Table I. Preparation of Dehydro Amino Acids

compd	CuCl, mol %	carbodiimide[a]	(mol %)	solvent	temp, °C	time, h	product	(% yield)[b]
5a	30	DiPCD	(110)	CH_3CN	40	6	7a	(82)
5b	4	DiPCD	(130)	CH_3CN	20	23	7b	(72)
5b	30	WSC	(110)	CH_2Cl_2	20	12	7b	(96.5)
5c	30	DiPCD	(110)	CH_3CN	40	24	7c (E + Z)	(65)[c]
8	30	DCCD	(110)	THF	50	3	10	(68)
8	90	WSC	(110)	CH_2Cl_2	20	12	10 + 11	(76-88) (12-20)
8	0	DiPCD	(110)	CH_3CN	20	5	11	(79)

[a] DiPCD = diisopropylcarbodiimide, WCS = the water-soluble carbodiimide 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate, DCCD = dicyclohexylcarbodiimide. [b] Isolated purified yields. [c] NMR spectrum of crude 7c showed a 1:1 mixture of E + Z; chromatographic separation gave the E and Z isomers in a 3:2 ratio. The geometry of these isomers was assigned by comparison of NMR and melting point data with that in the literature.[5,9]

presence of ether containing trace amounts of peroxide. The threonine derivative gave a 3:2 mixture of the E and Z isomers which could be chromatographically separated and characterized by comparison with literature data.[5,9] No reaction of the β-hydroxy amino acids **5a–c** occurred in the absence of CuCl. However, without added CuCl the cysteine derivative 8 gave the symmetrical thioether **11** in 79% yield as a mixture of two diastereomers. Since the starting material was an L-cysteine derivative, the formation of the diastereomers presumably occurred by an elimination–addition mechanism (Scheme II). In the presence of CuCl the dehydroalanine derivative **10** was preferentially formed from 8.

Some restrictions of this method of dehydro amino acid synthesis are apparent. The need to avoid peroxide-containing solvents has already been mentioned. Aqueous, alcoholic, and carboxylic acid solvents and similarly reactive substituents must be avoided since they would competitively consume the carbodiimide. A distinct advantage of this one-pot process, however, is the ability to use water-soluble reagents to facilitate the reaction workup.

Experimental Section

Melting points were taken on a Thomas-Hoover melting-point apparatus and are uncorrected. NMR spectra were determined in chloroform-*d* with tetramethylsilane as a reference, using a Varian A-60A spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord. Mass spectra were recorded on a Dupont DP102 spectrometer. THF was distilled from $LiAlH_4$ directly before use. High-pressure liquid chromatography was performed with a Beckman/Altex Model 332 system. Elemental analyses were performed by Midwest Microlabs.

***N*-Protected amino acid esters 5a–c and 8** were prepared by reaction of the appropriate amino acid derivative **4a–c** and *N*-acetylcysteine, respectively, with the appropriate isourea **3**, according to the reported procedures.[7] These esterifications proceeded in high yield as described. However, the reaction of *N*-acetylcysteine with *O*-benzyl-*N*,*N*′-diisopropylisourea gave a mixture of products. Chromatographic separation (silica gel, ethyl acetate–hexane, 3:7) gave the desired *N*-acetyl-L-cysteine benzyl ester 8 in 44% yield: mp 78.5–79.5 °C (after recrystallization from ethyl acetate–hexanes); NMR δ 1.25 (t, SH), 2.05 (s, 3 H), 2.98 (dd, 2 H), 4.9 (m, 1 H), 5.23 (s, 2 H), 6.5 (br, NH), 7.4 (s, 5 H); mass spectrum (CI with CH_4), m/e 254 (M + 1). A prior chromatographic fraction also contained *S*-benzyl-*N*-acetylcysteine benzyl ester in 6% yield: mp 64–66.5 °C dec; NMR δ 1.96 (s, 3 H), 2.85 (d, 2 H), 3.66 (s, 2 H), 4.85 (m, 1 H), 5.17 (s, 2 H), 6.6 (br d, NH), 7.27 (s, 5 H), 7.34 (s, 5 H); mass spectrum (CI with CH_4), m/e 344 (M + 1). Competitive carboxyl and sulfhydryl alkylation by *O*-alkylisoureas has been previously observed.[1]

