from acetylenic acid **26** (or *ent*-**26**) by a three step sequence involving lactonization, epimerization at C_3, and oxidative cleavage. **26** was obtained as a single enantiomer using a Nicholas-Schreiber reaction.

The paraconic acids are a family of trisubstituted γ-butyrolactones, examples of which have been isolated from various species of moss and lichens,[1] as well as culture filtrates of *penicillium* sp (Figure 1).[2] Recently, these materials have attracted considerable synthetic attention, in part because of their interesting biological activity.[3] A characteristic feature of this class is the C_4-carboxyl functionality, which is accompanied by an alkyl chain at C_5 that ranges in length from five to fifteen carbons. In some cases the C_5-alkyl chain is oxidized at one or more positions [*cf.* (-)-allo-pertusaric acid (**6**)]. Finally, C_3 is invariably substituted with either a methyl- or methylene group, which plays a significant role in determining the compound's physiological properties. For example, (-)-dihydroprotolichesterinic acid (**4**) is a potent anti-bacterial agent,[1f,3e] while (-)-protolichesterinic acid (**5**) is notable for its anti-tumor, anti-fungal and growth regulating properties.[2,3h]



(-)-phaseolinic acid (**1**)



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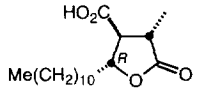

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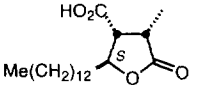
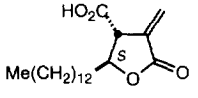
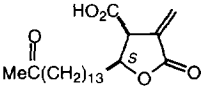


(-)-dihydroprotolichesterinic acid (**4**)



(-)-protolichesterinic acid (**5**)



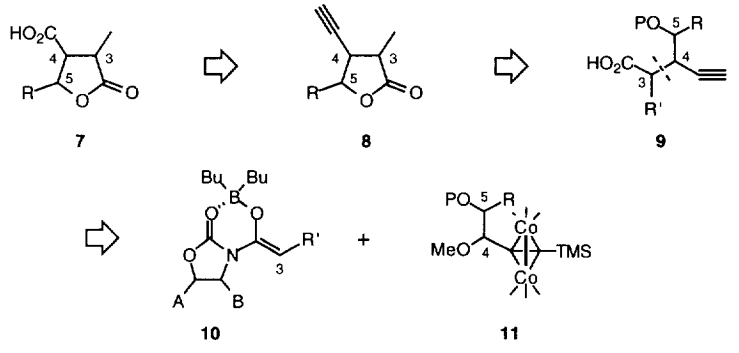
(-)-allo-pertusaric acid (**6**)

Figure 1

The stereochemical relationship between C_3, C_4 and C_5 in these lactones varies widely, and examples of nearly all possible combinations are known (*e.g. TT*, *TC*, *CT*, and *CC*).[3i] In addition, some members have been isolated in both dextro- and levorotatory forms.[3h] Each of these variants has an important influence on biological activity, which makes the stereoselective syntheses of these compounds an interesting and challenging goal. In this note we describe enantioselective syntheses of both (+)- and (-)-phaseolinic acid (**1**),[1h,3a] using methodology which allows for control of both relative and absolute stereochemistry at all stereogenic centers.

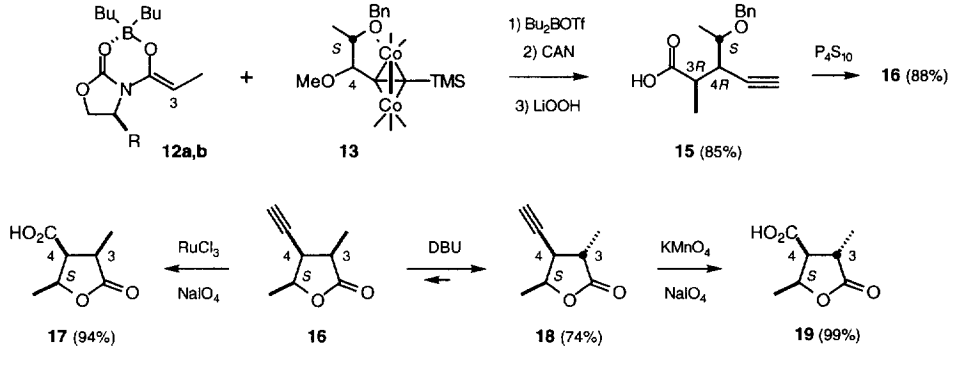
In a recent series of papers we described efficient syntheses of acetylenic acids of general structure **9**, which were readily obtained, in enantiomerically pure form, by Nicholas-Schreiber condensation of boron enolates **10** with acetylenic cobalt complexes **11** (Scheme 1; P = protecting group).[4,5] These acids were utilized in the syntheses of diverse natural products, including the carbapenem antibiotic thienamycin,[4a] and

