added 24 g of a 30% aqueous solution of methylglyoxal. After keeping the reaction mixture at room temperature, the solution was treated with 500 mL of Amberlite IR-120 (H^+), and the resin was eluted with 10 L of water. Evaporation of water left white crystals, 7.5 g (yield 32.5%). Recrystallization was carried out in water to yield 6.7 g of white needles: $[\alpha]^{16}_D$ −131.95° (c 1.2, water); mp 202–203 °C; NMR (D_2O) δ 2.55 (s, 3 H, CH_3). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 47.06; H, 6.03; N, 12.10.

Tetraacetate 14: $[\alpha]^{21}_D$ −23.75° (c 1.0, methanol); mp 110 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03. Found: C, 51.11; H, 5.49; N, 6.99.

Catalytic hydrogenation of **11** with palladium in methanol yielded the known 2-(D-*arabino*-tetrahydroxybutyl)-5-methylpyrazine (**12**): $[\alpha]^{21}_D$ −61.19° (c 1.0, water) (lit.[11] $[\alpha]^{13}_D$ −62.4°); mp 198 °C (lit.[11] mp 196 °C).

Tetraacetate 15: mp 103–104 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_8$: C, 53.40; H, 5.80; N, 7.33. Found: C, 54.21; H, 5.85; N, 7.44.

5-Methylpyrazine-2-carboxylic Acid (13). By the procedure described for **5**, 1.2 g of **12** afforded 230 mg of crystalline **13**, mp 164–165 °C (lit.[13] mp 166–167 °C).

Determination of Isomers 2 and 3 and Isomers 10 and 11. A small amount of the reaction mixture, after 1 h of reaction, was lyophilized and analyzed after being dissolved in D_2O with the sodium salt of 2-(trimethylsilyl)propanesulfonic acid as internal standard.

Registry No. 1, 21537-55-3; 2, 72938-69-3; 3, 32077-79-5; 4, 13440-26-1; 5, 5521-61-9; 6, 72938-70-6; 7, 72938-71-7; 8, 940-07-8; 9, 72938-72-8; 10, 72938-73-9; 11, 72938-74-0; 12, 13532-06-4; 13, 5521-55-1; 14, 72938-75-1; 15, 72938-76-2; methylglyoxal, 78-98-8.

2*H*-Cyclopenta[*d*]pyridazines. Polyhalogenation Studies. Evidence for a Radical Substitution with *N*-Chlorosuccinimide[1]

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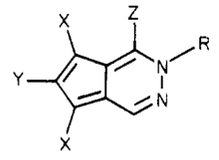
Previous results showed that the 2*H*-cyclopenta[*d*]-pyridazine system, a π-excessive heteroanalogue of azulene, underwent electrophilic substitution, including halogenation with *N*-halosuccinimides, readily at the 5- and 7-positions and more slowly at the 6-position.[3-5] We now report the reactions of 5,6,7-trichloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**1**) with NCS and also the preparation of several other new polyhalogen derivatives.

The parallels in reactivities, positions of substitution, and yields in the reactions of azulene and its π-excessive heteroanalogues with established electrophiles and with *N*-halosuccinimides[3-6] have demonstrated that the latter act as electrophilic reagents in effecting ring halogenation. Substitution of halogen for a benzylic hydrogen is known to proceed by a radical mechanism in nonpolar solvents with benzenoid compounds, however, and this provided a possible method for the preparation of chloromethyl derivatives in this nonbenzenoid series as intermediates for the formation of new functional substituents. Accordingly, this was investigated for the 2-methyl group in **1**.

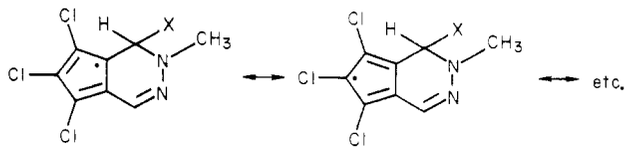


1, R = CH_3; X = Y = Cl; Z = H
2, R = CH_2Cl; X = Y = Cl; Z = H
3, R = $CHCl_2$; X = Y = Cl; Z = H
4, R = CCl_3; X = Y = Cl; Z = H
5, R = CH_2Cl; X = Y = Z = Cl
6, R = CH_3; X = Y = Cl; Z = *N*-succinimidyl
7, R = CH_3; X = Br; Y = Cl; Z = H
8, R = C_6H_5; X = Cl; Y = Br; Z = H
9, R = C_6H_5; X = Br; Y = Z = H
10, R = C_6H_5; X = Br; Y = Cl; Z = H
11, R = H; X = Br; Y = Z = H

