(.+-.)-Aspidofractinine derivatives

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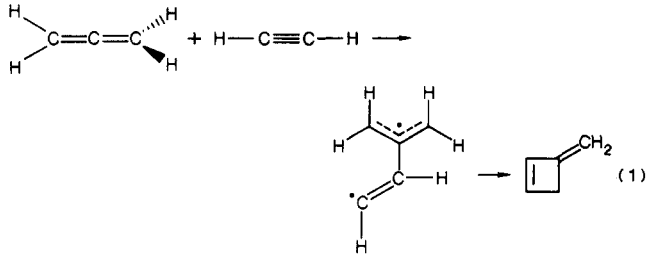
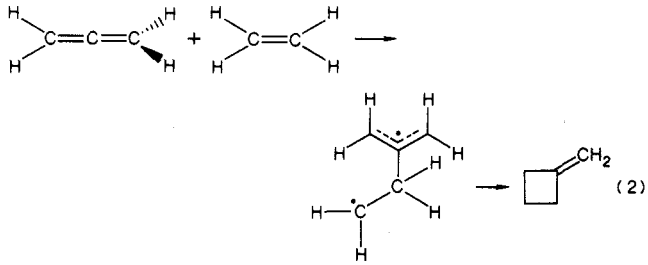
greater reactivity of the alkynes in the [2 + 2] cycloaddition reactions with DMA can be gained by consideration of the relative changes in the heats of formation on going from the reactants to the intermediate diradicals and on to the products, which are shown in Figure 1 for the hypothetical reactions shown in eq 1 and 2. The formation of **2** is



1



2

accompanied by a positive *increase* in the heat of formation as expected. The formation of **1**, however, is accompanied by a *decrease* (in a positive sense) in heat of formation, giving a heat of formation of **1** *lower* than that of the reactants! This is due to the considerably larger positive heat of formation of acetylene (54.2 kcal mol^{-1}) compared to that of ethene (12.5 kcal mol^{-1}).[9] The much lower heat of formation of **1** versus **2** relative to the heats of formation of the reactants would suggest that the energy barrier for the formation of **1** should be considerably lower than that for the formation of **2**, which is consistent with the presently observed relative reactivity data.

Experimental Section

Relative Rate Measurements. The competitive cycloaddition reactions were carried out by placing 0.5 mmol each of the substituted alkene and alkyne and DMA in 0.4 mL of toluene-d_8 in an NMR tube. Dioxane (20 μL) was added as an internal standard for NMR integration purposes, and 1 mg of hydroquinone was added as a polymerization inhibitor. The contents of the tubes were triply freeze degassed, and the tubes were sealed under reduced pressure. The NMR spectra of the reactant solutions were recorded and the tubes were then heated in a sand bath at 160 °C for 5 days. The NMR spectra of the reaction solutions were recorded, the integrals were measured and compared with those of the reactant solutions, and the extent of reaction of the substituted alkene and alkyne was calculated. The resonances in the reactions mixtures were identified by the comparison of chemical shifts with those recorded previously.[5,6]

Acknowledgment. This research was supported by National Science Foundation Grant CHE87-09725.

Registry No. DMA, 598-25-4; $H_2C{=}CHCO_2Et$, 140-88-5; $HC{\equiv}CCO_2Et$, 623-47-2; $H_2C{=}CHC_6H_5$, 100-42-5; $HC{\equiv}CC_6H_5$, 536-74-3.

(9) The heats of formation of the reactants, diradical intermediates, and the products have been calculated by the Benson group additivity approach (Benson, S. W. *Thermochemical Kinetics*; John Wiley & Sons: New York, 1976) using the group additivities in Table 2.14 (pg 73) and Appendix A.1. The group additivities for C-(C_d)(C)(H) and C_d-(H) were assumed to be -5 and +25, respectively, based on comparisons with other group values.

