aration of 3. The solvents were evaporated and the acid chloride resuspended in dry THF. To this was added 300 mol % of (+)-α-(phenylethyl)amine in dry THF, and the solution was stirred at 0° for 2 h. Isolation as described above for the amino acid isoxazolidides gave the crude amides which were taken up in EtOAc and analyzed by HPLC, eluting with EtOAc/hexanes, 35/65.

Acknowledgment. We thank Gregory A. Anderson for his assistance in the preparation of several of the starting materials used in this investigation and Saul Rosenberg for the preparation of **13**. This work was supported in part by NIH Postdoctoral Fellowship 5F32 GM08752 to T.L.C.

Registry No. **1a**, 16639-86-4; **1b**, 15761-38-3; **1c**, 29268-18-6; **1d**, 19887-32-2; **1e**, 5700-77-6; **2a**, 79821-79-7; **2b**, 97973-80-3; **2c**, 97973-81-4; **2d**, 89312-80-1; **2e**, 97973-82-5; **2f**, 97973-83-6; **2g**, 97973-84-7; **2h**, 97973-85-8; **2i**, 97973-86-9; **2j**, 97973-87-0; **3**, 3844-94-8; **4**, 97973-88-1; **5a**, 97973-89-2; **5b**, 97973-90-5; **6**, 97973-91-6; **7**, 97973-79-0; **8a**, 97973-92-7; **8b**, 97973-93-8; **8c**, 97973-94-9; **8d**, 97973-95-0; **8e**, 97973-96-1; **8f**, 97973-97-2; **8g**, 97973-98-3; **8h**, 97973-99-4; **9a**, 17689-03-1; **9b**, 1119-64-8; **9c**, 33589-44-5; **9d**, 1111-64-4; **9e**, 54655-07-1; **10**, 97974-00-0; L-alanine, 56-41-7; L-phenylalanine, 63-91-2; L-methionine, 63-68-3; L-proline, 147-85-3; phenylsulfonyl chloride, 98-09-9; ethyl chloroformate, 541-41-3; pyrrolidine, 123-75-1; 1-hexyne, 693-02-7; 3,5-dimethylpyrazole, 67-51-6; 2-mercaptopyridine, 2637-34-5; dimethylhydroxylamine hydrochloride, 16645-06-0; isoxazolidine hydrochloride, 39657-45-9; tetrahydro-2*H*-1,2-oxazine hydrochloride, 54722-74-6; phenylsulfonic acid, 98-11-3; (trimethylsilyl)acetylene, 1066-54-2; 1,3-dibromopropane, 109-64-8; hydroxyurethane, 589-41-3; *N*-(ethoxycarbonyl)isoxazolidine, 54020-55-2; *N*-(phenylsulfonyl)-L-proline, 88425-46-1.

Intramolecular Michael Reactions. Addition to the α-Carbon of Ynamides

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A number of substituted cinnamamides were synthesized to determine the feasibility of preparing 4-arylnipecotate derivatives via an intramolecular Michael reaction. With these substrates, β-elimination of the cinnamamide residue was the dominant reaction. 3-Phenylpropynamide substrates, however, underwent an unusual "anti-Michael" addition to the α-carbon of the acetylene to produce pyrrolidinones, whose structures were confirmed by independent synthesis.

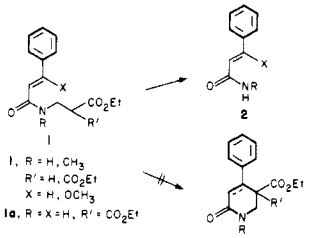
For some time we have been interested in the synthesis of 4-arylpiperidines as precursors to a variety of natural products.[1] As a route to such compounds, we envisioned employing an intramolecular Michael reaction of a suitably functionalized cinnamamide in a convergent synthesis of the piperidine ring.

Results and Discussion

A variety of cinnamamide substrates of the general structure **1** were subjected to ring-closure conditions (NaOEt/EtOH, LDA/THF, *t*-BuOK/DMF or Me_2SO). In all cases only elimination of acrylate occurred providing cinnamamides **2**. Even when the basicity of the enolate was less than that of the cinnamamide anion, as in compound **1a**, elimination was the only reaction observed (Scheme I).

