Enantioselective Biotransformation of Ethyl-n-propylarsinic Acid by the Mould *Scopulariopsis brevicaulis*: Asymmetric Synthesis of (*R*)-Ethylmethyl-n-propylarsine

Paul Gugger, Anthony C. Willis, and S. Bruce Wild*

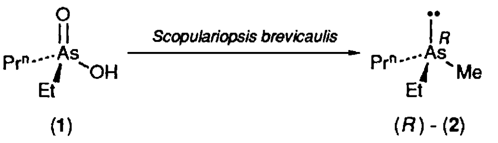
Research School of Chemistry, Australian National University, Canberra, ACT 2601, Australia

The mould *Scopulariopsis brevicaulis*, when growing on bread containing ethyl-n-propylarsinic acid, produces *R*-ethylmethyl-n-propylarsine of 60% optical purity.

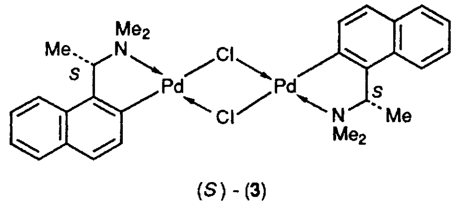
Arsenic, as a tri- or penta-valent oxide, is converted by a variety of micro-organisms[1] into trimethylarsine, a highly volatile arsenical with a morbid history.[2] The mould *Scopulariopsis brevicaulis* in bread cultures containing arsenious oxide or sodium arsenate produces the arsine (Gosio-gas[3]), which was positively identified by Challenger *et al.* in 1933.[4] Later, it was shown that ethyl-n-propylarsinic acid, (**1**), is converted into ethylmethyl-n-propylarsine, (**2**), by the bread mould,[5] although it was not known at that time that simple non-cyclic tertiary arsines, chiral at arsenic were configurationally stable and amenable to optical resolution.[6] We have repeated the earlier experiment with ethyl-n-propylarsinic acid and have shown that the reductive methylation by the mould is stereoselective in favour of the *R*-enantiomer of the tertiary arsine. To our knowledge, this is the first observation of the stereoselective biomethylation of an element other than carbon.

A flask containing moist bread (1.36 kg)[†] was sterilized, inoculated with a seven day old culture of *Scopulariopsis brevicaulis* (ATCC 7903), and incubated for 4 days at 25 °C; a sterile 1% solution of ethyl-n-propylarsinic acid (34 ml) was then sprayed onto the surface of the bread. Concentration: approximately 0.25%. The volatile products were aspirated in a stream of air into a flask containing a solution of (*S*)-(**3**)[7] (0.5 g, 0.7 mmol) in toluene (1 l). After an induction period of 3 days arsine evolution began and climbed steeply during a period of rapid growth of the mould; after 14 days arsine production was minimal and approximately 90% of the (*S*)-(**3**) had been converted into the diastereoisomers (S,R_{As})-(**4**) and (S,S_{As})-(**4**).[‡] Chemical yield based on arsenic: approximately 6.6%. The solution of diastereoisomers was dried ($MgSO_4$) and the toluene was evaporated off; the 500 MHz ^{1}H NMR spectrum of the mixture of diastereoisomers in the arsenic–ligand methyl region is shown in Figure 1. The ratio of the major to the minor peaks is approximately 4:1, which corresponds to an optical yield (enantiomeric excess, e.e.) of the tertiary arsine of 60%. (The co-ordination of tertiary arsines to (*S*)-(**3**) is known to be stereospecific.[9])

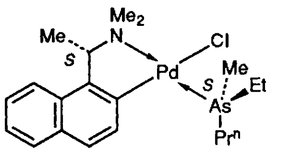
A resolution of synthetic (±)-(**2**) with (*S*)-(**3**) afforded, after nine recrystallizations of the initial mixture of diastereoisomers from benzene–n-pentane, pale-yellow crystals of (S,R_{As})-(**4**), as determined by an *X*-ray crystal structure



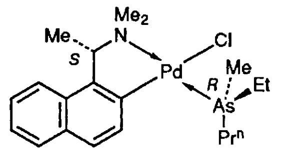
(**1**) (*R*)-(**2**)



(*S*)-(**3**)



(S,S_{As})-(**4**)



(S,R_{As})-(**4**)

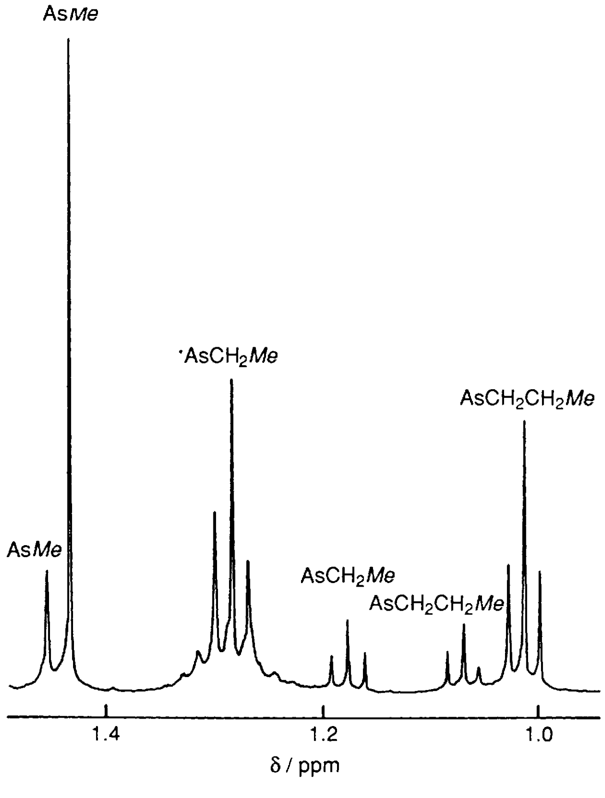


Figure 1. The 500 MHz ^{1}H NMR spectrum ($[^2H_2]$dichloromethane) in the arsenic-ligand methyl region of the mixture of diastereoisomers (S,R_{As})-(**4**) (minor) and (S,S_{As})-(**4**) (major) formed in the biotransformation.

