specimen prepared by the acid-catalyzed rearrangement of garryfoline.[11] The 100-MHz ^1H NMR spectrum shows a sharp singlet at δ 0.81 for the C(4) methyl group, a doublet centered at δ 1.11 for the C(16) methyl group, a broad singlet at δ 2.65 for the C(19) methylene group, and a broad singlet at δ 4.29 for the C(20) proton. Comparison of the ^{13}C NMR spectrum of cuauchichicine in $CDCl_3$ with that of veatchine and garryfoline revealed the presence of *a single set of signals* for the oxazolidine ring F, the piperidine ring E, and the methyl groups at C(4) and C(16). This result indicates that cuauchichicine exists as a single C(20) epimer with the C(20) proton in the α configuration. Early work on the configuration of garryfoline assumed, without evidence, a β configuration for the C(20) proton.[12] Since cuauchichicine had been chemically correlated with garryfoline,[11] the β configuration was presumed for the C(20) proton in cuauchichicine.[2b]

To establish the stereochemistry of the C(16) methyl group in cuauchichicine by ^{13}C NMR spectral analysis, isocuauchichicine (**8**) and its C(16) methyl epimer (**9**) were prepared from cuauchichicine by boiling them in a solution of 2% sodium hydroxide in methanol. These epimers were separated by careful column chromatography over alumina using hexane and benzene as eluants. Comparing molecular models of compound **8** and its epimer **9** reveals that the methyl group at C(16) is spatially crowded in the β position in contrast to the α position. The chemical shift of the β-methyl group should appear at higher field than that of the α-methyl group because of steric compression. Accordingly, we have assigned the chemical shifts at 10.15 and 15.95 ppm to the β- and α-methyl groups in **8** and **9**, respectively. These results provide evidence for the presence of the β-methyl group at C(16) (10.15 ppm) in cuauchichicine, and therefore structure **7** may be assigned to cuauchichicine. This assignment was confirmed subsequently by a single-crystal X-ray analysis of cuauchichicine.

Cuauchichicine formed large, clear crystals with orthorhombic symmetry, space group $P2_12_12_1$, $Z = 4$, $a = 7.373$ (3) Å, $b = 10.370$ (4) Å, $c = 24.877$ (8) Å, and $d_{calcd} = 1.19$ g/cm^3. All unique reflections with $\theta \leq 60°$ were measured with an ω–2θ scan technique on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation ($\lambda = 1.5418$ Å). There was no indication of crystal decomposition during data collection. Data were corrected for Lorentz and polarization effects before conversion to structure factor amplitudes. Out of 1672 measured reflections, 1180 (70.6%) were observed at the 3σ level of significance. The structure (Figure 1) was solved with a multiple-solution tangent formula program[9] and refined using the programs of the X-RAY system.[10] Anisotropic refinements of the nonhydrogen atoms and isotropic refinements of the hydrogens converged at $R = 0.071$ and $Rw = 0.083$ for the observed reflections. At the conclusion of refinement a difference electron density map showed no peaks >0.27 e Å^{-3}.

Cuauchichicine (**7**) has the veatchine skeleton with a C(16) β-methyl group and a carbonyl functionality at C(15). In contrast to veatchine, it exists as only one C(20) epimer in the solid state.[7] Comparison of the dihedral angles of cuauchichicine with those of veatchine shows that the major conformational differences between the two structures are in rings D and F. Ring D approximates an envelope conformation in veatchine with C(14) as flap, while in cuauchichicine it is in the twist conformation. The oxazolidine ring F is disordered in veatchine and exists both in the twist conformation and in the envelope conformation with C(20) as flap. In cuauchichicine this ring assumes an N-flap envelope conformation. One of the C(14) hydrogens is much closer to the α side of C(20) in cuauchichicine than in veatchine (2.65 compared to 2.96 Å), and it may be this close contact which prevents formation of the second cuauchichicine epimer during isolation via the ternary imminium salt. Both atisine[13] and cuauchichicine[2] have been correlated with veatchine. Cuauchichicine, therefore, has the absolute configuration determined for atisine by X-ray diffraction.

