From the Penicillin to the Nocardicin Skeleton: an Alternative Route

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Summary The nocardicin skeleton has been stereospecifically synthesised from readily available penicillin derivatives.

ATTENTION has been paid recently to the synthesis[1,2] of nocardicin A (**1a**), a monocyclic β-lactam antibiotic isolated from *Nocardia uniformis*.[3] During a study of the preparation of novel β-lactam antibiotics, we devised a synthetic access to the class of compounds (**6**), closely related to nocardicin, which has the advantage of introducing the desired final side chain R^3 at an early stage. This procedure by-passes 3-ANA (**1b**), which has been a necessary intermediate in previous syntheses.[1,2]

Treatment of the thiazoline (**2**), obtained from penicillin G by an established route,[4,5] with (±)-methyl α-bromophenylacetate in the presence of NaH at 0 °C, gave a 30% yield, after crystallisation of the crude product from Et_2O, of the synthon (**3**, $R^1 = R^2 = H$); $[\alpha]_D$ −175° ($CHCl_3$); δ(60 MHz, $CDCl_3$) 3·74 (s, MeO and CH_2), 5·57 (s, exocyclic C–H), 5·75–6·05 (m, β-lactam H), and 6·9–7·5 (m, Ar–H).

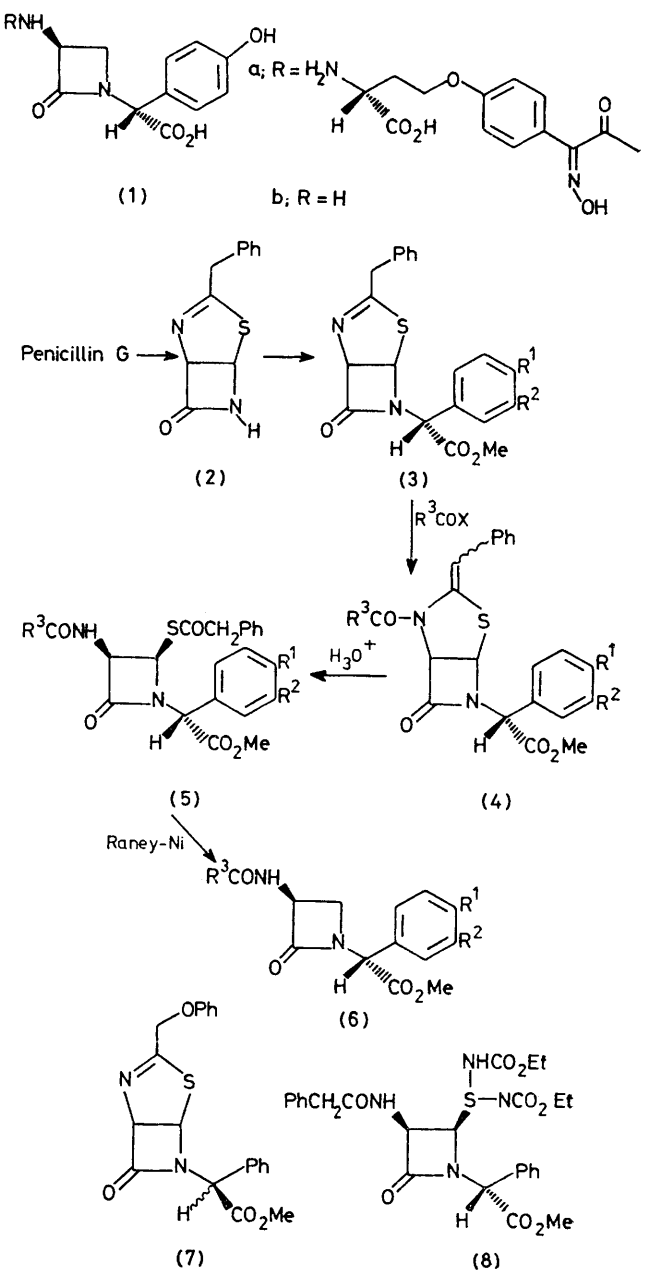
Identical treatment of the thiazoline obtained from penicillin V afforded (28% yield) compound (**7**) as a 6:4 mixture of epimers as shown in the n.m.r. spectrum by the splitting of the singlets due to the exocyclic C–H (δ5·50 and 5·40) and PhO–CH_2 (δ4·72 and 4·90), showing the loss of stereoselectivity in the alkylation at nitrogen in this case.