cyclic enamides of a type found in vitamin B_{12}.[4b] For the case where R'= Me, we expected that **9** would also be a useful precursor for the synthesis of paraconic acids of type **7**. Thus, deprotection of **9**, followed by cyclization, would afford the acetylenic lactone **8**, which upon oxidative cleavage would give **7** with predictable stereochemistry at C_3-C_5.[4,5] In addition to kinetic control, which favors *syn*-adducts with "matched" substrates of type **10** and **11**,[4a-c,5] this approach also offered the possibility of selective epimerization at either C_3 or C_4, depending upon the timing of the oxidative cleavage. As previously described, "mis-matched" condensations of this type exhibit *anti*-selectivity.[4a]



Scheme 1

The viability of this strategy was first tested with the model system **16**, which was prepared in excellent overall yield as diagrammed in Scheme 2. Chiral boron enolate **12a** (R = *i*-propyl) was prepared following the general procedure of Schreiber *et al.*,[5d] employing 1.0 equiv each of $(i\text{-}C_3H_7)_2NEt$ and Bu_2BOTf at 0 °C in CH_2Cl_2. Cobalt derivative **13** was prepared as described previously,[4a] by condensation of lithio(trimethylsilyl)acetylene with *S*-benzyloxyacetaldehyde,[6] followed by *in situ* methylation (DMS), and complexation of the resulting methylpropargyl ether with $Co_2(CO)_8$.[5] Matched condensation of **12a** and **13**,[7a] followed by LiOOH hydrolysis,[7b] then gave an 85% yield of the 3*R*,4*R*-acetylenic acid **15** with >98% *syn*-selectivity. Interestingly, in this case *achiral* oxazolidinone **12b** (R = H) also afforded enantiopure **15** in 83% yield and with >98% *syn*-selectivity. This last reaction illustrates the strong directing influence that chiral substrates can exert on the Nicholas reaction (note that the condensation of **12b** and **15** does not involve "double stereodifferentiation" [4c]).

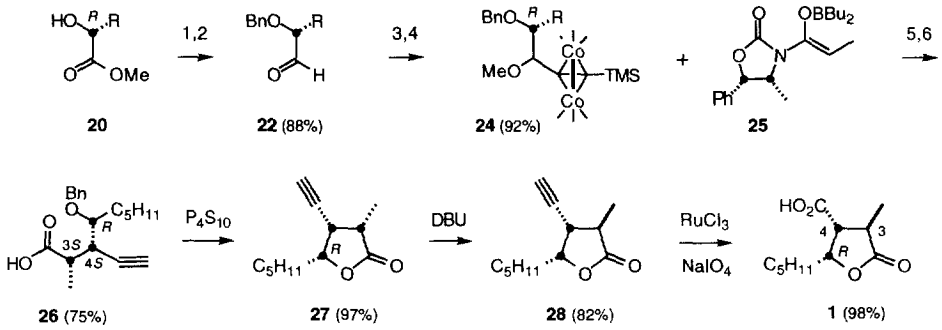


a: R = isopropyl; **b**: R = H

Scheme 2

Various methods were then explored in an attempt to cleave the benzyl protecting group in **15**. However, by far the most convenient reagent turned out to be P_4S_{10},[8a] which routinely afforded 85-95% yields of the 3*R*,4*R*,5*S*-lactone **16** upon stirring with **15** at RT in CH_2Cl_2. Cleavage of benzyl ethers with P_4S_{10} does not appear to be a general reaction, but this reagent works well with carboxylic acids where intramolecular participation is possible.[8a] Once in hand, **16** could be directly oxidized to the paraconic acid **17** having the 3*R*,4*S*,5*S*-configuration ($RuCl_3$, $NaIO_4$; *CC*-stereochemistry). Alternatively, **16** underwent facile equilibration with DBU/CH_2Cl_2 to afford a 74:20 equilibrium mixture of **18** and **16**, which was readily separated by chromatography. Oxidative cleavage of **18** then gave a virtually quantitative yield of the paraconic acid **19**,[8b] which was obtained as a single enantiomer having the 3*S*,4*S*,5*S*-configuration (*TC*-stereochemistry).

