Table III. ^{13}C NMR Data for Bebeerine *N*-Metho Salt 15 and Related Alkaloids[a]

carbons	chemical shift, ppm					
	13	14	15	16	17	18
1	68.7	68.5	65.9	66.5	61.9	69.2
3	54.5	54.7	55.0	55.3	45.0	54.3
4	23.6	23.6	23.6	24.3	21.1	23.8
4a	120.1	125.4	120.4	125.6	120.0	121.2
5	108.7	109.7	108.8	110.3	107.9	109.8
6	149.6	154.3	149.0	154.4	148.9	149.8
7	138.8	140.4	137.5	140.4	137.7	137.5
8	137.4	143.8	138.2	144.9	138.2	138.6
8a	119.8	119.9	119.9	121.2	120.0	119.2
α	38.6	39.7	36.8	37.4	40.2	37.7
9	129.0	130.8	129.1	130.2	128.0	127.4
10	124.0	123.6	123.3	124.0	120.0	129.8
11	142.4	142.5	142.0	143.0	142.1	118.2
12	148.8	149.2	147.7	149.4	147.7	154.6
13	116.7	114.5	117.1	114.1	116.5	114.9
14	127.4	127.8	123.9	124.6	126.0	129.4
1′	65.1	72.7	72.5	73.4	64.7	69.2
3′	45.9	54.2	55.0	55.5	44.4	54.3
4′	22.6	23.6	23.6	24.3	21.1	23.8
4a′	124.4	123.2	123.1	123.6	123.5	121.2
5′	112.3	112.9	113.0	113.7	112.3	109.8
6′	150.3	150.9	149.9	151.4	149.2	149.8
7′	146.4	146.0	145.2	145.4	144.2	137.5
8′	118.4	116.7	117.1	117.9	116.8	138.6
8a′	121.0	121.3	122.7	123.1	121.9	119.2
α′	40.0	37.0	38.0	38.8	39.7	37.7
9′	129.9	129.5	128.6	129.7	127.3	127.4
10′	134.0	134.1	131.6	132.3	131.9	129.8
11′	115.3	114.5	115.5	115.5	114.3	118.2
12′	156.4	156.5	155.7	156.6	155.1	154.6
13′	113.1	112.9	113.0	113.7	113.7	114.9
14′	130.8	131.2	129.9	130.9	130.1	129.4
$^{+}$NMe	40.5 (N′), 51.3 (N), 54.5 (N)	51.0, 51.2, 52.9, 54.7	51.1, 51.1, 52.4, 52.9	51.4, 51.6, 52.8, 53.5	40.4, 40.4	51.8, 51.8, 53.0, 53.0
OMe	56.4, 56.4	56.1, 56.5, 56.5, 60.7	56.4, 56.7	56.7, 56.9, 57.3, 61.4	55.9, 55.9	57.0, 57.0

[a] The spectra were obtained in (a) D_2O-MeOH for **13**, **14**, and **16**, (b) D_2O-Me_2SO for **18** and **19**, and (c) $CDCl_3$-MeOH for **15** and **17**. The chemical shifts are expressed on the Me_4Si scale according to the following equations: $\delta^{Me_4Si} = \delta^{MeOH} + 49.3$ ppm, $\delta^{Me_4Si} = \delta^{Me_2SO} + 40.4$ ppm, and $\delta^{Me_4Si} = \delta^{CDCl_3} + 76.9$ ppm for systems a-c, respectively.

O,O-dimethylbebeerine (**2**),[10] (*R,R*)-12-*O*-methylbebeerine (**4**),[10] (*R,R*)-7-*O*-acetyl-12-*O*-methylbebeerine (**6**),[10] (*R,S*)-*O,O*-dimethylchondrocurarine iodide (**14**),[11] (*R,R*)-*N,N*′-dimethylbebeerine iodide (**15**),[12] (*R,R*)-*N,N*′,*O,O*-tetramethylbebeerine iodide (**16**),[12] bebeerine hydrochloride (**17**),[12] *N,N*′-dimethylisochondrodendrine iodide (**18**).[12]

For better solution all iodide ions were exchanged by chloride by using freshly prepared silver chloride.[11]

(*R,R*)-7-*O*-Methylbebeerine (**3**) was obtained as follows. Monomethylation of **1** was carried out with CH_2N_2 by using a standard procedure,[13] yielding **3**: mp 119.2-124.0 °C; $[\alpha]^{25}_D$ -249 (*c* 0.10, $CHCl_3$); mass spectrum, *m/e* (relative intensity) 608 (M^+, 10), 204 (14), 192 (86), 190 (46), 158 (100); H^1 NMR ($CDCl_3$), see Table II; ^{13}C NMR, see Table I; $C_{37}H_{40}O_6N_2$ requires *m/e* 608.2886, found *m/e* 608.2897 (M^+).

