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SYNTHESIS OF BERNINAMYCINIC ACID

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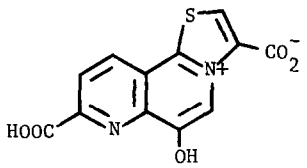
Abstract: A short, efficient synthesis of berninamycinic acid (1) is described.

Berninamycinic acid (1)[1] stands apart as the only known example of the pyridothiazolopyridinium ring system. First encountered as a degradation product of the cyclic polypeptide antibiotic berninamycin,[2] it is also produced upon exposure of sulfomycin[3] and 2[4] to peptide hydrolysis conditions,[5] but no efforts directed towards the rational



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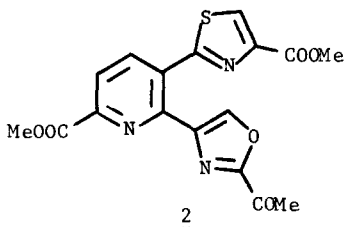

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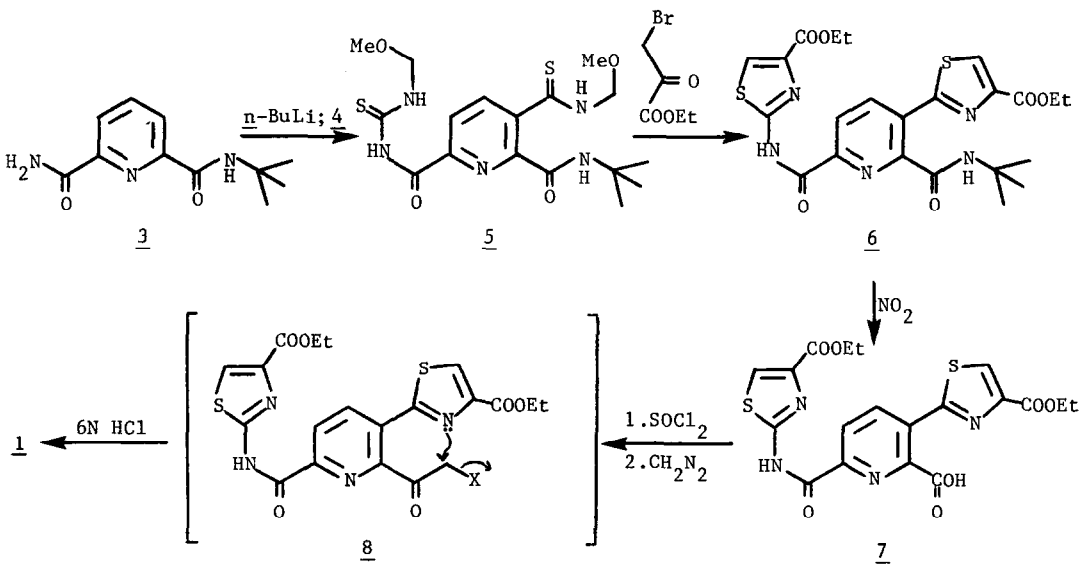
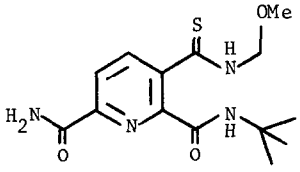
construction of 1 have been recorded. We now report an expeditious synthesis of this structurally remarkable molecule which also serves to illustrate the utility of heteroatom facilitated lithiation[6] for the fabrication of complex heteroaromatic assemblages (Scheme 1).

Scheme 1



3 5 6 7 8 1

Metalation of 3 with 4.2 equiv of n-BuLi in THF (0°C, ca. 1 h) followed by exposure to 2.2 equiv of $CH_3OCH_2N{=}C{=}S$ (4)[7] for 1 h at 24°C provides 5 in 67% yield. Use of only 1 equiv of 4 (0°C, 15 min) cleanly affords 9 (88%), which is also convertible to 1 (vide infra). The nature of the metalated species derived from 3 has not been rigorously established, but 10 is strongly implicated since neither 5 nor 9 is produced if metalation is effected with only 3



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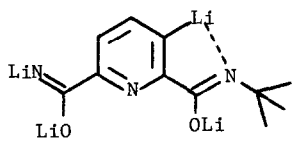