(±)-Aspidofractinine Derivatives

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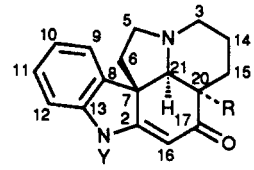
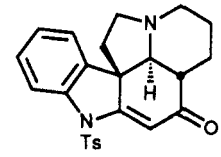
In connection with studies in the field of Aspidosperma alkaloid synthesis the pentacyclic intermediate **1a** has been prepared recently[2] and now has been used for the construction of some aspidofractinine derivatives.

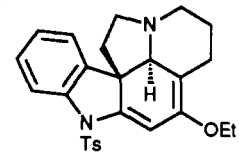
Exposure of pentacycle **1a** to *p*-tolylsulfonyl chloride and sodium hydroxide under phase-transfer conditions yielded a mixture of the *N*-tosyl derivatives **1b** and **2**. Treatment of either product with ethyl iodide and potassium hydride gave ketone **1c** (in 13% yield) and diene **3** (61%).[3]





2

1a: R = Y = H
b: R = H; Y = $SO_2C_6H_4Me(-p)$
c: R = Et; Y = $SO_2C_6H_4Me(-p)$
d: R = Et; Y = H



3

The acquisition of a fair amount of diene **3** permitted its use in Diels–Alder reactions en route to the kopsane skeleton (e.g. aspidofractinine, **5a**).[4] Interaction of the diene with methyl acrylate afforded hexacycle **4a** (82%). Acid-induced, partial hydrolysis of the latter yielded keto ester **5b** (87%), whose stereostructure was confirmed by single-crystal, X-ray crystallographic analysis.[6] Similarly, cycloaddition of diene **3** and phenyl vinyl sulfone produced a ca. 4:1 mixture (66%) of adducts **4b** and **6**. Hydrolysis of each enol ether furnished ketones **5c** (81%) and **7** (84%), respectively. Exposure of either product to sodium amalgam reduction led to 17-oxoaspidofractinine (**5d**) (70

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(2) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719.

(3) Hydrolysis of ketone **1c** with 2 N potassium hydroxide in methanol has led to colorless, amorphous 2,16-dihydro-17-oxoaspidospermidine (**1d**) (76%): UV λ_{max} 241 nm (log ε 4.08), 300 (3.85), 348 (4.10); IR NH 3140 (br m), NCH 2760 (m), 2700 (w), C=O 1680 (s), C=O, C=C 1625 (s), 1603 (s) cm^{-1}, ^1H NMR δ 0.25 (t, 3, *J* = 7 Hz, Me), 3.47 (s, 1, H-21), 5.46 (s, 1, H-16), 6.8–7.7 (m, 4, Ar Hs), 10.03 (s, 1, NH); *m/e* 294 (M^+, 6), 140 (9), 126 (37), 124 (base), 110 (7).

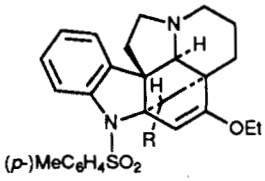
(4) For previous Diels–Alder reactions on 3-like substances, see: (a) Ohnuma, T.; Oishi, T.; Ban, Y,. *J. Chem. Soc., Chem. Commun.* **1973**, 301. (b) Ban, Y.; Honma, Y.; Oishi, T. *Tetrahedron Lett.* **1976**, 1111. (c) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (d) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790.[5] (e) Ogawa, M.; Kitagawa, Y.; Natsume, M. *Tetrahedron Lett.* **1987**, 3985.[5]

(5) Wenkert, E.; Pestchanker, M. J. *J. Org. Chem.* **1988**, *53*, 4875.

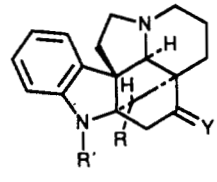
(6) Toffoli, P.; Rodier, N.; Le Ménez, P.; Kunesch, N., unpublished observation.

