

A Simple Preparation of (+)-4-Phenylthioazetidin-2-one and an Asymmetric Synthesis of (+)-Thienamycin

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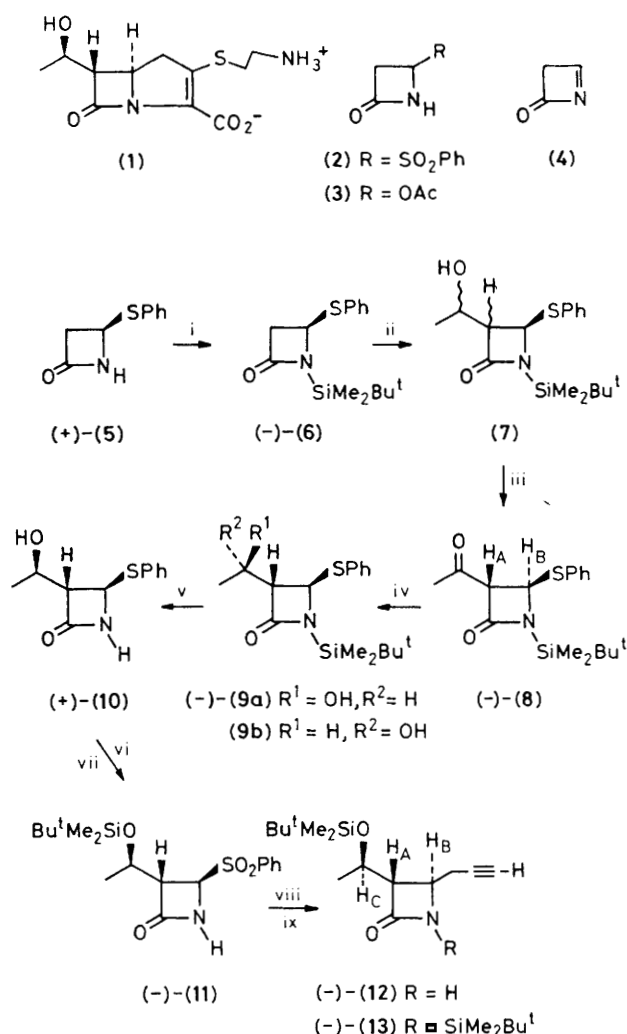
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Asymmetric induction provides a simple preparation of (+)-4-phenylthioazetidin-2-one, from which a key intermediate for (+)-thienamycin has been synthesised.

Thienamycin (**1**) has prompted considerable interest owing to its unprecedented biological properties; this has resulted in the elegant synthesis of (+)-(**1**) from L-aspartic acid,¹ dimethyl β -aminoglutarate involving chemicoenzymatic asymmetric induction,² penicillin,³ D-allothreonine,⁴ and L-threonine.⁴ In addition, the chiral synthesis of (+)-(**1**) *via* chemical asymmetric induction is also of great interest.⁵ In this communication we report the chiral synthesis of the key synthetic intermediate (**13**) for (+)-(**1**) using the asymmetric

introduction of a phenylthio-group to 4-phenylsulphonylazetidin-2-one (**2**)⁶ as a key step.

It is generally known that (**2**) and 4-acetoxyazetidin-2-one (**3**) easily undergo several types of nucleophilic substitution reactions probably *via* the azetidinone (**4**).^{6,7} Accordingly, it occurred to us that the asymmetric introduction of some group to (**2**) or (**3**) would be expected to afford the optically active 4-substituted azetidin-2-one which could be converted into (+)-(**1**) in a stereocontrolled manner. Indeed we found that



Scheme 1. i, Bu^tMe₂SiCl-imidazole-*N,N*-dimethylformamide (DMF); ii, lithium di-isopropylamide (3 equiv.)-MeCHO (5 equiv.); iii, Collins reagent-CH₂Cl₂; iv, NaBH₄-MeOH, -78 °C; v, (9a) → (10), 10% HCl-MeOH, 25 °C, (9b) → (10), diethyl azodicarboxylate (5 equiv.)-triphenylphosphine (5 equiv.)-formic acid (6.5 equiv.)-tetrahydrofuran (THF), 25 °C, then 10% HCl-MeOH, 25 °C; vi, Bu^tMe₂SiCl-imidazole-DMF; vii, *m*-ClC₆H₄CO₂H-CH₂Cl₂; viii, BrMgCH₂C≡CH (10 equiv.), ether-THF (1:1), -25 to ca. 0 °C; ix, Bu^tMe₂SiCl-Et₃N-DMF.