Treatment of **1** with 1 equiv of NCS in refluxing carbon tetrachloride in the presence of air resulted in rapid decomposition. Repetition of the procedure in the absence of NCS caused decomposition but at an appreciably slower rate. Thus oxygen in the air appeared to be acting as an oxidant as well as a radical scavenger. The same reaction under a nitrogen atmosphere produced the chloromethyl derivative **2** (64%) and a trace of material spectrally identified as **3**. The NMR spectrum of **2** showed doublets at δ 8.47 and 8.61 for H-1 and H-4 and a singlet at δ 5.95 (as compared to δ 4.34 for the CH_3 in **1**) for the CH_2Cl group. Further reaction of **2** with 1 equiv of NCS under nitrogen formed **3** (77%) and a trace amount of **4**. The NMR spectrum of **3** had doublets at δ 8.59 and 8.97 (H-1, H-4) and a singlet at δ 7.78 ($CHCl_2$). Finally, longer treatment of **3** with a slight excess of NCS gave **4** (62%), the NMR spectrum of which consisted of only doublets at δ 8.74 and 9.33 (H-1, H-4).

Attempts to introduce chlorine into the remaining ring positions by the above method were unsuccessful, the hexachloro compound **4** being recovered unchanged after more than 1 week at reflux temperature.

Irradiation of **1** and 3 equiv of NCS in the absence of oxygen, however, formed a complex mixture of products (at least seven) from which small amounts of two compounds were isolated and spectrally characterized as the 1,5,6,7-tetrachloro-2-chloromethyl (**5**) and 1-succinimidyl-5,6,7-trichloro (**6**) derivatives. The NMR spectrum of **5** showed singlets at δ 8.60 (H-4) and 6.27 (CH_2Cl), and that of **6** had singlets at δ 8.66 (H-4), 4.02 (CH_3), and 3.1 (succinimidyl group) with the corresponding areas. The choice of the 1-position for the radical substitution was based on the postulate of a resonance-stabilized intermediate (**12**), which is not possible for substitution at position



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4, and the correlation of the chemical shift of the remaining ring hydrogen with those observed in the spectra of **2**.

Additional electrophilic substitutions with *N*-halosuccinimides were also effected. Chlorination of the 5,7-

(1) Abbreviated NCS throughout this paper.
(2) From the Ph.D. Thesis of T. Y. Tober, University of Washington, 1977.
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dibromo-2-methyl compound gave the 5,7-dibromo-6-chloro derivative **7**. Bromination of the 5,7-dichloro-2-phenyl compound and chlorination of the 5,7-dibromo-2-phenyl derivative formed **8** and **10**, respectively. The 5,7-dibromo derivative **11** of the parent 2-H compound was also prepared.

Experimental Section

Melting points were taken on a Kofler hot stage and are uncorrected. Spectral data were recorded on the following instruments: UV and visible, Cary Model 14 spectrophotometer; NMR, Varian Model A-60, T-60, or EM-360 with Me_4Si as internal reference; mass spectra, Associated Electrical Industries MS-9 with perfluorotributylamine as the reference standard. Analyses were performed by Mr. David Harsch, Moscow, ID. All solvents were purified and dried prior to use. TLC plates (EM Reagents) were of silica gel 60F-254, 0.25 mm for analytical or monitoring and 2.0 mm for preparative separations unless otherwise specified.

