$-H_2O)^-$ peaks, which verify the diol nature of the compounds. Collisional activation seems to be most appropriate here to optimize anion spectral information.

The fraction of $(M-H)^-$ parent ions with little excess energy decomposing in the metastable ion region of the mass spectrometer should be highly sensitive to stereochemistry. Grützmacher et al.[16] have successfully applied the metastable ion spectra technique (DADI resp. MIKES)[17] to stereochemical problems of gas phase cations. Our findings on $(M-H)^-$ ions are also in keeping with this reasoning. The negative metastable ion (NMI) spectra of *cis*- and *trans*-1,3-cyclohexanediols (Figure 2C,D) strikingly show the intramolecular hydrogen bridge stabilization effect in the cis isomer.

These examples demonstrate the potential of negative ion mass spectrometry for the identification of stereoisomers. We are applying anion techniques now to a larger variety of cyclic diols and related compounds to obtain more information about the analytical utility of stereochemical effects on anion mass spectra.

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(12) The spectra were recorded on a ZAB-2F spectrometer, VG Micromass, fitted with a combination EI/CI source. A $N_2O/CH_4$ mixture was used to generate $OH^-$ reagent ions.[3] The reagent gas pressure was 0.5 Torr. At ~3% $N_2O$ in $CH_4$, the optimum yield of $OH^-$ was obtained (55–70% $OH^-$, 45–30% $O^{-\cdot}$). The diol spectra seemed to be insensitive to the $O^{-\cdot}$ reactant ions, constantly present under our conditions, as will be discussed in the full paper.
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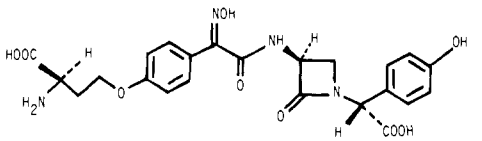
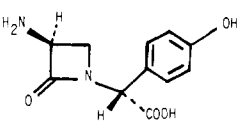
## A Synthesis of (±)-3-Aminonocardicinic Acid (3-ANA)

*Sir:*

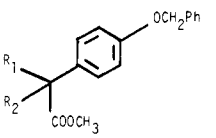
The nocardicins, monocyclic β-lactams recently isolated from the fermentation broth of a strain of actinomycetes,[1] exhibit activity against a broad spectrum of Gram-negative bacteria. The nucleus of this β-lactam system, 3-aminonocardicinic acid (3-ANA) (**2**), is an attractive target for synthesis since its availability permits the preparation of new derivatives of the nocardicins by acylation of the 3-amino group. Two syntheses of nocardicin A (**1**) have been reported,[2,3a] both involving the preparation of 3-ANA followed by a second-stage coupling with the side chain.[2,3b] We now report a novel, efficient synthesis of (±)-3-aminonocardicinic acid (**2**), which has




1




2




3, $R_1=R_2=H$
4, $R_1=H$; $R_2=COOCH_3$
5, $R_1=N_3$; $R_2=COOCH_3$
6, $R_1=NH_2$; $R_2=COOCH_3$

advantages over previous syntheses in that it involves few steps, proceeds in good yields, and utilizes readily available starting materials.

A suitably protected amine (**6**) was prepared from methyl *p*-(benzyloxy)phenylacetate (**3**).[4] Condensation of the ester **3** with dimethyl carbonate (NaH, ether, $CH_3OH$, 25 °C, 24 h) gave the malonate **4** (75%). The amine functionality was introduced by reaction of the malonate anion (NaH, THF, HMPA, 25 °C, 2 h) with *p*-toluenesulfonyl azide[5] (50 °C, 2.5 h) to yield the azido malonate **5** (76%) followed by reduction with zinc in 90% aqueous acetic acid (25 °C, 2 h) giving the amino malonate **6** (85%).