We presume that the different stereochemical course of the reactions of the two substrates may be ascribed to the influence of the bridged phenyl and phenoxy groups, respectively, on the stability of the final products (**3**) and (**7**) towards further epimerisation, although we cannot exclude the formation of traces of the other epimer of (**3**) which might have been eliminated during the crystallisation. Our assumption is supported also by the work of Cooper[4] in which epimerisation at the exocyclic C–H occurred for similar compounds bearing a dimethyl-thiazolidine group fused to the azetidinone ring.

Two-phase acylation (CH_2Cl_2–aq.$NaHCO_3$, 0 °C) of (**3**, $R^1 = R^2 = H$) in presence of an acyl halide R^3COX (*e.g.* R^3 = Ph, X = Cl) gave the crude thiazolidine (**4**, $R^1 = R^2 = H$, $R^3 = PhCH_2$) which was subjected to mild acidic hydrolysis (acetone–aq.HCl, room temp.) to give, without further purification and in almost quantitative yield, the fully substituted azetidinone (**5**, $R^1 = R^2 = H$, $R^3 = PhCH_2$); δ($CDCl_3$) 3·50 and 3·56 (2 × s, 2 × CH_2), 3·78 (s, MeO), 5·25–5·60 (m, 3–H and exocyclic C–H), 5·95 (d, 4-H), 6·53 (d, NH), and 7·05–7·70 (m, Ar–H).

Finally, Raney-Ni desulphurisation of this synthon produced the nocardicinoid (**6**; $R^1 = R^2 = H$, $R^3 = PhCH_2$) as white crystals; m.p. 143 °C; $[\alpha]_D$ −165° (MeOH); δ($CDCl_3$) 3·06 (dd, 4-H^A), 3·54 (s, CH_2), 3·77 (s, MeO), 3·60–4·16 (m, 4-H^B), 4·96 (m, 3-H), 5·63 (s, exocyclic C–H), 6·60 (d, NH), and 7·05–7·70 (m, Ar–H); ν_{max} ($CHCl_3$) 1750 and 1670 cm^{-1}.

Similarly, the reaction of (**2**) with (±)-methyl α-bromo-(3-bromo-4-methoxy)phenylacetate afforded compound (**3**; R^1 = OMe, R^2 = Br) in satisfactory yield; δ($CDCl_3$) 3·77 (s, MeO), 3·86 (s, MeO and CH_2), 5·43 (s, exocyclic C–H), 5·70–6·06 (m, β-lactam H), and 6·90–7·70 (m, Ar–H). Compound (**3**, R^1 = OMe, R^2 = Br) was then transformed into the nocardicinoid (**6**; R^1 = OMe, R^2 = Br, R^3 = $PhCH_2$) as previously described; $[\alpha]_D$ −180° (MeOH); δ($CDCl_3$) 3·07 (m, 4-H^A), 3·50 (s, CH_2), 3·74 and 3·90 (2 × s, 2 × OMe 3·30–4·00 (m, 4-H^B), 4·86 (m, 3-H), 5·50 (s, exocyclic C–H), 6·50 (d, NH), and 6·80–7·60 (m, Ar-H); ν_{max} (KBr) 1755 and 1675 cm^{-1}.



Spectral data and rotatory power values are in full agreement with those reported for derivatives obtained from natural 3-ANA.†

Compound (**6**; $R^1 = R^2 = H$, $R^3 = PhCH_2$) was also obtained by desulphurisation of the adduct (**8**) prepared from (**3**; $R^1 = R^2 = H$) by thiazoline ring opening.[6]

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† The methyl ester methyl ether of (**1**; R = $PhCH_2CO$) gave $[\alpha]_D$ −206° (MeOH) (T. Kamiya, Symposium on Recent Advances in the Chemistry of β-lactam Antibiotics, Cambridge, 1976) and [**1**; R = *p*-$HOC_6H_4C(NOH)CO$] gave $[\alpha]_D$ −192° and −181° (H_2O), respectively, for *syn* and *anti* oximes (ref. 1, p. 281). Spectral data are reported in Netherland P. 7,508,008 (Jan. 6, 1976) (Fujisawa Pharmaceutical Co., Japan).

[1] T. Kamiya in 'Recent Advances in the Chemistry of β-lactam Antibiotics,' ed. J. Elks, Chemical Society Special Publication No. 28, 1977.
[2] R. D. G. Cooper, 5th International Symposium on Synthesis in Organic Chemistry, Oxford 1977.
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[4] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[5] E. G. Brain, A. J. Eglinton, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.
[6] G. Franceschi, M. Foglio, P. Masi, A. Suarato, G. Palamidessi, L. Bernardi, F. Arcamone, and G. Cainelli, *J. Amer. Chem. Soc.*, 1977, **99**, 248.