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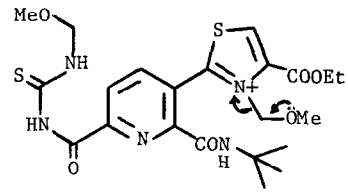
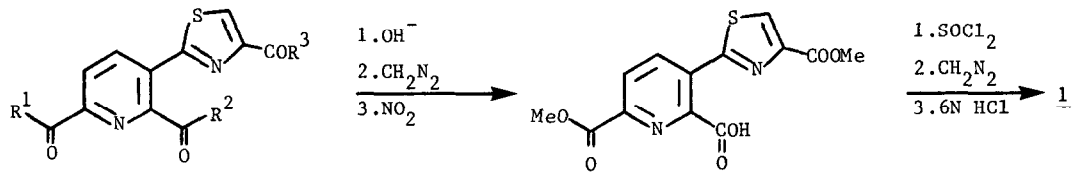


11

equiv of n-BuLi.[8,9] Condensation[10a] of 5 with ethyl bromopyruvate yields 6 (94%), presumably via intermediates such as 11; it is noteworthy that cleavage of the methoxymethylene groupings occurs spontaneously during the course of the reaction.[11]

While 12 can be similarly elaborated[10b] from 9, the thiazole substituent on the amide nitrogen in 6 serves to prevent that amide grouping from reacting with NO_2 and permits continued differentiation[12] of the two carboxyl functions in the conversion[10c,13] of 6 to 7 (92%). Subjection of the latter to a Nierenstein-type[14] homologation sequence[10d] followed without isolation by heating in 6 M HCl[10e] affords berninamycinic acid (1) directly, presumably via intermediates such as 8. The 1 so obtained is identical with naturally derived material[5b] and is produced in an overall yield of 30% based on 3.

In a somewhat longer but more efficient sequence (3→1: 40% overall yield) which is largely an exercise in carboxylic acid derivative chemistry, 12 can also be converted to 1 (Eq. 1).[10f]

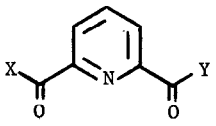


12, $R^1{=}NH_2$, $R^2{=}NHt\text{-}Bu$, $R^3{=}OEt$
13, $R^1{=}R^3{=}OH$, $R^2{=}NHt\text{-}Bu$
14, $R^1{=}R^3{=}OMe$, $R^2{=}NHt\text{-}Bu$

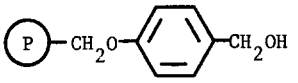
15

(Eq.1)

The starting material (3) in Scheme 1 was prepared by two independent routes. The less direct procedure exploits the susceptibility[15] of 16[10g] to suffer partial saponification to 17 in high yield.[10h] Elaboration of 17 to 3 is straightforward[10i] and amenable to large scale operation (>90% overall) but requires several operations. The more direct route utilizes solid phase synthesis technology[16] and affords 3 in a "one-pot" procedure from commercially available material. Thus attachment[10j] of one of the acid chloride residues of 18[10g] to an



16, X=Y=OMe
17, X=OMe, Y=O$^-$K$^+$
18, X=Y=Cl



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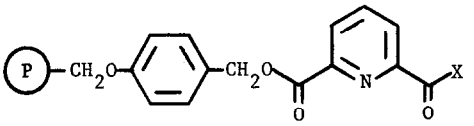

20, X=Cl
21, X=NHt-Bu

hydroxyl group of resin 19[17] simultaneously protects the second acid chloride grouping since its reaction with other polymer-bound nucleophiles is precluded by the spatial constraints inherent in the tertiary structure of cross-linked polymers.[18] Sequential reaction[10k] of the now-differentiated carboxyl functions in 20 with t-butylamine (→21) and NH_4OH affords 3 in 70-80% yield[10ℓ] based on 18.[19]