Formation of the β-lactam ring was accomplished by two methods. Initially **6** was added to a solution of cyclopropanone (ether, $CH_2Cl_2$) prepared from ketene and diazomethane at −78 °C.[6] The alkylaminocyclopropanol **7**, formed in quantitative yield, was chlorinated in situ to form **8** (not isolated) ($NaHCO_3$, $ClOC(CH_3)_3$, −10 °C, 40 min) and treated directly with silver nitrate ($CH_3CN$, 25 °C, 1.5 h) to give the β-lactam **9**,[7] mp 103–104 °C (40%). The cyclopropanone route which, in our earlier experience,[6b] generally proceeds in good yield to the β-lactam was complicated in this case by the formation of the chloroamide **10**,[8] mp 151–153 °C, as a side product (30%) (Scheme I).

In a more convenient route to **9**, 3-chloropropionamide (**10**)[9] in $DMF/CH_2Cl_2$ (1:4) (0.1 M) was added slowly (5.5 h) to a suspension (0.1 M) of NaH in $DMF/CH_2Cl_2$ (1:4) at 25 °C. Workup after 1 h yielded the β-lactam **9** (76%). This type of cyclization has previously been used to prepare β-lactams in special cases,[3a,10] but it has not been shown to be general for *N*-alkyl unsubstituted β-halopropionamides.[11] (In more concentrated solutions the reaction gives substantial amounts of the elimination product **11**.) Under the above conditions, a small amount (~5%) of **11** was observed.

The β-lactam malonate **9** was converted to the 3-azido derivative using the procedure of Kuhlein and Jensen[12] (Scheme

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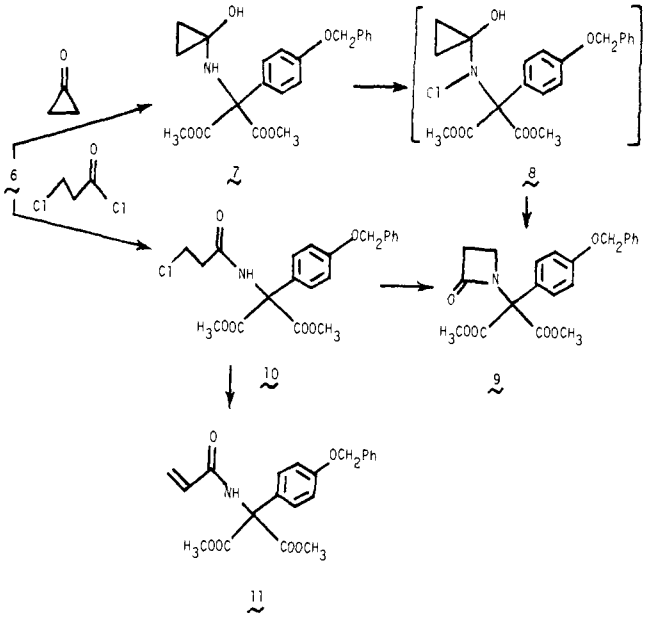
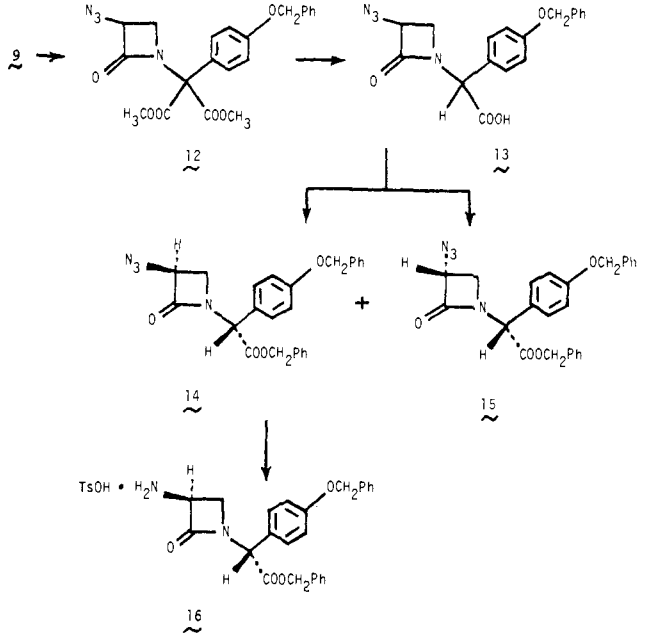
Scheme I



