or not the ring structure is invariant to substituents, we carried out empirical force field calculations. For all practical purposes, the ring structures of all bicyclic ketals studied in this paper were the same.

In contrast, axial substituents on the flexible portion of the pyran ring tend to distort the system toward a flattened chair structure. By not taking this into account, Gore et al. may have biased their results. It may be that real or force field optimized geometries will not allow PDIGM to differentiate between the four multistriatin isomers in a statistically meaningful way. We suggest that without a priori knowledge of detailed structural information, LSR studies may give misleading results and should be used with caution in the structural analyses of dioxabicyclic ketals.

Experimental Section

A preliminary report of the preparation of the bicyclic ketals has appeared,[7] and a typical preparation will be reported here. Satisfactory combustion analysis for new compounds in this study include the following. Calcd for **8a**: C, 69.2; H, 10.2. Found: C, 69.0; H, 9.9. Calcd for **8c**: C, 70.6; H, 10.6. Found: C, 70.6; H, 10.4. Calcd for **8d**: C, 77.0; H, 8.3. Found: C, 76.9; H, 8.4. The chemistry of **8e** has been well-documented.[14] The NMR spectrum for each compound is in accord with the assigned structure.

The procedure for **8c** was as follows. Methyl vinyl ketone dimer (0.007 mol) was slowly added to 1 equiv of ethyl Grignard in ether. After the addition was complete, the reaction mixture was stirred for an additional hour. Wet ether was added to the reaction mixture to hydrolyze the magnesium complex. The reaction mixture was extracted with dichloromethane. The extracts were dried and reduced in volume to 0.98 g of yellow liquid, composed of product and starting methyl vinyl ketone dimer in the ratio of 1:6.6. This constitutes a 72% yield of **8c**.

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Registry No. **1**, 28401-39-0; **α-2**, 59014-03-8; **β-2**, 59014-05-0; **γ-2**, 54832-21-2; **δ-2**, 54832-22-3; ***endo*-3**, 22625-19-0; ***exo*-3**, 20290-99-7; **8a**, 16566-96-4; ***exo*-8b**, 68378-84-7; ***endo*-8b**, 68378-85-8; ***exo*-8c**, 68378-86-9; ***endo*-8c**, 68378-87-0; ***exo*-8d**, 65899-46-9; ***endo*-8d**, 65899-47-0; ***exo*-8e**, 56057-15-9; ***endo*-8e**, 56057-16-0.

Preparation of 8-Alkyl-14-hydroxydihydrocodeinones[1]

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Reaction of 14-[(trimethylsilyl)oxy]codeinone (**1b**) with lithium dimethylcuprate gave a 2:1 isomeric mixture of the corresponding 8α-methyl (**2**) and 8β-methyl (**3**) 14-(trimethylsilyl)oxydihydro derivatives. Selective removal of the silyl group from α isomer **2** to give **4**, by use of silica gel, allowed resolution of the mixture. 8β-Methyl-14-hydroxydihydrocodeinone (**5**) was prepared from **3** by cleavage of the silyl ether with *n*-Bu_4NF. Treatment of 14-hydroxycodeinone with Me_2CuLi gave a 4:1 mixture of alkylated products **4** and **5**. The (*tert*-butyldimethylsilyl)oxy ether **1c** under similar conditions gave exclusively the stable 8α isomer **6**. Reaction of trimethylsilyl compound **1b** with Et_2CuLi or *n*-Bu_2CuLi gave approximately equal amounts of the corresponding 8-alkyl 14-O-silylated isomers. These results are in contrast to previous work with codeinone which demonstrated that lithium organocopper reagents add almost exclusively to the β face of "T-shaped" morphinone derivatives.

We have previously reported reaction of codeinone with lithium dialkylcuprates yields mainly 8β-alkylated dihydrocodeinones.[2] A minor product of some of these reactions was the corresponding 8α-alkyl isomer. As part of a program aimed at preparing morphine compounds modified in the C ring, a similar reaction of 14-hydroxycodeinone and some 14-*O*-silyl derivatives was investigated. We now report that such reactions yield a substantially higher proportion of the 8α-alkylated product.