5,6,7-Trichloro-2-(chloromethyl)-2*H*-cyclopenta[*d*]pyridazine (2). To a solution of 1.112 g (4.72 mmol) of **1** in 50 mL of CCl_4 under an O_2-free N_2 atmosphere was added dropwise over 30 min a solution of 650 mg (4.86 mmol) of NCS in 15 mL of CH_2Cl_2. The mixture was heated under reflux with stirring for 24 h. TLC monitoring (4:1 *n*-hexane–ether) showed a less polar product after 2 h and a second less polar product after 24 h. The cooled mixture was poured through a 1 in. × 4 in. CC-7 silica gel column (CH_2Cl_2). Rechromatography of the material from the yellow fraction (1 in. × 18 in. CC-7 silica gel column, 9:1 *n*-hexane–ether) gave three bands: a trace of material spectrally identified as **3**, a larger fraction, and unchanged **1** (78 mg, 7%). The second band afforded 759.2 mg (64%) of **2**: mp 158 °C (softening at 154 °C); NMR ($CDCl_3$) δ 5.95 (s, 2, NCH_2Cl), 8.47 (d, 1, H-1), 8.61 (d, 1, H-4); UV max (ether) 253 nm (ϵ 23 690), 261 (25 650), 282 (18 225), 320 (3710), 416 (1550); mass spectrum, m/z 267.9128 (M^+ calcd for $C_8H_4N_2{}^{35}Cl_4$: 267.9126), with the natural abundances of ^{35}Cl and ^{37}Cl.

5,6,7-Trichloro-2-(dichloromethyl)-2*H*-cyclopenta[*d*]pyridazine (3). In the manner described for the preparation of **2**, from 600 mg (2.22 mmol) of **2** in 25 mL of CCl_4 and 300 mg (2.25 mmol) of NCS in 10 mL of CH_2Cl_2, but with 93:7 *n*-hexane–ether as the final eluant, were obtained two products, a trace of material spectrally identified as **4** and, after sublimation, 521.2 mg (77%) of **3**: mp 163–164.5 °C; NMR ($CDCl_3$) δ 7.78 (s, 1, $NCHCl_2$), 8.59 (d, 1, H-1 (4)), 8.97 (d, 1, H-4 (1)); UV max (ether) 252 nm (ϵ 25 400), 260 (25 800), 282 (21 000), 284 (21 200), 286 (21 500), 291 (22 900), 300 (5400); mass spectrum, m/z 301.8710 (M^+ calcd for $C_8H_3N_2{}^{35}Cl_5$: 301.8735), with the natural abundances of ^{35}Cl and ^{37}Cl.

5,6,7-Trichloro-2-(trichloromethyl)-2*H*-cyclopenta[*d*]pyridazine (4). In the manner described for the preparation of **2** except that the reflux time was 72 h, the eluant for TLC monitoring was 97:3 *n*-hexane–ether, and the other eluant was 98:2 *n*-hexane–ether, from 220 mg (0.725 mmol) of **3** in 40 mL of CCl_4 and 100 mg of NCS in 5 mL of CH_2Cl_2 was obtained, after sublimation, 152 mg (62%) of **4**: mp 189–191 °C (with sublimation at 155 °C); NMR ($CDCl_3$) δ 8.74 (d, 1, H-1 (4)), 9.33 (d, 1, H-4 (1)); UV max (ether) 256 nm (ϵ 22 900), 259 (24 200), 261 (25 800), 263 (25 900), 278 (21 500), 282 (21 000), 320 (5320); mass spectrum, m/z 335.8308 (M^+ calcd for $C_8H_3N_2{}^{35}Cl_6$: 335.8345), with the natural abundances of ^{35}Cl and ^{37}Cl.

1,5,6,7-Tetrachloro-2-(chloromethyl)-2*H*-cyclopenta[*d*]pyridazine (5) and 1-Succinimidyl-5,6,7-trichloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (6). To a solution of 400 mg (1.70 mmol) of **1** in 25 mL of cyanomethane was added dropwise a solution of 700 mg (5.25 mmol) of NCS in 20 mL of cyanomethane. Irradiation with a medium-pressure 450-W Hg lamp for 15 min caused the solution to become red. TLC (88:12 *n*-hexane-ether) showed seven or more compounds. After solvent removal, chromatography on a 1.75 in. × 12 in. CC-7 silica gel column (9:1 *n*-hexane–ether) gave a continuous yellow band which was separated into ten approximately equal fractions which were recombined into two fractions on the basis of TLC analyses.

The major yellow component of the first fraction was separated from three minor products by preparative TLC (9:1 *n*-hexane–ether and then ether), and 47 mg (9%) of **5**, mp 125–127 °C, was obtained: NMR ($CDCl_3$) δ 6.27 (s, 2, NCH_2Cl), 8.60 (s, 1, H-4); UV max (ether) 256 nm (ϵ 22 900), 263 (25 700), 281 (22 100), 284 (22 400), 289 (22 400), 325 (4530); mass spectrum, m/z 301.8736 (M^+ calcd for $C_8H_3N_2{}^{35}Cl_5$: 301.8735), with the natural abundances of ^{35}Cl and ^{37}Cl.

