4.6 (s, HOD), 4.1 (m, 1 H, CHO), 3.0 (m, 2 H, CH_2N), 2.32 (d, J = 6 Hz, 2 H, CH_2CO_2H). IR (KBr): 3450, 3100–2500, 2150, 1650, 1575–1250, 1100, 1050, 900 cm^{-1}. IR (lit.[28g] KBr): 3100, 2150, 1650, 1575, 1400, 1150, 1100, 1050 cm^{-1}.

(*R*)-4-Amino-3-hydroxybutanoic Acid (8). (*R*)-Cyanoamine hydrochloride (**31**) (143 mg, 1.05 mmol) was dissolved in concentrated suulfuric acid (1.0 mL, 19 mmol) and heated on the steam bath for 15 min. Water (10 mL) was added and the solution refluxed for 3 h. After being cooled, it was neutralized with lead carbonate and heated on the steam bath for 1 h. After filtration and evaporation under reduced pressure, 189 mg of a thick yellow oil remained. Dissolution in a small amount of water and dilution with absolute ethanol (about 30 mL) provided 120 mg of white crystals (96%); mp 202–205 °C, lit.[28d] mp 212 °C. Rotation: $[\alpha]^{25}_D$ = −7.09° (c = 3.5, H_2O) (lit.[28d] $[\alpha]_D$ = −3.4° or −21.06°), $[\alpha]_{578}$ = −7.49°, $[\alpha]_{546}$ = −8.49°.

(DL)-2,2-Dimethyl-4-((*tert*-butylamino)methyl)-1,3-dioxolane (33). (DL)-Acetonide tosylate (**17**) (100 mg, 0.35 mmol) was weighed into a 10-mL round-bottomed flask and dissolved in 3 mL of dimethyl sulfoxide. Dry *tert*-butylamine (1.0 mL, 9.45 mmol, distilled from calcium hydride) was added, a condenser and calcium sulfate drying tube were attached, and the solution was heated to 85 °C for 21 h. After being cooled, it was poured into 25 mL of diethyl ether, extracted with 3 × 10 mL of saturated sodium bicarbonate, and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure provided 51 mg (78%) of the desired amine **33**. NMR (acetone-d_6): δ 4.3–3.7 (m, 3 H, CHO), 2.8–2.5 (m, 3 H, CH_2N and NH), 1.35 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.10 (s, 9 H, *t*-Bu). IR ($CHCl_3$): 3550, 3400, 2950, 1350, 1250 cm^{-1}. Mass spectrum: m/e 187 (M^+), 172, 155, 129, 116, 114, 86, 84. High-resolution mass spectrum: m/e 187.1570 (M^+), calcd for $C_{10}H_{21}NO_2$, 187.1572.

(DL)-3-(*tert*-butylamino)-1,2-propanediol (34). (DL)-(*tert*-butylamino)acetonide (**33**) (50 mg, 0.27 mmol) was dissolved in 1 N hydrochloric acid (5 mL) and stirred at room temperature for 3 h. After the solution was cooled to 0 °C, sodium hydroxide (0.3 g, 7.5 mmol) was added and it was stirred until dissolved. Water (10 mL) was added, and the aqueous solution was extracted with 3 × 25 mL of dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 13 mg (33%) of a yellow oil. NMR: δ 3.7 (m, 3 H, CHO), 2.92 (d, J = 5 Hz, 2 H, CH_2N), 2.6 (br s, 3 H, OH and NH), 1.1 (s, 9 H, CH_3). IR ($CHCl_3$): 3400, 2980, 1370, 1350, 1045 cm^{-1}. Mass spectrum: m/e 132 (M^+ − 15), 114, 70, 57. High-resolution mass spectrum: m/e 132.1022 ($M^+ - CH_3$), calcd for $C_6H_{14}NO_2$, 132.1024.

