(13) P. Tola, O. Kahn, C. Chauvel, and H. Coudanne, *Nouv. J. Chim.*, 1, 467 (1977).
(14) The measured susceptibilities are corrected for the temperature-independent susceptibility including the diamagnetism and the TIP. This correction is estimated at -320.10^{-6} cm^3 mol^{-1}.

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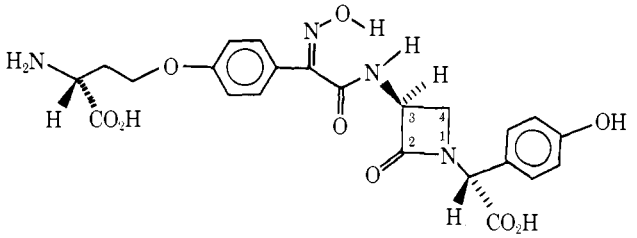
Total Synthesis of Nocardicin A. Synthesis of 3-ANA and Nocardicin A

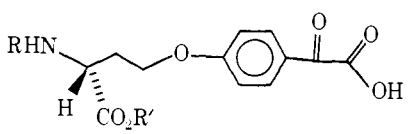
Sir:

In a concurrent communication[1] we have discussed the synthetic strategy involved in our synthesis of the side-chain fragment **2a** of nocardicin A (**1**). In this communication we wish to report the total synthesis of the nucleus **3** and of nocardicin A (**1**).

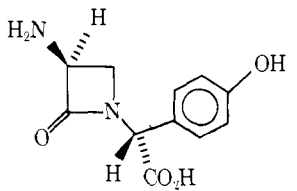
One restriction that we placed on the synthetic design which we elaborated for 3-ANA was that it use readily available



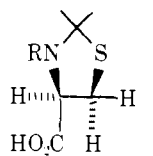
nocardicin A (**1**)



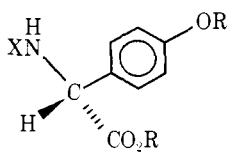
2a, R = R' = H
b, R = ^{t}Boc; R' = $CHPh_2$



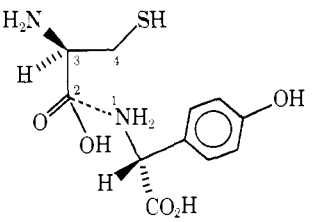
3



4a, R = H
b, R = PhC(=O)—



5, R = H; X = ^{t}Boc
6, R = $PhCH_2$; X = ^{t}Boc
7, R = $PhCH_2$; X = H·HCl
8, R = $PhCH_2$; X = H



L-cysteine D-*p*-hydroxyphenylglycine

Figure 1.

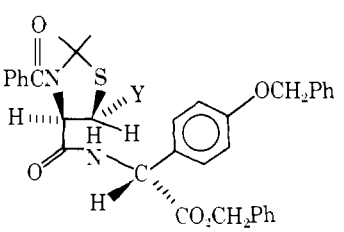
chiral starting materials. We chose L-cysteine and D-*p*-hydroxyphenylglycine. The construction of the crucial β-lactam ring requires the bond-forming reactions shown in Figure 1.

The bond formation between the α-amino group of D-*p*-hydroxyphenylglycine and the carboxyl of L-cysteine was a relatively trivial amide group synthesis. However, the second bond formation, that of the amino group to C-4 while retaining the chirality at C-3, represented a more challenging task. Our solution was to incorporate C-3 and C-4 in five-membered ring thus controlling stereochemistry by the geometry of the ring juncture.[4] The successful synthesis of 3-ANA (**3**) evolved in the following manner.

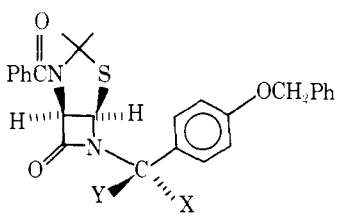
Condensation of L-cysteine with acetone (**4a**) (reflux, 3 days) followed by acylation with benzoyl chloride using propylene oxide as an acid scavenger (25 °C, 1 h) gave excellent yields of the thiazolidine **4b**: mp 170–175 °C; $[\alpha]_D$ (TFE) −165°; NMR ($CDCl_3$) δ 1.83 (3 H, s), 1.92 (3 H, s), 3.13 (2 H, m), 4.60 (1 H, m), 7.23 (5 H, s).

