class of compounds, as shown for compounds 1, 3, and 5, but also to study and optimize specific reactions either with hydrogenolytic systems as shown with compound 7 or with proteolytic systems as shown with the enkephaline analogue 6.

It should be mentioned, that the products of all successfully optimized deprotection reactions mentioned above were in fact isolated. The amounts (0.5 mg) suffice to give immediate access to further analytical data such as biochemical activities or chiral amino acid analysis. The latter is of great interest, as mass spectrometry, in general, supplies no information on enantiomeric purity.

Discussion

The monitoring of chemical reactions depends on the separation and identification of the different reaction products and intermediates. Usual methods for monitoring are TLC and HPLC. Both depend on the previous development of separation conditions. The identification of the different reaction products is usually achieved by a separate workup and isolation procedure. This involves automatically loss of time and material, while the amount needed finally depends on the method of identification.

By the application of FAB mass spectrometry, reactions can be monitored in real-time and components be identified immediately, and the sensitivity lies in the nanomolar range.

Consequently, we feel that the direct application of FAB mass spectrometry allows deprotection reactions to be optimized much more easily and efficiently than conventional methods.

Deprotection reactions of synthetic peptides can, of course, also be monitored via TLC or HPLC. But appropriate solvent systems have to be found that ensure complete separation of all the different reaction products and intermediates, which is usually followed by a separate identification step. We feel, that these alternative procedures are comparatively more time consuming than the direct application of FAB-MS.

Experimental Section

The purity of all protected peptides was assessed through amino acid analysis, TLC, HPLC, FAB-MS, and NMR spectroscopy. All reactions were carried out in Eppendorf micro test tubes 3815. The reaction mixtures were stirred occasionally and before sampling by using a mechanical shaker (Heidolph, Type Reax 1DR).

Hydrogenolysis. Hydrogen was led through a thin-glass capillary into the reaction mixture. To obtain constant gas flow, the hydrogen pressure was controlled with a microvalve. For workup, the reaction mixture was first diluted to 0.5 mL and then the catalyst concentrated by centrifugation for 15 min at 3500 rpm. The clear solution was pipetted and the catalyst suspended again in 0.5 mL of solvent. The process was repeated, and the combined solutions were centrifuged again to remove traces of catalyst. The solution was then lyophylized.

HBr/TFA Procedure. The reaction was carried out as described in Table I. The gas flow was regulated manually. Though cooling was supplied, the rapid evaporation of TFA made constant additions of new solvent necessary: as a rule 100 μL were added every 5 min with an Eppendorf pipet.

Other proteolytic reactions were carried out under argon atmosphere as described in Table I.

Sampling. All samples were drawn directly from the reaction mixture by quick immersion of a thin-glass capillary. The sample, mixed with equal amounts of glycerol, was then centered on the tip of the FAB probe of the mass spectrometer.

FAB mass spectra were recorded with a Vacuum Generator (VG) ZAB-3HF mass spectrometer (BEB configuration) equipped with a VG 250/11 data system at the following conditions: ion source pressure, 5×10^{-6} torr; ion source temperature, 20 °C; xenon as FAB gas, 8 keV xenon atoms; 0.1 mA emission current in the FAB gun; 8kV acceleration voltage for the secondary ions; 1300 mass resolution in the double focusing mode; scan speed, 5 s/decade.

Acknowledgment. Financial support of the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Registry No. 1, 99922-03-9; 2, 99901-80-1; 3, 99901-81-2; 4, 99901-82-3; 5, 99901-83-4; 6, 99901-84-5; 7, 96393-61-2.

Application of a Transition-Metal-Mediated Stereospecific Michael Reaction Equivalent to the Synthesis of Alloyohimbone

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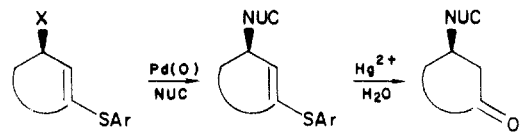
A stereospecific Michael reaction equivalent, based on a sulfur-substituted (π-allyl)palladium intermediate, has been applied as the key step in a synthesis of alloyohimbone (2). The use of the identical π-allyl precursor in the absence of palladium provided an entry into the opposite stereochemical series and could potentially be used in a synthesis of yohimbone (3).

We had previously reported a palladium-mediated equivalent to the Michael reaction which allowed complete stereospecificity by virtue of the intermediacy of a (π-allyl)Pd complex.[2,3]



This feature was particularly significant because of the notoriously poor stereochemical control associated with the "native" Michael reaction.[4] In tandem with a Diels–Alder reaction this process was also shown[3] to provide the alternative stereochemical outcome to that typically pre-

(1) Current address: Kodak Research Laboratories, Building 82, 1999 Lake Avenue, Rochester, NY 14650.

(2) Complete stereospecificity in (π-allyl)palladium reactions using "soft" carbon nucleophiles has been demonstrated in: Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611.

(3) The initial report on this methodology appeared in: Godleski, S. A.; Villhauer, E. B. *J. Org. Chem.* **1984**, *49*, 2246.

(4) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 367. Howe, R.; McQuillan, F. J. *J. Chem. Soc.* **1958**, 1194. Abramovitch, R. A.; Stuble, D. L. *Tetrahedron* **1968**, *24*, 357.

