Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6621-6624, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01533-5

Enantioselective Syntheses of (+)- and (-)-Blastmycinolactol

Peter A. Jacobi* and Prudencio Herradura

Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06459-0180

Abstract: (-)-Blastmycinolactol (**1b**) has been prepared in an enantioselective fashion from acetylenic acid **5** by a three step sequence involving debenzylation-lactonization, hydration with concurrent C_3-epimerization, and Baeyer-Villiger oxidation accompanied by ester cleavage. Acylation of **1b** with isovaleryl chloride then afforded (+)-blastmycinone (**1a**) in excellent overall yield.

(+)-Blastmycinone (**1a**) is a degradation product of the macrocyclic dilactone (+)-antimycin (blastmycin, **2a**), an antifungal-antibiotic isolated from several members of the *Streptomyces* species (Figure 1).[1,2] Recently **1a** has attracted considerable synthetic attention,[3a-d] in part because it is an attractive precursor to **2a**, and also because lactones of this type provide interesting stereochemical challenges. Related "*trans-trans*" (TT) lactones include (-)-blastmycinolactol (**1b**),[3d-f] from which **1a** is readily derived by acylation,[3a-c] and NFX-2 (**3a**) and

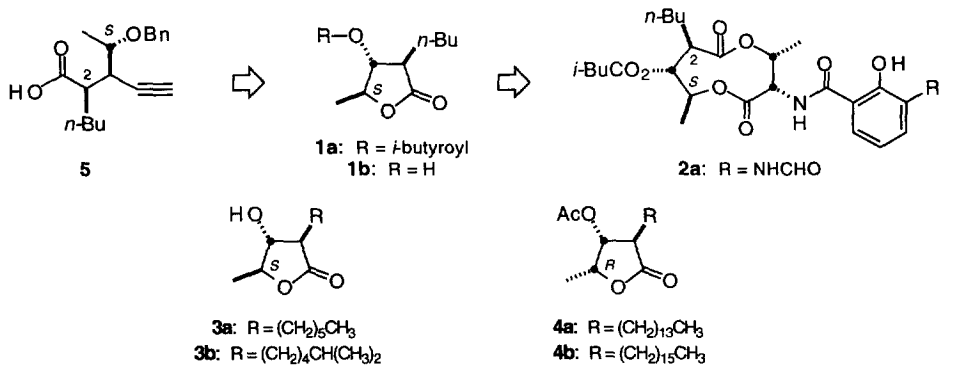
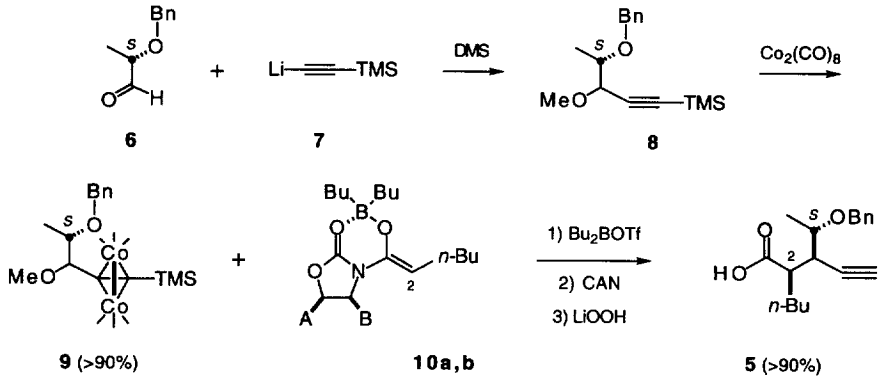


Figure 1

NFX-4 (**3b**), which are virginiamycin inducing factors isolated from the culture broth of *Streptomyces antibiotics* NF-18.[4] Examples of "*cis-trans*" (CT) hydroxylactones include **4a** and **4b**, which are lipid metabolites produced by the Gorgonian coral *Plexaura flava*.[5] The published syntheses of **1a** and **1b** vary in their ability to control relative stereochemistry about the γ-butyrolactone ring, and/or to prepare optical antipodes. In this note we describe an efficient solution to this problem that makes use of the alkyne acid **5**.

Acid **5** was readily prepared from the alkyne cobalt complex **9**, itself derived in two steps, as previously desribed,[6a] from 2-(*S*)-(benzyloxy)propionaldehyde (**6**)[2f,7] and lithio(trimethylsilyl)acetylene (**7**) (Scheme 1; >90% overall yield). Following literature precedent,[6,8] **9** underwent a highly *syn*-selective Nicholas-Schreiber condensation with boron enolates **10**, affording, after oxazolidinone cleavage,[9] a >90% overall yield of **5** as a single enantiomer.[10a] Interestingly, identical levels of asymmetric induction were obtained employing either chiral boron enolate **10a** ("matched" condensation),[6c] or achiral enolate **10b**. This last case illustrates the