Acetates **5** and **7** were prepared by standard methods. For (*R,R*)-12-*O*-acetyl-7-*O*-methylbebeerine (**5**): mp 95.7-99.0 °C; $[\alpha]^{25}_D$ -318 (*c* 0.12, $CHCl_3$); mass spectrum, *m/e* (relative intensity) 650 (M^+, 73), 340 (100), 312 (90); H^1 NMR ($CDCl_3$), see Table II; ^{13}C NMR, see Table I; $C_{39}H_{42}O_7N_2$ requires *m/e* 650.2992, found *m/e* 650.3020 (M^+). For (*R,R*)-*O,O*-diacetylbebeerine (**7**); mp 135.1-136.4 °C; $[\alpha]^{25}_D$ -242 (*c* 0.12, $CHCl_3$); mass spectrum, *m/e* (relative intensity) 678 (M^+, 22), 340 (100); H^1 NMR ($CDCl_3$), see Table II; ^{13}C NMR, see Table I; $C_{40}H_{42}O_8N_2$ requires *m/e* 678.2941, found *m/e* 678.2932 (M^+).

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Registry No. **1**, 436-05-5; **2**, 1812-55-1; **3**, 31944-97-5; **4**, 59685-16-4; **5**, 76947-03-0; **6**, 59685-17-5; **7**, 76947-04-1; **8**, 477-58-7; **13**, 57-94-3; **14**, 7601-55-0; **15**, 16202-76-9; **16**, 16240-52-1; **17**, 6059-41-2; **18**, 32434-25-6.

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3-Methyl-1*H*-indenones: A One-Step Conversion from 2,3-Dihydro-1*H*-indenones with *N*-Bromosuccinimide

Frank D. Mills

Northern Regional Research Center, Agricultural Research, Science and Education Administration, U.S. Department of Agriculture, Peoria, Illinois 61604

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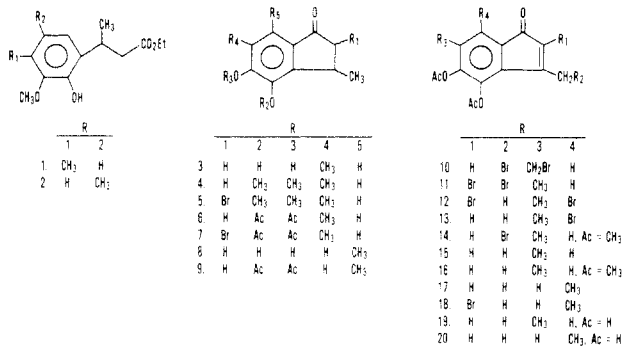
Preparation of strategically substituted 3-alkyl-1*H*-indenones and the precursor 2,3-dihydro-1*H*-indenones, which serve as intermediates to complex cyclic compounds of biological importance,[1-6] is usually not straightforward.

Chart I

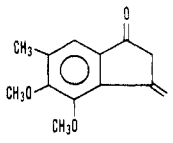


Approaches to the syntheses of 2,3-dihydro-3-methyl-1*H*-inden-1-ones that are less desirable include cyanoethylation of phenolic ethers, followed by hydrolysis and subsequent condensation with Lewis acid catalysts, or condensation of the derivatized phenol with the appropriate α,β-unsaturated acid. These reactions use tedious and multistep procedures and, in the former approach, the precursor nitrile may not be readily available.[7,8]

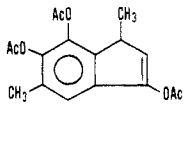
Easily obtained ethyl 3-arylbutanoates **1** and **2**[1] (Chart I) are used to prepare the hydroxylated 2,3-dihydro-1*H*-inden-1-ones **3** and **8** in 83% and 47% yields, respectively. Because of inertness to further reactions, the di-*O*-methyl ether **4** was used initially to ensure the definition of the reaction conditions and the products in the indenone synthesis. As predicted, lowered yields resulted when vigorous reaction conditions were used to convert the ether **16** to the free phenol. In subsequent reactions, the use of this group was abandoned in favor of the acetylated compounds **6** and **9**.

An approach using *N*-bromosuccinimide (NBS) and white-light catalysis produces the 3-methyl-1*H*-indenones directly. Indenone **4** did not yield the desired 3-bromo-2,3-dihydro-1*H*-indenone. Instead, **14** and **16** formed. When the reaction time is increased and **6** employed as the substrate, **10–12** and **15** are produced. Although more side-reaction products result, the yield of **15** increases from 30 to 51%. Similarly, dihydroindenone **9** forms **17** (in good yield) and **18**. The various products indicate that halogenation takes place initially and primarily at the 3 position. Because of high reactivity of the bromo derivative, concomitant dehydrohalogenation arising from succinimide catalysts produces the desired indenones (**15**, **16**, or **17**). Two successive competing reactions are present; some 2-halogenation of the 3 isomer occurs and the reaction is quickly followed by a dehyrohalogenation step; allylic substitution also occurs at one or more of the methyl positions. The extent of the side reactions is minor, except when the reaction time is extended or the NBS concentration is increased, then the multiple halogenation products predominate. Both methyl positions (**10** and **11**) are equally sensitive to the reagent, and some aromatic ring halogenation occurs (**12**) at longer reaction times. The derivatized indenones **15** and **17** are converted to the phenols, and the virtue of the acetate protecting group is demonstrated when methoxide-catalyzed hydrolysis of those compounds produces **19** and **20**, respectively, nearly quantitatively.