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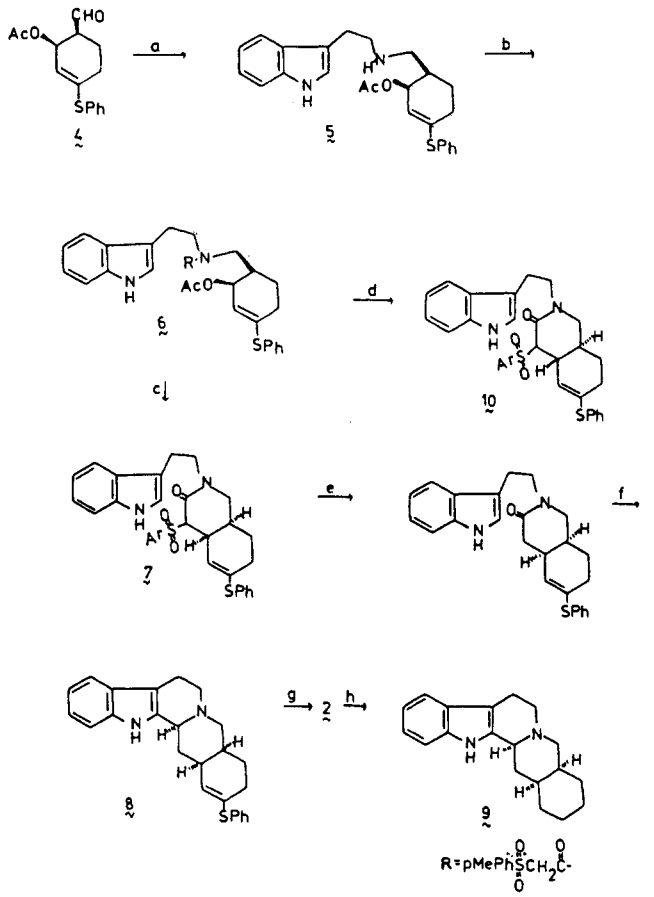
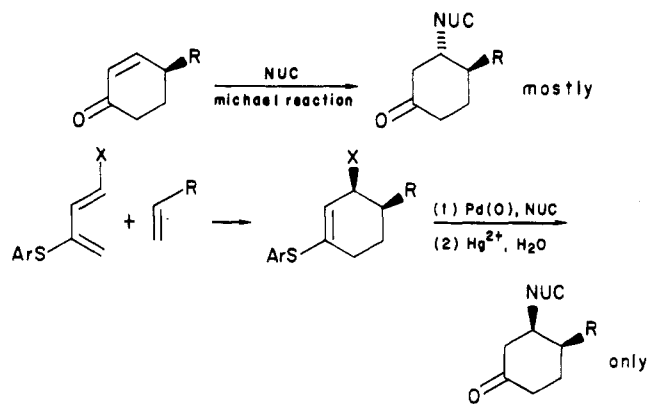
Scheme I. Synthesis of Alloyohimbone (2)[a]



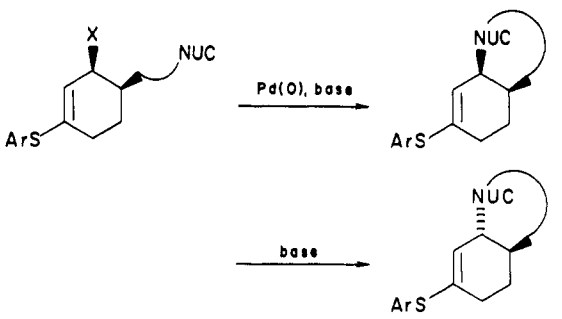
[a] (a) CH_2Cl_2, tryptamine, $MgSO_4$, −23 °C, 11 h, then MeOH, $NaBH_4$, −63 °C, 0.75 h, 85%. (b) CH_2Cl_2, $ClCOCH_2(SO_2Ar)$, Et_3N, −23 °C, 0.25 h, 94%. (c) DME, NaH, 0 °C, 40 min, then $Pd(diphos)_2$, 85 °C, 10 min, 84%. (d) DME, NaH, 0 °C, 10 min, then room temperature, 24 h, 73%. (e) MeOH, Na_2HPO_4, 6% (Na)Hg, room temperature, 1 h, 91%. (f) $POCl_3$, benzene, 80 °C, 2 h, then CH_2Cl_2, lithium tri-*tert*-butoxyaluminumhydride, −78 °C, 5 min, then −78 °C to room temperature, 1-1/2 h, 72%. (g) CH_3CN-6 N HCl, 80 °C, 3 h, 64%. (h) $(HOCH_2CH_2)O$, KOH, $H_2NNH_2 \cdot H_2O$ (64% in H_2O), 100 °C, 0.75 h, then 195 °C, 1.25 h; Huang-Minlon reduction.[12]

dominantly obtained from the Michael addition to a γ-substituted-α,β-unsaturated cyclohexenone as illustrated below.

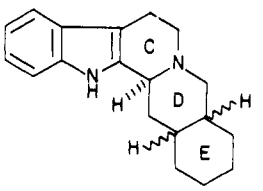


The palladium-based reaction also gave rise to an additional complementarity in comparison with a classic S_N2 process[3] as shown below. This result further enhanced the synthetic versatility of this methodology.

In order to fully demonstrate the synthetic utility of this metal-mediated process, we sought to apply it in the

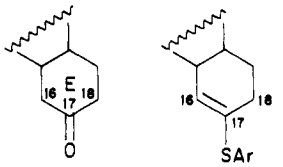


context of a synthesis of natural product. In this regard, the yohimbe family of alkaloids appeared to be particularly



yohimbe skeleton

well-suited targets on the basis of the following considerations: (1) they possess significant biological as well as synthetic interest;[5] (2) members of this class of alkaloids are known to contain both cis- and trans-fused D,E ring junctures[5] (the possible obtention of each of these completely stereospecifically from a single intermediate would be an extremely desirable feature and one that was typically not available in previous yohimbe alkaloid syntheses[5] but is obtainable via palladium methodology.) (3) An additional vexing problem in the synthesis of these alkaloids revolves around specific functionalization at C-16 from a ketone intermediate, e.g., 1 where predominant



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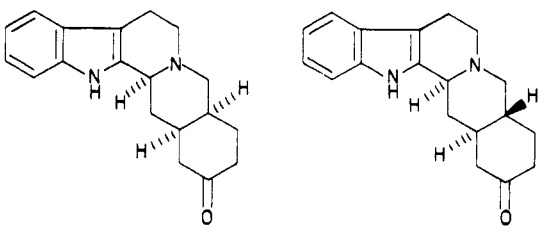
reaction at C-18 is generally known to occur.[6] As a result of the palladium process however, a vinyl sulfide is produced, potentially allowing a vehicle for specific reaction of C-16.

Our efforts employing the palladium-based methodology in the key cyclization step have resulted in an efficient synthesis of alloyohimbone (2).[7] In addition, the ability



2 3

(5) For summaries of synthetic efforts in this area, see: Manske, R. H. F. "The Alkaloids"; Academic: New York, 1983; Vol. XXII, pp 241-279. Toke, L.; Szantay, C. *Heterocycles* **1976**, *4*, 251. Manske, R. H. F. "The Alkaloids"; Academic: New York, 1968; Vol. XI, pp 145-187. Kutney, J. P. "The Total Synthesis of Natural Products"; Wiley-Interscience: New York, 1977; Vol. 3, p 273.