If elimination could not be suppressed relative to ring closure then perhaps a more active Michael acceptor would increase the rate of addition relative to that of elimination. The doubly activated α-cyanocinnamamide residue was examined first. α-Cyanocinnamamide **3** was prepared from α-cyanocinnamoyl chloride[2] and subjected to a variety of ring-closure conditions (Scheme II). No piperidone or elimination products were observed, with only unidentified polar products predominating. It is possible that 1,2-addition to the nitrile was occurring since reaction of α-methoxy carbonyl derivative **4**, in which the amide carbonyl is not present, results in Dieckmann cyclization product **5** rather than Michael condensation.[3]

Scheme I. Attempted Ring Closure of Cinnamamides



Scheme II

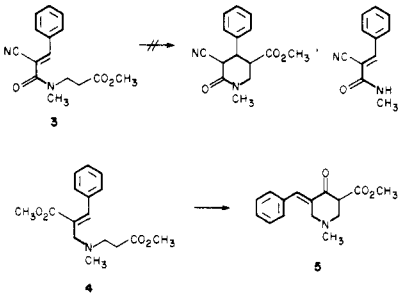


Table I. Effect of the Nitrogen Substituent on the Ratio of Ring Closure to Elimination for Acetylenic Amido Esters

substrate	R	9[a]	11[a]
6a	CH_3	48	39
6b	$CH(C_6H_5)_2$	31	52
6c	$C(CH_3)_3$	89	5

[a] Isolated yield after chromatography.

These results were encouraging in that they proved that reaction, albeit not the desired reaction, is possible without elimination of methyl acrylate provided a sufficiently reactive electrophilic center is present. An acetylenic Mi-

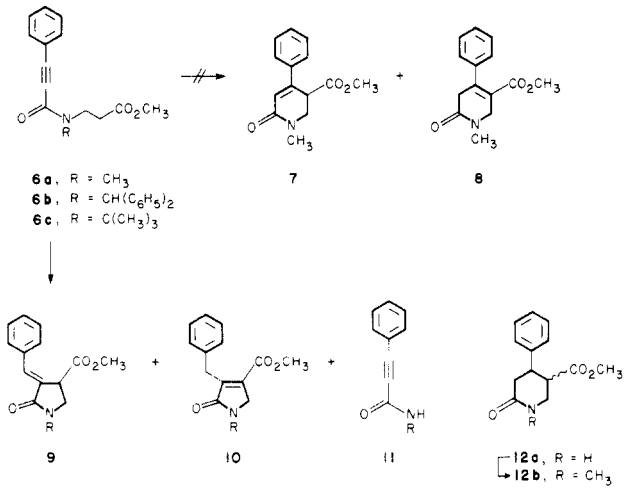
(1) (a) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 1831. (b) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064. (c) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485. (d) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.

(2) Dietz, G.; Fielder, W.; Faust, G. *Chem. Ber.* **1969**, *102*, 522.

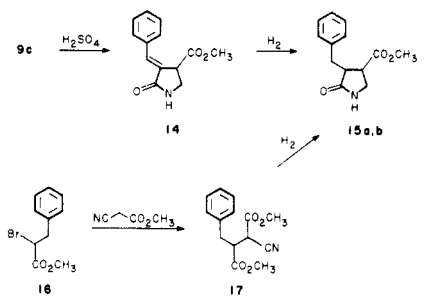
(3) Experiment performed by M. Peled, this laboratory.

0022-3263/85/1950-3979$01.50/0

Scheme III. Anti-Michael Reactions of Acetylenic Amido Esters



Scheme IV. Structure Proof of Anti-Michael Addition Products



chael acceptor should offer both increased reactivity and the means of introducing unsaturation into the final product (Scheme III). Reaction of phenylpropynoyl chloride with methyl 3-(methylamino)propanoate provided acetylenic amide **6a**. Treatment with potassium *tert*-butoxide afforded *N*-methylphenylpropynamide (**11a**) and a new product in 39% and 48% respective yields. On the basis of the proton NMR spectrum, which exhibited a downfield methine resonance at 4.22 ppm coupled to downfield diastereotopic methylene signals at 3.59 and 3.70 ppm, this new product was initially assigned the structure of dihydropyridone **7**. A third, minor component was also isolated which exhibited two downfield methylene singlets at 4.04 and 4.06 ppm and was assigned isomeric structure **8**. Other nitrogen substituents were examined in order to suppress elimination, the *tert*-butyl group affording 89% of the ring-closed product (Table I).