strong directing influence that stereogenic centers can exert on the Nicholas reaction (note that the condensation of **10b** and **9** does not involve "double stereodifferentiation" [6c]). The only apparent by-product in these reactions is a small amount (<2%) of the corresponding *anti*-acetylenic acid.[6,8d]



a: A = Ph, B = Me. **b**: A,B = H

Scheme 1

It was next necessary to cleave the benzyl protecting group in **5**, a transformation that required careful control of chemoselectivity. For example, hydrogenolysis was not practical due to competing reduction of the alkyne triple bond.[10b] Similar complications were anticipated with Na/NH_3 or Li/NH_3, and other reagents that work well in the absence of sensitive functionality.[11] A widely employed solution to this problem is based upon HSAB theory,[12] in which the "hard" ether oxygen is selectively complexed with a "hard" Lewis acid (HLA), affording an activated complex **12** (Figure 2). Under these conditions, nucleophilic attack at the adjacent "soft" sp^3 center (SE) is favorable with "soft" nucleophiles such as thiols (**11**).[12c] However, in model studies *inter*-molecular reactions of this type were uniformly unsuccessful, in part due to the harsh conditions required.[10b,c]

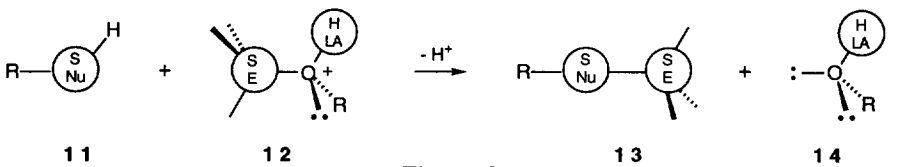
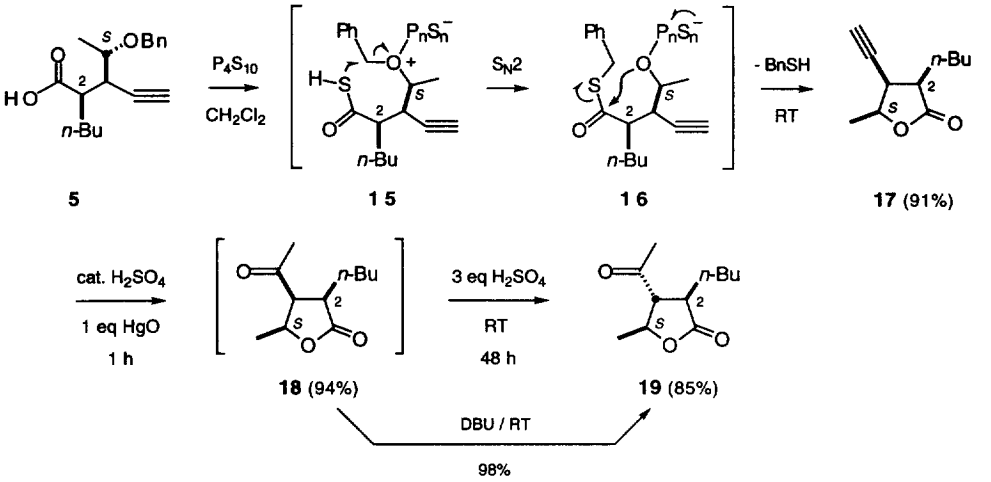


Figure 2

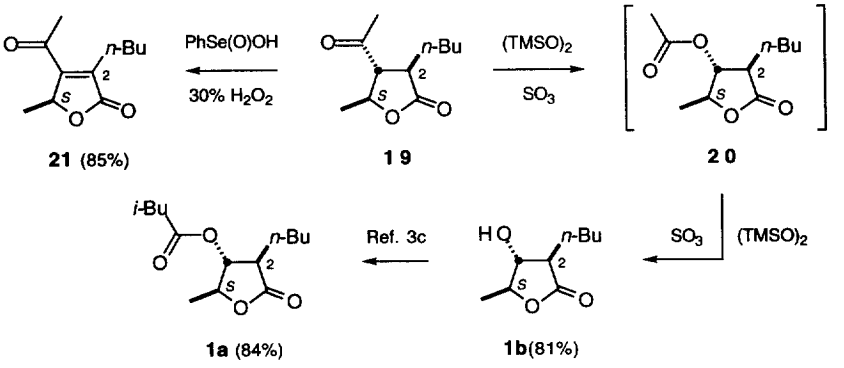
As a modification to this approach, we found that alkyne acid **5** reacted cleanly with P_4S_{10}, affording a >90% yield of lactone **17** (Scheme 2).[10a] We interpret this result as arising by initial conversion of **5** to the thioacid **15**, which is ideally composed to undergo an *intra*molecular displacement of the activated benzyl group. Transformations of this type find good precedent in thia-Mitsunobu reactions, where the active nucleophile is thioacetic acid.[13] Once formed, the presumed thioester intermediate **16** would undergo rapid lactonization to afford **17** with loss of benzyl mercaptan. Support for this mechanism derives from the fact that benzyl mercaptan, and not benzyl alcohol, is readily detected by GC-MS. This reduces, but does not eliminate,[10d] the possibility of an alternative pathway involving direct displacement of the benzyl group by the carboxyl functionality. Also, alkyne *esters* of general structure **5** are inert to P_4S_{10}-induced benzyl ether cleavage, even at elevated temperatures, and employing HOAc or TFA as solvent.[10b] With esters, intramolecular participation by the carboxyl group is presumably less favorable, since it cannot be converted to a thioacid. In contrast, with acid **5** the entire sequence is conveniently carried out with a slight excess of P_4S_{10} by stirring at RT in CH_2Cl_2.