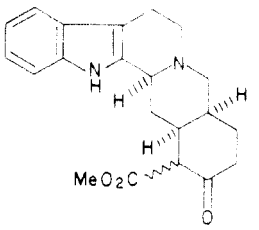
(6) Albright, J. D.; Mitcher, L. A.; Goldman, L. *J. Org. Chem.* **1963**, *28*, 38.

to obtain the opposite stereochemistry at the D,E ring juncture (as contained in yohimbone (3)) from the identical intermediate used in the preparation of 2 has been demonstrated. Disappointingly, efficient functionalization at C-16 and subsequent hydrolysis to produce alloyohimbinone could not be realized.

Synthesis of Alloyohimbone. A summary of the synthesis of alloyohimbone is shown in Scheme I. The sequence is initiated by reaction of the Diels–Alder adduct 4, whose preparation has been described previously,[3] with tryptamine followed by $NaBH_4$ to give the aminoallylic acetate 5 in 85% yield. Acylation of the amine 5 with $ClCOCH_2SO_2Ar$ (Ar = *p*-Me) provided the π-allyl precursor 6 (94%). Anion formation with NaH and reaction with $Pd(diphos)_2$ gave 7 possessing exclusively a cis-fused ring juncture in excellent yield (84%). Treatment with Na/Hg effected removal of the sulfone moiety (91% yield). The subsequent Bischler–Napieralski reaction completed the synthesis of the pentacyclic ring system 8 (72% yield). The stereochemistry at C-3 was established as the required αH by hydride reduction of the imminium ion intermediate in the Bischler–Napieralski reaction as precedented in closely related synthetic work.[8] Hydrolysis of the vinyl sulfide 8 (HCl–CH_3CN) gave alloyohimbone (2) in 64% yield. This material was found to possess identical physical and spectral properties to values reported in the literature.[7] Further verification of the structure of this product was obtained by Wolff–Kishner reduction of 2 to provide alloyohimbane (9), again possessing identical spectral characteristics to literature values[9] including ^{13}C NMR.

Preparation of the Trans D,E Ring Juncture. The alternative trans D,E ring juncture was obtained in a straightforward manner from 6 by treatment with NaH in the absence of a Pd(0) catalyst (Scheme I), producing 10 in 73% yield. This material could then in principle be transformed into yohimbone (3) by an analogous series of reactions to those performed in the allo series.

Attempted Synthesis of Alloyohimbinone. The vinyl sulfide 8 appeared to be a most attractive intermediate for further elaboration to alloyohimbinone (11), especially as



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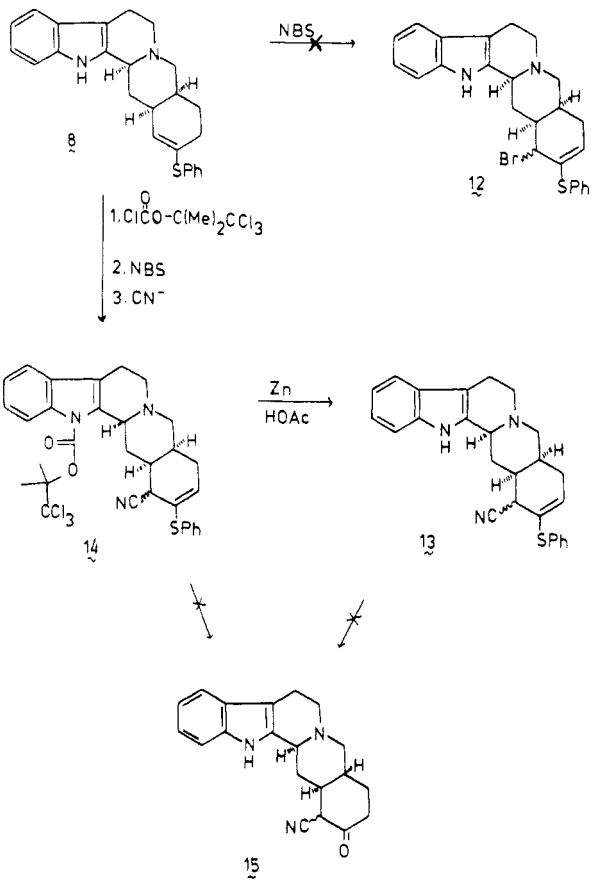
it could alleviate the difficulty of C-16 over C-18 functionalization normally encountered in transformations initiated from alloyohimbone (2). *N*-Bromosuccinamide

Scheme II. Attempted Synthesis of Alloyohimbinone



(NBS) reaction[10] with 8 was intended to give the allylic bromide vinyl sulfide 12 (Scheme II) which could be further transformed into the cyano vinyl sulfide 13. However, bromination of the indole ring was found to be competitive with that of the vinyl sulfide. Protection of the indole by acylation and subsequent bromination by NBS and cyanation did provide the protected cyano vinyl sulfide 14. Conditions for the direct hydrolysis of either 14 or the deprotected 13 to produce the known alloyohimbine intermediate alloyohimbinone 11 or 15 could not be found.

Experimental Section

General Data. Proton nuclear magnetic resonance spectra were recorded on a Varian Model EM-390 (90-MHz) or a Nicolet QE 300 (300-MHz) spectrometer. ^{13}C nuclear magnetic resonance spectra were recorded on a Nicolet QE 300 (300-MHz) spectrometer. Chemical shifts were expressed in δ units (ppm) with tetramethylsilane as an internal standard unless otherwise stated. Coupling constants (J) are reported in hertz; splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; b, broad.

Low resolution and precise mass spectra were obtained on a VG 7035 instrument. The ionizing voltage was 20 eV unless stated otherwise.

Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer and are calibrated with the 1601-cm^{-1} peak of polystyrene. All absorption frequencies are reported in reciprocal centimeters.

Flash chromatography[11] was run on Woelm silica gel (32–63 μm) in the indicated solvent. Preparative TLC plates were supplied by Analtech.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Unless otherwise noted, materials were obtained

(7) For previous syntheses of alloyohimbone, see: Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1983**, 1231. Naito, T.; Tada, Y.; Nishiguchi, Y.; Nindomiya, I. *Heterocycles* **1982**, *18*, 213. Szantay, C.; Honty, K.; Toke, L.; Szabo, L. *Chem. Ber.* **1976**, *109*, 1737. Toke, L.; Gombos, Z.; Blasko, G.; Honty, K.; Szabo, L.; Tamas, J.; Szantay, C. *J. Org. Chem.* **1973**, *38*, 2501. Philpott, P. G.; Parsons, A. M. *J. Chem. Soc.* **1958**, 3018. Poisson, J.; Neuss, N.; Goutarel, R.; Janot, M. M. *Bull. Soc. Chim. Fr.* **1958**, 1195. Chatterjee, A.; Pakrashi, S. *Naturwissenschaften* **1954**, *41*, 215; *J. Indian Chem. Soc.* **1959**, *36*, 685. LeHir, A.; Goutrel, R. *Bull. Soc. Chim. Fr.* **1953**, 1023. MacPhillamy, H. B.; Huebner, C. F.; Schlittler, E.; St. Andre, A. F.; Ulshafer, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 4335. LeHir, A. *C. R. Hebd. Seance Akad. Sci.* **1952**, *234*, 2613. Swan, G. A. *J. Chem. Soc.* **1950**, 1534.