treatment of (2) with 5 equiv. of thiophenol in benzene [95 ml/g of (2)] containing 1.2 equiv. of cinchonidine, [α]_D²⁵ -110.2° (*c* 1.04, EtOH), at 35 °C for 62.5 h provided optically active 4-phenylthioazetidin-2-one (5), [α]_D²⁵ +56.3° (*c* 0.80, CHCl₃) (54% optical yield, 96% chemical yield).^{8†} Both its absolute configuration and its optical purity were determined by converting (5) into the known sulphone (11).⁴ Likewise, it was found that (3) affords (+)-(5) (38% optical yield, 79% chemical yield).

There is another striking point in the present asymmetric reaction. Recrystallization of (+)-(5), [α]_D²⁵ +55° (*c* 0.95, CHCl₃), from benzene-cyclohexane gave (+)-(5) in low optical purity, [α]_D²⁵ +17.3° (*c* 1.27, CHCl₃) (64%), while optically pure (+)-(5), [α]_D²⁵ +105.1° (*c* 0.65, CHCl₃), m.p.

58–60 °C, was readily obtained from the mother liquor (28%). Oxidation of (+)-(5) with low optical purity (16%) to the sulphone (2) by the use of 2.6 mol. equiv. of *m*-chloroperbenzoic acid,⁶ followed by treatment under the same conditions as described above, again provided (+)-(5) of 50% optical purity (90%). Thus the present asymmetric synthesis offers a fairly practical method for the preparation of (+)-(5).

Protection of optically pure (+)-(5) by the *t*-butyldimethylsilyl group yielded (6), [α]_D²⁵ -164.3° (*c* 1.54, CHCl₃), which underwent an Aldol condensation to afford a diastereomeric mixture (7) of the alcohols [81% from (5)]. Subsequent oxidation of (7) gave the stereochemically pure ketone (8) (86%), ¹H n.m.r.: δ 4.25 (1H, d, *J*_{A,B} 2.2 Hz, H_A), [α]_D²⁵ -65.1° (*c* 2.55, CHCl₃). Reduction of (8) provided a diastereomeric mixture, (9a) and (9b), of the alcohols, from which (9a), [α]_D²⁵ -81.7° (*c* 1.24, CHCl₃), was separated (23%). Deprotection of (9a) afforded (10) (89%), [α]_D²⁵ +64.4° (*c* 0.65, CHCl₃). The undesired alcohol (9b) (55%) could be converted into (10) (99%) by the modified Mitsunobu reaction.⁹ Protection of (10) as the *t*-butyldimethylsilyl ether, followed by oxidation, provided the optically pure sulphone (11)⁴ (85%), [α]_D²⁵ -11.0° (*c* 0.91, CHCl₃) [lit.⁴ [α]_D²⁴ -12.4° (*c* 0.91, CHCl₃)], m.p. 170–171 °C (lit.⁴ m.p. 166–167 °C). The optical purity of (11) was confirmed by the aid of the chiral shift reagent Eu(hfc)₃ [hfc = 3-(heptafluoropropyl)-hydroxymethylene-(-)-camphorato]. The sulphone (11) was then subjected to the Grignard reaction, resulting in clean formation of (12) (90%), [α]_D²⁵ -4.2° (*c* 4.53, CHCl₃), m.p. 120–121 °C, ¹H n.m.r.: δ 2.93 (1H, dd, *J*_{A,B} 2.0 Hz, *J*_{A,C} 5.0 Hz, H_A). Protection of the NH group by a *t*-butyldimethylsilyl group led to the known intermediate (13) (80%), [α]_D²⁵ -43.2° (*c* 3.40, CHCl₃), which has already been converted into (1).¹⁰ Thus, we have accomplished a fairly efficient synthesis of (+)-thienamycin (1) *via* chemical asymmetric induction for the first time.

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† The unexpectedly high stability of (+)-(5) was demonstrated by the fact that it was recovered without any racemization after refluxing in benzene for 1 h.