0022-3263/89/1954-3216$01.50/0

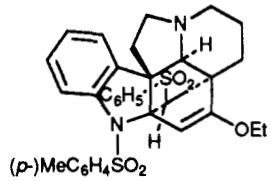
and 55%, respectively). N-Acylation of the latter with methyl chlorocarbonate and sodium hydride afforded ketourethane **5e**, spectrally identical with the product[7] of hydrogenation of the alkaloid kopsinone (8).[8]



4a: R = CO_2Me
b: R = $SO_2C_6H_5$



5a: R = R' = H; Y = H_2
b: R = CO_2Me; R' = $SO_2C_6H_4Me(-p)$; Y = O
c: R = $SO_2C_6H_5$; R' = $SO_2C_6H_4Me(-p)$; Y = O
d: R = R' = H; Y = O
e: R = H; R' = CO_2Me; Y = O



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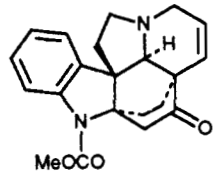

8

Experimental Section

Melting points were determined on a Kofler micro hotstage and are uncorrected. Infrared spectra of films and ultraviolet spectra of 95% ethanol solutions were recorded on Perkin-Elmer 257 and Unicam SP 1800 spectrophotometers, respectively. ^1H NMR spectra of deuteriochloroform solutions (internal standard: Me_4Si) were measured on a Bruker AM 200 spectrometer, and ^{13}C NMR spectra of deuteriochloroform solutions were obtained at 50.3 MHz on the same instrument.[9] The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Mass spectra were recorded on AE1 MS 902 and Nermag/Sidar V 2.3 spectrometers and exact mass measurements on a Varian MAT 311 spectrometer. Chromatographic separations were carried out on Merck silica gel 60 (70–230 mesh ASTM). All crude products were extracted with methylene chloride, and the extracts were dried over anhydrous Na_2SO_4.

20-Deethyl-2,16-didehydro-17-oxo-1-(*p*-tolylsulfonyl)aspidospermidine (1b) and Its C-20 Isomer (2). A mixture of 310 mg (1.1 mmol) of ketone **1a**, 60 mg of tetrabutylammonium hydrogen sulfate, and 15 mL of a 15% aqueous sodium hydroxide solution in 18 mL of methylene chloride was stirred at room temperature for 10 min. *p*-Tolylsulfonyl chloride (250 mg, 1.3 mmol) was added, and the mixture was stirred for 0.5 h. It then was poured into water, and the organic layer was separated, washed with water, dried, and evaporated. Chromatography of the residue (420 mg) and elution with 1:1 cyclohexane–ethyl acetate gave 46 mg (9%) of colorless, crystalline ketone **2**: mp 197–199 °C; IR (KBr) C=O 1660 (s), C=C 1625 (m), 1595 (s), SO_2 1370 (s), 1175 (s) cm^{-1}; ^1H NMR δ 2.33 (s, 3, Me), 3.30 (d, 1, J = 10 Hz, H-21), 6.23 (s, 1, H-16), 6.96 (td, 1, J = 8, 1 Hz Ar H), 7.3–7.4 (m, 3, Ar Hs), 7.70 (dd, 1, J = 8, 1 Hz Ar H), 7.80 (d, 2, J = 9 Hz, Ts *o*-Hs), 7.85 (d, 1, J = 8 Hz, H-12); m/e 420 (M^+, 21), 265 (34), 96 (base); exact mass m/e 420.1515 (calcd for $C_{24}H_{24}O_3N_2S$ m/e 420.1507).

Further elution yielded 180 mg (37%) of colorless, crystalline ketone **1a**: mp 206–208 °C; UV λ_{max} 228 nm (log ϵ 4.43), 274 (4.11), 308 (3.87); IR (KBr) NCH 2780 (m), 2720 (w), C=O 1675 (s), C=C 1630 (s), 1595 (s), SO_2 1368 (m) cm^{-1}; ^1H NMR δ 2.30 (s, 3, Me), 3.00 (d, 1, J = 5 Hz, H-21), 6.28 (s, 1, H-16), 6.9–7.3 (m, 5, Ar Hs), 7.5–7.8 (m, 3, Ar Hs); m/e 420 (M^+, 4), 265 (43), 96 (base). Anal. Calcd for $C_{24}H_{24}O_3N_2S$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.73; H, 5.69; N, 6.70.