The amino group of D-*p*-hydroxyphenylglycine was protected as the *tert*-butoxycarbonyl derivative **5** and then **5** was treated with 2 equiv of KO-*t*-Bu in DMF followed by 2 equiv of benzyl bromide (25 °C, 16 h) to give the dibenzyl derivative **6**. Treatment of **6** in methylene chloride with dry gaseous hydrogen chloride gave the crystalline salt **7** in 85% yield from *p*-hydroxyphenylglycine: mp 194–198 °C; $[\alpha]_D$ (MeOH) −40.1°; NMR (Me_2SO-d_6) δ 5.22 (2 H, s), 5.30 (2 H, s), 7.13 (2 H, d, J = 9 Hz), 7.33 (5 H, s), 7.43 (2 H, d, J = 9 Hz), 7.48 (5 H, s).

Coupling of the free amine **8** (liberated from **7** using sodium bicarbonate) with **4b** was accomplished using DCC in methylene chloride to give the dipeptide **9** in 90% yield: mp 125–128 °C; $[\alpha]_D$ (Me_2SO) −100.4°; NMR ($CDCl_3$) δ 1.93 (3 H, s), 2.08 (3 H, s), 3.20 (2 H, br d), 4.70 (1 H, tr), 5.05 (2 H, s), 5.17



9, Y = H
10, Y = OCC_6H_5
11, Y = Cl



12, X = CO_2CH_2Ph; Y = H
13, X = H; Y = CO_2CH_2Ph

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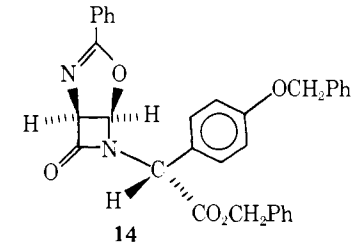

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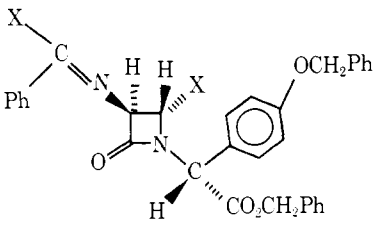
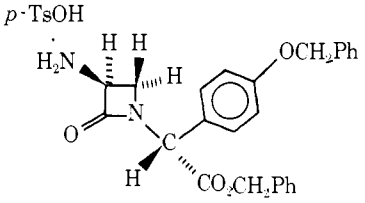
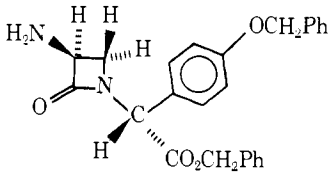


15, X = Cl
16, X = H



17



18

(2 H, s), 5.43 (1 H, d, J = 7 Hz), and 6.83–7.42 (19 H, m). During synthetic investigations of penam and cephem molecules, several methods[2-4] were used to form a N–C_4 bond in systems similar to the present one. We chose the method as described in ref 4 as most applicable to our present circumstance. Thus, treatment of **9** with benzoyl peroxide in refluxing benzene (4 equiv of $(PhCO_2)_2$, 80 °C, 4 h) gave the benzoate derivative **10** in 45–55% yield:[4] mp 168–170 °C; $[\alpha]_D$ ($CHCl_3$) +38.9°; NMR ($CDCl_3$) δ 2.17 (6 H, s), 5.07 (2 H, s), 5.12 (1 H, s), 5.18 (2 H, s), 5.37 (1 H, d, J = 7 Hz), 6.52 (1 H, s), 6.83–8.10 (24 H, m). This was then converted to the chloro derivative **11**[4] in quantitative yield (HCl in CH_2Cl_2, 0 °C, 2 h): mp 80–84 °C; NMR ($CDCl_3$) δ 2.08 (3 H, s), 2.23 (3 H, s), 5.03 (2 H, s), 5.15 (2 H, s), 5.15 (1 H, s), 5.40 (1 H, d, J = 7 Hz), 5.80 (1 H, s), 6.70–7.40 (19 H, m). Closure of the β-lactam ring was readily accomplished (1 equiv of NaH, 1:4 DMF–CH_2Cl_2, 25 °C, 1 h) in 85% yield. However, an isomeric mixture of two β-lactam-containing products was formed (**12** and **13**, ratio 3:1). **12**:[5] mp 175–177 °C; $[\alpha]_D$ (TFE) −290.6°; ν_{max} ($CHCl_3$) 1775, 1750, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (3 H, s), 1.93 (3 H, s), 5.07 (2 H, s), 5.15 (2 H, s), 5.43 (1 H, s), 5.48 (1 H, d, J = 4 Hz), 5.65 (1 H, d, J = 4 Hz), 6.92 (2 H, d, J = 9 Hz), 7.23 (2 H, d, J = 9 Hz), 7.2–7.5 (15 H, m). **13**:[6] mp 131–134 °C; $[\alpha]_D$ (TFE) −161.5°; ν_{max} ($CHCl_3$) 1770, 1745, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.91 (3 H, s), 2.02 (3 H, s), 4.98 (2 H, s), 5.15 (2 H, s), 5.18 (1 H, s), 5.35 (2 H, s), 6.83 (2 H, d, J = 9 Hz), 7.18 (2 H, d, J = 9 Hz), 7.2–7.8 (15 H, m).