No apparent alternative to **19** and **20** exists. Direct bromination efforts showed that the light-catalyzed NBS treatment of the acetate-protected 2,3-dihydro-3-methyl-1*H*-indenones was the best method for a synthesis of the related 1*H*-indenones in good yield, and the successful NBS route also presented an "oxidation" reaction that is in contrast to earlier work on the synthesis of 2-, 3-, and 2,3-bromo substitution compounds from 2-alkyl-2,3-dihydro-1*H*-inden-1ones.[9] When a typical bromination–dehydrobromination sequence of reactions is used, the yield of 3-methyl-1*H*-indenone is usually poor and additional compounds arise from the high reactivity of indenone toward further electrophilic and nucleophilic attack by the solvent or dehydrohalogenation reagent.[10,11] Preparation of hydroxylated 3-methyl-1*H*-indenones from *O*-methyl derivatives presents other difficulties, because commonly used conditions of demethylation can lead to a reduced yield of hydroxylated indenone. Attempts to convert **4**, **6**, or **9** to the analogous indenone with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) produced only minor amounts of product (verified by GC–MS analyses). Direct bromination of ketone **4** or **6** produces the monobromo product **5** or **7** in good yield; the results are similar to those obtained with non- and 2-alkyl-substituted 2,3-dihydro-1*H*-inden-1-ones.[7,9] Several bases [pyridine, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), lithium carbonate] dehydrobrominate halide **5** poorly to the predicted indenone; dilute hydroxide produces only a moderate yield of indenone. The cis relationship of the 2-bromo and 3-hydrogen atoms (shown by ^{1}H NMR) limited inversion of the C2 chiral center, and the high reactivity of the formed 1*H*-indenone directed ketone **5** to yield **16** (3–14%) and **21** (8–30%). An alternate attempt to encourage bromination of the 3 position in the dihydroindenones was made by changing its allylic character. Bromination of **22** produced only **7**, and halogenation of **22** with NBS yielded **13** as the only indenone; apparently, both brominations followed the route common to aliphatic enol ethers;[12,13] after halogen addition to the enol, hydrolysis removed the 1-bromo group.



21.



22.

Experimental Section

General Procedures. Melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 612 spectrophotometer from solutions in chloroform. The mass spectra were determined with a Nuclide 12-90-DF double-focusing spectrometer at 70 eV, and a direct or heated inlet (150–200 °C) was used. The ^{1}H NMR spectra were recorded from chloroform-*d*, Me_2SO-d_6,

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or methanol-d_4 solutions (the latter two are noted) with tetramethyl silane as an internal standard on a Varian HA-100 instrument, and various sweep widths were employed in coupling-constant evaluations. The UV spectra were measured on a Beckman Model DB recording photometer from either absolute or 95% ethanolic solutions. Gas–liquid chromatograms were obtained from a Hewlett-Packard Model 5750 chromatograph using a 4 ft × 0.125 in. glass column packed with 3% SE-30 on 80–100 Gaschrom Q and an isothermal program at 185 °C.

(±)-2,3-Dihydro-4,5-dihydroxy-3,6-dimethyl-1*H*-inden-1-one (3). (±)-Ethyl 3-(2-hydroxy-3-methoxy-4-methylphenyl)-butanoate (1), 5 g, was dissolved in 50 mL of tetrachloroethane and four 2.5-g additions, each 15 min apart, of anhydrous aluminum chloride were made. After 30 min, the reaction was refluxed for 1.5 h. When the mixture cooled, ice was added and the mixture was vigorously stirred while 40 mL of 3 M hydrochloric acid was added. The solid 3 was isolated by filtration: 3.2 g; mp 170 °C after two recrystallizations from aqueous methanol, treating the solution with Norit each time; yield 87%; exact mass calcd 192.0786, found 192.0791; mass spectrum, *m/e* (relative %) 192 (74), 178 (11), 177 (100), 149 (11), 131 (7), 119 (3), 103 (3), 91 (7), 77 (5); ^{1}H NMR δ 7.02 (1 H, aromatic), 3.48 (1 H, center of two different methines, sextuplet CD_3OD), 2.51 (2 H, center of two different methylenes, octet), 2.21 (3 H, aromatic methyl), 1.34 (3 H, alkyl methyl, J = 7 Hz).

(±)-2,3-Dihydro-4,5-dimethoxy-3,6-dimethyl-1*H*-inden-1-one (4). Anhydrous acetone, 400 mL, that contained 10 mL of methyl iodide, indenone 3, 2.54 g, and 8 g of anhydrous potassium carbonate was refluxed for 8 h. After cooling and filtration, the mixture was poured into water and the product was isolated by filtration. Indenone 4 was then distilled [175–180 °C (2 mmHg)], and the distillate crystallized on standing: 2.49 g; mp 55–58 °C; exact mass calcd 220.1099, found 220.1094; mass spectrum, *m/e* (relative %) 220 (100), 206 (17), 205 (85), 190 (8), 189 (9), 177 (13), 162 (6), 154 (11), 91 (9), 77 (5); ^{1}H NMR δ 7.29 (1 H, aromatic), 3.88 and 3.84 (6 H, methoxyl), 3.51 (1 H, center methine, two four-line patterns), 2.52 (2 H, center of methylene, an eight-line pattern), 2.26 (3 H, aromatic methyl), 1.39 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz).