2,16-Didehydro-17-oxo-1-(*p*-tolylsulfonyl)aspidospermidine (1c) and 20-Deethyl-17-ethoxy-1-(*p*-tolylsulfonyl)-2,16,17,20-tetradehydroaspidospermidine (3). A mixture of 100 mg (0.24 mmol) of ketone **1b** and 100 mg (0.60 mmol) of potassium hydride (25% mineral oil dispersion, washed three times with dry tetrahydrofuran) in 5 mL of anhydrous tetrahydrofuran was stirred at 0 °C under nitrogen for 0.5 h. Ethyl iodide (1 mL, 12.5 mmol) was added dropwise to the suspension, and the stirring was continued for another 0.5 h. Water (0.1 mL) was added cautiously, and the mixture was concentrated under vacuum. It then was diluted with water and extracted. Evaporation of the extract, chromatography of the residue (117 mg), and elution with 3:2 cyclohexane–ethyl acetate yielded 65 mg (61%) of colorless, crystalline ether **3**: mp 157–159 °C (MeOH); IR (KBr) C=O 1670 (s), C=C 1610 (w), 1595 (m), SO_2 1355 (s), 1165 (s) cm^{-1}; ^1H NMR δ 1.29 (t, 3, J = 7.5 Hz, Me), 2.35 (s, 3, Ts Me), 3.7–4.0 (m, 2, OCH_2), 3.81 (s, 1, H-21), 6.27 (s, 1, H-16), 7.03 (t, 1, J = 8 Hz, Ar H), 7.15 (d, 2, J = 8 Hz, Ts *m*-Hs), 7.22 (t, 1, J = 8 Hz, Ar H), 7.48 (d, 1, J = 8 Hz, H-9), 7.62 (d, 2, J = 8 Hz, Ts *o*-Hs), 7.77 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 15.1 (Me), 18.8 (C-14), 21.5 (Ts Me), 23.3 (C-15), 41.7 (C-6), 46.5 (C-3 or C-5), 47.2 (C-5 or C-3), 52.6 (C-7), 65.4 (OCH_2), 66.7 (C-21), 103.9 (C-16), 112.6 (C-20), 115.3 (C-12), 123.1 (C-10), 125.0 (Ts *o*-C), 127.0 (C-9 or C-11), 127.7 (C-11 or C-9), 129.3 (Ts *m*-C), 134.4 (C-2), 137.9 (C-8), 140.4 (Ts *ipso*-C), 143.1 (C-17), 144.3 (Ts *p*-C), 145.1 (C-13); m/e 448 (M^+, 9), 293 (base), 91 (8). Anal. Calcd for $C_{26}H_{28}O_3N_2S$: C, 69.61; H, 6.29; N, 6.24. Found: C, 68.98; H, 6.46; N, 6.44.

Further elution yielded 14 mg (13%) of colorless, crystalline ketone **1c**: mp 188–192 °C (MeOH); IR (KBr) NCH 2770 (m), 2710 (w), C=O 1698 (s), 1628 (s), C=C 1592 (s), SO_2 1368 (s) cm^{-1}; ^1H NMR δ 0.32 (t, 3, J = 7.5 Hz, Me), 0.5–0.7 (m, 2, Hs-18), 2.35 (s, 3, Ts Me), 6.21 (s, 1, H-16), 7.1-7.4 (m, 5, Ar Hs), 7.77 (d, 2, J = 8 Hz, Ts *o*-Hs), 7.95 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 7.5 (C-18), 21.5 (Ts Me), 21.7 (C-14), 28.0 (C-19), 34.7 (C-15), 46.3 (C-6), 50.0 (C-20), 51.1 (C-5 or C-3), 51.9 (C-3 or C-5), 53.5 (C-7), 67.0 (C-21), 104.8 (C-16), 114.5 (C-12), 120.6 (C-10), 125.0 (Ts *o*-C), 127.3 (C-9), 128.1 (C-11), 129.6 (Ts *m*-C), 133.5 (C-13), 139.5 (Ts *ipso*-C), 145.2 (Ts *p*-C), 162.6 (C-2), 199.9 (C-17); m/e 448 (M^+, 3), 293 (58), 124 (base), 110 (5); exact mass m/e 448.1829 (calcd for $C_{26}H_{28}O_3N_2S$, m/e 448.1820).