Difficulty was experienced in the conversion of thebaine to 14-hydroxycodeinone (**1a**) with use of *m*-chloroperbenzoic acid as reported.[3] Iijima and co-workers[4] have found that this reaction is sensitive to changes in reaction conditions. In our hands, this reaction at first gave mixtures containing polar products. We found that **1a** could smoothly be obtained from thebaine, in the reported yield, by the inclusion of 10% water during this reaction.[5]

To increase the solubility of **1a** in ethereal solvents, the 14-*O*-trimethylsilyl ether **1b** was prepared by refluxing **1a** in hexamethyldisilizane. Efforts to purify **1b** by chromatography resulted only in recovery of starting material **1a**. Addition of an ethereal solution of crude **1b** to 1.25 equiv of Me_2CuLi in Et_2O gave an approximately 2:1 mixture of alkylated products **2** and **3** as indicated by NMR. Attempted concurrent removal of the silyl group and resolution of this mixture by chromatography unexpectedly yielded the silylated 8β-methyl product **3** and the deprotected 14-hydroxy-8α-methyl compound **4**. Improved resolution of these products was obtained by stirring the crude alkylation products with silica gel in $CHCl_3$ prior to chromatography. The silyl group in 8β-methyl compound **3** could then be easily removed, to give **5**, by treatment with *n*-Bu_4NF in THF (Scheme I).

The NMR spectrum of the crude reaction mixture obtained above indicated that the α isomer was the major product in contrast to previous results in the codeinone series. The structure of the C-8 methylated products are easily assigned based on the observation that the NMR signal for the 8-methyl group in the α isomer is observed

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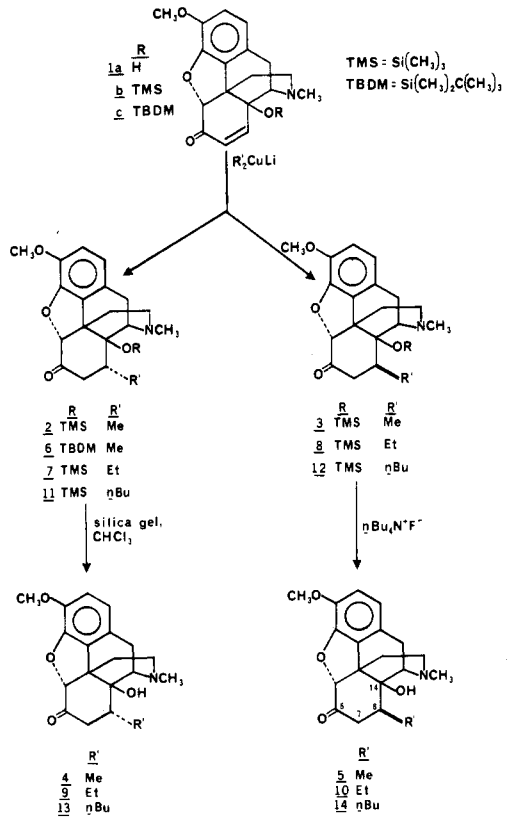
0022-3263/81/1946-4012$01.25/0

Scheme I



at a position upfield from that of the corresponding β isomer.[2] This upfield shift is due to the anisotropic effect the aromatic A ring has on the methyl group in the axial (α) orientation. These NMR spectra further show the aromatic region in 8α-alkyl derivatives as an unsymmetrical narrow doublet, while this region is observed as a sharp singlet for the 8β-alkyl compounds. Both of these observations were applicable in the current work.

Given the observed reversal in the preferred mode of attack of Me_2CuLi on this enone system, we investigated several other variations. Reaction of a methylene chloride solution of **1a** with Me_2CuLi gave mixtures containing **4** and **5** which could not be resolved by chromatography. NMR spectroscopy indicated that the crude mixture contained a greater proportion of the 8α-methyl isomer **4**. The *tert*-butyldimethylsilyl derivative **1c** yielded **6** as the sole product which was stable to chromatography. Treatment of trimethylsilyl derivative **1b** with Et_2CuLi or n-Bu_2CuLi gave mixtures containing approximately equal amounts of α and β isomers. The 8-ethyl compounds **9** and **10** were partially resolved after removal of the silyl group from the mixed isomers. Selective hydrolysis of **11**, to give **13**, was followed by chromatography. The purified silyl derivative **12** thus obtained was converted to **14** with use of n-Bu_4NF.

