A Total Synthesis of Actinobolin *via* the Intermolecular Diels–Alder Reaction of a Threonine-derived Diene[1]

Alan P. Kozikowski,* Toshiro Konoike, and Thaddeus R. Nieduzak

University of Pittsburgh, Department of Chemistry, Pittsburgh, Pennsylvania 15260, U.S.A.

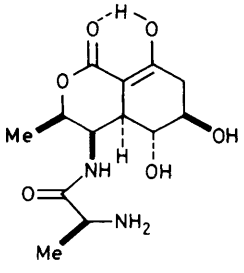
A sixteen-step synthetic route to (+)-actinobolin from L-threonine is described.

We have recently described a synthesis of tri-(*epi*)-actinobolin,[2] an isomer of the naturally occurring broad spectrum antibiotic actinobolin,[3] a compound isolated from cultures of *Streptomyces griseoviridus* var. *atrofaciens*. Closely related structurally to actinobolin is the chlorine containing antibiotic bactobolin,[4] a product isolated from the culture broths of *Pseudomonas* BMG 13—147. The antileukaemic properties of bactobolin are more pronounced than those of actinobolin.[5]

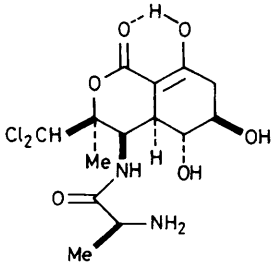
In continuing our synthetic efforts in this area, we have sought to prepare actinobolin itself from the threonine derived silyloxy diene (**1**). While various attempts have been made to improve the diastereoselectivity reported for the Diels–Alder reaction of this diene with methyl propiolate as the dienophilic component,[2] we have had little success in accomplishing this to date. By running the Diels–Alder reaction under high pressure conditions (6 kbar, room temp., 3 days) it was interesting to find that the ratio of diastereoisomers could be changed from the 1.7 : 1 (undesired to desired) ratio observed at 220 °C to 10 : 1.

Since earlier we have observed a shift in the product ratio in the undesired direction on lowering the Diels–Alder reaction temperature,[2] the change observed under the high pressure conditions was not particularly surprising. For both steric and electronic reasons the transition state (**4**) would appear to account best for the production of the major diastereoisomer.

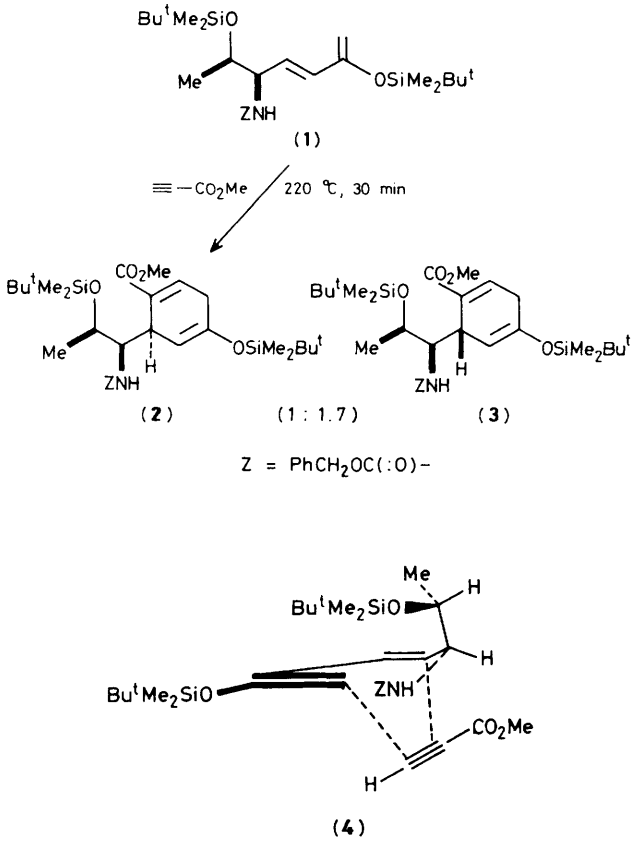
The minor isomer from the thermal reaction was thus separated and then hydroborated, oxidized, and treated with HF to provide the lactone (**5**) as described previously.[2] While in the case of the tri-(*epi*)-actinobolin synthesis we were able to introduce the enolic hydroxy group through a sequence of reactions involving osmylation, thioxocarbonate formation, tin hydride reduction, and oxidation, this particular sequence was not operative for the 'correct' diastereoisomer. Appar-