2-Bromo-2,3-dihydro-4,5-dimethoxy-3,6-dimethyl-1*H*-inden-1-one (5). Ether 4, 1.0 g, was dissolved in 30 mL of chloroform at 4 °C, and an equimolar amount of bromine in 20 mL of solvent was added dropwise to the stirred solution over 30 min. The reaction was then stirred for 3.75 h. The organic phase was washed with 5% sodium bicarbonate and twice with water and then dried (sodium sulfate). After solvent removal, the sample was chromatographed on an 80-g silica gel (Woelm TSC, ICN Biochemical, Inc., 2.0 cm diameter)[14] column that was eluted with benzene: 0.5 g; mp 46–49 °C from benzene; exact mass calcd 300.0150, found 300.0191; mass spectrum, *m/e* (relative %) 300 (35), 299 (7), 298 (36), 285 (4), 283 (4), 220 (22), 219 (100), 218 (8), 205 (10), 204 (22), 191 (13), 189 (13), 176 (12), 161 (10), 115 (8); ^{1}H NMR, δ 7.38 (1 H, aromatic), 4.84 (0.3 H, methine α to carbonyl, J_{cis} = 7 Hz) and 3.12 (0.7 H, methine α to carbonyl, J_{trans} = 2 Hz), 3.88 and 3.91 (6 H, methoxyl), 3.62 (1 H, methine β to carbonyl and is the center of a set of 2 m), 2.25 (3 H, aromatic methyl), 1.51 (3 H, alkyl methyl, doublet, $J_{CH_3,H}$ = 7 Hz). Irradiation at δ 3.62 collapsed the methine multiplet and the alkyl methyl doublet to singlet resonances. Also, the area ratio of the two different methine protons showed the product to be a 30:70 cis/trans mixture.

(±)-4,5-Diacetoxy-2,3-dihydro-3,6-dimethyl-1*H*-inden-1-one (6). A mixture of 3, 10 g, 0.5 g of freshly fused sodium acetate, and 10 mL of acetic anhydride in 30 mL of chloroform was refluxed for 2.5 h; 13.4 g; mp 188–190 °C from aqueous ethanol; exact mass calcd 276.0997, found 276.0998; mass spectrum, *m/e* (relative %) 276 (10), 266 (3), 238 (6), 234 (11), 220 (12), 193 (14), 192 (100), 178 (5), 177 (16), 150 (9), 91 (4); ^{1}H NMR δ 7.49 (1 H, aromatic), 3.38 (1 H, methine, d of q), 2.84 and 2.76, also 2.30 and 2.21 (2 H, H_A and $H_{A'}$ methylene and H_B and $H_{B'}$ methylene, each with J_{gem} = 18 Hz), 2.30 (6 H, acetoxymethyl), 2.22 (3 H, aromatic methyl), 1.31 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz); UV λ_{max} (95% EtOH) 248 nm (ε 13 390); IR 1768, 1705, 1590 cm^{-1}.

(±)-2-Bromo-4,5-diacetoxy-2,3-dihydro-3,6-dimethyl-1*H*-inden-1-one (7). The diacetoxyindanone 6, 1.0 g, was halogenated by using the reaction conditions that produced 5: 1.06 g of 7; mp 134–135 °C from ether; exact mass calcd 354.0103, found 354.0107; mass spectrum, *m/e* (relative %) 356 (6), 354 (6), 314 (21), 312 (21), 272 (53), 270 (54), 191 (100), 91 (6), 77 (5), 43 (97); ^{1}H NMR δ 7.27 (1 H, aromatic), 4.12 (1 H, C(2) methine, m), 3.62 (1 H, C(3) methine, d of q), 2.34 (6 H, acetoxy methyl), 2.27 (3 H, aromatic methyl), 1.52 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz).

(±)-2,3-Dihydro-4,5-dihydroxy-3,7-dimethyl-1*H*-inden-1-one (8). (±)-Ethyl 3-(2-hydroxy-3-methoxy-5-methylphenyl)-butanoate, 2, 7.3 g, was intimately mixed with 14.6 g of anhydrous aluminum chloride and 70 mL of tetrachloroethane. After the exothermic reaction subsided, the crushed mixture was heated for 2 h at 140 °C. After the mixture cooled, 100 mL of 3 M hydrochloric acid and 200 mL of ice–water were added with vigorous stirring. The solid was then isolated by filtration and purified by two crystallizations: 2.6 g of 8; mp 188–189 °C from aqueous methanol; exact mass calcd 192.0786, found 192.0792; mass spectrum, *m/e* (relative %) 192 (11), 178 (12), 177 (100), 175 (4), 164 (8), 149 (9), 131 (4), 103 (6), 91 (7), 79 (2); ^{1}H NMR δ (CD_3OD) 6.60 (1 H, aromatic), 3.36 (1 H, methine, 2 finely split qs), 2.42 (3 H, aromatic methyl), 2.31 (2 H, center of 2 different methylene octets), 1.35 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz) [irradiation at δ 1.35 simplifies the methine pattern, and irradiation at δ 3.36 collapses the octet centered at δ 2.31 to a methylene quartet (J_{AB} = 19 Hz, H_A = 2.56 and H_B = 2.36)]; UV λ_{max} (95% EtOH) 253 nm (ε 10 680).