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A Short New Azulene Synthesis

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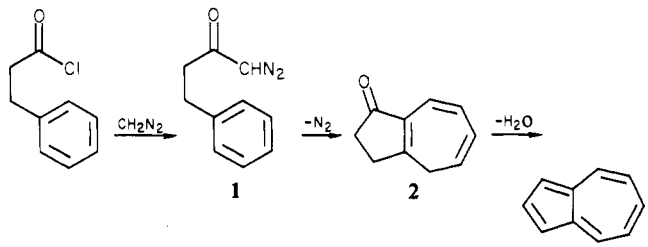
Abstract: A short new azulene synthesis, requiring no dehydrogenation step, has been developed (Scheme I). Intramolecular carbene addition creates the bicyclic ring system of azulene with a high degree of unsaturation and versatile functionality in a single step from a simple benzene derivative. The synthesis is particularly amenable to preparation of specific ^{13}C- and ^{2}H-labeled azulenes.

Azulene, the first and best known of all nonbenzenoid aromatic hydrocarbons, has played a major role in the advancement of our understanding of cyclic conjugation.[1] Since Plattner's original synthesis of this unusual, blue hydrocarbon in 1937,[2] a variety of new pathways to azulenes has been reported.[3] Prominent among these stands the remarkably simple and versatile Hafner–Ziegler synthesis[4] which avoids the low yield, dehydrogenation step typical of most other routes. Access to this class of compounds has resulted in the extensive exploration of azulene chemistry.[1]

One long-known reaction in this field, the thermal rearrangement of azulene to naphthalene,[5] continues to mystify mechanistic organic chemists.[6] We decided to study this unique interconversion of aromatic hydrocarbons by the use of ^{13}C labels. It soon became apparent, however, that none of the existing syntheses were suitable for preparation of the desired ^{13}C-azulenes. The Hafner–Ziegler method, for example, begins with cyclopentadiene anion and cannot be used to label specifically the five-membered ring positions. Consequently, we have developed the pathway outlined in Scheme I.[7]

Scheme I



This new azulene synthesis is short and simple. No dehydrogenation step is required. Furthermore, it can be easily adapted for the introduction of ^{13}C or ^{2}H at almost any position. We believe our new approach will prove useful in the rational preparation of many azulenes not previously accessible by existing methods.

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(5) Heilbronner, E.; Plattner, P. A.; Wieland, K. *Experientia* **1947**, *3*, 70. Heilbronner, E.; Wieland, K. *Helv. Chim. Acta* **1947**, *30*, 947–56.

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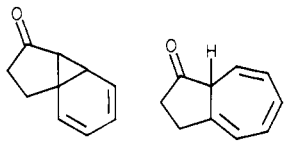
Details

Diazoketone **1** can be obtained in essentially quantitative yield from dihydrocinnamic acid by standard methods. For the synthesis of angularly labeled [^{13}C]-azulene, however, we have developed an alternative procedure which requires only 1.0 equiv of [^{13}C]-diazomethane.[8]

When added to refluxing benzene containing a catalytic amount of cuprous chloride, diazoketone **1** loses nitrogen rapidly to give bicyclic trienone **2** in 45–50% yield after purification. Steric constraints (Bredt's rule) presumably confine intramolecular addition of the intermediate ketocarbene to the 1,2-position of the benzene ring. The unstable norcaradiene (**3**) then opens to bicyclic trienone **4**, which can be identified[9] in the crude reaction



3 4

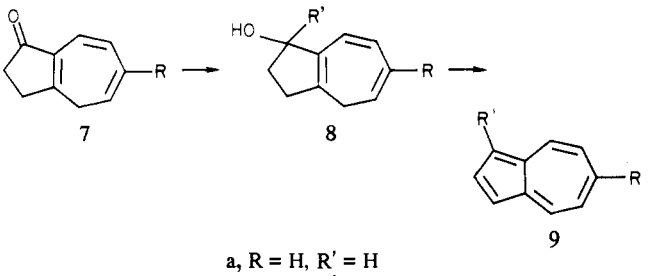
mixture but isomerizes to the cross-conjugated trienone (**2**) during isolation.