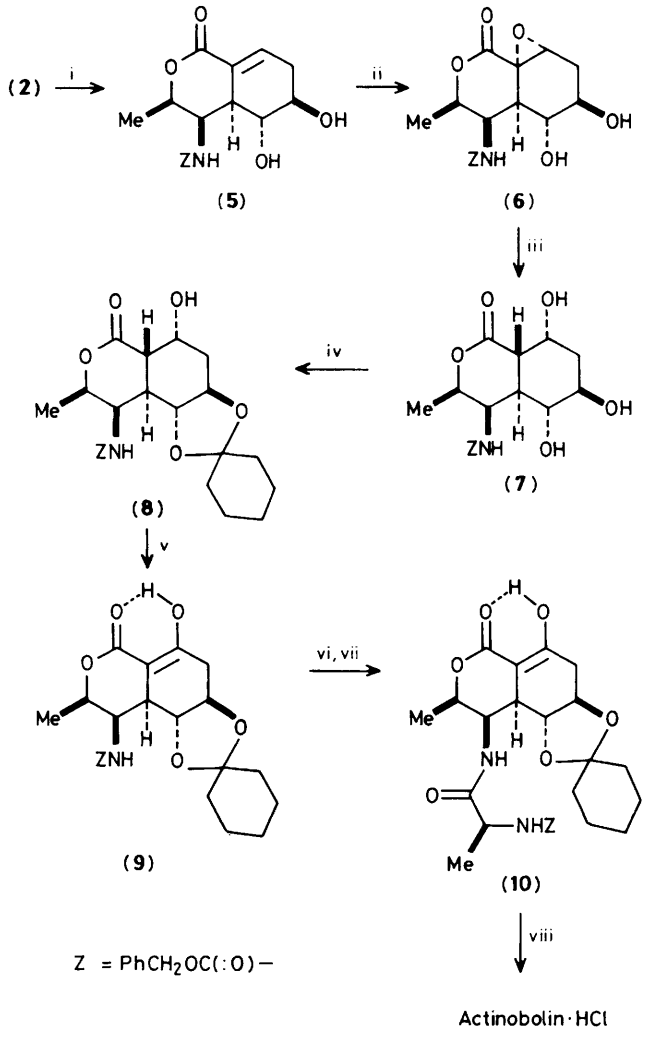


Actinobolin



Bactobolin





ently, various steric and conformational factors made both the osmylation and thioxocarbonate formation difficult in the case of (**5**).

Consequently, we developed an alternative scheme for introducing this enolic hydroxy group. *Only seven* additional steps were needed to complete the conversion of (**5**) into actinobolin. First, epoxidation using 3,5-dinitroperoxybenzoic acid–Na_2HPO_4 delivered (**6**).[6] Reduction with zinc dust in the presence of sodium acetate and acetic acid gave the triol (**7**).[7] After protection of the vicinal diol as its cyclohexylidene acetal, chromium trioxide–pyridine oxidation led to the desired enol-lactone (**9**). The benzyloxycarbonyl group was removed by hydrogenolysis, and a peptide coupling reaction with benzyloxycarbonyl-L-alanine was carried out to afford (**10**).

The newly introduced benzyloxycarbonyl group was then cleaved with concomitant diol deprotection by hydrogenolysis over palladium on charcoal in the presence of 1 M HCl and acetic acid to deliver actinobolin hydrochloride.