In order to apply these model studies to the syntheses of naturally occurring paraconic acids, it was first necessary to develop a flexible synthesis of cobalt complexes of type **24** and *ent*-**24** (Scheme 3; *ent* = mirror image of structure shown). This was accomplished by taking advantage of the ready availability of hydroxyacid derivatives of type **20** and *ent*-**20**. A number of such acids are available commercially,[9a] and they are also conveniently prepared by methods which include asymmetric reduction of the corresponding trichloromethyl-ketones,[9b] asymmetric hydroxylation,[9c] or resolution.[9d] For the case of (+)- and (-)-phaseolinic acid (**1**), enantiomerically pure **20b** and *ent*-**20b** (R = *n*-C_5H_{11}) were obtained in multigram quantities following the procedure of Hauser *et al.*[9d] Once in hand, ester **20b** was converted to the cobalt complex **24b** in >80% overall yield, employing a straightforward sequence involving benzylation (BnBr, Ag_2O), followed by reduction (DIBAL-H), condensation with lithio(trimethylsilyl)acetylene (LiTMSA), and complexation with $Co_2(CO)_8$.[4,5]



a: R = alkyl; **b**: R = *n*-C_5H_{11}

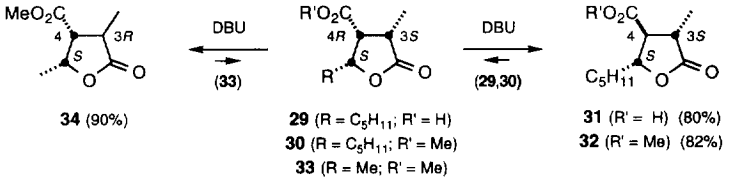
1. BnBr, Ag_2O 2. DIBAL-H 3. LiTMSA; DMS 4. $Co_2(CO)_8$ 5. Bu_2BOTf; CAN 6. LiOOH

Scheme 3

Condensation of **24b** with boron enolate **25** then occurred in a "matched" fashion,[4a-c,5] affording a 75% overall yield of acetylenic acid **26** after decomplexation and hydrolysis (>12:1 *syn*-selectivity). As described above for **15** (Scheme 2), enantiopure **26** was also obtained in 71% overall yield (>12:1 *syn*-selectivity) employing the *achiral* boron enolate **12b** (R = H). The synthesis of (-)-**1** was then completed by P_4S_{10} induced debenzylation and cyclization (97%), followed by C_3-epimerization (82%; 16% return of **27**), and oxidative cleavage (98%; *cf.* also Scheme 2). (-)-Phaseolinic acid (**1**) thus prepared had identical spectral data as that reported in the literature, and was obtained as a single enantiomer [mp 137-38 °C; lit. mp 139-40 °C;[1h] 138-40 °C.[3a] $[\alpha]_D^{26}$ = -147° (c = 0.37, $CHCl_3$); lit. $[\alpha]_D^{26}$ = -150° (c = 0.20, $CHCl_3$);[1h] -142° (c = 0.22, $CHCl_3$)[3a]]. In analogous fashion, we also prepared (+)-**1** beginning with *ent*-**20b** and utilizing either chiral oxazolidinone *ent*-**25** or achiral oxazolidinone **12b** [mp 138-39 °C; $[\alpha]_D^{26}$ = 146° (c = 0.16, $CHCl_3$)].

Finally, it was of interest to see if the "all trans" stereochemistry (*TT*) found in nephrosteranic acid (**3**) might be attained by epimerization at C_4 in preference to C_3. This was readily accomplished with lactone **27** (R = *n*-C_5H_{11}) by carrying out oxidative cleavage prior to equilibration (Scheme 4). Thus, $RuCl_3$/$NaIO_4$ mediated

cleavage of **27** gave a 95% yield of the paraconic acid **29**, which was esterified with CH_2N_2 to give the methyl ester **30** (95%). Treatment of *either* **29** or **30** with DBU gave predominantly epimerization at C_4, providing the *TT* isomers **31** and **32** in 80% and 82% yield, respectively (~1-10% return of **29** and **30**; ~1-10% epimerization at C_3). Preferential epimerization at C_4 might be a general phenomenon for relatively large R groups at C_5. However, as a cautionary note, lactone ester **33** (R = Me) underwent exclusive epimerization at C_3 to afford the *CT* isomer **34** (90%; 7% return of **33**). Further studies of this methodology for the synthesis of paraconic acids are underway and will be reported in due course.



34 (90%)

29 (R = C_5H_{11}; R' = H)
30 (R = C_5H_{11}; R' = Me)
33 (R = Me; R' = Me)

31 (R' = H) (80%)
32 (R' = Me) (82%)

Scheme 4

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