The compounds assigned as structures **7** and **8** were each reduced to the same new product, which was neither isomer of 4-phenylpiperidone **12**. Surprisingly, it appeared that addition had actually occurred to the α-position of the ynamide to provide **9a** and **10a**, whose structures are also consistent with the NMR data. That five-membered ring products were indeed being formed was confirmed by comparison with pyrrolidinones prepared via an alternate method (Scheme IV). Thus the *tert*-butyl group of **9c** was removed with strong acid, and the resulting NH pyrrolidinone **14** was hydrogenated to pyrrolidinone **15a**, which was identical with one isomer of 3-benzylpyrrolidone **15** prepared from methyl 2-bromo-3-phenylpropanoate (**16**).[4]

(4) (a) Testa, E.; Nicolaus, B. J. R.; Mariani, L.; Pagani, G. *Helv. Chim. Acta.* **1963**, *46*, 766. (b) Briggs, M. T.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2138.

For the cinnamamide substrates **1** and for phenylpropynamides **6**, closures to six-membered rings have been labeled as "favored" processes.[5] Models indicate, however, that significant strain is encountered when the ester enolate is brought close to the β-carbon on the cinnamamide or ynamide while retaining the planarity of the α,β-unsaturated carbonyl system. Thus in neither case can the amide carbonyl help stabilize the developing anion. This is especially so in the acetylenic series where the energetically unfavorable geometry of an allene within a six-membered ring would be required. The fact that all reactions took a course other than closure to a six-membered ring experimentally supports this interpretation.

Limited precedent exists for both the intermolecular[6] and intramolecular[7] "anti-Michael" addition of a carbanion to the α-carbon of an α,β-acetylenic carbonyl species. In the intermolecular example the ylide from the cyanomethyl diethyl sulfonium salt added to the β-carbon of phenylethynyl phenyl ketone but to the α-carbon of ethyl phenylpropynoate, indicating that a phenyl ring is indeed capable of stabilizing a developing anion even when the driving force of five-membered ring formation is not a factor.[8] The reaction of ynamide **6** to form pyrrolidine **9** represents the first example of an anti-Michael addition of a carbanion to an acetylenic amide and the first example in which a simple ester enolate has been the attacking carbanion.

Experimental Section

General Methods. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone. Dimethyl formamide (DMF) was purified as described earlier.[9] Methanol and ethanol were distilled from magnesium. Dimethyl sulfoxide (Me_4SO), triethylamine (TEA), and diisopropylamine were distilled from calcium hydride. Methylene chloride was distilled from P_2O_5. Oxalyl chloride and thionyl chloride were distilled. Methyl iodide was percolated through freshly activated basic alumina. Potassium *tert*-butoxide was freshly sublimed and transferred under an inert atmosphere.

Boiling points and melting points (Pyrex capillary) are uncorrected. Unless otherwise noted ^{13}C NMR and ^1H NMR spectra were recorded in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. UV spectra were determined in ethanol. Preparative medium-pressure liquid chromatography (MPLC) was performed with glass columns and 40–60 mesh silica. High-pressure liquid chromatography was done with 3.2 × 250 mm, 5-μm LiChrosorb Si 60 normal phase silica gel column and a flow rate of 1 mL/min. Column chromatography (gravity) was performed with 63–200 mesh silica gel. Unless otherwise noted, reactions were conducted under an argon atmosphere with magnetic stirring at room temperature. Final product solutions were dried over $MgSO_4$ and rotary evaporated at reduced pressure.