(8) Toke, L.; Honty, K.; Szabo, L.; Buasko, G.; Szantay, C. *J. Org. Chem.* **1973**, *38*, 2496.

(9) Wenkert, E.; Chang, C.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.

(10) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

from commercial suppliers and were used without further purification. In experiments requiring dry solvents, benzene, dimethoxyethane (DME), and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl immediately before use. Hexanes, methylene chloride (CH_2Cl_2), methanol (MeOH), and triethylamine (Et_3N) were distilled from calcium hydride.

$Pd(diphos)_2$ catalyst was handled in an inert atmosphere of nitrogen. All nonaqueous reactions were run under a positive pressure of nitrogen.

***cis*-3-Acetoxy-4-[((2-(3-indolyl)ethyl)amino)methyl]-1-(phenylthio)cyclohexene (5).** The aldehyde **4** (2.00 g, 7.25 mmol) was dissolved in 14.5 mL of CH_2Cl_2 and cooled to −23 °C under N_2. Anhydrous $MgSO_4$ (0.87 g, 7.25 mmol) was then added, followed by the tryptamine (1.17 g, 7.32 mmol). The solution was stirred at −23 °C for 11 h and then was cooled to −63 °C. Methanol (7.25 mL) was then added to the cloudy brown reaction mixture, followed by the addition of $NaBH_4$ (0.29 g, 7.61 mmol) in small amounts over 1 min. The reaction mixture was stirred at −63 °C for an additional 0.75 h and then diluted with 50 mL of chilled CH_2Cl_2 (−63 °C). The solution was partitioned between 100 mL of CH_2Cl_2 and 100 mL of ice-cold H_2O. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 phases were washed with 100 mL of H_2O and 100 mL of brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the resulting reddish brown oil (ethyl acetate/hexane, 16:1) yielded 2.59 g (85%) of the amine **5** as a dark, reddish brown, gummy oil: ^1H NMR ($CDCl_3$) δ 8.01 (br s, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.4–7.25 (m, 6 H), 7.17 (pseudo t, J = 7.4 Hz, 1 H), 7.09 (pseudo t, J = 7.4 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 5.66 (d, J = 4.8 Hz, 1 H), 5.22 (pseudo t, J = 4.8 Hz, 1 H), 2.94 (m, 4 H), 2.63 (d, d, J = 12, 7.0 Hz, 1 H), 2.53 (d, d, J = 12, 7.0 Hz, 1 H), 2.16 (m, 2 H), 1.87 (s, 3 H), 1.85 (m, 1 H), 1.64–1.53 (m, 3 H); IR ($CDCl_3$) 3490, 3040, 2940, 2835, 1730, 1625, 1580, 1460, 1375, 1350, 1250, 1010, 860 cm^{-1}; MS, m/e 420 (M^+), 360, 229, 216, 201, 188, 173, 144, 143, 130, 110, 109, 91, 79, 77, 60, 44, 43. Anal. Calcd for $C_{25}H_{28}O_2N_2S$: C, 71.40; H, 6.72; O, 7.61; N, 6.67; S, 7.61. Found: C, 71.41; H, 6.79; N, 6.46; S, 7.85.

***cis*-3-Acetoxy-4-[((2-(3-indolyl)ethyl)((*p*-tolylsulfonyl)-acetyl)amino)methyl]-1-(phenylthio)cyclohexene (6).** *cis*-3-Acetoxy-4-[((2-(3-indole)ethyl)amino)methyl]-1-(phenylthio)-cyclohexene (**5**) (3.56 g, 8.49 mmol) was dissolved in 84.9 mL of CH_2Cl_2, and the solution was cooled to −23 °C under N_2. Freshly distilled Et_3N (2.37 mL, 17.00 mmol) was added by syringe, followed by the addition of (*p*-tolylsulfonyl)acetyl chloride (2.95 g, 12.70 mmol). The solution was stirred at −23 °C for 15 min. The solution was then partitioned between 100 mL of CH_2Cl_2 and 100 mL of a saturated $NaHCO_3$ solution. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 100 mL of H_2O and 100 mL of brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residual oil was flash chromatographed on silica gel (hexane/ethyl acetate, 1:1), yielding 4.90 g (94%) of the amide **6** as a fluffy yellowish tan solid: ^1H NMR ($CDCl_3$) shows two diastereomers due to amide resonance (ratio 2.5:1). Major isomer: ^1H NMR δ 8.18 (br s, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.41–7.10 (m, 9 H), 6.92 (d, J = 1.8 Hz, 1 H), 5.72 (d, J = 4.7 Hz, 1 H), 5.06 (pseudo t, J = 4.7 Hz, 1 H), 3.66 (pseudo d, J = 5.48 Hz, 2 H), 3.78–3.60 (m, 1 H), 3.6–3.5 (m, 1 H), 3.45–3.22 (m, 2 H), 2.97 (t, J = 6.3 Hz, 2 H), 2.38 (s, 3 H), 2.31–1.82 (m, 3 H), 1.96 (s, 3 H), 1.68–1.60 (m, 2 H). Minor isomer: ^1H NMR δ 8.10 (br s, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.41–7.10 (m, 9 H), 7.03 (d, J = 1.8 Hz, 1 H), 5.64 (d, J = 4.8 Hz, 1 H), 4.99 (pseudo t, J = 4.8 Hz, 1 H), 3.71 (pseudo d, J = 8.4 Hz, 2 H), 3.78–3.60 (m, 1 H), 3.6–3.5 (m, 1 H), 3.45–3.22 (m, 2 H), 2.97 (t, J = 6.3 Hz, 2 H), 2.41 (s, 3 H), 2.31–1.82 (m, 3 H), 1.96 (s, 3 H), 1.62–1.58 (m, 2 H); IR ($CDCl_3$) 3479, 3140, 2950, 1730, 1650, 1458, 1375, 1325, 1250, 1155, 1080, 860, 640 cm^{-1}; MS, m/e 557, 556, 447, 414, 402, 401, 370, 356, 324, 277, 215, 213, 186, 185, 170, 164, 155, 144, 143, 130, 119, 109, 107, 105, 91, 79, 77, 60, 45, 43. Anal. Calcd for $C_{34}H_{36}O_5N_2S_2$: C, 66.21; H, 5.89; N, 4.54; S, 10.38. Found: C, 66.09; H, 5.99; N, 4.36; S, 10.64.