18(*R*)-Carbomethoxy-16,17-didehydro-17-ethoxy-1-(*p*-tolylsulfonyl)aspidofractinine (4a). A solution of 500 mg (1.1 mmol) of diene **3** and 5 mL (55 mmol) of freshly distilled methyl acrylate in 5 mL of methylene chloride was stirred under nitrogen at room temperature for 48 h. More methyl acrylate (5 mL) was added, and the stirring was continued for 72 h. The mixture was evaporated, and the residue (660 mg) was chromatographed. Elution with 1:1 methylene chloride–ethyl acetate led to the recovery of 50 mg of diene and 490 mg (91%, based on consumed diene) of colorless, crystalline adduct **4a**: mp 237–239 °C (MeOH); IR (film) C=O 1730 (s), C=C 1605 (m), SO_2 1345 (s), 1165 (s) cm^{-1}; ^1H NMR δ 1.1–1.3 (m, 1, H-19), 1.39 (t, 3, J = 7 Hz, Me), 1.65 (dd, 1, J = 12, 6 Hz, H-19), 2.38 (s, 3, Ts Me), 2.80 (dd, 1, J = 8, 6 Hz, H-18), 3.07 (s, 1, H-21), 3.5–3.8 (m, 1, OCH_2 H), 3.76 (s, 3, OMe), 3.8–4.0 (m, 1, OCH_2 H), 5.52 (s, 1, H-16), 7.05 (t, 1, J = 8 Hz, Ar H), 7.1–7.3 (m, 4, Ar Hs), 7.62 (d, 2, J = 8 Hz, Ts *o*-Hs), 7.87 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 14.1 (Me), 16.4 (C-14), 21.5 (Ts Me), 30.0 (C-19), 37.5 (C-15), 39.1 (C-6), 44.5 (C-18), 46.9 (C-3), 48.7 (C-5), 52.1 (OMe), 63.6 (OCH_2), 67.4 (C-21), 77.3 (C-2), 90.3 (C-16), 117.0 (C-12), 122.2 (C-10), 124.7 (C-9), 125.9 (Ts *o*-C), 127.8 (C-11), 129.4 (Ts *m*-C), 138.5 (C-13), 139.7 (C-8 or Ts *ipso*-C), 141.0 (Ts *ipso*-C or C-8), 143.3 (Ts *p*-C), 159.7 (C-17), 173.3 (CO_2); m/e 534 (M^+, 3), 448 (12), 379 (26), 293 (base), 91 (13); exact mass m/e 534.2160 (calcd for $C_{30}H_{34}O_5N_2S$ m/e 534.2188).

18(*R*)-Carbomethoxy-17-oxo-1-(*p*-tolylsulfonyl)aspidofractinine (5b). A mixture of 80 mg (0.15 mmol) of enol ether **4a** and 10 mL of a 1 N hydrochloric acid solution in 2 mL of

(7) The authors are indebted to Professor H.-P. Husson for a gift of a comparison sample.

(8) Do Carmo Carreiras, M.; Kan, C.; Deverre, J. R.; Hadi, A. H. A.; Quirion, J. C.; Husson, H.-P. *J. Nat. Prod.* **1988**, *51*, 806.

(9) The spectral determinations were performed in the Laboratoire de Chimie des Interactions Moléculaires (Collége de France, Paris).