General Method of Preparation of Dehydro Amino Acids. The reaction conditions for the β-elimination processes are given in Table I. All solvents were dried before use and the reactions were carried out under a drying tube or a nitrogen atmosphere. When the water-insoluble carbodiimides were used the following workup was employed. One volume of ethyl acetate or methylene chloride was added and the precipitated urea was removed by filtration. The organic solution was then extracted with two separate volumes of water, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel. When the water-soluble carbodiimide was used the chromotographic purification could be avoided, and the product was purified by recrystallization or vacuum distillation. The products were characterized by comparison of their physical and spectral properties with those reported.[1,5,9] The assignment of the E and Z isomers **7c** obtained from **5c** was made by comparison of the reported melting point and NMR data.[9]

Diasteromeric Thioether 11. *N*-Acetylcysteine benzyl ester 8 (253 mg, 1 mmol) was dissolved in 5 mL of CH_3CN and stirred under nitrogen at room temperature while 126 mg of freshly distilled diisopropylcarbodiimide (DiPCD) was added. The solvent was then evaporated, and the residue was chromatographed on silica gel with ethyl acetate–hexanes (1:1) and then pure ethyl acetate. The symmetrical thioether 11 was thereby obtained in 79% yield as a mixture of diastereomers: mp 128–138 °C (after recrystallization from ethyl acetate–hexanes); NMR δ 2.0 and 2.04 (2 s, 3 H total), 2.95 (d, 2 H), 4.8 (m, 1 H), 6.7 (br d, NH), 7.4 (s, 5 H). The two singlets at δ 2.0 and 2.04 correspond to the acetyl methyl groups of the two diastereomers. High-performance LC (RP-18 column; 70% CH_3OH, 30% H_2O at 1 mL/min) gave retention times of 5.4 and 5.6 min. With 65% CH_3OH the retention times increased to 15.5 and 16.6 min.

Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93; S, 6.79. Found: C, 60.63; H, 5.92; N, 5.92; S, 6.85.

Acknowledgment. Financial support from the National Institutes of Health is gratefully acknowledged as is the assistance of Mr. Donald Schifferl with the mass spectral determinations.

Registry No. L-**5a**, 1676-81-9; L-**5b**, 21209-51-8; L-**5c**, 57224-63-2; **7a**, 21149-17-7; **7b**, 59524-07-1; (*E*)-**7c**, 60027-55-6; (*Z*)-**7c**, 60027-61-4; L-**8**, 73908-42-6; **10**, 73908-43-7; D,L-**11**, 73908-44-8; L,L-**11**, 73908-45-9; *S*-benzyl-*N*-acetyl-L-cystein benzyl ester, 73908-46-0.

(9) Srinivasan, A.; Richards, K. D.; Olsen, R. K. *Tetrahedron Lett.* 1976, 891–894.

Constituents of *Trichilia hispida* (Meliaceae). 2. A New Triterpenoid, Hispidone, and Bourjotinolone A

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In an earlier paper we reported the isolation and characterization of two major constituents, sapelins A (1) and

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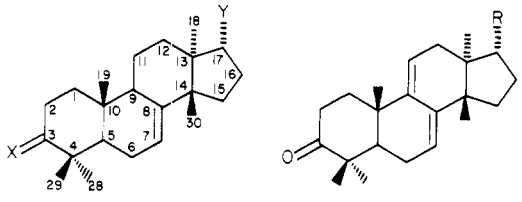
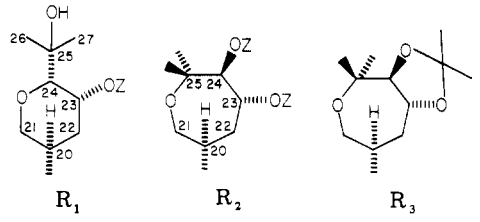
B (4), from the ethanol extract of leaves of *Trichilia hispida* Penning. (ined.) (Meliaceae).[1,2] Further fractionation of this extract has now afforded two isomeric triterpenoids and three tetranortriterpenoids (limonoids). We have identified one of the triterpenoids as bourjotinolone A (2), a constituent of the leaves of the Australian *Flindersia* species, *F. bourjotiana* F. Muell.,[3] and fully characterized the other one, which we name hispidone (5). The characterization of the three limonoids, which we term hispidins A, B, and C, will be discussed in the next paper of this series.