Methyl 3-(Methylamino)propanoate. Methyl 3-[(*N*-(phenylmethyl)-*N*-methylamino]propanoate (25.1 g, 120 mmol)[10] in methanol (250 mL) and cyclohexene (125 mL) was treated with 10% Pd/C (7.0 g). The mixture was heated at reflux for 3 h, filtered, carefully evaporated, and distilled to afford 10.9 g (77%) of a colorless oil: bp 50 °C (15 mm) [lit.[11] bp 71–73 °C, (29 mm)].

Diethyl 2-[(Cinnamoylamino)methyl]malonate (1a). Cinnamoyl chloride (328 mg, 1.98 mmol) and diethyl (aminomethyl)malonate hydrochloride[12] (474 mg, 2.10 mmol) in CH_2Cl_2

(5) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(6) Jeckel, D.; Gosselk, J. *Tetrahedron Lett.* **1972**, 2101.
(7) Metler, T.; Uchida, A.; Miller, S. I. *Tetrahedron* **1968**, *24*, 4285.
(8) Other sulfur ylides add to the β-carbon of ethyl phenylpropynoate. Ide, J.; Kishida, Y. *Tetrahedron. Lett.* **1966**, 1787.
(9) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 56.
(10) Leonard, N. J.; Durand, D. A. *J. Org. Chem.* **1968**, *33*, 1322.
(11) Phillips, A. P. *J. Am. Chem. Soc.* **1950**, *72*, 3298.
(12) Prepared by hydrogenating diethyl cyanomalonate (ref 13) with PtO_2 in 3.5 M HCl/EtOH, filtering, and evaporating to dryness.

(10 mL) were treated with triethylamine (1.2 mL, 8.6 mmol). The mixture was stirred for 4 h, diluted with $CHCl_3$, washed with 1 M HCl and saturated $NaHCO_3$ solution, then dried, and evaporated to afford 530 mg (85%) of **1a** as a pale yellow solid: mp 62–68 °C; ^1H NMR δ 7.47 (d, 1 H, J = 15 Hz), 7.20 (m, 5 H), 6.53 (br t, 1 H), 6.28 (d, 1 H, J = 15 Hz), 4.10 (q, 4 H, J = 6 Hz), 3.80 (m, 3 H), 1.22 (t, 5 H, J = 6 Hz); exact mass calcd for $C_{17}H_{21}NO_5$ m/z 319.1420, found m/z 319.1419.

Cinnamamide (2a). Malonate derivative **1a** (395 mg, 1.24 mmol) was treated with Na (401 mg, 17.4 mmol) dissolved in ethanol (27 mL), and the mixture was kept at reflux for 18 h. The cooled solution was poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$ and then was dried and evaporated. Chromatography (gravity, EtOAc) afforded 209 mg (52%) of recovered **1a** followed by 45 mg (25%) of cinnamamide (**2a**): mp 147–148 °C (lit.[14] mp 145–146 °C).

***N*-*tert*-Butyl-*N*-[2-(methoxycarbonyl)ethyl]-3-phenylpropynamide (6c).** Phenylpropynoic acid (3.00 g, 20.5 mmol) in $SOCl_2$ (14.0 mL) was heated at 60 °C for 3 h, then the excess $SOCl_2$ was evaporated, and the residue was distilled [50 °C, (0.6 mm)] and protected from light. The distillate was dissolved in THF (50 mL) and cooled to 0 °C, and triethylamine (5.0 mL, 36 mmol) and methyl 3-(*tert*-butylamino)propanoate[15] (3.30 g, 20.7 mmol) were added. The mixture was stirred at 0 °C for 45 min and then evaporated, and the residue was dissolved in ether (60 mL) and then was washed with 1 M HCl solution (2×), saturated $NaHCO_3$ solution (2×), dried, evaporated, and distilled to afford 4.51 g (77%) of **6c**: bp 75–80 °C (0.03 mm); mp 70–73 °C; HPLC (70 isooctane/30 Et_2O) t_R 6.0 min; ^1H NMR δ 7.5–7.6 (m, 2 H), 7.3–7.5 (m, 3 H), 4.04 (t, 2 H, J = 7.9 Hz), 3.69 (s, 3 H), 2.73 (t, 2 H, J = 7.9 Hz), 1.50 (s, 9 H); ^{13}C NMR δ 171.2, 155.2, 132.5, 130.0, 128.6, 121.0, 88.1, 83.8, 57.6, 51.7, 42.8, 36.4, 28.9. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.1; H, 7.4; N, 4.9. Found: C, 71.1; H, 7.3; N, 4.8.