It is interesting to note that cuauchichicine is the first normal-type oxazolidine-ring-containing alkaloid which does not exist in the epimeric form at C(20) either in solution or in the solid state. This result is compatible with our earlier conclusion[6,14] that the C(20) epimers of normal-type oxazolidine-ring-containing alkaloids, in nonionic solvents, are not interconvertible via a zwitterion. Because the stereochemistry of the C(16) methyl group in cuauchichicine is reassigned, *certain previously assigned[2] structures for the degradation products of cuauchichicine, garryfoline, and veatchine must be revised.* By analogy, the acid-catalyzed rearrangement of napelline to isonapelline[15,16] would result in a C(16) β-methyl group in isonapelline.

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Supplementary Material Available: Fractional coordinates, bond distances, bond angles, and structure factors for cuauchichicine and (−)-"α"-dihydrokaurene (24 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Pelletier, S. W.; Mody, N. V.; Seigler, D. S. *Heterocycles* **1978**, *9*, 1409.
(2) Vorbrueggen, H.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 2990. Hanson, J. R. "The Tetracyclic Diterpenes"; Pergamon Press: Oxford, 1968; Chapter 5, p 68.
(3) The names, "α"- and "β"-dihydrokaurene, were assigned before the configuration of the C(16) methyl group was determined. The actual configuration at C(16) is opposite to that implied by the prefixes.
(4) Cross, B. E.; Galt, R. H. B.; Hanson, J. R. *Tetrahedron Lett.* **1962**, 145.
(5) Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R.; Rutledge, P. S.; Wilmshurst, J. K. *J. Chem. Soc.* **1963**, 1345.
(6) Mody, N. V.; Pelletier, S. W. *Tetrahedron* **1978**, *34*, 2421.
(7) Pelletier, S. W.; DeCamp, W. H.; Mody, N. V. *J. Am. Chem. Soc.* **1978**, *100*, 7976.
(8) Dolder, F.; Lichti, H.; Mosettig, E.; Quitt, P. *J. Am. Chem. Soc.* **1960**, *82*, 246.
(9) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.
(10) Stewart, J. M., Ed., "The X-RAY System—Version of June, 1976", Technical Report TR-446, Computer Science Center, University of Maryland, College Park, Md.
(11) Djerassi, C.; Smith, C. R.; Lippman, A. E.; Figdor, S. K.; Herran, J. *J. Am. Chem. Soc.* **1955**, *77*, 4801, 6633.
(12) Klyne, W. and Buckingham, J. "Atlas of Stereochemistry. Absolute Configurations of Organic Molecules"; Oxford University Press: New York, 1974; p 171 and references cited therein.
(13) Pelletier, S. W.; Locke, D. M. *J. Am. Chem. Soc.* **1965**, *87*, 761.
(14) Pelletier, S. W.; Mody, N. V. *Tetrahedron Lett.* **1977**, 1477.
(15) Wiesner, K.; Valenta, Z.; King, J. F.; Maudgal, R. K.; Humber, L. G.; Ito, S. *Chem. Ind. (London)*, **1957**, 173. Wiesner, K.; Ito, S.; Valenta, Z. *Experientia* **1958**, *14*, 167.
(16) Okamoto, T.; Natsume, M.; Iitaka, Y.; Yoskino, A.; Amiya, T. *Chem. Pharm. Bull.* **1965**, *13*, 1270.

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Asymmetric Synthesis of *allo*-Heteroyohimbine Alkaloids

Sir:

The synthesis of pharmacologically interesting heteroyohimbine alkaloids has been extensively investigated in the past

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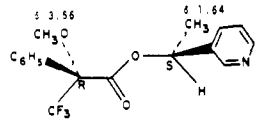
10 years.[1-18] Previously, we have shown that a preformed D,E-ring bicyclic fragment, bearing three of the four chiral centers, can be used efficiently in a convergent synthesis of these alkaloids.[4] Thus, N-alkylation of racemic bicyclic amino ester **2** with tryptophyl bromide (**1**) gave the seco alkaloid **3** (Scheme I). Oxidative C-ring closure with 1:1 mercuric acetate-ethylenediaminetetraacetic acid disodio salt, followed by reduction with sodium borohydride, led to 43% racemic tetrahydroalstonine (**4**) and 10% racemic akuammigine (**5**).[4] Subsequently, cyclization of the optically active seco alkaloid **3** by Sakai with mercuric acetate in hot acetic acid was reported to give approximately equal amounts of **4** and **5**.[6] The original conditions[4] were also applied in the synthesis of aricine (10-OCH_3, **4**) and reserpinine (11-OCH_3, **4**).[7] In this communication we report an efficient asymmetric synthesis of the key intermediate 15*S*,19*S*,20*S*-bicyclic amino ester **2**.

