that the  $Fl^-$ , /Fl: reversible redox couple was observed in the cyclic voltammetric reduction of  $FlN_2$ .<sup>2</sup> The chemical reductions of  $FlN_2$  and  $FlBr_2$  lead us to conclude that reduction of diazo compounds is the only efficient method presently available for producing these aryl carbene anion radicals in solution. As to the question of whether the reduction of carbene anion radicals  $\rightarrow$  carbene dianions will be observed generally or will be strongly structure dependent, the answer must await the results of studies in progress.

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# Total Synthesis of (-)-Axisonitrile-3. An Application of the Reductive Ring Opening of Vinylcyclopropanes

# Sir:

Recently, Sica and co-workers isolated the isonitrile sesquiterpene (+)-axisonitrile-3 from the marine sponge *Axinella cannabina* and determined that it has a novel spiro[4.5]decane ring system by X-ray crystallography.<sup>1</sup> We report the total synthesis of (-)-axisonitrile-3 (1a) from (+)-dihydrocarvone. This synthesis establishes that the absolute configuration of the natural product is opposite to that shown in structure 1a.

It is well known that reductive cleavage of 1-methyltricyclo[4.4.0.0<sup>2,6</sup>]decan-3-ones provides a general method of

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b. R<sub>1</sub>=H; R<sub>2</sub>=OH e. R<sub>1</sub>=N<sub>3</sub>; R<sub>2</sub>=E c. R<sub>1</sub>=H; R<sub>2</sub>=OTs f. R<sub>1</sub>=NH<sub>2</sub>; R<sub>2</sub>=H 4. R<sub>1</sub>=R<sub>2</sub>=H; R<sub>3</sub>=0
 b. R<sub>1</sub>=H; R<sub>2</sub>=OH; R<sub>3</sub>=0
 c. R<sub>1</sub>=R<sub>2</sub>=H; R<sub>3</sub>=CH<sub>2</sub>
 d. R<sub>1</sub>=H; R<sub>2</sub>=OH; R<sub>3</sub>=CH<sub>2</sub>

synthesis of spiro[4.5]decanone derivatives.<sup>2</sup> Our recent work on the lithium/liquid ammonia cleavage of the tricyclodecanone **2a** demonstrated that opening of the cyclopropane ring to the corresponding spiro ketone occurred exclusively with inversion of configuration at the  $\beta$  carbon (C-1).<sup>2c</sup> We have now found that the related vinylcyclopropanes (cf. **2c**,**d**) undergo reductive ring opening with lithium in ethylamine to produce spiro[4.5]decenes such as **1b**,**d**. Again, exclusive inversion of configuration at C-1 was observed. This suggested that an *exo*-methylene compound of the type **2** having a substituent at C-7 which would allow elaboration to an isonitrile group would serve as a useful precursor of **1a**. From a number of possibilities, we selected a route which utilized the  $7\alpha$ hydroxy compound **2d**.

The known ketol  $3,^3$  which was prepared in 50% yield by annulation of (+)-dihydrocarvone<sup>4</sup> with methyl vinyl ketone followed by catalytic hydrogenation of the double bond of the isopropenyl group, was the starting material for the synthesis.



Treatment of 3 with acetic anhydride containing a catalytic amount of sulfuric acid (12 h, 25°C) gave the dienol acetate 4 (NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.88 (d, J = 6 Hz, 3 H), 0.91 (d, J =6 Hz, 3 H), 1.02 (s, 3 H), 2.03 (s, 3 H), 5.33 (d, J = 3 Hz, 1 H), 5.62 (d, J = 2 Hz, 1 H)) in 80% yield. Oxidation of 4 with m-chloroperbenzoic acid in 20:1 isopropyl alcohol-water<sup>5</sup> (4 h, 25 °C) gave a mixture of products containing 42% of the enone derived from dehydration of the ketol 3 and 56% (96% based upon unrecovered enone) of an  $\sim$ 6:1 mixture of the hydroxy enone **5a** and its  $6\beta$  epimer. Hydroxy enone **5a**<sup>6</sup> (mp 116.0-118.0 °C (from benzene-hexane); NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.93 (br m, 6 H), 1.40 (s, 3 H), 3.75 (s, 1 H), 4.20 (br s, 1 H), 5.67 (s, 1 H)) was isolated by chromatography by Florisil. The  $6\beta$  epimer was not obtained completely pure, but the crude material showed NMR  $\delta_{Me4Si}$  (CCl<sub>4</sub>) 0.92 (br m, 6 H), 1.25 (s, 3 H), 4.53 (br s, 1 H), 6.05 (d, J = 1.5 Hz, 1 H).