Lithium organocuprates usually react with cyclic enones to form addition products in which the newly introduced group is axial.[6] In contrast, the addition of these reagents to the morphinane skeleton results in the introduction of the alkyl group into the equatorial position.[2,7,8] The steric bulk of the A and B rings, forming the stem of the "T-shaped" molecule,[9] forces reagents to approach from the more accessible β face. As expected, the presence of additional steric bulk on the top of the juncture of the "T-arms" causes alkylation to occur to a greater extent from the α face. An examination of a structural model of the silyl derivative **1b** indicates that approach to the β face is so hindered, it is indeed remarkable that any reaction occurs from this side of the molecule.

Table I. Approximate Product Distribution and Ratio of Alkylated Products

compd	R	organocuprate	products	8α/8β
1a	H	Me_2CuLi	4, 5	4:1
1b	TMS[a]	Me_2CuLi	2, 3	2:1
1c	TBDM[b]	Me_2CuLi	6	1:0
1b	TMS	Et_2CuLi	7, 8	1:1
1b	TMS	n-Bu_2CuLi	11, 12	1:1

[a] TMS = trimethylsilyl. [b] TBDM = *tert*-butyldimethylsilyl.

The difference in the ratio of products obtained with **1b** (summarized in Table I) may further be influenced by the alkylating reagent. We have noted in similar reactions with codeinone[2] that as the size of the alkyl group in the organocopper reagent increases, there is little or no formation of the α product.

The stereospecific preparation of these novel ring C 8α- or 8β-alkylated 14-hydroxydihydrocodeinones has now allowed us to extend our pharmacological studies. The preparation of the corresponding *N*-cycloalkylmethyl-14-hydroxy compounds with either 8α- or 8β-alkyl groups, and their pharmacological evaluation, will be published by others.[10]

Experimental Section

Methods have previously been described.[2] All reactions involving organometallic reagents were performed under an atmosphere of argon. Processing in the usual fashion implies that the organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), and evaporated at 40 °C bath temperature. The residue was further dried at 50–60 °C bath temperature under high vacuum. Column chromatography was carried out over silica gel 60 G (E. Merck) with $CHCl_3$–MeOH mixtures (10:1–30:1) containing 1–0.2% (v/v) concentrated NH_4OH as eluant. NMR spectra were recorded in $CDCl_3$. Mass spectra were determined by using a Hewlett-Packard 5985A GC/MS system.

14-Hydroxycodeinone (1a). To a stirred solution of thebaine (30.1 g, 0.1 mol) in glacial HOAc (120 mL) were added H_2O (12 mL) and CF_3COOH (10.1 mL). *m*-Chloroperbenzoic acid (12.5 g, 85% technical grade) was then added portionwise over 15 min, and the remainder of the reaction was conducted exactly as described.[3] Workup gave 24.8 g (79%) of crude **1a** as a light tan solid, mp 262–264 °C (lit.[3] mp 262–264 °C).

14-[(Trimethylsilyl)oxy]codeinone (1b). A suspension of **1a** (20.0 g, 64 mmol) in hexamethyldisilizane (75 mL) containing $(NH_4)_2SO_4$ (50 mg) was refluxed for 3 h and then cooled. The cream-colored crystals were collected by filtration to give 23.1 g (94%) of **1b**: mp 110–113 °C; NMR δ 6.18 (m, 3 H, H-1,2,7), 5.98 (d, 1 H, H-8, J = 10 Hz), 4.60 (s, 1 H, H-5), 3.80 (OCH_3), 2.37 (NCH_3), 0.17 (silyl CH_3); mass spectrum, m/e 385 (M^+, 23), 313 (9), 230 (17), 229 (100).

14-[(*tert*-Butyldimethylsilyl)oxy]codeinone (1c). A mixture of **1a** (3.13 g, 10 mmol), *tert*-butyldimethylsilyl chloride (1.66 g, 11 mmol), and imidazole (1.70 g, 25 mmol) in DMF (15 mL) was heated at 100 °C for 4 h. The cooled mixture was partitioned between dilute NH_4OH and toluene. Processing of the organic phase gave a residue which was chromatographed to give 1.57 g

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(37%) of crystalline **1c**: NMR δ 6.70 (d, 1 H, H-7), 6.63 (s, 2 H, H-1,2), 6.05 (d, 1 H, H-8, J = 10 Hz), 4.62 (s, H-5), 3.85 (OCH_3), 2.40 (NCH_3), 0.87 (s, $SiC(CH_3)_3$), 0.20 ($SiCH_3$), 0.07 ($SiCH_3$); mass spectrum, m/e 427 (M^+, 24), 370 (76), 229 (100). Recrystallization from hexane gave **1c**, mp 170.5–171.5 °C.

Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.27. Found: C, 67.35; H, 7.59; N, 3.11.

Reaction of 1a with Me_2CuLi. A solution of **1a** (5.26 g, 16.8 mmol) in CH_2Cl_2 (125 mL) was added rapidly dropwise to a solution of Me_2CuLi (prepared from 75.6 mmol of ethereal MeLi and 37.8 mmol of CuI) in Et_2O (125 mL) at 0 °C. After stirring in the cold for 1 h, the mixture was poured into saturated NH_4Cl solution and stirred for 15 min. The mixture was made basic with NH_4OH and extracted with CH_2Cl_2. Processing in the usual manner gave 5.94 g of a crystalline reside. The NMR spectra of this material indicated an approximately 4:1 mixture of **4** and **5** together with about 1 part of a 4,5-epoxy bond cleaved product. Crystallization of this mixture from EtOH gave 3.44 g (62%) of white crystals, mp 166–173 °C, which, by integration of the NMR signals for the methyl group doublets, indicated a 4:1 mixture of **4** and **5**.

Reaction of 1b with Me_2CuLi. Preparation of 4. A solution of **1b** (5.50 g, 14.3 mmol) in Et_2O (125 mL) was added rapidly dropwise to a solution of Me_2CuLi (17.8 mmol) in Et_2O (60 mL) at 0 °C. After stirring for 1 h, the mixture was processed as above and extracted with 5 portions of Et_2O. Evaporation of the Et_2O gave 5.70 g (99%) of a yellow solid which was shown to be an approximately 2:1 mixture of **2** and **3** by integration of the NMR signals for H-5, δ 4.67 and 4.58, respectively.

The solid was stirred with silica gel 60 G (125 g) in $CHCl_3$ (500 mL) for 18 h. After removal of the gel by filtration, the filtrate was evaporated and the residue chromatographed. First eluted was 1.78 g (31%) of **3**, obtained as a syrup. Continued elution gave 1.86 g (40%) of crystalline **4**, which was recrystallized from EtOH to give pure **4**: mp 177–179 °C; NMR δ 6.70 (m, 2 H, H-1,2), 5.70 (14-OH), 4.70 (s, 1 H, H-5), 3.95 (OCH_3), 2.43 (NCH_3), 0.47 (d, 3 H, 8α-CH_3, J = 8 Hz); mass spectrum, m/e 329 (M^+, 100).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; h, 6.98; N, 4.24.

14-Hydroxy-8β-methyldihydrocodeinone (5). To a solution of **3** (1.23 g, 3.0 mmol) in THF (30 mL) was added n-Bu_4NF (10 mL of a 0.5 M THF solution). The mixture was stirred for 15 min and then evaporated. The residue was partitioned between $CHCl_3$ and H_2O. Processing of the organic extracts gave a residue which was chromatographed to give 709 mg (70%) of crystalline **5**. Recrystallization from EtOH gave pure material: mp 174.5–175.5 °C; NMR δ 6.70 (s, 2 H, H-1,2), 4.68 (14-OH), 4.65 (s, H-5), 1.00 (d, 3 H, 8β-CH_3, J = 6 Hz); mass spectrum, m/e 329 (M^+, 100).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.46; H, 7.07; N, 4.23.

14-[(*tert*-Butyldimethylsilyl)oxy]-8α-methyldihydrocodeinone (6). To a solution of Me_2CuLi (4.6 mmol) in Et_2O (25 mL) at 0 °C was added a solution of **1c** (1.57 g, 3.7 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred in the cold for 1 h and processed in the usual fashion. Chromatography of the residue gave 1.19 g (72%) of crystalline **6**. Recrystallization from EtOH gave pure **6**: mp 145–146 °C; NMR δ 6.63 (m, H-1,2), 4.60 (H-5), 3.93, 2.27, 0.93 (s, 9 H, $SiC(CH_3)_3$), 0.57 (d, 8α-CH_3, J = 8Hz), 0.23 and 0.13 (singlets, $SiCH_3$); mass spectrum, m/e 443 (M^+, 13), 386 (100).