3-[2-(3-Indolyl)ethyl]-4-oxo-5-(*p*-tolylsulfonyl)-8-(phenylthio)-*cis*-3-azabicyclo[4.4.0]dec-7-ene (7). Sodium hydride (0.082 g, 3.41 mmol) was transferred to a flame-dried, 25-mL round-bottomed flask under N_2. DME (3.25 mL) was syringed in, and the resulting grey suspension was then cooled in an ice-cold H_2O bath. The allylic acetate **6** (2.00 g, 3.25 mmol) was added over a period of 2 min, and the bubbling reaction was then stirred in an ice-cold H_2O bath for 40 min under N_2. DME (3.25 mL) and $Pd(diphos)_2$ (0.59 g, 0.65 mmol) were then added under N_2 to the dark olive-colored solution, and the reaction was immediately brought to reflux and stirred for 10 min. The blackish red reaction was cooled to room temperature and partitioned between 50 mL of CH_2Cl_2 and 50 mL of H_2O. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residual oil was flash chromatographed on silica gel (hexane/ethyl acetate, 6:1), yielding 1.51 g (94%) of **7** as a fluffy white precipitate: ^1H NMR ($CDCl_3$) single diastereomer at C-5 δ 8.08 (br s, 1 H), 7.71 (d, J = 8.1 Hz, 2 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.34–7.23 (m, 7 H), 7.19 (pseudo t, J = 7.5 Hz, 1 H), 7.11 (pseudo t, J = 7.5 Hz, 1 H), 7.07 (d, J = 1.9 Hz, 1 H), 5.76 (d, J = 1.9 Hz, 1 H), 3.80 (m, 2 H), 3.56 (br s, 1 H), 3.47 (m, 2 H), 2.97 (m, 3 H), 2.42 (s, 3 H), 2.41 (m, 1 H), 2.12 (m, 1 H), 2.04 (m, 1 H), 1.60 (m, 1 H), 1.49 (m, 1 H); IR ($CDCl_3$) 3479, 3059, 2930, 2860, 1643, 1595, 1487, 1437, 1315, 1301, 1289, 1248, 1145, 1081, 1042, 810 cm^{-1}; MS, m/e 556 (M^+), 402, 401, 268, 267, 212, 144, 143, 135, 130, 110, 91, 71, 57. Anal. Calcd for $C_{32}H_{32}O_3N_2S_2$: C, 69.04; H, 5.80; N, 5.04; S, 11.50. Found: C, 68.80; H, 6.02; N, 4.68; S, 11.61.

3-[2-(3-Indolyl)ethyl]-4-oxo-5-(*p*-tolylsulfonyl)-8-(phenylthio)-*trans*-3-azabicyclo[4.4.0]dec-7-ene (10). Sodium hydride (0.009 g, 0.375 mmol) was transferred to a flame-dried, 10-mL round-bottomed flask under N_2. DME (0.724 mL) was syringed in, and the resulting grey suspension was then cooled in an ice-cold H_2O bath. The allylic acetate **6** (0.11 g, 0.181 mmol) was added, and the bubbling reaction was stirred in an ice-cold H_2O bath for 10 min and then at room temperature for 24 h under N_2. One drop of H_2O was then added to the dark, olive-colored reaction mixture, and the solution was chromatographed on a preparative-layer silica gel plate (hexane/ethyl acetate, 1:1), yielding 0.074 g (73%) of **10** as a fluffy, white precipitate, mp from methanol 151–152 °C: ^1H NMR ($CDCl_3$) shows two diastereomers at C-5 (ratio 7:1). Major isomer: ^1H NMR δ 8.26 (br s, 1 H), 7.56 (d, J = 8.2 Hz, 2 H), 7.51 (d, J = 7.7 Hz, 1 H), 7.40 (d, J = 6.2 Hz, 1 H), 7.39–7.06 (m, 9 H), 6.95 (d, J = 1.9 Hz, 1 H), 5.86 (d, J = 5.4 Hz, 1 H), 4.06–3.96 (m, 2 H), 3.92 (t, J = 5.0 Hz, 2 H), 3.75, 3.41 (AB quartet, J = 14.0 Hz, 2 H), 3.59 (d, t, J = 15.4, 5.8 Hz, 1 H), 3.12–2.97 (m, 2 H), 2.86 (d, d, J = 13.8, 1.9 Hz, 1 H), 2.37 (s, 3 H), 2.25–2.11 (m, 2 H), 1.80–1.65 (m, 1 H). Minor isomer: ^1H NMR δ 8.16 (br s, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 7.56 (d, J = 8.2 Hz, 2 H), 7.40 (d, J = 6.2 Hz, 1 H), 7.39–7.06 (m, 9 H), 7.05 (d, J = 1.9 Hz, 1 H), 5.62 (d, J = 5.9 Hz, 1 H), 4.06–3.96 (m, 2 H), 3.92 (t, J = 5.0 Hz, 2 H), 3.75, 3.41 (AB quartet, J = 14.0 Hz, 2 H), 3.59 (d, t, J = 15.4, 5.8 Hz, 1 H), 3.12–2.97 (m, 2 H), 2.86 (d, d, J = 13.8, 1.9 Hz, 1 H), 2.39 (s, 3 H), 2.25–2.11 (m, 2 H), 1.80–1.65 (m, 1 H); IR ($CDCl_3$) 3480, 3390, 3160, 2940, 1635, 1460, 1375, 1322, 1252, 1156, 1090 cm^{-1}; MS, m/e 556 (M^+), 447, 402, 401, 369, 258, 201, 186, 173, 144, 143, 130, 110, 109, 91, 86, 84, 57, 47; exact mass calcd for $C_{32}H_{32}O_3N_2S_2$ 556.1853, found 556.1822.