Separation of **12** and **13** was possible using fractional crystallization (ethyl acetate).

Subsequent experiments indicated that isomer **13** evolved from a base-catalyzed epimerization of the p-hydroxyphenylglycine after β-lactam closure and that this epimerization was an extremely facile one, being very rapid even in the presence of weak amine bases, e.g., pyridine.

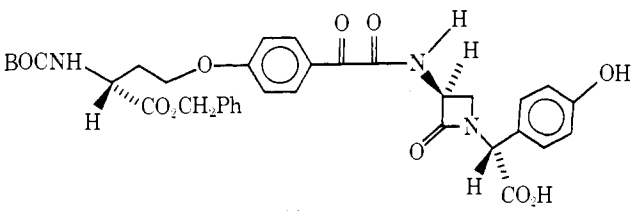
It was also noted that crystallization of a mixture of **12** and **13** from aqueous pyridine under equilibrating conditions gave only crystalline isomer **12**; thus the β-lactam closure reaction could be used to produce **12** selectively in >85% yield from **11**.

Treatment of **12** with mercuric acetate (4 equiv) in aqueous THF (25 °C, 4 h) gave a high yield of the crystalline oxazoline **14**: mp 92–95 °C; $[\alpha]_D$ (CH_3OH) −156.8°; ν_{max} ($CHCl_3$) 1780, 1745 cm^{-1}; NMR ($CDCl_3$) δ 4.98 (2 H, s), 5.20 (2 H, s), 5.33 (1 H, d, J = 4 Hz), 5.53 (1 H, s), 6.32 (1 H, d, J = 4 Hz), 6.86 (2 H, d, J = 9 Hz), 7.19 (2 H, d, J = 9 Hz), 7.2–7.8 (15 H, m). The oxazoline **15** was cleaved with PCl_5 in methylene chloride (3 equiv of PCl_5, 25 °C for 20 min, followed by quenching of the reaction wtih 3 equiv of pyridine) to give crystalline **15**: mp 109–112 °C; $[\alpha]_D$ (EtOAc) −169.2°; ν_{max} ($CHCl_3$) 1785, 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.07 (2 H, s), 5.24 (2 H, s), 5.40 (1 H, s). 5.43 (1 H, d, J = 0.5 Hz), 5.56 (1 H, d, J = 0.5 Hz), 6.97 (2 H, d, J = 9 Hz), 7.27 (2 H, d, J = 9 Hz), 7.3–8.1 (15 H, m). **15** was then reduced using tributyltin hydride (2 equiv of Bu_3SnH, 2 equiv of AIBN, 80 °C, 2 h) to yield the Schiff base **16**. Isolation was not attempted. Direct treatment of **16** with p-TsOH·H_2O in ethyl acetate (25 °C, ½ h) gave the 3-ANA salt **17** in an overall yield of 34% from **11**.

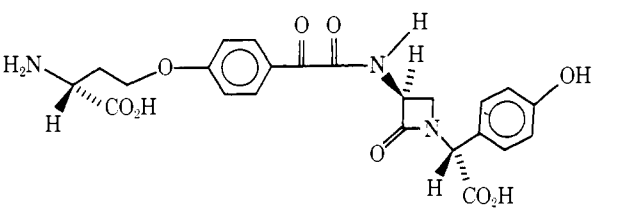
Neutralization of **17** with $NaHCO_3$ gave the 3-ANA ester **18** as a white foam: $[\alpha]_D$ (TFE) −138°; ν_{max} ($CHCl_3$) 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (2 H, s, exchanges with D_2O), 2.80 (1 H, m), 3.87 (1 H, m), 4.23 (1 H, m), 5.07 (2 H, s), 5.17 (2 H, s), 5.58 (1 H, s), 6.92 (2 H, d, J = 9 Hz), 7.17 (2 H, d, J = 9 Hz), 7.28 (5 H, s), 7.40 (5 H, s).