The spectra and combustion analysis of **2** all support the assigned structure, but ^{1}H NMR studies provide the most convincing evidence for distinguishing among double bond isomers. At 100 MHz, the upfield signals in the ^{1}H NMR spectrum of **2** appear as an A_2B_2 pattern (δ 2.58, 4 H, cyclopentenone moiety) plus a two-proton doublet (δ 2.83, J = 6 Hz, allylic methylene in cycloheptatriene moiety). The integration and multiplicity of the allylic hydrogen signal demand that the lone sp^3 carbon of the seven-membered ring lie adjacent to one of the two angular positions. Eu(dpm)$_3$ induces a relatively large downfield shift in the NMR signal of the olefinic hydrogen adjacent to the other angular position (δ 6.68, d, 1 H, J = 10 Hz) compared to that of the allylic hydrogen signal, however, and only structure **2** agrees with this observation.

In optimizing the yield for the cyclization in Scheme I, we have determined the importance of several variables. Carbene addition to the solvent (benzene) competes with cyclization to some extent but can be completely suppressed by conducting the reaction in bromobenzene; use of other solvents (e.g., cyclohexane, carbon tetrachloride, chlorobenzene, tetrahydrofuran, and dimethoxyethane) invariably gave inferior yields. The reaction mixture must also be kept dilute in order to minimize interception of the intermediate carbene by other species in solution. Several catalysts all appear to effect the cyclization reaction equally well (e.g., cuprous chloride, anhydrous cupric chloride, cupric sulfate, and copper metal).

Creation of the bicyclic ring system of azulene with a high degree of unsaturation and versatile functionality in a single step from a simple benzene derivative represents perhaps the most attractive feature of this synthesis. Independent cyclization of diazoketone **1** by a French group[10] has been reported to give a bicyclic trienone with double bonds arranged differently than in either **2** or **4**. This isomerized product, obtained in 13% yield by preparative GLC, presumably results from 1,5-hydrogen shifts at the high reaction temperatures employed (refluxing decalin).[10] Few other intramolecular carbene additions to benzene rings have been reported,[11] although the transition-metal-catalyzed rearrangement of phenyl-substituted bicyclobutanes to bicyclo[5.3.0]decatetraenes may represent an additional example.[12]

Scheme II

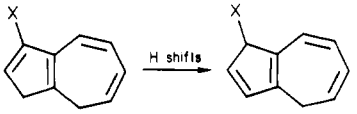


7 8 9

a, R = H, R' = H
b, R = H, R' = CH_3
c, R = CH_3, R' = H
d, R = CH_3, R' = CH_3

Some substituted azulenes have actually been obtained from the products of this latter reaction.[12]

Final conversion of trienone **2** to azulene presented a modest, but interesting, synthetic challenge. Formally, the transformation requires conversion of a ketone to a diene by elimination of the elements of water with no change in overall oxidation state. Multistep pathways[13] can be devised to solve this general problem, of course, but a direct solution has yet to be found. In the present case, it occurred to us that an enol derivative such as **5** would contain a cyclopentadiene ring capable of ready isomerization via sequential hydrogen shifts and that isomer **6**, if formed, should aromatize with ease by loss of HX. Indeed, azulene can be obtained directly from **2** simply by warming with phosphorous pentoxide in methanesulfonic acid.[21] We have no evidence that this reaction does involve intermediates resembling **5** and **6**; however, attempts to apply the method to other systems (e.g., cyclohexenone and α-tetralone) were not successful.[14]



5 6

Extensions

We have prepared both [1-^{13}C]-azulene and [3a-^{13}C]-azulene by this route and have studied their thermal rearrangements to ^{13}C-labeled naphthalene.[15] Substituted azulenes can also be prepared, although this aspect of the project has not been pursued in earnest. The cyclization reaction does tolerate benzannulation and electron-donating substituents but not halogens on the benzene ring.[16] Bicyclic trienone **2** undergoes Grignard addition and aluminum hydride reduction without complication and thus can be used for the introduction of alkyl substituents and, presumably, deuterium on the five-membered ring. The change in oxidation state which accompanies these carbonyl additions, however, necessitates a classical dehydration–dehydrogenation to generate

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(9) 2,3-Dihydro-1(8a*H*)-azulenone **4**: IR (neat) 1757 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 6.4–6.2 (m, 2), 6.2–5.9 (m, 2), 5.0 (dd, 1, J = 9, 4 Hz, C_8H), 3.0–2.2 (m, 5); decoupling experiments are consistent with the assignment.