***N*-[2-(Methoxycarbonyl)ethyl]-*N*-methyl-3-phenylpropynamide (6a)** was prepared as described for **6c** from methyl 3-(methylamino)propanoate: HPLC (Et_2O) t_R 3.4 min; ^1H NMR δ 7.25 (m, 5 H), 3.80 (m, 2 H), 3.65 (s, 3 H), 3.25, 2.98 (2 s, total 3 H), 2.63, 2.60 (t, total 2 H, J = 7 Hz); ^{13}C NMR 172.0, 171.3, 154.7, 154.5, 132.8, 130.1, 128.6, 120.7, 90.4, 90.0, 81.8, 81.5, 51.8, 51.7, 47.1, 43.3, 37.2, 33.6, 32.5, 32.1; IR (film) 2207, 1730, 1625 cm^{-1}; UV λ_{max} 275 (ϵ 14900), 258 (17500), 249 nm (17100); exact mass calcd for $C_{14}H_{15}NO_3$ m/z 245.1052, found m/z 245.1042.

4-(Methoxycarbonyl)-1-methyl-2-oxo-3-benzylidenepyrrolidine (9a) and 4-(Methoxycarbonyl)-1-methyl-2-oxo-3-benzyl-3-pyrroline (10a). Acetylenic amido ester **6a** (300 mg, 1.22 mmol) was dried at 50 °C (0.05 mm) for 9 h, dissolved in DMF (5 mL), cooled to −69 °C, and treated with potassium *tert*-butoxide (160 mg, 1.5 mmol) in DMF (5 mL) precooled to −69 °C. After 15 min, acetic acid (0.5 mL, 9 mmol) was added, the solvent was removed by bulb-to-bulb distillation (50 °C, −78 °C receiver), and the residue was suspended in ether and washed with saturated $NaHCO_3$ solution, which was then back-extracted with ether. The combined organic phases were dried and evaporated, and the residue was chromatographed (MPLC, Et_2O) to afford in order of elution, 75.5 mg (39%) of *N*-methyl-3-phenylpropynamide (**11a**), 12.5 mg (4%) of **10a**, and 144.0 mg (48%) of **9a**.

9a: mp 100–101 °C; HPLC (Et_2O) t_R 6.9 min; ^1H NMR δ 7.6–7.3 (m, 6 H), 4.22 (ddd, 1 H, J = 8.2, 2.8, 2.8 Hz), 3.70 (dd, 1 H, J = 10.1, 8.2 Hz), 3.60 (s, 3 H), 3.59 (dd, 1 H, J = 10.1, 2.8 Hz), 3.02 (s, 3 H); ^{13}C NMR δ 171.3, 167.7, 134.5, 133.0, 129.8, 129.4, 128.9, 128.5, 52.2, 50.1, 41.2, 29.9; UV λ_{max} 280 nm (ϵ 16900); mass spectrum, m/z (relative intensity) 245 (23), 185 (36), 161 (12), 138 (22), 115 (15), 82 (100). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.4; H, 6.2; N, 5.6.

10a: mp 117–119 °C; HPLC (Et_2O) t_R 4.2 min; ^1H NMR δ 7.4–7.5 (m, 2 H), 7.2–7.3 (m, 3 H), 4.06 (s, 2 H), 4.04 (s, 2 H), 3.86 (s, 3 H), 3.05 (s, 3 H); ^{13}C NMR δ 170.0, 163.3, 147.1, 138.1, 135.6, 129.3, 128.5, 126.5, 52.7, 52.0, 30.9, 29.4; UV λ_{max} 275 (ϵ 3100), 231 (8400), 208 nm (8800); mass spectrum, m/z (relative intensity) 245 (76), 186 (100), 154 (35), 91 (65). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.8; H, 6.1; N, 5.7.