methylene chloride and 4 mL of methanol was refluxed for 4 h. After vacuum removal of the volatile solvents the mixture was poured into water, neutralized with a saturated sodium bicarbonate solution, and extracted. Drying and evaporation of the latter, chromatography of the residue, and elution with 1:1 methylene chloride–ethyl acetate gave 65 mg (87%) of ketone **5b**: mp 285–290 °C dec (MeOH); IR (KBr) C=O 1730 (s), 1710 (s), C=C 1595 (m), SO_2 1355 (s), 1170 (s) cm^{-1}; ^1H NMR δ 2.30 (s, 3, Ts Me), 2.82 (d, 1, J = 19 Hz, H-16), 3.37 (s, 1, H-21), 3.62 (d, 1, J = 19 Hz, H-16), 3.78 (s, 3, OMe), 7.1–7.4 (m, 5, Ar Hs), 7.62 (d, 2, J = 8 Hz, Ts *o*-Hs), 7.90 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 15.9 (C-14), 21.5 (Ts Me), 29.3 (C-19), 32.5 (C-16), 36.3 (C-15), 39.0 (C-6), 42.5 (C-18), 43.6 (C-20), 47.0 (C-3), 48.3 (C-5), 52.6 (OMe), 58.7 (C-7), 68.8 (C-21), 71.8 (C-2), 116.7 (C-12), 122.0 (C-10), 125.1 (C-9), 125.8 (Ts *o*-C), 128.3 (C-11), 129.7 (Ts *m*-C), 138.4 (C-13), 139.9 (C-8 or Ts *ipso*-C), 140.1 (Ts *ipso*-C or C-8), 143.7 (Ts *p*-C), 172.6 (CO_2), 210.1 (C-17); m/e 506 (M^+, 33), 420 (8), 351 (68), 293 (29), 265 (base), 91 (16); exact mass m/e 506.1854 (calcd for $C_{28}H_{30}O_5N_2S$ m/e 506.1875).

16,17-Didehydro-17-ethoxy-18(*R*)-(phenylsulfonyl)-1-(*p*-tolylsulfonyl)aspidofractinine (4b) and Its 18*S* Isomer (6). A solution of 280 mg (0.63 mmol) of diene **3** and 600 mg (3.6 mmol) of phenyl vinyl sulfone in 5 mL of dry toluene was stirred and refluxed under nitrogen for 48 h. It then was concentrated, and the residue was chromatographed twice on Merck alumina 90 (activity II–III). Elution with 4:1 ethyl acetate–cyclohexane yielded 56 mg (14%) of the colorless, crystalline adduct **6**: mp 258–260 °C (MeOH); IR C=C 1610 (s), SO_2 1350 (s), 1145 (s) cm^{-1}; ^1H NMR δ 1.29 (t, 3, J = 7.5 Hz, Me) 2.43 (s, 3, Ts Me), 3.4–3.6 (m, 1, OCH_2 H), 3.57 (s, 1, H-21), 3.6–3.9 (m, 1, OCH_2 H, H-18), 5.58 (s, 1, H-16), 7.1–7.6 (m, 8, Ar Hs), 7.71 (d, 2, J = 8 Hz, Ts *o*-Hs), 7.86 (d, 3, J = 8 Hz, Ar Hs); ^{13}C NMR δ 13.9 (Me), 16.0 (C-14), 21.4 (Ts Me), 29.9 (C-19), 37.1 (C-15), 37.4 (C-20), 42.2 (C-6), 46.7 (C-3), 47.9 (C-5), 62.2 (C-18), 63.6 (OCH_2), 65.7 (C-7), 66.3 (C-21), 76.8 (C-2), 95.6 (C-16), 116.3 (C-12), 161.5 (C-17); m/e 616 (M^+, 1), 475 (4), 461 (20), 448 (7), 320 (6), 293 (base), 125 (22), 91 (13). Anal. Calcd for $C_{34}H_{36}O_5N_2S_2$: C, 66.21; H, 5.88; N, 4.54. Found: C, 66.10; H, 5.96; N, 5.02.