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(16) Scott, L. T.; Minton, M. A.; Fong, L. K.; Reeder, W. D., unpublished results.

the azulene nucleus (Scheme II). By this procedure we have prepared azulenes **9a–d**.

Experimental Section

General. All ^1H NMR spectra were recorded at 60 MHz unless otherwise specified and are reported relative to internal tetramethylsilane. All melting points and boiling points are uncorrected. Diethyl ether, tetrahydrofuran (THF), and benzene were all dried by distillation under nitrogen from sodium benzophenone ketyl. The MeMgCl in THF was obtained from Ventron Corp.; Silica gel PF254+366 (Brinkmann) was used for all preparative layer chromatography. Combustion analyses were performed by Spang, Mich.

3-Phylpropanoyl Chloride. A mixutre of 15.0 g (0.1 mol) of 3-phenylpropanoic acid and 18.0 mL (0.25 mol) of thionyl chloride, protected from the atmosphere by a drying tube, was heated under reflux for 2 h. Excess thionyl chloride was removed at reduced pressure, and the residue was vacuum distilled, giving 16.3 g (97%) of 3-phenylpropanoyl chloride as a colorless liquid: bp 43–48 °C (0.04mm) [lit.[10] bp 72 °C (0.4mm)]; IR (neat) 1812 cm^{-1}; ^1H NMR (CCl_4) δ 7.04 (s, 5), 2.93 (m, 4).

1-Diazo-4-phenyl-2-butanone (1). A solution of diazomethane (ca. 100 mmol) in 300 mL of anhydrous ether was prepared in the standard way[17] from 30 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. To this solution, cooled in an ice–salt bath under a drying tube, was added an additional 35 mL of anhydrous ether containing 4.94 mL (33 mmol) of 3-phenylpropanoyl chloride dropwise during 1 h with magnetic stirring. At the end of the addition, the reaction mixture was stirred 1 h more in the cold bath and then 1 h more while being warmed to room temperature. Concentration of the reaction mixture under reduced pressure gave 5.80 g (100%) of **1** as a yellow oil: IR (neat) 2083, 1631 cm^{-1} [lit.[10] IR (neat) 2096, 1637 cm^{-1}]; ^1H NMR (CCl_4) δ 7.07 (s, 5), 5.07 (s, 1), 3.00–2.29 (m, 4); duplicate N_2 evolution[18] established the purity as 97%.

Caution! Diazomethane is toxic and explosive; all operations should be carried out in a well-ventilated hood with adequate shielding.

3,4-Dihydro-1(2*H*)-azulenone (2 = 7a). A suspension of 0.8 g of fresh,[19] anhydrous CuCl in 3 L of bromobenzene, freshly distilled from CaH_2, was heated to 80 °C under nitrogen in an oven-dried, 5-L, three-neck flask fitted with a mechanical stirrer, a constant addition funnel, and a reflux condenser. To this vigorously stirred suspension was added 1 L of dry bromobenzene containing 20.4 g (0.117 mol) of **1** dropwise during 7 h. Heating and stirring were continued for an additional 1 h; then the pale yellow reaction mixture was cooled and filtered through 30 g of alumina to remove CuCl and isomerize the unconjugated trienone (**4**)[9] to the more stable isomer (**2**). The alumina was washed with 500 mL of EtOAc, and the combined organic filtrates were concentrated at 40 °C (20–0.5 mm) to a brown oil. Chromatography on 200 g of silica gel using 15% EtOAc/petroleum ether as the eluant gave 8.9 g (52%) of **2** (=**7a**) as a light brown oil. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.23; H, 6.89. ^1H NMR ($CDCl_3$): δ 6.68 (d, 1, J = 10Hz, C_8H), 6.48 (dd, 1, J = 10, 6 Hz, C_7H), 6.09 (dd, 1, J = 6, 9 Hz, C_6H), 5.39 (dt, 1, J = 9, 6 Hz, C_5H), 2.83 (d, 2, J = 6 Hz, C_4H_2), 2.58 (sym m, 4). IR (neat): 1690 (C=O), 1620 (C=C) cm^{-1}. UV max (EtOH): 232 nm (ϵ 15 200), 265 (4800) [cf. 2,3-dimethyl-2-cyclopentenone: UV max 235 nm[20]]. Mass spectrum (70 eV): m/e 146 (M^+).