3-[2-(3-Indolyl)ethyl]-4-oxo-8-(phenylthio)-*cis*-3-azabicyclo[4.4.0]dec-7-ene. The lactam **7** (1.51 g, 2.72 mmol) was dissolved in warm methanol (54.40 mL) and then cooled to room temperature under N_2. Na_2HPO_4 (3.09 g, 21.80 mmol) and 6% (Na)Hg (10.90 g, 54.40 mmol) were then added, and the mixture was stirred at room temperature for 1 h. The cloudy grey reaction was then filtered through Celite, and the filtrate was concentrated. The oily residue was then partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residual was flash chromatographed on silica gel (hexane/ethyl acetate, 1:1), yielding 0.994 g (90.9%) of the lactam as a white solid, mp 134–135 °C: ^1H NMR ($CDCl_3$) δ 8.07 (br s, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.35 (d, J = 7.9 Hz, 1 H), 7.31–7.20 (m, 5 H), 7.18 (pseudo t, J = 7.1 Hz, 1 H), 7.11 (pseudo t, J = 7.1 Hz, 1 H), 7.02 (d, J = 1.7 Hz, 1 H), 5.86 (s, 1 H), 3.71, 3.59 (AB dectet, J = 13.2, 7.0, 7.0 Hz, 2 H), 3.25 (d, d, J = 12.6, 5.8 Hz, 1 H), 3.05–2.96 (m, 3 H), 2.66–2.52 (m, 2 H), 2.30–2.20 (m, 1 H), 2.20–1.98 (m, 3 H), 1.66–1.45 (m, 2 H); IR ($CDCl_3$) 3479, 3280, 3060, 2925, 2855, 1620, 1580, 1495, 1472, 1450, 1438, 1418,

1338, 1293, 1250, 1150, 1122, 1040, 810 cm^{-1}; MS, *m/e* 402 (M^+), 400, 322, 260, 258, 236, 218, 201, 200, 187, 144, 130, 123, 110, 109, 88, 86, 84, 71, 57. Anal. Calcd for $C_{25}H_{26}O_1N_2S_1$: C, 74.59; H, 6.51; N, 6.96; S, 7.95. Found: C, 74.40; H, 6.63; N, 6.67; S, 7.88.

17-(Phenylthio)alloyohimb-16-ene (8). The reduced lactam (0.400 g, 1.00 mmol) was dissolved in 29.4 mL of benzene under N_2. $POCl_3$ (0.649 mL, 7.00 mmol) was syringed in and the initially clear, colorless solution was refluxed for 2 h. Toluene (5 mL) was then added to the reaction followed by aspirator distillation of the solvent and excess $POCl_3$ at 40 mm to leave a dark brown oil. The oil was placed in a vacuum (1.0 mm) for 1 h to give the imminium salt as a bright orange precipitate. The salt was dissolved in CH_2Cl_2 (10.0 mL) and syringed, over a 5-min period, into a stirring, −78 °C solution of lithium tri-*tert*-butoxyaluminumhydride (0.509 g, 2.00 mmol) and 10 mL of CH_2Cl_2 under N_2. The hazy bright orange solution was then stirred at −78 °C for 5 min, allowed to warm to room temperature over 15 min, and stirred for an additional 75 min under N_2. The solution was cooled in an ice bath, and H_2O (4 mL) was added slowly. The quenched orange mixture was partitioned between 50 mL of CH_2Cl_2 and 50 mL of saturated NH_4Cl solution. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 phases were washed with 100 mL of brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the resulting oil (hexane/ethyl acetate, 8:1) yielded 0.277 g (71.8%) of the amine **8** as a yellowish white precipitate, mp from diethyl ether/hexanes 174–176 °C dec: ^1H NMR ($CDCl_3$) δ 7.66 (br s, 1 H), 7.46 (d, J = 7.4 Hz, 1 H), 7.36–7.20 (m, 5 H), 7.19 (d, J = 6.7 Hz, 1 H), 7.12 (pseudo t, J = 7.6 Hz, 1 H), 7.07 (pseudo t, J = 7.6 Hz, 1 H), 6.02 (pseudo t, J = 2.2 Hz, 1 H), 3.22 (d, J = 10.4 Hz, 1 H), 3.00–2.90 (m, 2 H), 2.90–2.78 (m, 2 H), 2.74–2.64 (m, 1 H), 2.62–2.50 (m, 3 H), 2.17–1.88 (m, 4 H), 1.76 (d, d, d, J = 11.7, 11.5, 11.5 Hz, 1 H), 1.68 (d, t, J = 12, 3 Hz, 1 H); IR ($CDCl_3$) 3475, 3155, 3058, 3025, 2905, 2845, 2800, 2745, 1578, 1470, 1460, 1445, 1438, 1372, 1342, 1318, 1300, 1288, 1272, 1258, 1238, 1220, 1205, 1192, 1170, 1150, 1105, 1082, 1055, 1021, 1010, 985 cm^{-1}; MS, *m/e* 386 (M^+), 353, 309, 278, 277, 256, 235, 221, 184, 171, 149, 111, 110, 109, 97, 91, 83, 71, 57. Anal. Calcd for $C_{25}H_{28}N_2S$: C, 77.68; H, 6.79; N, 7.25; S, 8.28. Found: C, 77.51; H, 6.86; N, 7.26; S, 8.28.

Alloyohimbone (2). Recrystallized vinyl sulfide **8** (0.072 g, 0.187 mmol) was dissolved in 1.10 mL of CH_3CN. The cloudy white solution was heated to reflux and 1.10 mL of 6 N HCl was syringed in over 10 s. After 2 min, the reaction cleared to a light yellow and was stirred at reflux for 3 h. The cooled, clear, light yellow solution was then added to a separatory funnel containing 40 mL of saturated aqueous $NaHCO_3$ and 40 mL of CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted twice with 40 mL of CH_2Cl_2. The CH_2Cl_2 solutions were combined, washed with 60 mL of brine, dried over anhydrous Na_2SO_4, and concentrated to give a beige-colored precipitate. Flash chromatography (ethyl acetate/hexane, 1:1) followed by recrystallization (methanol) yielded 0.036 g (64%) of alloyohimbone (**2**) as a white crystalline solid, mp 266–269 °C (lit.[7] mp 265–267 °C): ^1H NMR ($CDCl_3$) δ 7.72 (br s, 1 H), 7.44 (d, J = 7.4 Hz, 1 H), 7.28 (d, J = 7.8 Hz, 1 H), 7.11 (pseudo t, J = 7 Hz, 1 H), 7.06 (pseudo t, J = 7 Hz, 1 H), 3.22 (d, d, J = 11.5, 1.4 Hz, 1 H), 3.00–2.88 (m, 3 H), 2.71–2.63 (m, 3 H), 2.58–2.28 (m, 5 H), 2.23 (d, J = 14.0 Hz, 2 H), 1.90–1.81 (m, 2 H), 1.63 (d, d, d, J = 11.5, 12.7, 12.7 Hz, 1 H); IR (KBr) 3305, 2925, 2910, 2880, 2825, 2805, 2735, 1688, 1489, 1468, 1450, 1430, 1410, 1370, 1342, 1312, 1288, 1268, 1241, 1230, 1212, 1182, 1158, 1142, 1125, 1107, 1092, 1072, 1040, 1010, 997, 889, 841, 799, 772, 732, 671, 620 cm^{-1}; MS (70 eV), *m/e* 294 (M^+), 293, 279, 277, 261, 235, 223, 221, 211, 184, 170, 169, 156; exact mass calcd for $C_{19}H_{22}ON_2$ 294.1730, found 294.1708; ^{13}C NMR (2:1 $CDCl_3/Me_2SO$-d_6) C(2) 135.1, C(3) 60.2, C(5) 52.9, C(6) 21.6, C(7) 106.6, C(8) 236.8, C(9) 117.3, C(10) 118.3, C(11) 120.2, C(12) 110.8, C(13) 136.2, C(14) 31.2, C(15) 37.5, C(16) 46.5, C(17) 209.9, C(18) 40.8, C(19) 26.5, C(20) 34.9, C(21) 59.6 ppm. Huang-Minlon reduction[12] gave alloyohimbane (**9**), whose ^{13}C NMR spectral data matched exactly with literature.[9]