1-*tert*-Butyl-4-(methoxycarbonyl)-2-oxo-3-benzylidenepyrrolidine (9c). Acetylenic amido ester **6c** (340 mg, 1.18 mmol) was treated as described above for the *N*-methyl compound **6a**. Chromatography (MPLC, 3/1 isooctane/ether) afforded 304 mg (89%) of **9c**: mp 82–85 °C; HPLC (70 isooctane/30 Et_2O) t_R 6.0 min; ^1H NMR δ 7.3–7.6 (m, 6 H), 4.13 (ddd, 1 H, J = 2.3, 5.1, 5.7 Hz), 3.714 (d, 1 H, J = 5.7 Hz), 3.712 (d, 1 H, J = 5.1 Hz), 3.60 (s, 3 H), 1.49 (s, 9 H). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.1; H, 7.4; N, 4.9. Found: C, 71.0; H, 7.4; N, 4.8.

4-(Methoxycarbonyl)-2-oxo-4-benzylidenepyrrolidine (14). *N*-*tert*-Butylpyrrolidine **9c** (70 mg, 0.24 mmol) was heated in H_2SO_4 (1.0 mL) at 50 °C for 2 h and then allowed to come 20 °C and stirred for 1 h. The mixture was poured into cooled (5 °C) water (20 mL) and extracted with $CHCl_3$, which was then dried and evaporated. Chromatography (MPLC, Et_2O) of the residue afforded 46 mg (82%) of **14**: mp 142–144 °C; HPLC (Et_2O) t_R 12.0 min; ^1H NMR δ 8.23 (br s, 1 H), 7.5–7.1 (m, 6 H), 4.3–4.1 (m, 1 H), 3.6–3.5 (m, 2 H), 3.53 (s, 3 H). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.7; H, 5.7; N, 6.0.

Dimethyl 3-Benzyl-2-cyano-1,4-butanedioate (17). Sodium (602 mg, 26.2 mmol) was dissolved in methanol (13 mL), methyl cyanoacetate (2.30 mL, 26.1 mmol) was added, and the mixture was stirred for 30 min. Methyl 2-bromo-3-phenylpropanoate (**16**; 5.60 g, 23.0 mmol)[4] in methanol (15 mL) was added, and the mixture was stirred for 24 h, quenched with acetic acid, poured into saturated $NaHCO_3$ solution, and extracted with chloroform to afford 6.61 g of a green oil. Distillation [100–115 °C (0.05 mm)] gave 4.15 mg (69%) of a colorless oil, which was a mixture of diastereomers of **17** (from 25–80 °C the starting bromo ester and a trace of methyl cinnamate were recovered): ^1H NMR δ 7.4–7.2 (m, 5 H), 3.8–4.0 (m, 1 H), 3.79, 3.78 (2 s, total 3 H), 3.69, 3.68 (2 s, total 3 H), 3.55–3.35 (m, 2 H), 3.25–3.15, 2.95–2.80 (m, total 1 H); exact mass calcd for $C_{14}H_{15}NO_4$ m/z 261.1002, found m/z 261.0998.

3-Benzyl-4-(methoxycarbonyl)-2-oxopyrrolidine (15). To cyano diester **17** (4.00 g, 15.3 mmol) in 3.3 M HCl in CH_3OH (26 mL) was added PtO_2 (0.12 g), and the mixture was hydrogenated at 50–55 psi for 24 h, then filtered, and evaporated. The residue was taken up in 1 M H_3PO_4 (80 mL), washed with benzene (3 × 30 mL), made basic with K_2CO_3, and extracted with $CHCl_3$, which was then dried and evaporated. Heating the residue at reflux in toluene (50 mL) for 2 h and then evaporating the solvent afforded 2.02 g of a light yellow solid. Chromatography (MPLC, 50 $CHCl_3$/50 EtOAc) gave 751 mg (21%) of isomer **15a** followed by 1.038 g (29%) of isomer **15b**.