The synthesis is outlined in Scheme II. The incipient center of chirality was introduced asymmetrically by microbiological reduction of 3-acetylpyridine (**6**) with *Sporotrichum exile* (QM-1250) under the anaerobic conditions described previously[19] (substrate concentration, 1 g/L). A 60% isolated yield of optically pure, oily (1*S*)-(3-pyridyl)ethanol (**7**, $[\alpha]^{25}_D$ −47.2°; hydrochloride mp 126–128 °C, $[\alpha]^{25}_D$ −33.4°) was achieved. The required *R* enantiomer **10** was obtained by a carefully controlled inversion sequence. Exposure of **7** to sodium hydride in tetrahydrofuran at 0 °C, followed by treatment with *p*-toluenesulfonyl chloride, gave the unstable tosylate **8**. The S_N2 displacement was effected with an excess of tetraethylammonium acetate in acetone at 60 °C to furnish the *R* acetate **9** ($[\alpha]^{25}_D$ +92.2°; hydrochloride mp 180–182 °C, $[\alpha]^{25}_D$ + 55.8°). Hydrolysis with sodium hydroxide in methanol then led to (1*R*)-(3-pyridyl)ethanol (**10**, $[\alpha]^{25}_D$ +46.7°; hydrochloride mp 128–130 °C, $[\alpha]^{25}_D$ +32.0°) in 90% overall yield from **7**.

The absolute configuration of enantiomers **7** and **10** was ascertained by an NMR analysis of the corresponding *R,S* and *R,R* esters I and II obtained by treatment with optically pure (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[20,21] According to Mosher, the most populated conformation, the *R,R* diastereomer II, would have the secondary methyl eclipsed

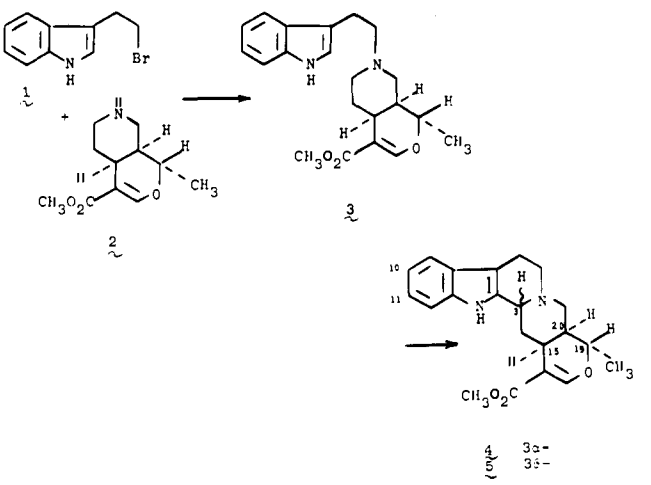


I II

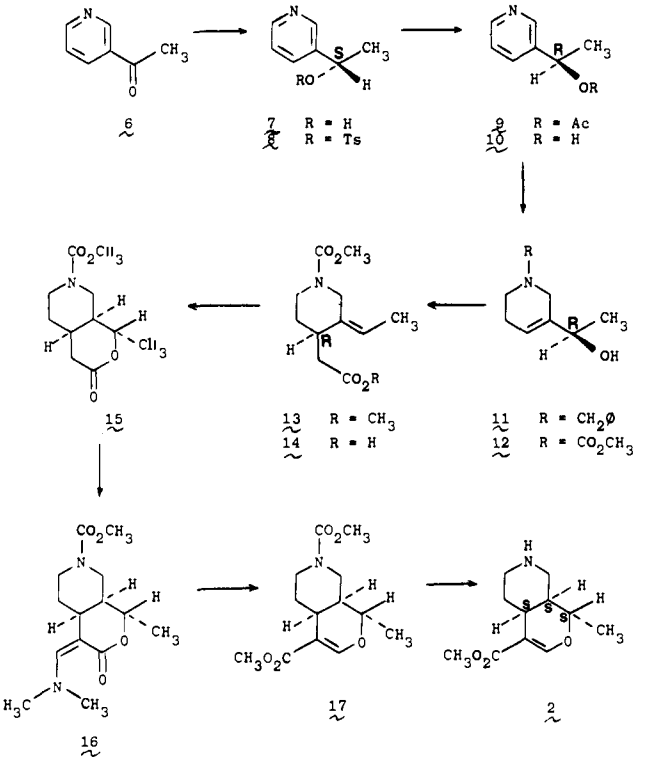
with the phenyl group and the methoxy methyl with the pyridine ring.[21,22] Owing to shielding effects of the aromatic rings, both methyls of II should be positioned upfield relative to those of the *R,S* diastereomer I, as was observed.[23,24] Since neither of the NMR spectra of crude I or II showed a signal corresponding to the other diastereomer within the limits of sensitivity (0.5%), the alcohols **7** and **10** were judged to be at least 99% optically pure.