(±)-4,5-Diacetoxy-2,3-dihydro-3,7-dimethyl-1*H*-inden-1-one (9). 2,3-Dihydroindenone 8, 2 g, was acetylated by using the procedure for the preparation 6: mp 136–137.5 °C from aqueous ethanol; exact mass calcd 276.0997, found 276.0994; mass spectrum, *m/e* (relative %) 276 (7), 234 (11), 193 (12), 192 (100), 178 (2), 177 (19), 164 (2), 91 (6), 43 (55); ^{1}H NMR δ 6.98 (1 H, aromatic), 3.36 (1 H, center of methine d of q), 2.57 (2 H, center of methylene octet, no individual assignments were made), 2.58 (3 H, aromatic methyl), 2.32 (3 H, acetoxy methyl), 2.27 (3 H, acetyl methyl), 1.30 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz); IR 1772, 1708, 1615 cm^{-1}.

4,5-Diacetoxy-3,6-bis(bromomethyl)-1*H*-indenone, 10. Compound 6, 2.86 g, was dissolved in 500 mL of carbon tetrachloride and NBS, 2.89 g, was added in three portions at 20-min intervals. During this time, the reaction was irradiated with a 200-W white-light bulb. The reaction was refluxed for 3 h. After cooling and filtration, the solvent was removed and the residue was chromatographed, using benzene, on a 400-g, dry-packed, silica gel column. Four products (10–12 and 15) were isolated and crystallized from aqueous ethanol. Compound 10: 8%; mp 188–190 °C; mass spectrum, *m/e* (relative %) no parent ion, 391 (15), 389 (30), 387 (16), 349 (49), 348 (28), 347 (100), 346 (37), 345 (55), 344 (15), 286 (29), 267 (22), 266 (30), 265 (18), 239 (8), 237 (9), 186 (21), 102 (17), 101 (19), 82 (74), 81 (28), 80 (75), 79 (29); ^{1}H NMR δ 7.58 (1 H, aromatic), 6.48 (2 H, vinyl bromomethyl), 6.38 (2 H, aromatic bromomethyl), 4.68 (1 H, vinyl, finely split d), 2.42 (6 H acetoxy methyl).

2-Bromo-4,5-diacetoxy-3-(bromomethyl)-6-methyl-1*H*-indenone, 11. Compound 11 was formed as a coproduct when 10 was treated with NBS: 7%; mp 203–205 °C; exact mass calcd 431.8974, found 431.9013; mass spectrum, *m/e* (relative %) 434 (7), 432 (14), 430 (8), 392 (16), 390 (32), 388 (16), 350 (20), 348 (41), 346 (21), 311 (18), 309 (18), 270 (16), 269 (97), 268 (43), 267 (100), 266 (28), 149 (5), 131 (8), 103 (12), 102 (14), 82 (27), 80 (27); ^{1}H NMR δ 7.49 (1 H, aromatic), 6.48 (2 H, bromomethylene), 2.41 and 2.38 (6 H, acetoxy methyl), 2.28 (3 H, arylmethyl).

4,5-Diacetoxy-2,7-dibromo-3,6-dimethyl-1*H*-indenone, 12. Compound 12 was isolated as a coproduct when 10 was treated with NBS: 3%; mp 135–140 °C; exact mass calcd 431.8974, found 431.9015; mass spectrum, *m/e* (relative %) 432 (2), 354 (10), 352 (11), 348 (6), 312 (21), 310 (21), 271 (10), 270 (81), 269 (20), 268 (85), 267 (10), 189 (15), 161 (3), 160 (4), 131 (3), 104 (2), 103 (5), 102 (3), 77 (8), 43 (100); ^{1}H NMR δ 2.48 (6 H, acetoxy methyl), 2.26 (3 H vinyl methyl), 2.18 (3 H, arylmethyl).

7-Bromo-4,5-diacetoxy-3,6-dimethyl-1*H*-indenone, 13. Compound 22, 100 mg, was dissolved in 15 mL of carbon tetrachloride and two 28-mg additions of NBS were made. The re-

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action mixture was refluxed for 12 h, and, after cooling and filtration, the solvent was evaporated. The residue was chromatographed on a 2-mm thick, silica gel prep plate (Brinkmann), using methylene chloride as the developing solvent. The yellow band was removed from the plate and extracted with methylene chloride: 65 mg of **13**; mp 151–154 °C; yellow crystals from chloroform–hexane; exact mass calcd 351.9942, found 351.9946, mass spectrum, *m/e* (relative %) 354 (6), 352 (5), 312 (16), 310 (16), 270 (68), 269 (12), 268 (69), 223 (10), 191 (8), 190 (42), 189 (23), 161 (7), 43 (100); ^{1}H NMR δ 5.27 (1 H, vinyl), 2.29 and 2.28 (6 H, acetoxy methyl), 2.18 (3 H, aromatic methyl), 2.12 (3 H, vinyl methyl).

3-(Bromomethyl)-4,5-dimethoxy-6-methyl-1*H*-indenone, 14. Compound **14** was isolated from the reaction mixture of **4** with NBS. Column chromatography (see **16**) allowed isolation of **14** as the slower of the two eluting components; this compound did not crystallize; exact mass calcd 296.9954, found 296.9939; mass spectrum, *m/e* (relative %) 298 (62), 296 (66), 218 (16), 217 (100), 203 (24), 202 (75), 189 (18), 187 (17), 175 (24), 174 (27), 173 (13), 146 (15), 145 (17), 144 (12), 131 (23), 129 (31), 128 (32), 115 (54), 103 (36), 91 (15), 89 (10), 77 (45); ^{1}H NMR δ 7.04 (1 H, aromatic), 5.62 (1 H, vinyl), 4.48 (2 H, bromomethylene), 3.92 and 3.90 (6 H, methoxyl), 2.30 (3 H, aromatic methyl).