	X	Y	Z		R	Z
1	H, α-OH	R_1	H	9	R_2	H
2	O	R_1	H	10	R_1	H
3	O	R_1	Ac			
4	H, α-OH	R_2	H			
5	O	R_2	H			
6	O	R_2	Ac			
7	H, α-OH	R_3				
8	O	R_3				



Hispidone (5) failed to crystallize but was homogeneous as judged by TLC and ^{13}C NMR. Elemental analysis and a molecular ion peak at m/e 472 in the mass spectrum indicated the molecular formula $C_{30}H_{48}O_4$. Except for the band at 1700 cm^{-1} due to a carbonyl, the spectrum was very similar to that of sapelin B (4), which contains two more hydrogens. Similarly, hispidone (5) provided a mass spectrum very close to that of sapelin B (4) but with appropriate shifts to mass numbers lower by two for almost all the major fragment ions in the upper mass region (m/e 250–472). The ^1H NMR spectrum of hispidone (5) indicated seven tertiary methyl groups, an olefinic proton (δ 5.3), and a primary–tertiary ether linkage (broadened AB pattern at δ 3.4 and 3.6, J = 10 Hz).

The formation of a crystalline diacetate [6, M^+ 556], with accompanying disappearance of the OH band in the IR spectrum and the appearance of signals for two acetate groups (δ 2.00 and 2.05) in the ^1H NMR spectrum, clearly suggested that both hydroxyl groups were secondary. Hispidone (5), when subjected to oxidation with mercuric acetate in acetic acid, yielded diene **9** which exhibited UV absorption bands (λ_{max} 231, 237, and 246 nm) characteristic of a 7,9(11)-heteroannular diene in a euphane-type skeleton.[4]

The above structural features suggested that hispidone (5) might be the 3-oxo compound corresponding to sapelin B (4). ^{13}C NMR spectral comparison of **5** and **4** (Table I) supported this view with almost perfect identity of the shifts except in the vicinity of ring A. This close correspondence in shifts suggests that the stereochemistry at all centers is the same in the two compounds. Since the stereochemistry of sapelin B (4) has been established,[6,7] hispidone must be **5**.

Table I. ^{13}C NMR Chemical Shifts of Hispidone (5) and Bourjotinoline A (2) Compared with Chemical Shifts of Sapelins A (1) and B (4)[5]

atom	1	2	4	5
C-1	31.3	38.5	31.3	38.6
C-2	25.4	34.9	25.4	34.9
C-3	76.3	217.1	76.3	217.1
C-4	37.6	47.9	37.4	47 9
C-5	44.6	52.4	44.6	52.4
C-6	23.9	24.3	23.9	24.4
C-7	118.2	118.1	118.1	118.1
C-8	145.9	145.7	146.0	145.8
C-9	48.6	48.4	48.6	48.4
C-10	34.8	34.9	34.8	34.9
C-11	17.9	18.2	17.9	18.1
C-12	33.1	32.9	32.8	32.6
C-13	43.3	43.2	43.4	43.4
C-14	51.4	51.2	51.4	51.3
C-15	33.9	33.9	33.9	33.9
C-16	27.3	27.4	28.2	28.2
C-17	44.8	44.7	47.7	47.5
C-18	13.0	12.8	13.0	12.8
C-19	21.9	21.6	21.9	21.6
C-20	37.6	37.5	38.6	38.6
C-21	70.2	70.1	64.6	64.4
C-22	36.5	36.4	37.4	37.5
C-23	64.7	64.6	68.7	68.7
C-24	86.5	86.4	80.8	80.8
C-25	74.2	74.1	76.3	76.2
C-26	23.9	23.9	22.2	22.4
C-27	28.5	28.4	26.5	26.3
C-28	27.4	27.4	27.3	27.4
C-29	27.8	24.5	27.8	24.6
C-30	22.2	22.3	22.2	22.4

