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

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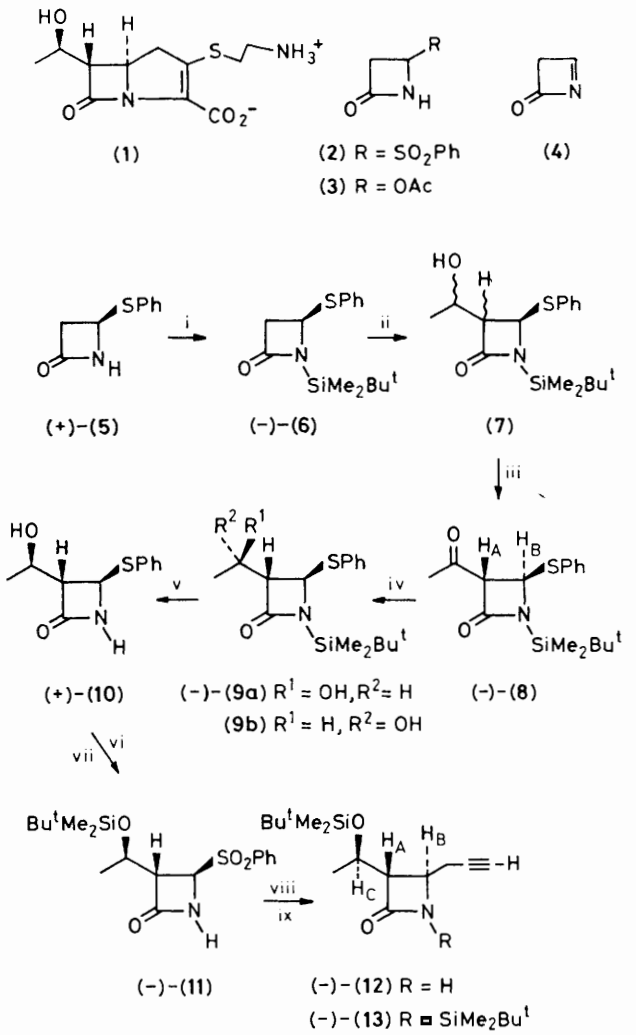
Asymmetric induction provides a simple preparation of (+)-4-phenylthioazetidin-2-one, from which a key intermediate for (+)-thienamycin has been synthesised.

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 azetinone (**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^tMe_2SiCl–imidazole–*N*,*N*-dimethylformamide (DMF); ii, lithium di-isopropylamide (3 equiv.)–MeCHO (5 equiv.); iii, Collins reagent–CH_2Cl_2; iv, $NaBH_4$–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^tMe_2SiCl–imidazole–DMF; vii, *m*-$ClC_6H_4CO_3H$–CH_2Cl_2; viii, $BrMgCH_2C{\equiv}CH$ (10 equiv.), ether–THF (1 : 1), −25 to *ca.* 0 °C; ix, Bu^tMe_2SiCl–Et_3N–DMF.

treatment of (**2**) with 5 equiv. of thiophenol in benzene [95 ml/g of (**2**)] containing 1.2 equiv. of cinchonidine, $[\alpha]_D^{25}$ −110.2° (*c* 1.04, EtOH), at 35 °C for 62.5 h provided optically active 4-phenylthioazetidin-2-one (**5**), $[\alpha]_D^{25}$ +56.3° (*c* 0.80, $CHCl_3$) (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**), $[\alpha]_D^{25}$ +55° (*c* 0.95, $CHCl_3$), from benzene–cyclohexane gave (+)-(**5**) in low optical purity, $[\alpha]_D^{25}$ +17.3° (*c* 1.27, $CHCl_3$) (64%), while optically pure (+)-(**5**), $[\alpha]_D^{25}$ +105.1° (*c* 0.65, $CHCl_3$), 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**), $[\alpha]_D^{25}$ −164.3° (*c* 1.54, $CHCl_3$), 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), $[\alpha]_D^{25}$ −65.1° (*c* 2.55, $CHCl_3$). Reduction of (**8**) provided a diastereomeric mixture, (**9a**) and (**9b**), of the alcohols, from which (**9a**), $[\alpha]_D^{25}$ −81.7° (*c* 1.24, $CHCl_3$), was separated (23%). Deprotection of (**9a**) afforded (**10**) (89%), $[\alpha]_D^{25}$ +64.4° (*c* 0.65, $CHCl_3$). 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%), $[\alpha]_D^{25}$ −11.0° (*c* 0.91, $CHCl_3$) {lit.[4] $[\alpha]_D^{24}$ −12.4° (*c* 0.91, $CHCl_3$)}, 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-(heptafluoropropylhydroxymethylene)-(−)-camphorato]. The sulphone (**11**) was then subjected to the Grignard reaction, resulting in clean formation of (**12**) (90%), $[\alpha]_D^{25}$ −4.2° (*c* 4.53, $CHCl_3$), 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%), $[\alpha]_D^{25}$ −43.2° (*c* 3.40, $CHCl_3$), 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.

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