15a: mp 130–131 °C; HPLC (Et_2O) t_R 8.0 min; ^1H NMR δ 7.4–7.2 (m, 5 H), 6.70 (br s, 1 H), 3.56 (s, 3 H), 3.44 (dd, 1 H, J = 8.0, 9.7 Hz), 3.36 (dd, 1 H, J = 8.5, 9.7 Hz), 3.16 (dd, 1 H, J = 3.8, 12.4 Hz), 3.1–2.9 (m, 3 H). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 67.0; H, 6.5; N, 6.0.

15b: mp 98–99 °C; HPLC (Et_2O) t_R 13.8 min; ^1H NMR δ 7.2–7.4 (m, 5 H), 6.4–6.8 (br, 1 H), 3.53 (s, 3 H), 3.4–3.5 (m, 2 H), 3.33 (ddd, 1 H, J = 5.9, 7.2, 8.2 Hz), 3.22 (dd, 1 H, J = 4.2, 14.4 Hz), 3.02 (ddd, 1 H, J = 4.2, 8.2, 9.8 Hz), 2.78 (dd, 1 H, J = 9.8, 14.4 Hz). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 67.0; H, 6.5; N, 6.0.

Alternatively benzylidenepyrrolidinone **14** (76.0 mg, 0.33 mmol) in methanol (5 mL) was hydrogenated at 50–55 psi with PtO_2 (6.5 mg) for 30 h. The mixture was filtered and chromatographed (MPLC, 50 EtOAc/50 $CHCl_3$) to afford 56.5 mg (74%) of **15b**, identical with the compound obtained above.

5-(Methoxycarbonyl)-1-methyl-2-oxo-4-phenylpiperidine (12b). To piperidone **12a** (11.72 g, 50.2 mmol)[16] in CH_2Cl_2 (60 mL) was added $(CH_3)_3OBF_4$ (9.30 g, 62.0 mmol). The mixture was stirred in the dark for 23 h, poured into saturated $NaHCO_3$ solution (200 mL) and ice (200 g), and extracted with CH_2Cl_2, which was then dried and evaporated. The crude imidate, dissolved in toluene (220 mL), was treated with dimethyl sulfate (3.3 mL, 35 mmol) at reflux for 20 h, cooled, and poured into water. The toluene layer was separated, the aqueous phase was extracted with $CHCl_3$, and the combined organic phases were dried and evaporated to afford 14.5 g of a brown solid which slowly crys-

(13) Haller, A. *C. R. Hebd. Seances Acad. Sci.* **1882**, *95*, 142.
(14) Posner, T. *Chem. Ber.* **1905**, *38*, 2316.
(15) Aelony, D. *J. Appl. Polym. Sci.* **1969**, *13*, 227.
(16) Prepared as described for the ethyl ester: Koelsch, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 2459.

tallized. Recrystallization from acetone afforded 4.60 g (37%) of *trans*-**12b**. The mother liquors were distilled bulb-to-bulb [100–160 °C (0.1 mm)], and the 1.25 g of white solid collected was chromatographed (MPLC, EtOAc) to afford an additional 500 mg (4%) of the *trans*-**12b** followed by 750 mg (6%) of the *cis*-**12b**.

trans-**12b**: mp 117–118 °C; HPLC (EtOAc) t_R 6.2 min; ^{1}H NMR δ 7.1–7.4 (m, 5 H), 3.64 (dd, 1 H, J = 9.5, 12.2 Hz), 3.50 (s, 3 H), 3.45–3.35 (m, 2 H), 3.11–3.00 (m, 1 H), 3.01 (s, 3 H), 2.75 (dd, 1 H, J = 5.7, 17.7 Hz), 2.59 (dd, 1 H, J = 10.3, 17.7 Hz). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 60.2; H, 7.0; N, 5.6.

cis-**12b**: mp 95–96 °C; HPLC (EtOAc) t_R 7.5 min; ^{1}H NMR δ 7.2–7.4 (m, 3 H), 7.0–7.1 (m, 2 H), 3.74 (dd, 1 H, J = 5.0, 9.2 Hz), 3.65 (s, 3 H), 3.42 (d, 1 H, J = 3.7 Hz), 3.39 (s, 1 H), 3.25–3.15 (m, 1 H), 3.03 (s, 3 H), 2.85 (d, 2 H, J = 5.0 Hz).