In the next phase of the synthesis, N-benzylation of the pure *R*-alcohol **10** with benzyl chloride, followed by reduction with sodium borohydride led to the tetrahydropyridine **11** in 62% yield. The air-sensitive amine **11** required extensive chromatography for complete purification. When, instead, the crude reduction product **11** was treated with methyl chloroformate in methylene chloride, the *N*-carbomethoxy analogue **12** (oil; NMR δ 1.29 (d, 3, *J* = 6 Hz, $-CH_3$); 3.68 (s, 3, OCH_3), 4.24 (q, 1, *J* = 6 Hz, $-CH(OH)CH_3$), 5.77 ppm (br s, 1, $-CH{=}C$); *m/e* 185} was obtained in 78% yield after chromatography. Formation of the desired *R*-*Z*-olefinic ester **13** from **12** with transfer of chirality from the side chain to C_4 was

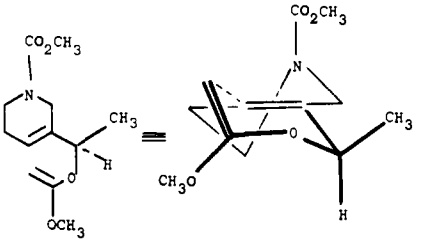
Scheme I



Scheme II

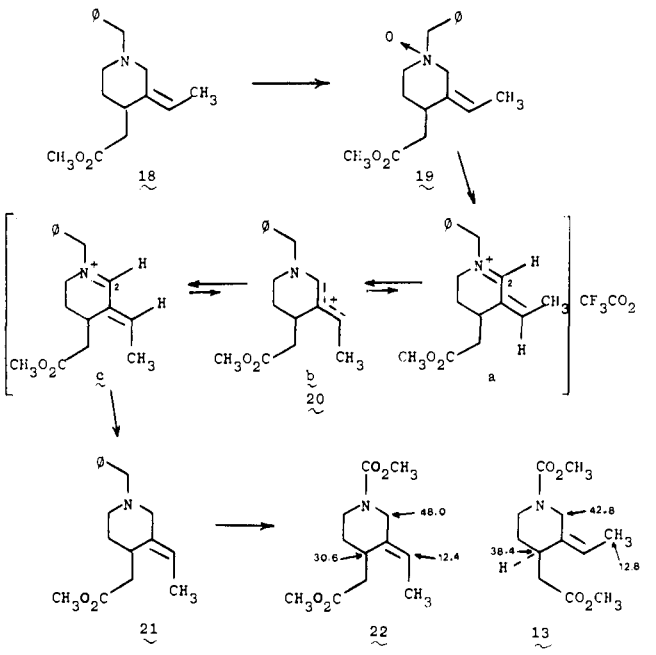


achieved predictably by a 3,3-sigmatropic rearrangement of the intermediate pyro ester III *via* the most stable chair-like transition state bearing the equatorial methyl group.[25] The product **13** (oil; 68% yield; $[\alpha]^{25}_D$ +13.4°; NMR δ 1.68 (d, 3, *J* = 7 Hz, $-CH_3$), 3.67 (s, 3, $-OCH_3$), 3.69 (s, 3, $-OCH_3$), 5.23 ppm (q, 1, *J* = 7 Hz, $=CHCH_3$), *m/e* 241) was optically pure on the basis of a comparison of the corresponding acid **14** (mp 62–65 °C, $[\alpha]^{25}_D$ +19.2°) with a sample (mp 62–65 °C,



III

Scheme III



$[\alpha]^{25}_D$ +18.5°) obtained by resolution. The *Z*-configuration of the double bond was determined by the ^{13}C NMR comparison[26] of **13** with the corresponding racemic isomer **22** having the *E*-configuration (values in parts per million, Scheme III).