Removal of the benzyl groups of **18** using 5% Pd/C (THF/MeOH, H_2 at 60 psi, 25 °C) gave 3-ANA as a white foam.

The nucleus, 3-ANA, was then coupled with the keto acid form of the side chain **2b** using bis(trimethylsilyl)acetamide and ethyl chloroformate as described by Kamiya et al.[7] to yield **19**. The final deblocking of **19** with trifluoroacetic acid and



19



nocardicin D (**20**)

anisole (3 min, room temperature) cleanly gave nocardicin D (**20**). Aqueous hydroxylamine hydrochloride treatment (pH 7.0, 50 °C, 1 h)[7] of nocardicin D yielded crystalline nocardicin A (**1**) which was identical with the naturally occurring material.[8,9]

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References and Notes

(1) Total Synthesis of Nocardicin A. The Side Chain. R. D. G. Cooper, F. Jose, L. McShane, and G. A. Koppel, *Tetrahedron Lett.*, in press.
(2) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).
(3) S. I. Nakatsuki, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, **97**, 5010 (1975).
(4) J. E. Baldwin, A. Au, M. Christie, S. B. Haber, and D. Hesson, *J. Am. Chem. Soc.*, **97**, 5957 (1975).
(5) The proof of structure of **12** and **13** was achieved by measurement of the individual circular dichroism spectra and that of a 1:1 mixture of both isomers. By subtraction of the curve of the mixture from the curves of the two pure isomers, it was thus possible to compute an approximate curve for the contribution of the C-5 chiral center to the overall curve of **12** or **13**. Comparison of the computed curves with those obtained from the derivatives prepared from both D- and L-*p*-hydroxyphenylglycine showed that the structures for the two diasteromers were as written.
(6) This structure was defined by x-ray crystallography by Dr. N. Jones and Dr. M. Chaney of the Lilly Research Laboratories.
(7) For a total synthesis, see T. Kamiya, "Recent Advances in the Chemistry of β-Lactam Antibiotics", Chemical Society, Cambridge, England, 1976.
(8) For the isolation of nocardicin A, see H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosoda, Y. Kubochi, E. Iguchi, and H. Imanaka, *J. Antibiot.*, **29**, 492 (1976).
(9) For the structure elucidation of nocardicin A, see M. Hashimoto, T. Komori, and T. Kamiya, *J. Am. Chem. Soc.*, **98**, 3023 (1976), and *J. Antibiot.*, **29**, 890 (1976).

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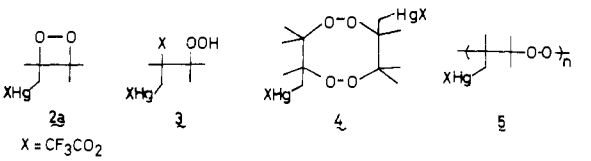
Mercuric Trifluoroacetate Catalyzed Decomposition of an Allylic Hydroperoxide via a Mercury-Substituted 1,2-Dioxetane[1]

Sir:

Peroxymercuration and cycloperoxymercuration have been studied extensively;[2] however, to the best of our knowledge allylic hydroperoxides have not been employed for this purpose. Attempted cyclomercuration of the allylic hydroperoxide **1** led to acetone, the expected Hock cleavage product,[3] but with chemiluminescence. Since 1,2-dioxetanes are likely precursors to this chemiluminescence,[4] we searched for and confirmed the intervention of the mercury-substituted 1,2-dioxetane **2.** Presently we communicate our unusual findings because they constitute (1) a rare example of four-membered-ring formation in cyclomercuration,[5] in particular the first example of the formation of the labile four-membered-ring cyclic peroxides via mercuration, (2) a novel synthetic entry into functionalized 1,2-dioxetanes, and (3) an intriguing allylic mercuration as major process.