Azulene from 2. A mixture of 5 g (35 mmol) of P_2O_5 (weighed under nitrogen) and 34 mL of distilled methanesulfonic acid was heated under nitrogen to 60 °C with mechanical stirring.[21] When the mixture was homogeneous, 0.48 g (3.3 mmol) of **2** was added neat dropwise during 7 min. The solution rapidly darkened to orange-brown. Progress of the reaction was followed by removing one-drop aliquots and quenching them into H_2O/hexane. The UV spectra of the hexane layer showed a gradual decrease in the absorption at 226 nm due to **2** and corresponding growth of the characteristic three-line pattern due to azulene around 274 nm. When the 226-nm absorption of **2** was no longer discernible (about 6 h), the reaction mixture was poured into 500 mL of ice cold water and extracted twice with pentane. The dark blue pentane layers were combined, washed with water until neutral, washed with saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The oily blue residue was purified by preparative layer chromatography on silica gel by using pentane as the eluant to give 130–210 mg (30–50%) of azulene as beautiful dark blue crystals, mp 98–98.5 °C [lit.[2] 98.5–99 °C].

6-Methyl-3,4-dihydro-1(2*H*)-azulenone (7c). A suspension of 10 mg of fresh,[19] anhydrous CuCl in 100 mL of dry benzene was heated to reflux under nitrogen in an oven-dried, 250 mL, three-neck flask fitted with a mechanical stirrer, a constant-addition dropping funnel, and reflux condenser. To this vigorously stirred suspension was added 20 mL of dry benzene containing 188 mg (1.0 mmol) of 1-diazo-4-(*p*-tolyl)-2-butanone[22] dropwise during 35 min. Heating and stirring were continued for 10 min more; then the reaction mixture was cooled, filtered, and concentrated under reduced pressure to give 161 mg of a brown oil which contained the 6-methyl derivative of the unconjugated trienone **4**: ^1H NMR ($CDCl_3$) δ 6.13 (d, 1, J = 7 Hz, C_5H), 6.04 (d, 1, J = 7 Hz, C_4H), 6.00 (d, 1, J = 10Hz, C_7H), 5.00 (dd, 1, J = 10, 4 Hz, C_8H), 3.00–2.30 (m, 5), 1.92 (s, 3, CH_3). Preparative layer chromatography on silica gel using 15% EtOAc/petroleum ether as eluant gave 72 mg (45%) of 6-methyl-3,4-dihydro-1(2*H*)-azulenone (**7c**) as an orange oil. Molecular distillation (100 °C (0.4mm)) provided a pure sample as a yellow oil. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.33; H, 7.41. ^1H NMR($CDCl_3$): δ 6.54 (d, 1, J = 12 Hz, C_8H), 6.44 (d, 1, J = 12 Hz, C_7H), 5.15 (t, 1, J = 6 Hz, C_5H), 2.80–2.30 (m, 6), 1.82 (s, 3, CH_3). IR (neat): 1695 (C=O), 1620 (C=C) cm^{-1}. UV max (EtOH): 235 nm (ϵ 13 500), and 268 (sh, 3100). Mass spectrum (70 eV): m/e 160 (M^+).

Aluminum Hydride Reduction of 7a. A suspension of AlH_3 (ca. 1.1 mmol) in 2.2 mL of dry THF was freshly prepared[23] and added dropwise with stirring to 160 mg (1.1 mmol) of **7a** in 2 mL of dry THF under nitrogen at 0 °C. After 30 min the reaction mixture was quenched by the dropwise addition of 2 mL of 50% aqueous THF. The mixture was stirred 1 h more, diluted with saturated NaCl, and extracted twice with ether. The ethereal extracts were combined, dried (Na_2SO_4), and concentrated to give 141 mg (87%) of 1,2,3,4-tetrahydroazulen-1-ol (**8a**) as a yellow oil: IR (neat) 3400 cm^{-1} (br, OH); ^1H NMR ($CDCl_3$) δ 6.55 (d, 1, J = 11 Hz, C_8H), 6.29 (dd, 1, J = 11, 4 Hz, C_7H), 5.99 (ddd, 1, J = 10, 4, 2 Hz, C_6H), 5.30 (dt, 1, J = 10, 6 Hz, C_5H), 4.7 (br d, 1, C_1H), 2.7 (br s, 1, OH), 2.6–1.4 (m, 6; includes δ 2.5, d, 2, J = 6 Hz, C_4H_2); single spot on thin-layer chromatography; used without further purification.