4,5-Diacetoxy-3,6-dimethyl-1*H*-indenone, 15. Indenone **15** was a coproduct with **10** when **6** was treated with NBS: 51%, mp 127–130 °C; exact mass calcd 274.0842, found 274.0849; mass spectrum, *m/e* (relative %) 274 (7), 232 (21), 191 (13), 190 (100), 189 (4), 162 (3), 161 (5), 115 (2), 77 (3), 43 (34); ^{1}H NMR δ 7.17 (1 H, aromatic, s, finely split), 5.63 (1 H, vinyl, finely split d, $J_{CH_3,H}$ = 2 Hz), 2.28 (6 H, acetoxy methyl), 2.22 (3 H, methyl, d) 2.14 (3 H, aromatic methyl); UV λ_{max} (95% EtOH) 242 nm (ε 34 760); IR 1765, 1702, 1610 cm^{-1}.

Reaction of 6 with DDQ. Compound **6**, 0.1 g, and 25 mg of DDQ were added to 10 mL of anhydrous dioxane. The solution was refluxed for 22 h. Following filtration and solvent evaporation, examination of the resulting oil by GLC showed a 4% yield of compound **15**.

4,5-Dimethoxy-3,6-dimethyl-1*H*-indenone, 16. Compound **5**, 3.4 g, and lithium carbonate, 1.65 g, were added to 100 mL of DMF. After the mixture was placed under nitrogen, the solution was refluxed for 2.75 h. The cooled solution was poured into 200 mL of ice–water and 200 mL of chloroform. The organic phase was separated after shaking and the organic phase was dried (sodium sulfate), filtered, and concentrated to a syrup. The remaining DMF was then removed at 50 °C (0.2 mmHg). The residue was chromatographed on 300 g of dry-packed silica gel, employing toluene as the eluting solvent. Various fractions were combined to yield a faster moving component, **16** (14%): mp 153–156 °C; exact mass calcd 218.0943, found 218.0950; mass spectrum, *m/e* (relative %) 218 (100), 203 (35), 189 (4), 188 (9), 175 (10), 167 (1), 147 (11), 115 (6), 104 (5), 103 (5), 77 (6); ^{1}H NMR δ 6.97 (1 H, aromatic), 5.59 (1 H, vinyl, q), 3.85 (6 H, methoxy methyl), 2.34 (3 H, vinyl methyl, d, $J_{CH_3,H}$ = 2 Hz), 2.20 (3 H, aromatic methyl). Compound **21** (8%, oil) was isolated as a slower eluting component.

Preparation of 16 and 21 from 5. Ether **5**, 0.5 g, was dissolved in 20 mL of anhydrous benzene, and 2 equiv of DBU in 25 mL of benzene was added over 25 min to the stirred solution; the mixture was then refluxed for 2.5 h. The cooled solution was washed with 3 M hydrochloric acid (25 mL), 5% sodium bicarbonate (25 mL) and 25 mL of water. After the solution was dried (magnesium sulfate), the solvent was removed and the sample was chromatographed on a 15 × 3 cm, dry-packed, silica gel column, which was developed with benzene; **16** was isolated in 7.7% yield and **21** in 22% yield.

In a second experiment, 0.1 g of **5** was added to 35 mL of water containing 6 mL of 1 M sodium hydroxide. After 1.5 h under reflux and subsequent cooling, the solution was acidified and then extracted with 30 mL of chloroform. The organic phase was dried (sodium sulfate). Following filtration and solvent evaporation, the resulting oil was chromatographed on a 2-mm thick silica gel TLC plate, and 15% ethyl acetate in benzene was used as the developing solvent. The yield of **16** was 17% and of **21** 25%.

When a solution of 0.1 g of **5** in 10 mL of pyridine was refluxed for 4 h, only 3% **17** formed (shown by gas chromatographic analysis).

Reaction of 4 with NBS. Dihydroindenone **4**, 0.2 g, and 0.16 g of NBS were added to 35 mL of CCl_4. The solution was refluxed for 1.75 h under white-light irradiation (200-W light). After the mixture was cooled and filtered, the solvent was removed and the residue was applied to a 90-g silica gel column. Elution with 10% ethyl acetate in benzene yielded the faster moving of two yellow components. Solvent removal provided **16**, 30% yield.

Demethylation of 16. Several methods were used to remove the methyl protecting group from **16**.[15–18] In each reaction, only minor amounts of **19** could be found, as observed by gas–liquid chromatography, in the reaction media. In all reactions, the mixture was highly colored, a good indication of phenolic decomposition.