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(5) (a) The structure originally proposed for berninamycin contains the ring system of berninamycinic acid, but the subsequent finding[4] that 2 is converted to 1 under conditions similar to those used for the degradation of berninamycin to 1 raises yet-unresolved doubts about the structure of berninamycin: Rinehart, K.L. Jr.; Weller, D.D. Pearce, C.J. J. Nat. Prod. **1980**, 43, 1-20. (b) The ^1H NMR spectrum of the sodium salt of 1 in D_2O exhibits[2b] singlets at δ9.21 and 8.39. Rinehart et al.[2b] find that the peak at δ9.21 disappears over time (deuterium exchange). We find that under seemingly identical conditions it is the proton at δ8.39, not at 9.21, which suffers deuterium exchange. While this difference is real and not attributable to errors in transcribing data, its origin is unclear. It is perhaps germane, however, to note that in the case of the ammonium salt of 1 in D_2O, it is the more upfield of the two signals which exchanges (K.L. Rinehart, Jr., personal communication).
(6) For a review see Gschwend, H.W.; Rodriguez, H.R. Org. React. **1979**, 26, 1-360.
(7) Schmidt, E.; Striewsky, W. Chem. Ber. **1940**, 73B, 286-293; 4 is also available from Trans World Chemicals.
(8) The ability of butyllithium to effect removal of both of the NH_2 protons of a 1° carboxamide has been invoked previously: Kaiser, E.M.; Vaulx, R.L.; Hauser, C.R. J. Org. Chem. **1967**, 32, 3640- 3645; Smith, H.A.; Hauser, C.R. J. Am. Chem. Soc. **1969**, 91, 7774.
(9) In contrast to 2° and 3° carboxamides, 1° carboxamides are reported to not promote ortho lithiation (Puterbaugh, W.H.; Hauser, C.R. J. Org. Chem. **1964**, 29, 853-856). Those authors suggested that this failure of ortho lithiation might be due to insolubility of the resulting dianion. But the formation of 5 in the present instance ipso facto invalidates insolubility as a general explanation since 10 is soluble enough to give 5. At a minimum we can infer that a 2° amide is a better directing group than a 1° amide, possibly because ortho lithiation of the dianion of a 1° carboxamide is opposed by the further accumulation of negative charge which would necessarily attend it.

(10) (a) 2.0 equiv $BrCH_2COCOOEt$ 18 h in refluxing MeCN; (b) 1.0 equiv $BrCH_2COCOOEt$ 18 h in refluxing MeCN; typically 12 was not isolated as such but hydrolyzed (10% aq KOH, 80°C) to 13 (70–75% overall yield from 9 (c) excess NO_2 in CF_3COOH, 50°C, 3 h; (d) $SOCl_2$, 60–70°C, 30 min; excess CH_2N_2 in THF/Et_2O, 0°C, 30 min; (e) 6M HCl, 90–105°C, 22 h, then evaporate, 1 purified by washing with acetone and recrystallization of the sodium salt;[1] (f) 12→13 see[10b]; 13→14 CH_2N_2, Et_2O (96%), 14→15 see[10c] (92%); 15→1 as in[10d] then 6M HCl 30 min at 90°C (68%, purification of 1 not necessary); (g) 2,6-pyridinedicarboxylic acid was converted (reflux 24 h in $SOCl_2$) to 18 (which is also commercially available) and the latter reacted with CH_3OH (0°C, 1 h) to give 16 in ca. 97% overall yield; (h) 16 in MeOH reacted with 1 equiv of solid KOH at ≤4°C for 1 h; remove volatiles in vacuo; 17 used without purification; (i) without purification of intermediates 17 was converted successively to the ester acid chloride [$(COCl)_2$, THF, 20°], ester 2° amide (t-$BuNH_2$, Et_2O, 0°C) and thence 3 (conc NH_4OH, 20°C) in 93% overall yield; (j) 18 plus 0.9 equiv resin 19[17] in THF with 1 equiv i-Pr_2NEt in a Schlenk apparatus under N_2 6 h at 20°C; (k) 3 equiv t-$BuNH_2$ in THF, 1 h, 20°C (Schlenk apparatus); neat conc NH_4OH 3 h at 20°C; wash resin/3 mixture with H_2O and extract 3 from resin with EtOAc; (l) conversion of 18 approx. 40%.

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(12) Such differentiation is necessary since 1 is destroyed (unpublished observation of A. Echavarren) by haloform reaction conditions and other reagents (e.g. HIO_4) necessary for the degradation to carboxylic acid residues of any superfluous chloromethyl ketone groupings which would be introduced if 7 were replaced in Scheme 1 by 12 (R^1=R^2=R^3=OH or R^1=R^2=OH, R^3=OEt).

