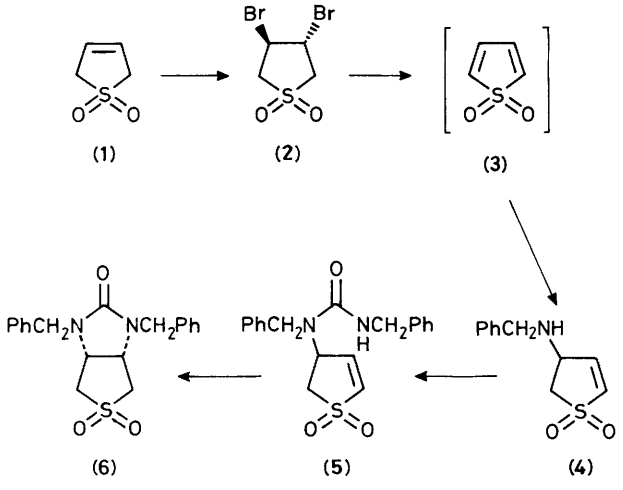
A Practical Stereospecific Synthesis of the Biotin Precursor (3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 1,1-Dioxide

Hans Aaron Bates,* Lloyd Smilowitz, and Stuart B. Rosenblum

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794–3400, U.S.A.

A highly efficient stereospecific synthesis of the biotin precursor (3aα,6aα)-1,3-dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 1,1-dioxide (**6**) is reported, by the cyclisation of the urea (**5**), which was obtained from the amine (**4**), (**4**) itself being prepared by the reaction of the dibromide (**2**) with benzylamine.

Recently we described two methods for the preparation of (3aα,6aα)-1,3-dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 1,1-dioxide (**6**), a valuable precursor for the vitamin biotin, from the abundantly available 2,5-dihydrothiophene 1,1-dioxide (**1**).[1] Both syntheses were improvements on previous methods,[2—5] but neither was as efficient as we wished. Treatment of the dibromo compound (**2**), generated from the dihydrothiophene dioxide (**1**), with excess of benzylamine afforded a mixture of *cis*- and *trans*-3,4-bis(benzylamino)tetrahydrothiophene 1,1-dioxides *via* conjugate addition to the unstable thiophene 1,1-dioxide (**3**).[1,2,6,7]



(1) (2) (3) (4) (5) (6)

While this isomeric mixture could be used to synthesise biotin without recourse to chromatographic separation,[1] we required a more efficient, practical, stereospecific route to (**6**). We reasoned that the transition state for intramolecular conjugate addition of the unsaturated ureido-sulphone (**5**) would favour formation of the *cis*-fused (**6**) rather than the *trans*-fused isomer.[8]

We thought that the unsaturated ureido-sulphone (**5**) might be generated if the dioxides (**2**) or (**3**) could be intercepted by 1,3-dibenzylurea, and that (**5**) would spontaneously cyclise to give (**6**), but this proved not to be the case. When (**2**) was treated with 1,3-dibenzylurea,[9] benzylurea,[9] or urea, with or without base and in various solvents, no product was formed. Evidently the ureas, though moderately nucleophilic,[10,11] did not add to the unstable[6] thiophene 1,1-dioxide (**3**) more rapidly than (**3**) decomposed, and only the unchanged ureas could be recovered from these reactions.

An alternative approach to (**6**) from (**2**) involved the dihydrothiophene (**4**) as an intermediate.† Reaction of (**2**) with ammonia and various anilines has been reported to afford analogues of (**4**),[2,6,12,13] and several amines related to (**4**) have also been synthesised by less direct routes.[13—16] Although derivatives of (**4**) have been reported to dimerise and undergo facile double bond migration to generate vinylogous sulphonamides,[6,8,15—17] treatment of (**2**) with excess of triethylamine followed by 1 equiv. of benzylamine did in fact afford a good yield of stable (**4**) without rearrangement.

† Although (**4**) has been alluded to previously, no means of preparation or characterization has been described.[2,18]

Reaction of the amine (**4**) with benzyl isocyanate furnished the acyclic urea (**5**), which was stable in nonpolar aprotic solvents, but spontaneously cyclised in slightly alkaline aqueous methanol to produce essentially quantitatively the desired *cis*-fused compound (**6**)[8,18] [in 63% overall yield from (**2**). The present synthesis of (**6**) from the abundantly available 2,5-dihydrothiophene (**1**) in a stereospecific, efficient, and convenient fashion allows this key biotin precursor to be prepared readily on a large scale.

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Institutes of Health for support.

Received, 12th November 1984; Com. 1595

References

1 H. A. Bates, L. Smilowitz, and J. Lin, *J. Org. Chem.*, 1985, **50**, in the press.
2 H. Kotake, K. Inomata, Y. Murata, H. Kinoshita, and M. Katsuragawa, *Chem. Lett.*, 1976, 1073.
3 An alternative synthesis of (**6**) has recently been published: H. Kinoshita, M. Futagami, K. Inomata, and H. Kotake, *Chem. Lett.*, 1983, 1275.
4 S. Lavielle, S. Bory, B. Moreau, M. J. Luche, and A. Marquet, *J. Am. Chem. Soc.*, 1978, **100**, 1558; S. Bory, M. J. Luche, B. Moreau, S. Lavielle, and A. Marquet, *Tetrahedron Lett.*, 1975, 827.
5 For an independent synthesis see: A. V. R. Rao, T. Ravindranathan, S. V. Hiremath, and D. R. Reddy, *Indian J. Chem., Sect. B*, 1983, **22**, 419.
6 M. Procházka and V. Horák, *Coll. Czech. Chem. Commun.*, 1959, **24**, 2278.
7 H. J. Backer and T. A. H. Blaas, *Recl. Trav. Chim. Pays-Bas*, 1942, **61**, 785.
8 F. Ellis and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2866.
9 T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, 1923, **45**, 1816.
10 G. C. Corfield, A. Crawshaw, and H. H. Monks, *J. Macromol. Sci., Chem.*, 1975, **A9**, 1085.
11 W. V. Curran and R. B. Angier, *J. Org. Chem.*, 1966, **31**, 201; V. E. Marquez, P. S. Liu, and J. K. Linevsky, *J. Org. Chem.*, 1982, **47**, 1712.
12 F. Ellis, P. G. Sammes, M. B. Hursthouse, and S. Neidle, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1560.
13 T. E. Bezmenova and P. G. Dul'nev, *Chem. Heterocycl. Compd. USSR*, 1972, 1078.
14 W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, 1954, **76**, 1932.
15 S. M. Lukashkov and T. E. Bezmenova, *Chem. Heterocycl. Compd. USSR*, 1974, 541.
16 K. Ohba, T. Kitahara, K. Mori, and M. Matsui, *Agric. Biol. Chem.*, 1974, **38**, 2431; K. Ohba, K. Mori, T. Kitahara, S. Kitamura, and M. Matsui, *ibid.*, 1974, **38**, 1679.
17 P. G. Dul'nev and T. E. Bezmenova, *Chem. Heterocycl. Compd. USSR*, 1974, 1159; T. E. Bezmenova, A. F. Rekasheva, T. S. Lutsii, P. G. Dul'nev, and V. P. Tantsyura, *ibid.*, 1975, 548.
18 G. I. Khaskin, T. E. Bezmenova, and P. G. Dul'nev, *Chem. Heterocycl. Compounds U.S.S.R.*, 1982, 246.