4,5-Diacetoxy-3,7-dimethyl-1*H*-indenone, 17. Dihydroindenone **9**, 5.0 g, was dissolved in 0.5 L of carbon tetrachloride and an equivalent amount of NBS was added to the reaction in two portions at a 30-min interval. The reaction was treated as described in the preparation of **15**. Two separate yellow fractions were obtained. The latter fraction contained **17** (60%): mp 149–52 °C from aqueous ethanol; exact mass calcd 274.0842, found 274.0849, mass spectrum, *m/e* (relative %) 274 (7), 232 (20), 191 (13), 190 (100), 162 (3), 161 (6), 77 (3), 43 (34); ^{1}H NMR δ 6.80 (1 H, aromatic), 5.64 (1 H, vinyl, q, $J_{CH_3,H}$ = 2 Hz), 2.30 and 2.34 (6 H, acetoxy methyl), 2.23 (3 H, aromatic methyl), 2.18 (3 H, vinyl methyl); UV λ_{max} (EtOH) 247 nm (ε 21 380); IR 1770, 1710, 1590 cm^{-1}.

2-Bromo-4,5-diacetoxy-3,7-dimethyl-1*H*-indenone, 18. The dibromoindenone was formed as a coproduct in the NBS treatment of **9** and was isolated as the faster moving component in the subsequent chromatography: 60%, mp 149–52 °C (from aqueous ethanol); mass spectrum, *m/e* (relative %) 354 (7), 352 (7), 312 (16), 310 (19), 270 (66), 269 (11), 268 (71), 190 (9), 189 (22), 103 (6) 77 (5), 43 (100); ^{1}H NMR δ 6.82 (1 H, aromatic), 2.30 (6 H, acetoxy methyl), 2.26 (3 H, vinyl methyl), 2.18 (3 H, aromatic methyl).

4,5-Dihydroxy-3,6-dimethyl-1*H*-indenone, 19. Indenone **15**, 0.5 g, was dissolved in 100 mL of anhydrous methanol and the reaction was placed under nitrogen. A 10% molar excess of sodium methoxide in methanol was added and the solution was stirred for 1 min. After neutralization with 0.1 M HCl, the solvent was removed and the residue was reprecipitated from aqueous ethanol: 94% yield of **19**; sinters at 220 °C; exact mass calcd 190.0631, found 190.0625; ^{1}H NMR δ (CD_3OD) 6.52 (1 H, aromatic), 2.25 (3 H, aromatic), 2.22 (3 H, vinyl methyl) (the vinyl proton was hidden under solvent resonance); UV λ_{max} (EtOH) 250 nm (ε 3300).

4,5-Dihydroxy-3,7-dimethyl-1*H*-indenone, 20. Indenone **17**, 0.5 g, was treated as described for the preparation of indenone **19**: 96% yield; mp 250 °C; exact mass calcd 190.0631, found 190.0636; ^{1}H NMR δ (CD_3OD) 6.27 (1 H, aromatic), 2.34 (3 H, aryl methyl), 2.28 (3 H, vinyl methyl) (the vinyl proton resonance was hidden under the water peak at δ 4.82); UV δ_{max} (EtOH) 248 (ε 3100).

2,3-Dihydro-4,5-dimethoxy-6-methyl-3-methyleneinden-1-one, 21. Compound **5**, 0.5 g, was used to prepare **21** in 30% yield when it was treated with a molar excess of DBU in refluxing benzene, using the workup procedure that produced **17** and **23** above; **17** was isolated in 6% yield. Compound **21**: oil; mass spectrum, *m/e* (relative %) 218 (100), 203 (41), 190 (10), 189 (14), 175 (38), 160 (7), 159 (7), 158 (8), 147 (10), 132 (10), 115 (12), 103 (9), 77 (11); ^{1}H NMR δ 7.36 (1 H, aromatic), 6.24 (1 H, exomethylene, t), 5.34 (1 H, exomethylene, t), 3.93 and 3.88 (6 H, methoxyl), 3.24 (2 H, alkyl methylene, finely split t), 2.29 (3 H, aromatic methyl).

(±)-3,6,7-Triacetoxy-1,5-dimethyl-1*H*-indene, 22. Dihydroindenone **3**, 1.0 g, *p*-toluenesulfonic acid, 40 mg, and isopropenyl acetate, 25 mL, were mixed and the resulting solution was refluxed for 2 h. After cooling, the reaction mixture was extracted with 30 mL of 5% sodium carbonate and 30 mL of water.

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The organic phase was then dried (sodium sulfate), filtered, and concentrated to a small volume. Column chromatography, as described in the isolation of **7**, using methylene chloride as an eluent, yielded **22** in 77% yield: mp 101–104 °C from ethyl acetate–hexane; mass spectrum, *m/e* (relative %) 318 (9), 276 (21), 235 (7), 234 (51), 193 (13), 192 (100), 191 (22), 177 (12), 174 (12), 91 (3), 43 (27); ^{1}H NMR δ 7.00 (1 H, aromatic), 6.22 (1 H, vinyl, d), 3.56 (1 H, methine, d of q), 2.26 (3 H, vinyl acyl methyl), 2.24 (6 H, acetoxy methyl), 2.18 (3 H, aromatic methyl), 1.24 (3 H, alkyl methyl, $J_{CH_3,H}$ = 7 Hz).

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Registry No. (±)-1, 77028-39-8; (±)-2, 77028-40-1; (±)-3, 77028-41-2; (±)-4, 77028-42-3; *cis*-(±)-5, 77028-43-4; *trans*-(±)-5, 77028-44-5; (±)-6, 77028-45-6; (±)-7, 77028-46-7; (±)-8, 77028-47-8; (±)-9, 77028-48-9; **10**, 77028-49-0; **11**, 77028-50-3; **12**, 77028-51-4; **13**, 77028-52-5; **14**, 77028-53-6; **15**, 77028-54-7; **16**, 77028-55-8; **17**, 77028-56-9; **18**, 77028-57-0; **19**, 77028-58-1; **20**, 77028-59-2; **21**, 77028-60-5; (±)-**22**, 77028-61-6.