Direct proof for the suggested structure of hispidone (5) was accomplished by converting sapelin B (4) to the corresponding acetonide (7) which when oxidized with Jones reagent yielded 8, identical in all respects [TLC, melting point, mixture melting point (no depression), and IR] with a sample prepared by treatment of hispidone (5) with acetone and catalytic amount of concentrated H_2SO_4 at room temperature. It may be pointed out that the easy formation of hispidone acetonide (8) under mild conditions precluded the possibility of a cis (erythro) configuration for the 1,2-diol.[3]

The other triterpenoid, isomeric with hispidone (5), was identified as bourjotinolone A (2) as follows. Elemental analysis and a molecular ion peak at m/e 472 in the mass spectrum indicated the molecular formula $C_{30}H_{48}O_4$. The melting point (167–168 °C) and specific rotation (−30.3°) were fairly close to those reported (176 °C, −34°) for bourjotinolone A.[3] Except for the carbonyl peak, the IR spectrum of this triterpenoid was very similar to that of sapelin A (1) and the mass spectrum exhibited a fragmentation pattern nearly identical with that of 1 but with appropriate shifts to mass numbers lower by two. The $\Delta^{7,9(11)}$-diene (10) from mercuric acetate oxidation of 2 had

(1) Formerly *Bursera klugii* (Burseraceae).
(2) Jolad, S. D.; Wiedhopf, R. M.; Cole, J. R. *J. Pharm. Sci.* **1977**, *66*, 889.
(3) Breen, G. J. W.; Ritchie, E.; Sidwell, W. T. L.; Taylor, W. C. *Aust. J. Chem.* **1966**, *19*, 455.
(4) Halsall, T. G.; Meakins, G. D.; Swayne, R. E. M. *J. Chem. Soc.* **1953**, 4139.
(5) ^{13}C NMR shift assignments were made as follows. (a) Off-resonance spectra were used to distinguish methyl, methylene, methinyl, and quaternary carbons. (b) Within each of these groups, assignments were made to give the best correspondence with calculated values (Lindeman, L. P.; Adams, J. Q. *Anal. Chem.* **1971**, *43*, 1245) that would lead to a self-consistent set of shifts for the four compounds in the table.
(6) Chan, W. R.; Taylor, D. R.; Yee, T. H. *J. Chem. Soc. C* **1970**, 311.
(7) Lyons, C. W.; Taylor, D. R. *J. Chem. Soc., Chem. Commun.* **1976**, 647.

virtually the same UV spectrum as the diene from hispidone (9), indicating a Δ^7-tirucallane nucleus as in 5. The ^{1}H NMR spectrum of this triterpenoid and its monoacetate (3) (IR, 3500 cm^{-1}; M$^+$ 514) closely matched the values resported for bourjotinolone A and its monoacetate. 3 had mp 145–146 °C and $[\alpha]_D$ −50° (reported[3] for bourjotinolone A monoacetate, 148 °C and −107°). The ^{13}C NMR shifts given in Table I coupled with the data presented above show clearly that our triterpenoid has structure 2; the shifts which should be similar in the four compounds in Table I are all within 0.2 ppm of one another and in the vast majority of cases are within 0.1 ppm. 2 is the structure proposed for bourjotinolone A,[3] which unfortunately was not available for direct comparison. While we do not understand the descrepancy of 57° in the specific rotation of our monoacetate (3) and that reported[3] for bourjotinolone A monoacetate, the weight of evidence strongly indicates that our triterpenoid and bourjotinolone A are indeed both 2.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Carbon and hydrogen analyses were carried out by University Analytical Center, Tucson, AZ. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Ultraviolet (UV) and infrared (IR) spectra were run on Cary-15 and Beckman IR-33 spectrometers, respectively. ^{1}H NMR spectra were run at 60 MHz on a Varian EM360L spectrometer and ^{13}C NMR spectra were run at 22.63 MHz with a Bruker WH-90 spectrometer; in both cases shifts are given as parts per million downfield from Me_4Si (δ). Mass spectra were recorded on Hewlett-Packard 5930A and Varian MAT 311A spectrometers.