The *E* isomer **22** was obtained by inversion of the double bond as outlined in Scheme III. The racemic *Z*-olefinic ester **18,** obtained from racemic **11,** was converted into the *N*-oxide **19** with *m*-chloroperbenzoic acid. Treatment with trifluoroacetic anhydride led smoothly to the conjugated (*Z*)-iminium cation **20a** which spontaneously rearranged to the more stable *E* isomer **20c.** Quenching with sodium borohydride gave the oily *E*-olefinic ester **21.** The exchange of *N*-benzyl for *N*-carbomethoxy furnished **22** (oil: NMR δ 1.60 (dd, 3, J = 7, 2 Hz, $-CH_3$), 2.50 (d, 2, J = 8 Hz, $CH_2CO_2CH_3$), 3.67 (s, 6, $-OCH_3$), 5.47 ppm (q, 1, J = 7 Hz, $=CHCH_3$); *m/e* 241) in a 54% overall yield from **18.** This inversion sequence was based on consideration of the difference in steric nonbonding interactions between the C-2 hydrogen and either the allylic methyl in **20a** or the vinyl hydrogen in **20c.**

The completion of the asymmetric synthesis of the bicyclic amino ester **2** required the introduction of two additional chiral centers. This was accomplished by hydroboration of the double bond of **13** from the less hindered side with 9-borabicyclo[3.3.1]nonane[27] in tetrahydrofuran at 0 °C. Oxidation of the intermediate borane with 30% hydrogen peroxide and 6 N sodium hydroxide in ethanol and acidification with 1 N hydrochloric acid gave exclusively, and in 65% yield, the 15*R*,19*S*,20*S* lactone **15** (mp 78–80 °C; $[\alpha]^{25}_D$ +32.2°; NMR δ 1.46 (d, 3, J = 6.5 Hz, CH_3), 3.68 (s, 3, $-OCH_3$), 4.45 ppm (dq, 1, J = 10, 6.5 Hz, $-CH(-O)CH_3$); *m/e* 227).

We found that the formation of the vinylogous carbonate function (**17**), characteristic of the E ring of heteroyohimbine alkaloids, can be performed most effectively by direct rearrangement of the vinylogous carbamate (**16**).[28] Treatment of the lactone **15** with bis(dimethylamino)-*tert*-butoxymethane at room temperature for 60 h and evaporation of the excess reagent gave crude **16.** The rearrangement was carried out in 10% hydrogen chloride–methanol in a sealed tube at 120 °C for 24 h. After chromatography, the desired **17** (oil: $[\alpha]^{25}_D$ +11.2°; λ_{max} 240 nm (ϵ 10 700); IR 1690, 1633 cm^{-1}; NMR δ 1.42 (d, 3, J = 6.5 Hz, $-CH_3$), 3.65 (s, 3, $-OCH_3$), 3.67 (s, 3, $-OCH_3$), 4.13 (dq, 1, J = 10, 6.5 Hz, $-CH(-O)CH_3$), 7.48 ppm (s, 1, $-OCH=$); *m/e* 269) was isolated in 66% yield. The synthesis was then completed by removal of the *N*-carbomethoxy protecting group, effected at 50 °C with glacial acetic acid saturated with hydrogen bromide. Chromatographic purification gave 83% of pure oily bicyclic amine **2** ($[\alpha]^{25}_D$ −63.9° ($CHCl_3$); IR 1698, 1630 cm^{-1}; λ_{max} 242–243 nm (ϵ 8525); NMR δ 1.37 (d, 3, J = 6.5 Hz, CH_3), 1.74 (s, 1, NH), 3.70 (s, 3, $-OCH_3$), 4.51 (dq, 1, J = 10, 6.5 Hz, $-CH(-O)-CH_3$), 7.52 ppm (s, 1, $=CHO$); *m/e* 211); the crystalline 1-tartrate salt had mp 163–165 °C, $[\alpha]^{25}_D$ −30.5°.[7]

In summary, we have completed our previously described synthesis of natural *allo*-heteroyohimbine alkaloids[4] by an efficient asymmetric and stereospecific preparation of the key intermediate 15*S*,19*S*,20*S*-bicyclic amino ester **2.** A practical, general method is now available for the synthesis of this type of alkaloid.[29]