The yellow, most polar of the ca. six components of the second fraction was separated through repetitive preparative TLC (88:12 *n*-hexane–ether and then CH_2Cl_2). After solvent removal, sublimation (100 °C at 0.1 torr) gave 102 mg (18%) of **6**: mp 177 °C; NMR ($CDCl_3$) δ 3.1 (s, 4, succinimidyl hydrogens), 4.02 (s, 3, NCH_3), 8.66 (s, 1, H-4); IR (Nujol) 1704, 1735, 1790 cm^{-1}; UV max (ether) 247 nm (ϵ 24 500), 254 (27 800), 259 (25 700), 283 (sh, 18 600), 287 (19 300), 295 (19 800), 335 (14 100), 360 (sh, 13 200); mass spectrum, m/z 330.9736 (M^+ calcd for $C_{12}H_8N_3O_2{}^{35}Cl_3$: 330.9680), with the natural abundances of ^{35}Cl and ^{37}Cl.

5,7-Dibromo-6-chloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (7). To 178 mg (0.61 mmol) of 5,7-dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine[4] in 5 mL of CH_2Cl_2 was added 94 mg (0.70 mmol) of NCS under an atmosphere of Ar. After 2 days, the mixture was extracted with water, dried ($MgSO_4$), and chromatographed on a 1 in. × 10 in. CC-7 silica gel column (CH_2Cl_2). Two bands separated, of which the second was unchanged starting material. Rechromatography of the yellow crystals from the first band on a 20 cm × 10 cm preparative plate with 1:3:1 *n*-hexane–ether–CH_2Cl_2 separated a small, less polar substance. Recrystallization of the major component from 90:10 cyanomethane–water gave 121 mg (37%) of **7**: mp 118–119 °C; NMR ($CDCl_3$) 4.17 (s, 3, NCH_3), 8.33 (d, 1, H-1), 8.54 (d, 1, H-4); UV max (ether) 262 nm (ϵ 34 200), 273 (sh, 22 400), 320 (1960), 408 (1140); mass spectrum, m/z 321.8522 (M^+ calcd for $C_8H_5N_2{}^{79}Br_2{}^{35}Cl$: 321.8508), with the natural abundances of ^{79}Br, ^{81}Br, ^{35}Cl, and ^{37}Cl.

5,7-Dichloro-6-bromo-2-phenyl-2*H*-cyclopenta[*d*]pyridazine (8). To a solution of 181 mg (0.688 mmol) of 5,7-dichloro-2-phenyl-2*H*-cyclopenta[*d*]pyridazine[4] in 7 mL of CH_2Cl_2 under a N_2 atmosphere was added 123 mg (0.707 mmol) of NBS[7] and the mixture was allowed to stand overnight. The solvent was removed and TLC (1:1:3 CH_2Cl_2–ether–*n*-hexane) revealed but did not completely separate two products. Further separation was achieved by crystallization from 90:10 cyanomethane–water, and recrystallization of one component three more times gave 94.1 mg (40%) of **8**: mp 183–184 °C; NMR ($CDCl_3$) δ 7.67 (m, 5, C_6H_5), 8.87 (overlapping ds, 2, H-1 and H-4); UV max (ether) 268 nm (ϵ 32 200), 295 (36 700), 322 (7520), 424 (3100); mass spectrum, m/z 339.9170 (M^+ calcd for $C_{13}H_7N_2{}^{79}Br{}^{35}Cl_2$: 339.9170), with the natural abundances of ^{79}Br, ^{81}Br, ^{35}Cl, and ^{37}Cl. Anal. Calcd for $C_{13}H_7N_2BrCl_2$: C, 45.63; H, 2.05; N, 8.19. Found: C, 45.88; H, 2.26; N, 8.06.

The other product was not obtained in pure form. The NMR spectrum showed a peak ratio of H-1 plus H-4 to phenyl hydrogens of ca. 1:2 which indicated monobromination on the phenyl ring.