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Coronopifoliol, a Diterpene Based on an Unprecedented Tetracyclic Skeleton from the Red Algae *Sphaerococcus coronopifolius*

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The structure of coronopifoliol (1), a novel tetracyclic diterpene isolated from the $CHCl_3$ extracts of *Sphaerococcus coronopifolius*, had been determined on the basis of physicochemical data including 2D NMR spectroscopies, and its biogenetic origin is briefly discussed.

Diterpenes, which are common metabolites of marine brown algae, are much less widespread in Rhodophyta[1], having been found, up to date, only in some algae belonging to the genus *Laurencia*[2] and in the unrelated species *Sphaerococcus coronopifolius*.[3] Particularly, the last organism is yielding an expanding variety of interesting diterpenes based on carbon skeletons that seem to be peculiar to this algae. We wish to describe here the structure of coronopifoliol (1), a novel brominated diterpene possessing an unprecedented tetracyclic ring system.

The dried algae was exhaustively extracted with chloroform, and the residue was subjected to separation on a combination of column chromatography over silica gel and HPLC on RP18 to give 1 (0.001%, based on dry weight). Coronopifoliol had the molecular formula $C_{20}H_{33}BrO_2$, established from HRMS. The mass spectrum showed, in addition to the two very weak molecular ion peaks of equal intensity at m/z 384 and 386, strong peaks at m/z 366, 368 [$(M - H_2O)^+$], 287 [$(M - H_2O - Br)^+$], and 269 [$(M - 2H_2O - Br)^+$], suggesting that the two oxygen atoms are as two hydroxyl groups. This was confirmed by IR absorption at ν_{max} 3450–3300 cm^{-1} and by the ^{13}C NMR spectrum of 1, which also indicated the nature of the two alcoholic functions showing in the lower field region resonances attributable to a ≡C–OH (δ 73.00) and to a =CHOH (δ 75.85) group in addition to that of the bromomethine carbon atom (δ 69.46). The ^{1}H NMR spectrum (C_6D_6, 500 MHz, Table I) of 1 confirmed the last two functionalities [δ 3.41 (1 H, br dd, 14-H) and 3.76 (1 H, dd, 8-H)] and showed the presence of two methyl groups linked to quaternary carbon atoms [3 H singlets at δ 1.13 (16-H_3) and 1.36 (17-H_3)] and of two secondary methyls belonging to an isopropyl function [δ 0.83 and 0.81 (3 H each, d's, 19-H_3 and 20-H_3)].

^{1}H NMR decoupling studies allowed us to formulate the partial structures A, B, and C, showing the interrelation of the pertinent protons as reported in Table II. The values of the coupling constants (see Table I) suggested that the last two structural fragments were most likely parts of six-membered rings.

Very useful information was obtained from two-dimensional ^{13}C–^{1}H shift correlated spectroscopy,[4] which led to the assignment of all the protonated carbon resonances in 1, thus confirming the above partial structures. ^{13}C NMR spectrum of 1 also comprised the signals of two quaternary carbon atoms [δ 49.75 (C4) and 41.75 (C7)] which, together with the carbon atom bearing the tertiary OH group (C11), connect the substructures A, B, and C to give structure 1. The positioning of these three fully substituted carbon atoms in structure 1 was accomplished with the aid of long-range 2D ^{13}C–^{1}H shift correlation spectroscopy. By this technique only a limited number of ^2J and ^3J C–H couplings could be evidenced, but these were essential for the confident structural assignment of 1. Thus, the two signals at δ 41.75 (C7) and 73.00 (C11) were observed to correlate with the two Me groups resonating at δ 1.36 (17-H_3) and 1.13 (16-H_3) in the ^{1}H NMR spectrum, respectively. These data in conjunction with the correlations of C12 with 16-H_3 and 17-H_3 and of C10 with 16-H_3 led to the combination of substructures A and C through the carbon atoms C11 and C7.

Ultimately, the correlation of C6 with 17-H_3 clearly indicated that substructure B was linked to C7, thus une-

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