Scheme 2

Once in hand, lactone **17** underwent facile hydration of the alkyne triple bond, affording a 94% yield of the methyl ketone **18** after stirring 1 h at RT with 1 eq of HgO and .04 eq of 1 M H_2SO_4 (Scheme 2). Ketone **18** has the *S*-configuration at C_3, which is opposite to that found in both (+)-(**1a**) and (-)-(**1b**).[10a] However, the desired 3-(*R*)-configuration was readily attained by increasing the concentration of H_2SO_4 (3 eq), and extending the reaction period to 48 h. Under these conditions **18** underwent clean acid-catalyzed epimerization to afford **19** in 85% overall yield.[10a] Alternatively, this same epimerization could be accomplished in 98% yield by employing DBU in CH_2Cl_2 at RT.

The remaining steps necessary in order to convert methyl ketone **19** to (-)-blastmycinolactol (**1b**) involved Baeyer-Villiger oxidation to the acetate derivative **20**, followed by ester hydrolysis (Scheme 3). However, our initial experiments in this direction were disappointing, since **19** was unreactive to most of the usual reagents employed for this purpose.[14] These included *m*-CPBA,[14a] CH_3CO_3H,[14b] and CF_3CO_3H,[14c] all of which returned mainly starting materials after extended reaction periods. Eventually some degree of success was achieved with the reagent system $PhSe(O)OH/H_2O_2$,[14d] which afforded up to 20% yields of the desired ester **20**, together with much larger quantities of the dehydrogenation product **21**. However, by far the best results were obtained employing bis(trimethylsilyl) peroxide [$(TMSO)_2$], which was initially introduced by Noyori for the chemoselective oxidation of ketones in the presence of alkene double bonds.[14e] With SO_3 as activator,[14f]



Scheme 3

this reagent system not only effected smooth Baeyer-Villiger oxidation, but also led directly to the target compound (-)-**1b** by *in situ* cleavage of the acetate group. Although some precedent exists for ester cleavages of this type,[14g] this last transformation warrants further study.

(-)-Blastmycinolactol (**1b**) thus obtained, in three steps from alkyne acid **5**, and in >60% overall yield, had identical spectral and physical properties as those published for the naturally derived material,[3a-d,15] and was readily converted to (+)-blastmycinone (**1a**) following the literature procedure.[3c] Finally, in analogous fashion, but beginning with *ent*-**5** (*ent* = enantiomer of structure shown), we have also prepared the optical antipodes (+)-**1b** and (-)-**1a** in enantiomerically pure form.[15,16]

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10. (a) Stereochemical assignments were based upon literature precedent,[6,8] spectral data,[6] and by conversion to the target compounds (+)-**1a** and (-)-**1b**. (b) Unpublished results, Dr. Wanjun Zheng, Wesleyan University. (c) At T > 80 °C, mercaptans undergo competitive addition to the triple bond. (d) BnOH is slowly converted to BnSH under the reaction conditions, but it is easily detectable when admixed.
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15. (+)-**1a**: colorless oil; $[\alpha]_D^{26}$ = 10.2° (c = 1.2, $CHCl_3$); lit.[2f] $[\alpha]_D^{23}$ = 10° (c = 1.5, $CHCl_3$). (-)-**1a**: oil; $[\alpha]_D^{26}$ = -10.0° (c = 2.0, $CHCl_3$); lit.[2f] $[\alpha]_D^{25}$ = -10° (c = 2.26, $CHCl_3$). (-)-**1b**: mp 49-50 °C; lit.[2f] mp 50-51 °C. $[\alpha]_D^{26}$ = -18.1° (c = 0.80, MeOH); lit.[2f] $[\alpha]_D^{22}$ = -18° (c = 1.61, MeOH). (+)-**1b**: mp 50-51 °C; lit.[2f] mp 50-51 °C. $[\alpha]_D^{26}$ = 17.9° (c = 1.4, MeOH); lit.[2f] $[\alpha]_D^{23}$ = 16° (c = 1.60, MeOH).

16. Financial support of this work by NSF Grant No. CHE-9424476 is gratefully acknowledged.

(*Received in USA* 9 *June* 1997; *accepted* 17 *July* 1997)