5,7-Dibromo-2-phenyl-2*H*-cyclopenta[*d*]pyridazine (9). To a stirred solution of 262 mg (1.35 mmol) of 2-phenyl-2*H*-cyclopenta[*d*]pyridazine[8] in 20 mL of cyanomethane was added a solution of 500 mg (2.84 mmol) of NBS[7] in 10 mL of cyanomethane over a period of 10 min. A TLC (95:5 *n*-hexane–EtOAc) monitor showed essential completion of the reaction in 30 min. After an additional 15 min the solvent was removed (rotary evaporator), and the residue was chromatographed on a 4.5 in. × 1.5 in. CC-7 silica gel column (CH_2Cl_2). Recrystallization of the residue from the leading orange band twice from cyanomethane–water gave 290 mg (61%) of **9** as orange needles: mp 114–115 °C; NMR ($CDCl_3$) δ 7.15 (s, 1, H-6), 7.57 (m, 5, C_6H_5), 8.60 (s, 2, H-1 and H-4); UV max (ether) 255 nm (ϵ 15 700), 260 (15 700), 291 (26 700), 330 (4080), 430 (2700); mass spectrum, m/z 349.8998 (M^+ calcd for $C_{13}H_8N_2{}^{79}Br_2$: 349.9056), with the natural abundances of ^{79}Br and ^{81}Br. Anal. Calcd for $C_{13}H_8N_2Br_2$: C, 44.34; H, 2.27; N, 7.96. Found: C, 43.81; H, 2.48; N, 7.63.

5,7-Dibromo-6-chloro-2-phenyl-2*H*-cyclopenta[*d*]pyridazine (10). To 560 mg (1.58 mmol of **9** in 15 mL of cyanomethane was added slowly a solution of 237 mg (1.78 mmol) of NCS in ca. 10 mL of cyanomethane. After 1.5 h, the yellow

(7) *N*-Bromosuccinimide.
(8) Anderson, A. G., Jr.; Forkey, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 924.

crystals which had formed were separated by filtration and washed with a little cold cyanomethane. Chromatography on a 1 in. × 18 in. CC-7 silica gel column (CH_2Cl_2) gave yellow needles from the yellow-orange band. Recrystallization from cyanomethane–water afforded 420 mg (68%) of **10**: mp 173–174 °C; NMR ($CDCl_3$) δ 7.67 (m, 5, C_6H_5), 8.72 (d, 1, H-1), 8.80 (d, 1, H-4); UV max (ether) 268 nm (ε 38 600), 295 (43 400), 322 (sh, 9650), 422 (3380); mass spectrum, *m/z* 383.8676 (M^+ calcd for $C_{13}H_7N_2{}^{79}Br_2{}^{35}Cl$: 383.8666), with the natural abundances of ^{79}Br, ^{81}Br, ^{35}Cl, and ^{37}Cl.

7-Bromo- and 5,7-Dibromo-2*H*-cyclopenta[*d*]pyridazine (11). To a stirred solution of 230 mg (1.95 mmol) of 2*H*-cyclopenta[*d*]pyridazine[8] in 60 mL of cyanomethane cooled by a dry ice bath was added a solution of 357 mg (2.01 mmol) of NBS[7] in ca. 15 mL of cyanomethane over a period of 1 h. TLC (9:1 CH_2Cl_2–ether) showed three components, one corresponding to starting material. NMR indicated a 2:5:3 ratio for starting material and the two products, respectively. Additional NBS solution was added slowly with periodic TLC monitoring until no starting material was present [ca. 200 mg (1.12 mmol) of NBS]. A mixture of the products was isolated by solvent removal (rotary evaporator) and chromatography on a 1 in. × 2 in. CC-7 silica gel column (CH_2Cl_2). The separation of the products was accomplished with difficulty on an analytical TLC plate with 90:10 CH_2Cl_2–acetone. The 7-bromo compound was removed with ether and amounted to 29.1 mg (8%) of yellow plates: mp 120 °C dec; NMR ($CDCl_3$) δ 6.96 (d, 1, J = 2 Hz, H-5), 7.43 (d, 1, J = 2 Hz, H-6), 8.66 (d, 2, J = 1 Hz, H-1 and H-4); UV max (ether) 243 nm (ε 35 600), 248 (sh, 34 000), 262 (sh, 21 000), 312 (2610), 325 (2600), 401 (887); mass spectrum, *m/z* 195.9634 (M^+ calcd for $C_7H_5N_2{}^{79}Br$: 195.9632), with the natural abundances of ^{79}Br and ^{81}Br.