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(15) Compare: Vasa, V.B.; Parameswaran, V.K.; Khorana, M.L.; Tipnis, H.P. Indian J. Pharm. **1968**, 30, 252–253.

(16) For reviews see (a) Stewart, J.M.; Young, J.D. "Solid Phase Peptide Synthesis"; W.H. Freeman and Co., San Francisco, **1969** (we thank the technical service staff of Sigma Chemical Co. for bringing the existence of this book to our attention). (b) Fiechet, J.M.J. In "Polymer-Supported Reactions in Organic Synthesis;" Hodge, P.; Scherrington, D.C. Eds; John Wiley and Sons, New York, **1980**; Chapter 6.

(17) Wang, S.S. J. Am. Chem. Soc. **1973**, 95, 1328–1333. A p-alkoxybenzyl alcohol resin obtained from Chemical Dynamics Corp. (catalog # 57-8620-80) was employed. Hydroxymethylpolystyrene resins (see ref 16a, p 27) gave inferior results.

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(19) Mp and ^1H NMR data for new compounds (all gave satisfactory combustion analysis results): 3, mp 193–195°C (from 1.2:1 EtOAc/$CHCl_3$), ^1H NMR [$(CD_3)_2SO$] δ1.47 (s, 9 H), 7.72 (br s, 1 H), 8.13 (br s, 3 H), 8.40 (br s, 1 H), 8.84 (br s, 1 H). 5, mp 153–154°C (dec) (from 2:1 EtOAc/n-hexane), ^1H NMR ($CDCl_3$) δ1.46 (s, 9 H), 3.49 (s, 3 H), 3.56 (s, 3 H), 5.17 (d, J=6Hz, 2 H, becomes s, 2 H after D_2O exchange), 5.22 (s, 2 H), 6.94 (br s, 2 H), AB quartet (δ_A=7.97, δ_B=8.15, J_{AB}=8 Hz). 6, mp 268–270°C (from EtOAc), ^1H NMR ($CDCl_3$) δ1.42 (t, J=7 Hz, 6H), 1.53 (s, 9 H), 4.44 (q, J=7 Hz, 4 H), 6.64 (br s, 1 H), 7.94 (s, 1 H), 8.35 (s, 1 H), 8.43 (s, 2 H), 11.06 (br s, 1 H). 7, mp 207–208°C (dec) (from 2:1 MeOH/MeCN), ^1H NMR [9:1 $CDCl_3$/ $(CD_3)_2SO$] δ1.41 (t, J=7 Hz, 6 H), 4.40 and 4.44 (overlapping q's, J=7 Hz, 4 H), 7.94 (s, 1 H), 8.42 (s, 1 H), 8.50 (br s, 2 H), 13.17 (s, 1 H). 9, mp 176–177°C (dec) (from EtOAc), ^1H NMR ($CDCl_3$) δ1.45 (s, 9 H), 3.58 (s, 3 H), 5.26 (d, J=5.2 Hz, 2 H becomes s, 2 H after D_2O exchange), 6.65 (br s, 1 H), 6.79 (br s, 1 H), 7.53 (br s, 1 H), AB quartet (δ_A=7.67, δ_B=8.33, J_{AB}=8.1 Hz, 2 H). 13, mp 144–146°C (from 1:1 EtOH/H_2O), ^1H NMR [$(CD_3)SO$] δ1.38 (s, 9 H), 8.36 (br s, 1 H), AB quartet (δ_A=8.30, δ_B=8.44, J_{AB}=8 Hz, 2 H), 8.64 (s, 1 H). 14, mp 193–194°C (from 2:1 benzene/cyclohexane), ^1H NMR ($CDCl_3$) δ1.45 (s, 9 H), 3.95 (s, 3 H), 4.03 (s, 3 H), 7.73 (br s, 1 H), 8.27 (br s, 2 H), 8.37 (s, 1 H). 15, mp 195–196°C (from 10:1 EtOAc/MeOH), ^1H NMR [9:1 $CDCl_3/(CD_3)_2SO$] δ3.96 (s, 3 H), 4.03 (s , 3 H), 8.35 (s, 1 H), AB quartet (δ_A=8.31, δ_B=8.37, J_{AB}=8.2 Hz, 2 H), 9.31 (br s, 1 H).

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