Further elution led to 200 mg (52%) of colorless, crystalline adduct **4b**: mp 245–246 °C (MeOH); IR C=C 1612 (s), SO_2 1355 (s), 1145 (s) cm^{-1}; ^1H NMR δ 1.38 (t, 3, J = 7.5 Hz, Me), 1.64 (dd, 1, J = 13, 8 Hz, H-19), 1.87 (dd, 1, J = 13, 8 Hz, H-19), 2.31 (s, 3, Ts Me), 3.00 (s, 1, H-21), 3.58 (t, 1, J = 8 Hz, H-18), 3.7–3.9 (m, 1, OCH_2 H), 3.9–4.1 (m, 1, OCH_2 H), 5.92 (s, 1, H-16), 6.87 (d, 1, J = 8 Hz, Ar H), 7.0–7.2 (m, 5, Ar Hs), 7.4–7.7 (m, 5, Ar Hs), 7.82 (d, 2, J = 8 Hz, Ar Hs); ^{13}C NMR δ 14.0 (Me), 16.2 (C-14), 21.3 (Ts Me), 30.1 (C-19), 36.1 (C-15), 38.0 (C-20), 38.0 (C-6), 46.8 (C-3), 48.7 (C-5), 63.1 (C-18), 63.8 (OCH_2), 65.0 (C-7), 67.5 (C-21), 76.3 (C-2), 90.4 (C-16), 119.9 (C-12), 159.3 (C-17); m/e 616 (M^+, 3), 475 (5), 461 (base), 448 (26), 125 (13). Anal. Calcd for $C_{34}H_{36}O_5N_2S_2$: C, 66.21; H, 5.88; N, 4.54. Found: C, 65.98; H, 6.00; N, 5.08.

17-Oxo-18(*R*)-(phenylsulfonyl)-1-(*p*-tolylsulfonyl)aspidofractinine (5c). A solution of 220 mg (0.36 mmol) of enol ether **4b** and 10 mL of a 1 N hydrochloric acid solution in 30 mL of methanol was refluxed for 16 h. After vacuum removal of methanol, the mixture was poured into water, neutralized with a saturated sodium bicarbonate solution, and extracted. Drying of the extract, flash chromatography[10] of the residue, and elution with 49:1 methylene chloride–methanol gave 170 mg (81%) of the ketone **5c**: mp 257–259 °C (MeOH); IR C=O 1710 (s), C=C 1595 (m), SO_2 1360 (s), 1145 (s) cm^{-1}; ^1H NMR δ 2.31 (s, 3, Ts Me), 3.04 (dd, 1, J = 19, 2.5 Hz, H-16), 3.31 (s, 1, H-21), 4.20 (d, 1, J = 19 Hz, H-16), 6.74 (d, 1, J = 8 Hz, Ar H), 7.0–7.7 (m, 10, Ar Hs), 7.80 (d, 2, J = 8 Hz, Ts *o*-Hs); ^{13}C NMR δ 15.7 (C-14), 21.3 (Ts Me), 29.5 (C-19), 30.5 (C-16), 34.9 (C-15), 38.8 (C-6), 44.7 (C-20), 46.8 (C-3), 48.2 (C-5), 59.3 (C-18), 60.3 (C-7), 68.9 (C-21), 71.7 (C-2), 119.5 (C-12), 208.6 (C-17); m/e 588 (M^+, 12), 447 (7), 433 (46), 420 (12), 265 (base), 123 (35), 91 (38); exact mass m/e 588.1755 (calcd for $C_{32}H_{32}O_5N_2S_2$ m/e 588.1752).

17-Oxoaspidofractinine (5d). Hydrolysis of 50 mg of enol ether **6** under the above conditions and workup (5:1 ethyl acetate–cyclohexane elution) afforded 40 mg (84%) of colorless, amorphous ketone **7**: IR C=O 1715 (s), C=C 1600 (m), SO_2 1355 (s), 1150 (s) cm^{-1}; ^1H NMR δ 2.40 (s, 3, Ts Me), 2.05 (s, 1, H-21), 2.94 (d, 1, J = 19 Hz, H-16), 3.15 (d, 1, J = 19 Hz, H-16), 7.1–7.8 (m, 13, Ar Hs); m/e 588 (M^+, 17), 433 (32), 420 (31), 405 (11), 265 (base), 156 (15), 123 (12), 91 (18).