Anal. Calcd for $C_{25}H_{37}NO_4Si$: C, 67.99; H, 8.41; N, 3.16. Found: C, 67.66; H, 8.39; N, 2.94.

Reaction of 1b with Et_2CuLi. Preparation of 9 and 10. Et_2CuLi (16.3 mmol) was prepared in Et_2O (200 mL) at −60 °C as described.[2] After warming to −40 °C, a solution of **1b** (5.00 g, 13 mmol) in Et_2O (125 mL) was added rapidly dropwise, and the mixture was stirred at −40 °C for 10 min. After warming to room temperature, the mixture was poured into saturated NH_4Cl solution and further processed with $CHCl_3$ in the usual manner to give 5.2 g of a syrup. The NMR spectra of this material indicated an approximately 1:1 mixture of **7** and **8**.

The syrup was dissolved in THF (150 mL) and n-Bu_4NF (50 mL of a 0.5 M THF solution) added. After stirring for 30 m, the mixture was evaporated to a small volume and the residue partitioned between $CHCl_3$ and H_2O. Evaporation of the $CHCl_3$ extracts gave a syrup from which the individual isomers were isolated by a combination of repetitive chromatography and fractional crystallization. Compound **9** was obtained as crystals, mp 203–205 °C, from EtOH: NMR δ 6.71 (m, H-1,2), 4.67 (H-5), 0.67 (t, 3 H, CH_2CH_3, J = 6 Hz). The corresponding HCl salt, **9**·HCl, mp > 265 °C, crystallized from EtOH: mass spectrum, m/e 343 (M^+, 100).

Anal. Calcd for $C_{20}H_{25}NO_4$·HCl: C, 63.24; H, 6.90; N, 3.69. Found: C, 63.48; H, 7.04; N, 3.56.

Compound **10** [NMR δ 6.72 (s, H-1,2), 4.67 (H-5), 0.80 (unsymmetrical t)] was not obtained as crystals but was converted to the HCl salt, mp > 265 °C, which was crystallized from EtOAc and recrystallized from MeOH–EtOAc: mass spectrum, m/e 343 (M^+, 96).

Anal. Found: C, 63.43; H, 6.91; N, 3.66.

Reaction of 1b with n-Bu_2CuLi. Preparation of 13 and 14. A solution of n-Bu_2CuLi was prepared at −10 °C from CuI (3.09 g, 16.3 mmol) and n-BuLi (20 mL of a 1.6 M solution in hexane) in Et_2O (100 mL). To this was added a solution of **1b** (5.00 g, 13 mmol) in Et_2O (125 mL), and the mixture was stirred in the cold for 1 h. Processing as above gave a syrup, which was stirred with silica gel 60 G (50 g) and $CHCl_3$ (200 mL) overnight. The residue obtained after removal of the gel was chromatographed to give 1.30 g (23%) of **12** as a crystalline residue. Continued elution gave 1.94 g (40%) of **13** as a yellow syrup: NMR δ 6.65 (m), 4.67 (H-5). The HCl salt of **13**, mp 270–275 °C dec, was obtained as crystals from EtOH–EtOAc: mass spectrum, m/e 371 (M^+, 96).

Anal. Calcd for $C_{22}H_{29}NO_4$·HCl: C, 64.78; H, 7.41; N, 3.43. Found: C, 64.69; H, 7.22; N, 3.43.

Treatment of **12** (815 mg) with n-Bu_4NF in THF as above, followed by chromatography, gave 656 mg (96%) of crystalline **14**: NMR δ 6.70 (s), 4.67 (H-5). The salt, **14**·HCl, was obtained in pure form by crystallization from EtOH–EtOAc: mass spectrum, m/e 371 (M^+, 85).

Anal. Found: C, 64.84; H, 7.47; N, 3.40.

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Registry No. **1a**, 508-54-3; **1b**, 78514-16-6; **1c**, 78529-64-3; **2**, 78514-17-7; **3**, 78514-18-8; **4**, 78514-19-9; **5**, 78514-20-2; **6**, 78514-21-3; **7**, 78514-22-4; **8**, 78514-23-5; **9**, 78514-24-6; **9**·HCl, 78529-65-4; **10**·HCl, 78514-25-7; **11**, 78514-26-8; **12**, 78514-27-9; **13**, 78514-28-0; **13**·HCl, 78514-29-1; **14**, 78514-30-4; **14**·HCl, 78514-31-5; thebaine, 115-37-7.