Grignard Addition to 7a. A solution of CH_3MgCl (1.0 mmol) in 0.33 mL of tetrahydrofuran was diluted with 1 mL of dry ether and cooled in an ice bath under nitrogen. To this Grignard reagent was added 94 mg (0.65 mmol) of **7a** in 2 mL of dry ether dropwise with stirring. Stirring was continued for 15 min at 0 °C and for 45 min at room temperature. The reaction mixture was then diluted with cold, saturated NH_4Cl and extracted twice with ether. The ethereal extracts were combined, dried (Na_2SO_4), and concentrated to give 94 mg of crude product which was purified by preparative layer chromatography on silica gel using 20% EtOAc/petroleum ether as eluant. The major band contained 54 mg (51%) of 1-methyl-1,2,3,4-tetrahydroazulen-1-ol (**8b**) as a thick oil: IR ($CHCl_3$) 3580, 3420 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60–5.65 (m, 3, pattern similar to that of the secondary alcohol above C_8H, C_7H, C_6H), 5.25 (dt, 1, J = 10, 6 Hz, C_5H), 3.0–1.7 (m, 7), 1.33 (s, 3, CH_3).

Azulenes (9a–d) from 1,2,3,4-Tetrahydroazulen-1-ols. A simple dehydrogenation apparatus was constructed from a Pyrex tube (35 cm × 25 mm o.d.) fitted with standard taper 24/40 ground-glass joints. The bottom of the tube was plugged with glass wool, and 2.0 g of 10% Pd/C was poured thereupon. The remainder of the tube was packed with glass helices. Heating was achieved by means of a 2.4 m × 1.0 cm heating tape wrapped the entire length around the tube, and the temperature was monitored by a thermometer held against the tube by the heating tape. A pressure equalizing addition funnel was attached to the top of the tube and capped with a nitrogen inlet. A trap at the bottom of the tube was cooled in a dry ice/acetone bath. Use of a more sophisticated apparatus such as that reported by Plattner[24] would undoubtedly give higher yields than those obtained with this crude device.

A 0.01 M solution of **8a** in 1:1 dry benzene/hexane was divided into several 10-mL aliquots which were each passed through the dehydration–dehydrogenation tube under different conditions. Yields were established by quantitative visible absorption spectroscopy. The best conditions found (temperature = 480 °C, nitrogen flow rate = 3.75 L/min, addition rate = 1 mL/6 s) gave azulene (**9a**) in 37% yield.

Trienol **8b** was similarly treated (temperature = 400 °C, nitrogen flow rate = 1.5 L/min, addition rate = 1 mL/21 s) to give 1-methylazulene (**9b**)[25] in 27% yield.

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6-Methyl-1,2,3,4-tetrahydroazulen-1-ol (**8c**), obtained from trienone **7c** by AlH_3 reduction as above (92%), was treated similarly (temperature = 445 °C, nitrogen flow rate = 3.3 L/min, addition rate = 1 mL/8 s) to give 6-methylazulene (**9c**)[25] in 22% yield.