A mixture of 40 mg (0.067 mmol) of ketone **7**, 0.58 g of sodium monohydrogenphosphate, and 0.40 g of freshly prepared 6% sodium amalgam in 20 mL of methanol was stirred under nitrogen at room temperature for 12 h. It then was poured into water and filtered. Upon evaporation of the methanol of the filtrate the latter was extracted. The organic solution was washed with water, dried, and evaporated. Flash chromatography of the residue and elution with 19:1 methylene chloride–methanol gave 11 mg (55%) of colorless, amorphous ketone **5d**: IR NH 3330 (m), C=O 1705 (s), C=C 1605 (m) cm^{-1}; ^1H NMR δ 2.39 (d, 1, J = 19 Hz, H-16), 2.88 (dd, 1, J = 19, 3.5 Hz, H-16), 3.48 (s, 1, H-21), 6.72 (d, 1, J = 8 Hz, H-9), 7.08 (t, 1, J = 8 Hz, H-11), 6.85 (t, 1, J = 8 Hz, H-10), 7.30 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 16.6 (C-14), 29.5 (C-15), 29.8 (C-19 or C-18), 30.0 (C-18 or C-19), 35.5 (C-16), 44.3 (C-20), 44.7 (C-6), 47.5 (C-3), 48.7 (C-5), 56.9 (C-7), 64.6 (C-21), 70.0 (C-2), 110.8 (C-12), 120.2 (C-10), 122.0 (C-9), 127.1 (C-11), 138.3 (C-8), 149.1 (C-13), 213.2 (C-17); m/e 294 (M^+, base), 266 (33), 251 (50), 238 (75), 144 (31), 143 (27), 130 (17), 123 (67), 109 (28), 95 (43); exact mass m/e 294.1734 (calcd for $C_{19}H_{22}ON_2$ m/e 294.1732).

Reduction of sulfone **5c** under the identical conditions led to a 70% yield of ketone **5d**.

1-Carbomethoxy-17-oxoaspidofractinine (5e). A solution of 0.25 mL of methyl chloroformate in 1 mL of anhydrous dioxane was added to a mixture of 19 mg (0.07 mmol) of ketone **5d** and 14 mg of sodium hydride (80% mineral oil dispersion) in 1 mL of dry dioxane. The mixture was stirred at 60 °C under nitrogen for 2 h. It then was poured into water and extracted. Evaporation of the extract, chromatography of the residue, and elution with 2:1 methylene chloride–ethyl acetate yielded 16 mg (70%) of colorless, amorphous ketone **5e**: UV λ_{max} 244 nm (log ϵ 4.19), 282 (3.56), 289 (3.54); IR C=O 1705 (s), C=C 1600 (w) cm^{-1}; ^1H NMR δ 3.0–3.3 (m, 3, H-3, H-16, H-5), 3.57 (s, 1, H-21), 3.87 (s, 3, OMe), 7.08 (t, 1, J = 7.5 Hz, H-10), 7.23 (t, 1, J = 7.5 Hz, H-11), 7.47 (d, 1, J = 7.5 Hz, H-9), 7.6–7.9 (m, 1, H-12); m/e 352 (M^+, base), 324 (4), 309 (30), 296 (2), 123 (8); exact mass m/e 352.1782 (calcd for $C_{21}H_{24}O_3N_2$ m/e 352.1787).

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Registry No. (±)-**1a**, 89240-74-4; (±)-**1b**, 120385-49-1; (±)-**1c**, 120385-50-4; (±)-**1d**, 120385-54-8; (±)-**2**, 120444-79-3; (±)-**3**, 120385-45-7; (±)-**4a**, 120385-46-8; (±)-**4b**, 120411-03-2; (±)-**5b**, 120385-47-9; (±)-**5c**, 120411-04-3; (±)-**5d**, 120385-51-5; (±)-**5e**, 120385-53-7; (±)-**6**, 120385-48-0; (±)-**7**, 120385-52-6; CH_2=$CHCO_2Me$, 96-33-3; CH_2=$CHSO_2C_6H_5$, 5535-48-8.

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Reverse Micelles, an Alternative to Aqueous Medium for Microbial Reactions: Yeast-Mediated Resolution of α-Amino Acids in Reverse Micelles†

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The use of enzymes and microbial cells in organic synthesis although fast increasing[1-3] is limited by the reactant solubility in aqueous medium. The problem of using organic solvents for these reactions can be occasionally solved by using a two-phase enzyme in aqueous substrate in water-immiscible organic solvent system[4,5] or more gen-

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