The synthetic actinobolin which was isolated as its hydrochloride salt was found to be identical in its spectral properties to natural actinobolin hydrochloride prepared from the corresponding sulphate[8] by exchange over Amberlite IRA-400 resin. The optical rotations of our synthetic hydrochloride {$[\alpha]_D^{24}$ + 50° (*c* 0.52, H_2O)} and the natural hydrochloride {$[\alpha]_D^{24}$ + 53° (*c* 0.65, H_2O)} were between those reported by Weinreb[8] and Ohno.[9]

In summary, the intramolecular Diels–Alder chemistry recorded herein provides a short (16 steps) route to (+)-actinobolin.[10] The major shortcoming of our scheme stems from the inability to control properly the π-facial course of the cycloaddition step. However, since few examples of Diels–Alder reactions employing chiral dienes[11—13] were known prior to our work on the actinobolin synthesis, the present study does provide information which should prove valuable to other researchers wishing to make use of related dienes in their synthetic strategies. Also, it is important to note here that the diene (**1**) fails to follow the rules set forth by Franck regarding the *re* and *si* face directing character of dienes containing an allylic asymmetric centre.[12] The failure of our diene to follow the same stereochemical course as that exhibited by Franck's and Carrie's[13] allylic oxygen bearing dienes may be due to some special steric property of the amide nitrogen substituent, to the presence of the electron donating silyloxy group on the diene which is coupled to a change in the concertedness of the cycloaddition process, or to the nature of the dienophile itself (ethylenic *vs.* acetylenic). Additional studies will be required to sort out the importance of these factors in controlling such π-facial stereoselection.

Scheme 1. Synthesis of (+)-actinobolin from (**2**). *Reagents:* i, BH_3·tetrahydrofuran, then H_2O_2, then HF, H_2O, tetrahydrofuran; ii, 3,5-dinitroperoxybenzoic acid, Na_2HPO_4 (42%); iii, Zn dust, NaOAc, 90% HOAc (50%); iv, cyclohexanone dimethyl acetal, pyridinium toluene-*p*-sulphonate (PPTS), dimethylformamide (68%); v, CrO_3–pyridine, Ac_2O, CH_2Cl_2 (51%); vi, H_2, 5% Pd/C, CH_2Cl_2; vii, benzyloxycarbonyl-L-alanine, dicyclohexylcarbodiimide, CH_2Cl_2 (90%); viii, H_2, 5% Pd/C, MeOH, HOAc, 1 M HCl (100%).

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References

1 Taken in part from the Ph.D. thesis of T. R. N., University of Pittsburgh, 1985.
2 A. P. Kozikowski, T. R. Nieduzak, and J. P. Springer, *Tetrahedron Lett.*, 1986, **27**, 819.
3 F. J. Antosz, D. B. Nelson, D. L. Herald, and M. E. Munk, *J. Am. Chem. Soc.*, 1970, **92**, 4933.
4 S. Kondo, Y. Horiuchi, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 1069.
5 M. Ishizaka, S. Fukasawa, T. Masuda, J. Sato, N. Kanbayashi, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 1054.
6 W. H. Rastetter, T. J. Richard, and M. D. Lewis, *J. Org. Chem.*, 1978, **43**, 3163.
7 W. S. Knowes and Q. E. Thompson, *J. Am. Chem. Soc.*, 1959, **79**, 3212.
8 The optical rotations reported by Weinreb for the synthetic and natural actinobolin hydrochlorides are $[\alpha]_D^{20}$ + 44° (*c* 0.40, H_2O) and +48° (*c* 0.51, H_2O), respectively: R. S. Garigipati, P. M. Tschaen, and S. M. Weinreb, *J. Am. Chem. Soc.*, 1985, **107**, 7790.
9 The optical rotations reported by Ohno for the synthetic and natural actinobolin hydrochlorides are $[\alpha]_D^{22}$ + 55° (*c* 0.47, H_2O) and +59° (*c* 0.41, H_2O) respectively: M. Yoshioka, H. Nakai, and M. Ohno, *J. Am. Chem. Soc.*, 1984, **106**, 1133.
10 For a synthesis of racemic *N*-acetylactinobolamine, see: D. Askin, C. Angst, and S. Danishefsky, *J. Org. Chem.*, 1985, **50**, 5005; optically active *N*-acetylactinobolamine: M. A. Rahman and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1985, **107**, 5576.
11 B. M. Trost, D. O'Krongly, and J. L. Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7595.
12 R. W. Franck, S. Argade, C. S. Subramaniam, and D. M. Frechet, *Tetrahedron Lett.*, 1985, **26**, 3187.
13 R. Greé, J. Kessabi, P. Mosset, J. Martelli, and R. Carrié, *Tetrahedron Lett.*, 1984, **25**, 3697.