Scheme II



II). Thus, formation of the anion at the 3 position of the β-lactam with LDA in THF (−78 °C, 2 h) was followed by treatment with *p*-toluenesulfonyl azide and then trimethylsilyl chloride affording the 3-azido lactam **12** (80%). Hydrolysis of **12** with 1 N NaOH in methanol (0 °C, 4 h), followed by acidification to pH 2 with 1 N HCl, resulted in decarboxylation with the formation of **13** as a 1:1 mixture of diastereomers (70%). Treatment of the mixture with benzyl bromide and triethylamine in acetonitrile (reflux, 6 h) gave the benzyl esters **14**[13] and **15**[14] (80%). The diastereomers were separated at this stage using a Waters Prep LC/System 500 liquid chromatograph,[15] and each isomer was reduced with hydrogen sulfide ($Et_3N$, $CH_2Cl_2$, 25 °C, 15 min).[16] In this way, the amine tosylate **16** and its epimer were separately isolated (70%). Comparison of **16** and its epimer with an authentic sample[17] showed **16** to be identical (IR, NMR, and TLC behavior) with the chiral product synthesized by the Lilly group.[3a] Additional quantities of the desired benzyl ester **14** could be obtained by equilibration of **15** with potassium *tert*-butoxide (*tert*-butyl alcohol, THF, 0 °C, 2 h) whereby a 1:1 mixture of **14** and **15** was formed in quantitative yield. The final conversion of the dibenzylamine tosylate **16** to 3-ANA by reduction has already been reported,[3a] as has the introduction of the side chain at position 3. Our preparation of the dibenzyl 3-ANA tosylate salt **16** thus constitutes a formal total synthesis of (±)-nocardicin A.[18]

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(8) IR ($CHCl_3$) 3400, 1740, 1680, 1500 $cm^{-1}$; NMR ($CDCl_3$) δ 2.73 (t, $J$ = 6 Hz, 2 H), 3.76 (m, 8 H), 5.04 (s, 2 H), 6.94 (d, $J$ = 9 Hz, 2 H), 7.2–7.5 (m) and 7.53 (d, $J$ = 9 Hz) (8 H); mass spectrum *m/e* 419 ($M^+$).
(9) Prepared by acylation of **6** with 3-chloropropionyl chloride ($CH_2Cl_2$, *N,N*-dimethylaniline, 25 °C, 4 H) (86%).
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(14) IR ($CHCl_3$) 2120, 1760, 1740 $cm^{-1}$; NMR ($CDCl_3$) δ 3.36 (apparent t, $J$ = 6 Hz, 1 H), 3.57 (dd, $J$ = 3, $J$ = 6 Hz, 1 H), 4.47 (dd, $J$ = 3, $J$ = 5 Hz, 1 H), 5.05 (s, 2 H), 5.21 (s, 2 H), 5.58 (s, 1 H), 6.94 (d, $J$ = 9 Hz, 2 H), 7.12 (d, $J$ = 9 Hz, 2 H), 7.26–7.42 (m, 10 H); mass spectrum *m/e* 414 ($M^+ - 28$).
(15) We thank Mr. Kenneth Conroe of Waters Associates for help in the separation of the diastereomers.
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(17) Provided by Dr. G. A. Koppel, The Lilly Research Laboratories, Eli Lilly and Co.
(18) Yields given in this synthesis are for pure isolated products having satisfactory spectroscopic properties and elemental analyses.

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## Classical Configurations Associated with Nonclassical Molecules: Three Carboranes as Examples

*Sir:*

The boranes and carboranes, two well-known classes of "nonclassical" molecules, have been the subject of extensive

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