Treatment of 2,3-dimethyl-3-hydroperoxy-1-butene (**1**) with mercuric trifluoroacetate in $CDCl_3$ at 35 °C under rigorously anhydrous conditions gave 75% acetone and 100% trifluoroacetic acid within 1 h. When $CDCl_3$ solutions of the reagents were mixed at −40 °C, ^1H NMR monitoring revealed that mercuration was essentially instantaneous. Although the ^1H NMR spectrum of the reaction was complex, the proton of trifluoroacetic acid was immediately visible at δ 8.7 ppm, but the methyl protons of acetone at δ 2.1 ppm grew in slowly only on warmup and was accompanied by light emission. In fact, the rates of acetone production and light emission were the same within the experimental error, but much slower than trifluoroacetic acid formation. Unfortunately the mercurated 1,2-dioxetane **2a** intermediate could as yet not be isolated by low temperature silica gel chromatography, but the following chemical trapping experiments convincingly demonstrate its intervention.

Since $LiAlH_4$ cleanly reduces 1,2-dioxetanes to their respective 1,2-diols,[6] reduction of the mercurated reaction mixture of the allylic hydroperoxide **1** in $CFCl_3$ at −70 °C afforded the expected pinacol in ~15% yield (by VPC). Such pinacol formation suggested that **2a** was formed in the mercuration of **1**, but the noncyclic mercurial **3,** the cyclodimer



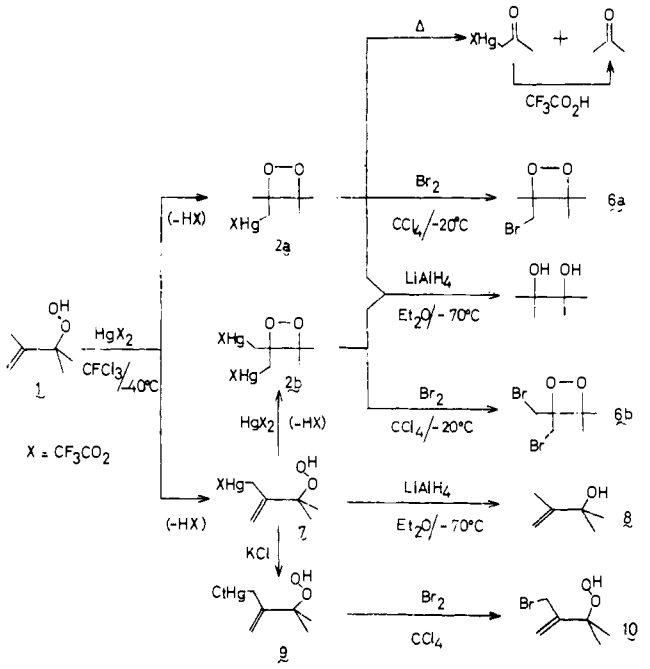
2a X = CF_3CO_2 **3** **4** **5**

4, and the polymer **5** are all plausible precursors to pinacol on $LiAlH_4$ reduction. However, since it was not possible to isolate a pure sample of the postulated mercurated 1,2-dioxetane intermediate **2a,** it was difficult to differentiate among these alternatives.

Consequently, bromodemercuration of **2a** was performed. On treatment of the mercurated reaction mixture with Br_2 in CCl_4 at −20 °C, followed by silica gel chromatography at −45 °C eluting with CH_2Cl_2, the chemiluminescent fractions were collected, rotaevaporated, and rechromatographed at −45 °C eluting with *n*-pentane/CH_2Cl_2 (6:4), affording the bromo-1,2-dioxetanes **6a**[7] and **6b**[8] in ~10 and ~8% yields, respectively. The new dioxetane **6a** was identical with an authentic sample prepared via the Kopecky route[6] by bromination of the allylic hydroperoxide **1** and cyclization of the resulting dibromide with silver trifluoroacetate.[9]

Formation of the dibromodioxetane **6b** implies that the unusual dimercurio-1,2-dioxetane **2b** was also formed. A reasonable pathway to **2b** is cycloperoxymercuration of **7** which is formed from **1** by allylic mercuration[10] (Scheme I). Several lines of evidence confirm that allylic mercuration was the major process in the reaction of **1** with mercuric trifluoroacetate. First of all, $LiAlH_4$ reduction of the mercurated reaction mixture at −40 °C in $CFCl_3$ gave ~80% allylic alcohol **8.** That **8** was not derived from unreacted **1** was easily ruled out since the ^1H NMR spectrum of the mercurated reaction mixture showed that the proton of trifluoroacetic acid was formed at the expense of the allylic protons of **1.** Furthermore, the allylic

Scheme I



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