[(2,2,2-Trichloro-1,1-dimethylethoxy)carbonyl]-16-cyano-17-(phenylthio)alloyohimb-17-ene (14). The vinyl sulfide **8** (0.200 g, 0.518 mmol) was dissolved in 5.18 mL of THF and cooled to −63 °C under N_2, followed by the addition of *sec*-BuLi (1.11 mL, 1.4 N in cyclohexane) over 1 min. The clear, dark maroon-brown solution was then allowed to stir at −63 °C under N_2 for 1 h. 2,2,2-Trichloro-*tert*-butyl chloroformate (1.1 equiv) was added and the solution was stirred at −63 °C under N_2 for 10 min. The clear, light yellow reaction was then partitioned between 20 mL of H_2O and 20 mL of EtOAc. The aqueous phase was then separated and further extracted with 2 × 20 mL of EtOAc. The combined EtOAc layers were washed with 40 mL of brine, dried over Na_2SO_4, filtered, and concentrated. The resulting oil was then purified by flash chromatography (first hexane then hexane/ethyl acetate, 15:1), yielding 0.216 g (71%) of [(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]-17-(phenylthio)alloyohimb-16-ene as a white fluffy precipitate. This carbamate was carried on to the next reaction without complete purification. Spectral data on crude material: ^1H NMR ($CDCl_3$) δ 8.20 (d, J = 8 Hz, 1 H), 7.40 (d, J = 8 Hz, 1 H), 7.32–7.11 (m, 7 H), 6.01 (t, J = 1 Hz, 1 H), 3.69 (d, J = 11 Hz, 1 H), 2.94–2.66 (m, 6 H), 2.64–2.44 (m, 2 H), 2.18–1.81 (m, 5 H), 2.02 (s, 6 H), 1.67–1.48 (m, 1 H); MS, *m/e* 593–588 (M^+), 513, 483, 482, 481, 480, 479, 429, 386, 385, 384, 353, 321, 309, 277, 229, 221, 159, 124, 123, 111, 110, 109, 96, 91, 89, 86, 85, 84, 70, 59, 53, 49, 44.

This carbamate (0.055 g, 0.0935 mmol) was dissolved in 0.925 mL of CH_2Cl_2 followed by the addition of NBS (0.018 g, 0.103 mmol) under N_2. The solution was then stirred at room temperature under N_2 for 10 min. The clear, dark reddish brown solution was then flash chromatographed through alumina (hexane/ethyl acetate, 15:1) and concentrated. This yellow, oily allylic bromide was dissolved in 1.00 mL of CH_2Cl_2 followed by the addition of the Et_4NCN (0.016 g, 0.103 mmol). The clear, dark reddish orange solution was then wrapped in aluminum foil and stirred at room temperature under N_2 for 1.5 h. The reaction was then purified by preparative plate chromatography (hexane/ethyl acetate, 3:1), yielding 0.004 g (7%) of **14** as a fluffy, tan precipitate: ^1H NMR ($CDCl_3$) δ 8.22 (d, J = 8 Hz, 1 H), 7.40 (d, J = 8 Hz, 1 H), 7.34–7.17 (m, 7 H), 6.34 (d, J = 4 Hz, 1 H), 3.79 (d, J = 10 Hz, 1 H), 3.23 (d, J = 4 Hz, 1 H), 3.08–2.55 (m, 6 H), 2.41–2.21 (m, 4 H), 2.16 (s, 3 H), 2.09 (s, 3 H), 1.89 (d, J = 14 Hz, 1 H), 1.40–1.29 (m, 1 H); MS, *m/e* 616–613 (M^+), 612, 580, 578, 454, 453, 410, 409, 377, 353, 303, 302, 280, 222, 221, 185, 184, 170, 163, 156, 149, 143, 127, 124, 111, 110, 101, 97, 89, 86, 85, 84, 71, 57.

16-Cyano-17-(phenylthio)alloyohimb-17-ene (13). Zn Reduction of 14. The carbamate **14** (0.0031 g, 0.0048 mmol) was dissolved in 0.24 mL of a MeOH/HOAc (100:1) solution followed by 0.0094 g (0.14 mmol) of powdered zinc. The cloudy, grey mixture was then stirred at 0 °C for 0.5 h and at room temperature for 3.5 h. The reaction was partitioned between 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 40 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 0.0014 g (70%) of **13** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.81 (br s, 1 H), 7.51–7.19 (m, 7 H), 7.15 (pseudo t, J = 8 Hz, 1 H), 7.10 (pseudo t, J = 8 Hz, 1 H), 6.35 (d, J = 5 Hz, 1 H), 3.30–3.16 (m, 2 H), 3.06–2.79 (m, 3 H), 2.79–2.46 (m, 3 H), 2.42–2.10 (m, 3 H), 2.10–1.85 (m, 2 H), 1.63–1.47 (m, 1 H); IR (KBr) 3380, 2920, 2200, 1500, 1370, 1340, 1315, 1295, 1275, 1250, 1205, 1150, 1110, 1065, 1010 cm^{-1}; MS, *m/e* 411 (M^+), 410, 385, 334, 303, 302, 296, 222, 221, 184, 170, 156, 143, 111, 110, 109, 97, 88, 86, 85, 84, 71, 57, 47, 43.