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References and Notes

(1) van Tamelen, E. E.; Placeway, C. *J. Am. Chem. Soc.* **1961**, *83*, 2594. van Tamelen, E. E.; Placeway, C.; Schiemenz, G. P.; Wright, I. G. *Ibid.* **1969**, *91*, 7359.
(2) Winterfeldt, E.; Radunz, H.; Korth, T. *Chem. Ber.* **1968**, *101*, 3172.
(3) Winterfeldt, E.; Gaskell, A. J.; Korth, T.; Radunz, H.; Walkowiak, M. *Ibid.* **1969**, *102*, 3558.
(4) Gutzwiller, J.; Pizzolato, G.; Uskoković, M. *J. Am. Chem. Soc.* **1971**, *93*, 5907.
(5) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1972**, 1081.
(6) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015.
(7) Sakai, S.; Aimi, N.; Endo, J.; Shimizu, M.; Yamanaka, E.; Katano, K.; Kashiwazaki, M.; Fujiu, M.; Yamamoto, Y. *Yakugaku Zasshi* **1978**, *98*, 850.
(8) Djakouré, L.; Jarreau, F.-X.; Goutarel, R; Janot, M.-M. *C. R. Acad. Sci., Paris, Ser. C* **1972**, *274*, 1520.
(9) Djakouré, L. A.; Jarreau, F.-X.; Goutarel, R. *Tetrahedron* **1975**, *31*, 2695.
(10) Boivin, J.; Pais, M.; Goutarel, R. *Tetrahedron* **1977**, *33*, 305.
(11) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.
(12) Scott, A. I.; Lee, S.-L. *J. Am. Chem. Soc.* **1975**, *97*, 6906.
(13) Stöckigt, J.; Treimer, J.; Zenk, M. H. *FEBS Lett.* **1976**, *70*, 267.
(14) Stöckigt, J.; Husson, H.-P.; Kan-Fan, C.; Zenk, M. H. *J. Chem. Soc., Chem. Commun.* **1977**, 164.
(15) Kan-Fan, C.; Husson, H.-P. *J. Chem. Soc., Chem. Commun.* **1978**, 618.
(16) MacKellar, F. A.; Kelly, R. C.; van Tamelen, E. E.; Dorschel, C. *J. Am. Chem. Soc.* **1973**, *95*, 7155.
(17) Brown, R. T.; Chapple, C. L.; Duckworth, D. M.; Platt, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 160.
(18) Brown, R. T.; Leonard, J.; Sleigh, S. K. *J. Chem. Soc., Chem. Commun.* **1977**, 636.
(19) Uskoković, M. R.; Pruess, D. L.; Despreaux, C. W.; Shiuey, S.-J.; Pizzolato, G.; Gutzwiller, J. *Helv. Chim. Acta* **1973**, *56*, 2834.
(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969** *34*, 2543. (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride, $[\alpha]^{25}_D$ +133° (*c* 1.62, CCl_4), was prepared from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, $[\alpha]^{25}_D$ +76° (*c* 1.56, CH_3OH), which had been *fully resolved* with (*R*)-α-methylbenzylamine. Commercial samples of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid vary in optical purity from 94 to 99%.
(21) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(22) Yasuhara, K.; Kabuto, K.; Yamaguchi, S. *Tetrahedron Lett.* **1978**, 4289.
(23) This finding is also in agreement with the originally assigned *S* absolute configuration of the alcohol **7**. The assignment was made by the method of Horeau on a sample of low optical purity, obtained by partial resolution. See Gottarelli, G.; Samori, B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1462.
(24) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 3530.
(25) Three other transition states should each lead to uniquely different products: equatorial methyl-boat–*S*-*Z* enantiomer of **13**; axial methyl-chair–*S*-*E* diastereomer of **13**; and axial methyl-boat–*R*-*E* diastereomer of **13.**
(26) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 69–85.
(27) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280, 5281.
(28) Ban, Y.; Taga, N.; Oishi, T. *Chem. Pharm. Bull. (Tokyo)* **1976**, *24*, 736.
(29) Specific rotations $[\alpha]_D$ were measured in methanol (concentration, 10 mg/mL) if not otherwise indicated. The IR spectra were taken in chloroform, the UV in methanol, and the NMR in deuteriochloroform.

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