Conversion of **5a** to its MIP (methoxyisopropylidine) derivative,<sup>7</sup> followed by the introduction of a 1,2 double bond using the phenylselenenylation-selenoxide elimination procedure,<sup>8</sup> gave **5b**<sup>6</sup> (mp 92.5-93.5 °C (from benzene-hexane); NMR  $\delta_{Me4Si}$  (CCl<sub>4</sub>) 0.83 (d, J = 5 Hz, 3 H), 0.93 (d, J = 5 Hz, 3 H), 1.41 (s, 3 H), 4.38 (br s, 1 H), 5.93 (dd, J = 1.6, 10 Hz, 1 H), 5.97 (d, J = 1.6 Hz, 1 H), 6.57 (d, J = 10 Hz, 1 H)) in 85% yield. Irradiation of a 0.04 M solution of **5b** in anhydrous dioxane at room temperature gave a single crude tricyclodecenone<sup>9</sup> (NMR  $\delta_{Me4Si}$  (CCl<sub>4</sub>) 0.81 (d, J = 6 Hz, 3 H), 0.93 (d, J = 6 Hz, 3 H), 1.17 (s, 3 H), 4.03 (d, J = 7 Hz, 1 H), 5.73 (d, J = 6 Hz, 1 H), 7.33 (d, J = 6 Hz, 1 H)) which was catalytically reduced (Pd/C, ethanol) to the hydroxy ketone **2b**<sup>6</sup> (mp 70.5-72.0 °C (from hexane); NMR  $\delta_{Me4Si}$  (CCl<sub>4</sub>) 0.78 (d, J

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= 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.17 (s, 3 H), 3.60 (d, J = 7 Hz, 1 H)) in 52% yield from **5b**.

Treatment of the hydroxy ketone 2b with triphenylmethylenephosphorane in dimethyl sulfoxide  $(12 h, 55 \circ C)^{10}$  gave the exo-methylene compound 2d<sup>6</sup> (mp 68.0-69.0 °C (from hexane); NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.74 (d, J = 7 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 3.60 (d, J = 7.5 Hz, 1 H), 4.63 (br s, 1 H), 4.75 (br s, 1 H)) in 92% yield. Reductive cleavage of 2d with lithium in ethylamine (1 min, 16 °C) gave a single alcohol, 1b, in 90% crude yield.<sup>11</sup> There was no evidence that any of the  $10\beta$  epimer of **1b** (retention of configuration in the ring opening) was obtained in this reaction. Without purification 1b was converted into the tosylate 1c<sup>6</sup> (mp 81-82 °C (from hexane); NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.75 (d, J = 6 Hz, 3 H), 0.78 (d, J = 6 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H), 1.63 (br s, 3 H)H), 2.45 (s, 3 H), 4.52 (d, J = 8 Hz, 1 H), 5.13 (br s, 1 H), 7.23 (d, J = 8 Hz, 2 H), 7.72 (d, J = 8 Hz, 2 H)) using tosyl chloride in pyridine (96 h, 25 °C) in 60% overall yield from 2d.

We also carried out the conversion of the model tricyclodecanone **2a** into (+)-spiroaxene (**1d**)<sup>1</sup> in a similar manner. Methylenation of **2a** as above gave **2c** (NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.82 (d, J = 6 Hz, 6 H), 0.97 (s, 3 H), 4.64 (br s, 1 H), 4.47 (br s, 1 H)) which upon reaction with lithium in ethylamine gave **1d**<sup>6</sup> (NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.75 (d, J = 6 Hz, 3 H), 0.83 (d, J = 6 Hz, 6 H), 1.72 (br s, 3 H), 5.28 (br s, 1 H);  $[\alpha]^{25}_{D}$ +11.6° (c 2.0, ether).<sup>11</sup>