[†] Two loaves Pritikin Diet. (This bread was found to be the best for the growth of the mould.)

[‡] The progress of the reaction was monitored by observing the decrease in intensity of the charge transfer band at 320 cm^{-1} in the electronic spectrum of the trapping agent (*S*)-(**3**). As a consequence of the Cahn–Ingold–Prelog rules for the specification of absolute configurations,[8] (*R*)-(**2**) gives (S,S_{As})-(**4**) and (*S*)-(**2**) gives (S,R_{As})-(**4**).

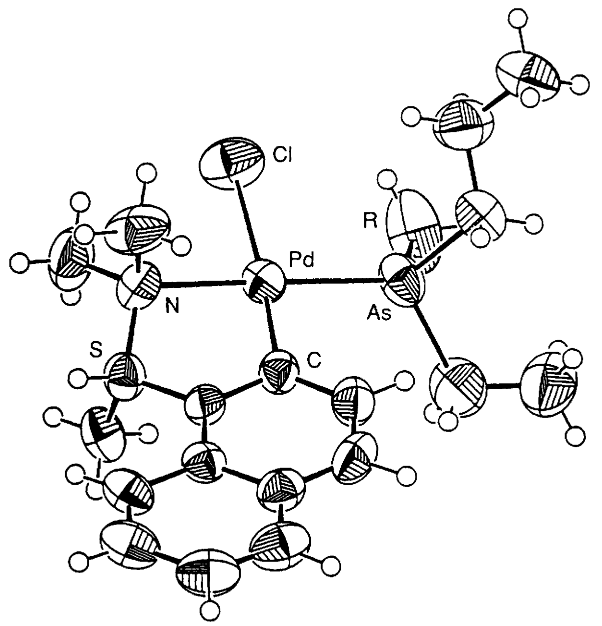


Figure 2. Molecular structure of (S,R_{As})-(**4**). Selected bond distances (Å) and angles (°) are as follows: Pd–As 2.3694(7), Pd–Cl 2.391(2), Pd–N 2.131(5), Pd–C 1.985(5), As–Pd–Cl 90.05(5), Cl–Pd–N 91.9(1), N–Pd–C 81.3(2), C–Pd–As 96.7(1).

analysis of a single crystal.§ The structure is shown in Figure 2. As observed by us previously, co-ordination of the 'soft' arsenic donor to the palladium asymmetric auxiliary was completely regioselective and *trans* to the dimethylamino group.[10] The ^{1}H NMR spectrum of the pure diastereoisomer is identical to that of the minor component of the mixture of palladium diastereoisomers obtained as a result of the biotransformation. Thus, the reductive methylation of (**1**) by *Scopulariopsis brevicaulis* yields (*R*)-(**2**) in 60% e.e. Present work is concerned with the optimization of the chemical yield of the fungal biotransformation and with a study of the effect of steric bulk of substituents on the arsenic on the stereoselectivity of the reaction.

We thank Mrs. M. Anderson and Mrs. J. Rothschild of the Research School of Chemistry for assistance with the microbiology.

Received, 9th May 1990; Com. 0/02035D

References

1 W. R. Cullen and K. J. Reimer, *Chem. Rev.*, 1989, **89**, 713.
2 F. Challenger, *Chem. Rev.*, 1945, **36**, 315.
3 B. Gosio, *Arch. Ital. Biol.*, 1893, **18**, 253, 298; B. Gosio, *Arch. Ital. Biol.*, 1901, **35**, 201; B. Gosio, *Chem. Ber.*, 1897, **30**, 1024.
4 F. Challenger, C. Higginbottom, and L. Ellis, *J. Chem. Soc.*, 1933, 95.
5 F. Challenger and A. A. Rawlings, *J. Chem. Soc.*, 1936, 264.
6 For the first resolution of a simple tertiary arsine, see L. Horner and H. Fuchs, *Tetrahedron Lett.*, 1962, 203; 1963, 1573.
7 The compound used was the hemidichloromethane solvate: P.-H. Leung, G. M. McLaughlin, J. W. L. Martin, and S. B. Wild, *Inorg. Chem.*, 1986, **25**, 3392.
8 R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. (Engl.)*, 1966, **5**, 385.
9 J. W. L. Martin, F. S. Stephens, K. D. V. Weerasuria, and S. B. Wild, *J. Am. Chem. Soc.*, 1988, **110**, 4346 and references cited therein.
10 P. G. Kerr, P.-H. Leung, and S. B. Wild, *J. Am. Chem. Soc.*, 1987, **109**, 4321 and references cited therein.

---

§ *Crystal data*: (S,R_{As})-(**4**), $C_{20}H_{31}AsClNPd$, M = 502.27, orthorhombic, space group $P2_12_12_1$, a = 10.189(1), b = 13.378(1), c = 15.663(2) Å, U = 2135.0 Å^3, D_c = 1.563 g cm^{-3} for Z = 4, $F(000)$ = 1016, λ (Mo-K_α) = 0.71069 Å. Of 4397 measured reflections (Phillips PW 1100/20; 25 °C), 2793 were considered observed [$I > 3\sigma(I)$]. After Lorentz, polarization, and absorption corrections, the structure was solved by the heavy-atom method. Subsequent refinement (full-matrix least-squares) afforded R and R' values of 0.028 and 0.037, respectively. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors Issue No. 1.