Summary

A palladium-based stereospecific Michael reaction equivalent has been employed in an efficient synthesis of alloyohimbone (**2**). The flexibility of this methodology also allowed facile entry into the yohimbone (**3**) series from an identical synthetic intermediate. The potential further utility of the derived vinyl sulfide intermediate was also explored.

Acknowledgment. We thank the National Institutes of Health, Grant GM-27328, for support of this research.

Registry No. (±)-**2**, 40088-10-6; (±)-**4**, 99766-07-1; (±)-**5**, 99766-08-2; (±)-**6**, 99766-09-3; **7**, 99766-10-6; (±)-**7** (desulfonyl deriv.), 99766-15-1; (±)-**8**, 99766-11-7; (±)-**8** (1-(2,2,2-trichloro-

(12) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487.

1,1-dimethylethoxy)carbonyl deriv.), 99766-18-4; (±)-**9**, 69349-93-5; (±)-**10** (isomer 1), 99766-12-8; (±)-**10** (isomer 2), 99766-20-8; (±)-**12** (1-(trichloro-1,1-dimethylethoxy)carbonyl deriv.), 99766-19-5; (±)-**13**, 99783-13-8; (±)-**14**, 99766-13-9; $Pd(diphos)_2$, 31277-98-2; $ClCOCH_2SO_2C_6H_4Me$-*p*, 997766-14-0; $ClCO_2C(Me_2)CCl_3$, 66270-36-8; tryptamine, 61-54-1; (±)-3-[2-(3-indolyl)ethyl]-4-chloro-8-(phenylthio)-*cis*-3-azoniabicyclo[4.4.0]-3,7-decadiene phosphorodichloridate, 99766-17-3.

Identification of New Constituents of Quince Fruit Flavor (*Cydonia oblonga* Mill. = *C. vulgaris* Pers.)[1]

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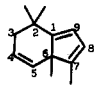
As a flavor of quince fruit, four new bicyclo[4.3.0]nonanes, 2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,7,9(1)-triene (**1**), (+)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (**2**), (−)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-ol (**3**), and (−)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-diene-7,8-diol (**4**), have been identified. Racemic compounds **1**–**4** have been synthesized from 4-oxoisophorone by direct and regioselective reduction to 4-hydroxy-2,6,6-trimethyl-2-cyclohexen-1-one followed by ketal Claisen rearrangement. 3,4-Didehydro-β-ionol (**5**) has also been found to be one of the constituents of quince fruit oil.

In previous papers,[2-4] we reported the occurrence of 62 compounds as the volatile components in quince fruit (*Cydonia oblonga* Mill. = *C. vulgaris* Pers.). Among them, (2*R*,4*S*)-(+)- and (2*R*,4*R*)-(−)-2,7-dimethyl-5(*E*),7-octadien-4-olides and *cis*- and *trans*-3-methyl-5-(3-methyl-1-(*E*),3-butadien-1-yl)tetrahydrofurans, which have a characteristic sweet odor and are regarded as the important contributors of quince fruit flavor, were isolated and identified. Extending our study on the structural elucidation of the volatile components, we have found four new bicyclo[4.3.0]nonanes (**1**, **2**, **3**, and **4**) and 3,4-didehydro-β-ionol (**5**). In this report, we describe the isolation, structural elucidation, and synthesis of these compounds.



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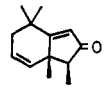
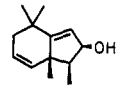


2



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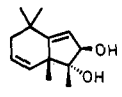

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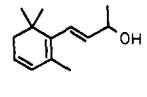
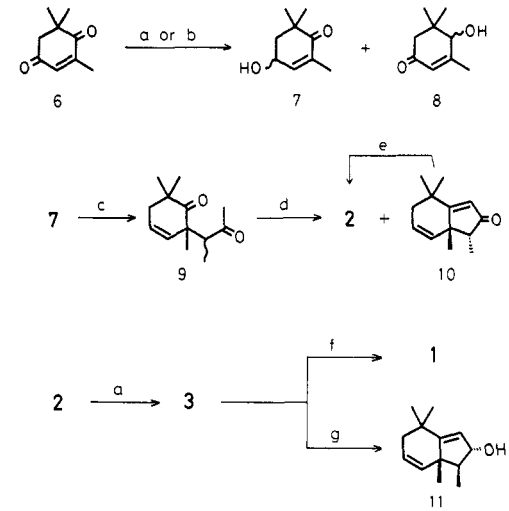


5

Results and Discussion

Isolation and Structural Elucidation. Workup of the oil was described in the foregoing paper,[4] each compound was isolated in a pure state for instrumental analysis by repeated silica gel column chromatography followed by preparative GC or preparative HPLC. In the previous paper,[4] we discussed structures of hydrocarbon **1** and alcohol **3** on the basis of spectral data, although the exact position of a double bond on the cyclohexene ring was not clear at that time. In the present work, this problem was solved by detailed analysis of the ^1H NMR spectral data and synthesis of these compounds.

Scheme I[a]



[a] (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$/MeOH. (b) $NaBH_4$/MeOH. (c) $CH_3C(OEt)_2CH_2CH_3$, H^+. (d) 0.5 N KOH/aqueous EtOH, reflux. (e) (1) LDA/THF, −78 °C; (2) H^+. (f) $POCl_3$/pyridine. (g) (1) $(=NCO_2Et)_2$, Ph_3P, $PhCO_2H$/THF; (2) 10% KOH/aqueous MeOH.

High-resolution mass spectroscopy (HRMS) revealed that the ketone **2**, $[\alpha]_D^{26}$ +11° (c 0.2, MeOH), has the molecular formula $C_{13}H_{18}O$. The α,β-unsaturated cyclopentenone skeleton was confirmed by IR bands at 1710 and 1605 cm^{-1}. When one of the *gem*-dimethyl's signals at δ 1.33 in the ^1H NMR spectrum (360 MHz) was irra-

(1) A part of this work was presented at the 9th International Congress of Essential Oils, Singapore, March 1983.
(2) Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1980**, *44*, 957.
(3) Ishihara, M.; Tsuneya, T.; Shiota, H.; Shiga, M.; Yokoyama, Y. *Agric. Biol. Chem.* **1983**, *47*, 2121.
(4) Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1983**, *47*, 2495.

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