Bose, Kistner, and Farber<sup>12</sup> have reported the conversion of menthyl tosylate into neomenthylamine via S<sub>N</sub>2 reaction with sodium azide in aqueous dimethylformamide followed by lithium aluminum hydride reduction of the azide. However, attempted conversion of 1c to the azide 1e using their procedure led primarily to the formation of elimination products as did the use of potassium azide in acetonitrile containing 18crown-6. It was clear that it would be necessary to carry out the tosylate displacement under conditions which would be more favorable to an  $S_N 2$  reaction. This was accomplished by treating 1c with 3 equiv of potassium azide in benzene containing 5 equiv of 18-crown-6 (48 h, 80 °C).<sup>13</sup> The azide 1e showed NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.71 (d, J = 6 Hz, 3 H), 0.93 (d, J = 6 Hz, 3 H), 0.97 (d, J = 6 Hz, 3 H), 1.77 (br s, 3 H), 3.47 (s, 1 H), 5.20 (br s, 1 H); mass spectrum (70 eV), no  $M^+$ , m/e219 (M - N<sub>2</sub>, weak), 204 (M - HN<sub>3</sub>, strong). Reduction of 1e with LiAlH<sub>4</sub> in ether at reflux gave the amine 1f (NMR  $\delta_{\text{Me4Si}}$  (CCl<sub>4</sub>) 0.71 (d, J = 6 Hz, 3 H), 0.87 (d, J = 5 Hz, 6 H), 1.73 (br s, 3 H), 2.63 (br s, 1 H), 5.27 (br s, 1 H)) in 30% overall yield<sup>14</sup> from 1c.

Using a procedure analogous to that of Hertler and Corey,<sup>15</sup> **If** was converted into (-)-axisonitrile-3 (**1a**) in 85% overall yield by treatment with a 2:1 mixture of formic acid in acetic anhydride at reflux for 2 h followed by reaction with tosyl chloride in pyridine at 25 °C for 1 h. (The formamide derivative, presumably (+)-axamide-3,<sup>1,16</sup> was isolated as an intermediate in this sequence.) The synthetic material<sup>6</sup> showed mp 97–99 °C (from hexane); NMR  $\delta_{Me_4Si}$  (CCl<sub>4</sub>) 0.75 (d, J = 6.5Hz, 3 H), 0.93 (br d, J = 6.5 Hz, 6 H), 1,75 (br s, 3 H), 3.52 (br s, 1 H), 5.14 (br s, 1 H); IR (CCl<sub>4</sub>) 2120 cm<sup>-1</sup>;  $[\alpha]^{25}$ <sub>D</sub> -71° (c 0.35, CHCl<sub>3</sub>).

These physical properties generally agreed with those reported for (+)-axisonitrile-3,<sup>1</sup> the enantiomer of **1a**, except for the sign of the optical rotation.<sup>1</sup> However, there were small discrepancies between the observed NMR chemical shifts, particularly for the methyl groups of the isopropyl group, and those reported by Sica and co-workers.<sup>1</sup> Therefore, verification of the structure of the synthetic material was desirable. Unfortunately, a direct comparison of the synthetic material with the natural product could not be made since neither a pure authentic sample nor copies of the original spectral data were available to us. In order to confirm the structure of the synthetic material was desirable.

thetic compound, a single crystal X-ray study was carried out using a Syntex P2<sub>1</sub> four-circle diffractometer. A complete data set was collected; the published coordinates<sup>1</sup> were refined using Sheldrick's SHELX-76 least-squares program. The refinement converged, with a residual of 0.13, using isotropic thermal parameters and without the hydrogen atoms being included. A difference Fourier synthesis showed no peaks of electron density greater than  $0.5e/Å^3$ . This conclusively demonstrated that the synthetic material was in fact (–)-axisonitrile-3 (1a).<sup>17</sup>

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# Stereospecific Total Synthesis of Gibberellic Acid. A Key Tricyclic Intermediate

#### Sir:

Since the recognition of the central biological role of gibberellic acid (gibberellin  $A_3$ ,  $GA_3$ ) (1) in the plant kingdom,<sup>1</sup> the clarification of its chemical structure,<sup>2</sup> and commercial production on a large scale from the fungus *Gibberella fujikuroi*, this substance has occupied a major position in the field of natural products.<sup>3</sup> The biosynthesis of gibberellic acid from prenyl units, though long and involved, is known in considerable detail.<sup>1,3,4</sup> Despite extensive efforts (some 150 published papers from about 25 different laboratories), the total chemical synthesis of gibberellic acid has not previously been achieved,<sup>5</sup> largely because the combination of overall molecular complexity, centers of high sensitivity toward many reagents, and

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