The 5,7-dibromo derivative (**11**) was removed with ether and amounted to 141 mg (24%) of yellow plates: mp 125 °C dec; NMR (acetone) δ 7.26 (s, 1, H-6), 8.83 (s, 2, H-1 and H-4); UV max (ether) 248 nm (ε 22 100), 265 (19 400), 321 (1550), 330 (1530), 412 (1240); mass spectrum, *m/z* 273.8756 (M^+ calcd for $C_4H_7N_2{}^{79}Br_2$: 273.8742), with the natural abundances of ^{79}Br and ^{81}Br.

Registry No. 1, 55268-18-3; 2, 73038-13-8; 3, 73038-14-9; 4, 73038-15-0; 5, 73038-16-1; 6, 73038-17-2; 7, 73038-18-3; 8, 73038-19-4; 9, 73038-20-7; 10, 73038-21-8; 11, 73038-22-9; NCS, 128-09-6; 5,7-dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine, 55268-20-7; 5,7-dichloro-2-phenyl-2*H*-cyclopenta[*d*]pyridazine, 55268-27-4; 2-phenyl-2*H*-cyclopenta[*d*]pyridazine, 22291-84-5; 2*H*-cyclopenta[*d*]-pyridazine, 270-64-4; 7-bromo-2*H*-cyclopenta[*d*]pyridazine, 73038-23-0.

A Method for Transfer of Labeled Methyl Groups

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Since their inception a decade ago,[1,2] the use of chiral methyl groups has become an established tool of bioorganic investigation. Generation of chiral methyl groups on biotransformation of an appropriately labeled substrate to product followed by excision, typically by Kuhn–Roth oxidation, of the labeled groups as acetic acid and determination of their absolute configuration by established methodology[1,2] has allowed the stereochemical course of a variety of enzymatic reactions to be defined. Conversely, examples where a substrate has borne a chiral methyl group which, in the course of a biochemical reaction, undergoes conversion to a methylene group or transfer or migration of the methyl group have generally been limited to cases in primary metabolism wherein acetate or pyruvate has been the reactant. Instances where substrates more complex than acetic acid have been employed have been fewer in number. These investigations[3] exemplify two general approaches to the synthesis of substances having chiral methyl groups. The first involves elaboration of chiral acetic acid itself by (a) reaction of the corresponding ester,[4] (b) reduction to ethanol and reaction of the derived sulfonate ester,[9] or (c) Schmidt degradation to methylamine (retention) and transfer of the chiral methyl group by displacement of ditosylimide **2a** (R = CHDT) (inversion).[5,6] The second relies upon the fact that aldehydes of considerable structural diversity can be reduced stereospecifically with horse liver alcohol dehydrogenase.[11] In principle, the resulting primary alcohol may be converted to the tosylate and the latter displaced by labeled lithium aluminum hydride. In practice, three potential experimental difficulties must be faced with this second approach: (a) although the stereochemical course of the enzymic reduction may be presumed by analogy with known examples, in principle, it should be proved for each new case;[12] (b) the dehydrogenase is not completely indiscriminate with respect to substrate and, in general, those which are largely nonpolar fare best;[11,13] and (c) the displacement of sulfonate esters by hydride is sensitive to steric effects,[14] and, owing to isotope effects, the efficiency of tritium transfer from radiolabeled lithium aluminum hydride is low.

The introduction of chiral methyl groups, therefore, by the alcohol dehydrogenase route may be fraught with serious experimental restrictions. Similarly, the use of chiral acetate or ethyl tosylate, while suited to the particular applications noted above, is synthetically limiting. In this paper we describe a partial solution to this problem which exploits the availability of chiral acetic acid of high optical purity and high specific radioactivity[1,2,15] to develop the

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(3) These notable exceptions include the following: investigation of methyl migration in lanosterol biosynthesis[4] wherein mevalolactone having a chiral C-6 methyl was required; studies of *S*-adenosylmethionine as a biological methylating agent which necessitated the synthesis of methionine having CHDT groups of known absolute configurations;[5,6] independent investigations by two groups[7,8] of cyclopropane formation in the last step of cycloartenol biosynthesis which required the synthesis of 2,3-oxidosqualene having a chiral C-6 methyl group; and recently the stereochemical studies of ω-hydroxylation of hydrocarbons.[9,10]

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