1,6-Dimethyl-1,2,3,4-tetrahydroazulen-1-ol (**8d**), obtained from trienone **7d** by CH_3MgCl addition as above (96%), was treated similarly (temperature = 428 °C, nitrogen flow rate = 2.2 L/min, addition rate = 1 mL/18 s) to give 1,6-dimethylazulene (**9d**) in 15% yield. A pure sample of this previously unknown azulene derivative was obtained as a blue oil by preparative GLC. Anal. Calcd for $C_{12}H_{12}$: C, 92.26; H, 7.74. Found: C, 91.99; H, 7.91. UV-Vis max (hexane): 270 nm (ϵ 60 000), 276 (61 000), 301 (7100), 349 (5100), 366 (2200), 550 (sh, 230), 573 (270), 595 (320), 622 (280), 651 (290), 688 (130), 722 (130) [Vis max predicted by Plattner's empirical rules:[26] calcd, 594 nm; found, 595 nm].

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Stereochemistry of Indolmycin Biosynthesis. Steric Course of C- and N-Methylation Reactions[1a]

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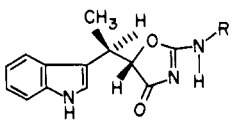
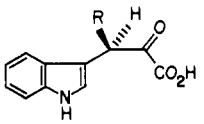
Abstract: (2*S*,*methyl-R*)- and (2*S*,*methyl-S*)-[*methyl*-^{14}C,$^{2}H_1$,$^{3}H_1$]methionine were synthesized from (*S*)- and (*R*)-[2-^{14}C,$^{2}H_1$,$^{3}H_1$]acetate. Key steps in the synthesis were Schmidt reaction of the acetate to give methylamine and use of methylditosylimide, derived from the latter, to alkylate the *S* anion of L-homocysteine. The two chiral methionine samples were fed to cultures of *Streptomyces griseus* producing the antibiotic indolmycin (Ia) and its precursor indolmycenic acid (III). Both compounds were degraded to convert the *C*- and the *N*-methyl groups into the methyl group of acetic acid, using reactions or reaction sequences of known stereochemistry. Chirality analysis of these acetic acid samples by the method of Cornforth et al. and Arigoni and co-workers indicated that the enzymatic transfer of the methyl group of (*S*)-adenosylmethionine both to carbon and to nitrogen as acceptor occurs with inversion of configuration.

The biosynthesis of the antibiotic indolmycin (Ia) by *Streptomyces griseus* (ATCC 12648) has been shown[2,3] to involve the transfer of the methyl group of methionine, in the form of (*S*)-adenosylmethionine, to the methylene carbon of indolpyruvate (IIa), which is generated by transamination of tryptophan, and



Ia: R = CH_3; indolmycin
b: R = H; N-desmethylindolmycin



IIa: R = H; indolepyruvate
b: R = CH_3; 3-methylindolepyruvate

to the exocyclic nitrogen of the amidino group in the oxazolinone ring of *N*-demethylindolmycin (Ib). The biosynthesis of indolmycin poses several stereochemical questions. The answers to some of these are evident, but several others involve cryptic stereochemistry, because they relate to reactions at centers which are not chiral. The latter reactions nevertheless can be expected to be stereospecific and their steric course can be deduced by experiments using suitable stereospecifically isotope-labeled precursors. The main stereochemical questions are (a) does replacement of a methylene hydrogen in IIa by a methyl group proceed in an inversion or retention mode at C-3, (b) does the methyl group itself undergo inversion or retention of configuration (or racemization) upon transfer to the methyl carbon, and (c) does the methyl group transfer to the nitrogen occur with inversion, retention or racemization. Question a was answered in previous work from this laboratory.[4] In this paper we report results which answer questions b and c. A preliminary account of some of this work has been published earlier.[5]

Results

The experimental approach to the study of the stereochemical fate of the methyl group of methionine in indolmycin biosynthesis required use of the chiral methyl group methodology[6] developed by the laboratories of Cornforth[7] and Arigoni.[8] This method involves the use of all three isotopes of hydrogen (^{1}H, ^{2}H, ^{3}H) to generate a methyl group which is chiral by virtue of isotopic substitution. For the present study the following three tasks had to be performed: (a) synthesis of methionine carrying a chiral methyl group of known absolute configuration, (b) incorporation of the chiral methyl group of methionine into Ia, and (c) degradation of Ia to convert each methyl group into the methyl group of acetate by a series of stereochemically unambiguous reactions followed by chirality analysis of these acetate samples. The latter was carried out as indicated by the laboratories of Cornforth[7] and

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