Pseudodipeptides: A Novel Route to Serine-Containing Diastereomeric Analogues

Arno F. Spatola* and Anthony L. Bettag

Department of Chemistry, University of Louisville, Louisville, Kentucky 40292

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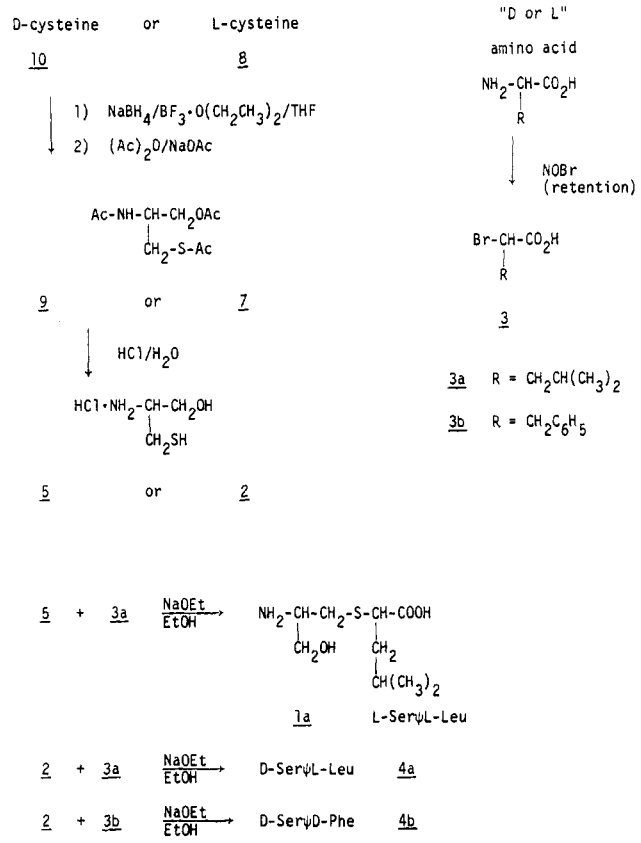
Continued interest in peptide analogues which contain methylenethio groups substituted for the peptide bond atoms has led us to explore synthetic routes to dipeptide analogues of the type SerψX (1) where ψ = CH_2S substituted for CONH and X may be one of a variety of amino acids. We have recently reported synthetic routes leading to XψGly pseudodipeptides[1] but this report represents the first example of a dipeptide analogue in which neither portion is formally derived from glycine. The presence of a serine side chain is of considerable interest in view of the many peptides and proteins in which serine residues perform important and apparently essential roles. Previous studies on a GlyψLeu analogue, first prepared by Yankeelov et al.,[2] have demonstrated that this analogue binds several times more tightly to aminopeptidase M than the natural substrate. Model building as well as enzymatic studies indicate that such analogues may satisfy binding requirements while being resistant to enzymatic hydrolysis.[2]

The serine-containing analogues can be easily prepared by utilizing the sulfur of cysteinol (**2**) as the nucleophile to displace the bromide of α-bromo acids (**3**). The cysteine side chain thus effectively undergoes a role reversal with the carboxyl-derived hydroxymethyl group and becomes part of the modified dipeptide linkage. Thus the resulting inversion of the chiral center forms the D-serine analogue (**4**) from L-cysteinol (**2**). It is of interest that a similar but inverse role reversal was utilized by Patchornik and coworkers in the synthesis of cysteine derivatives from serine analogues.[3]

Scheme I



The diastereomeric analogues L-SerψL-Leu (**1a**) and D-SerψL-Leu (**4a**) were prepared by the treatment of (*R*)-2-bromo-4-methylpentanoic acid (**3a**) with D-cysteinol (**5**) and L-cysteinol (**2**), respectively. The two diastereomers (**1a** and **4a**) could be completely resolved by reversed-phase high-performance liquid chromatography (HPLC) with retention times of 10.95 and 9.38 min, respectively. The HPLC chromatograms showed that neither analogue was contaminated by its diastereomer. To ensure that one diastereomer was not selectively crystallized from the other, chromatograms were obtained with the crude fraction prior to crystallization. The syntheses therefore proceed without racemization in either the formation of the bromo acid or the displacement of the bromide by the sulfur nucleophile, since racemization at *either* step would result in the formation of diastereomeric compounds.

The (*tert*-butyloxy)carbonyl (Boc)-derivatized dipeptide analogues can be prepared by standard procedures using di-*tert*-butyl dicarbonate,[4] and the analogues can be quantified by normal amino acid analysis. The preparation of peptides containing these pseudodipeptide units blocked as their *N*-α-*t*-Boc derivatives can proceed according to established methods of solution- and solid-phase peptide synthesis. By use of the latter method, analogues of LH–RH containing the dipeptide surrogates GlyψLeu and D-SerψLeu were recently prepared.[5] Thus, the availability of synthetic routes leading to XψY pseudodipeptides (Scheme I) should permit their facile incorporation into a wide variety of peptides of biological interest.

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