Isolation of Hispidone (5) and Bourjotinolone A (2). The dried leaves of *Trichilia hispida*, collected in Peru in July 1977, were milled in a Wiley mill and stored at −10 °C prior to extraction. The ground material was extracted exhaustively in a Lloyd-type extractor with 95% ethanol. A portion of the air-dried ethanol extract (500 g) was stirred with ethyl acetate (3 L) for 4 h, left in the refigerator overnight, and filtered. The air-dried ethyl acetate-soluble residue (269 g) was stirred with ether (3 L) for 4 h, left in the refrigerator overnight, and filtered. The solvent from the filtrate was evaporated in vacuo, and the resulting residue (128 g) was subjected to partitioning between cyclohexane (2.1 L), methanol (1.5 L), and water (300 mL). All the lower phases were combined, air dried, and finally dried in vacuo to yield 80 g. This material (172 g) was then subjected to EM silica gel 60 (2 kg) column chromatography. The column was eluted with dichloromethane followed by dichloromethane/ethyl acetate (99:1), with gradually increasing concentration of the latter. Several 20-mL fractions were collected.

Fractions 4–290 were combined and the solvent was evaporated in vacuo. The residue was stirred with isopropyl ether, cooled, and filtered. TLC of the isopropyl ether-insoluble residue displayed three major spots corresponding to three limonoids, hispidins A, B, and C, the separation of which was effected by preparative TLC [dichloromethane/ethyl acetate (70:30)]. The structure elucidation of these limonoids will be discussed in the next paper of this series.

Fractions 291–350 were combined and the solvent was distilled off in vacuo. TLC examination of the resulting residue showed four major spots corresponding (in order of elution) to bourjotinolone A (2), hispidone (5), sapelin A (1), and sapelin B (4). Separation of this mixture by repeated preparative TLC provided pure hispidone (5) and bourjotinolone A (2).

Hispidone (5). This substance remained amorphous but was homogeneous on TLC, $[\alpha]^{25}_D$ −35° (*c* 1.355, $CHCl_3$). The IR [($CHCl_3$) 3440, 1700, 1385, 1370, and 835 cm^{-1}], ^{1}H NMR [($CDCl_3$) 5.3 (m, 1 H, 7-H), 3.3–3.9 (m, 4 H, 21-H_2, 23-H, 24-H), 1.3 (s, 3 H, 26-Me or 27-Me), 1.15 (s, 3 H, 26-Me or 27-Me), 1.1 (s, 3 H, 19-Me), 1.05 (s, 6 H, 28-Me and 29-Me), 1.0 (s, 3 H, 30-Me), and 0.8 (s, 3 H, 18-Me)], and mass [*m/e* 472 (M$^+$), 457, 454, 439, 421, 399, 396, 381 (base), 367, 363, 337, 323, 311, 299, 297, 271, and 245] spectra were in accord with structure 5. Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.2; H, 10.2. Found: C, 75.8; H, 10.6.

Hispidone Diacetate (6). Acetylation of hispidone (5) in pyridine–acetic anhydride at room temperature overnight yielded a residue which was crystallized from methanol as colorless rods, mp 210 °C, $[\alpha]^{25}_D$ −45° (*c* 1.4, $CHCl_3$). The IR [(KBr) 1735, 1700, 1380, 1365, 1240, and 830 cm^{-1}], ^{1}H NMR [($CDCl_3$) 5.3 (m, 1 H, 7-H), 5.05 (m, 2 H, 23-H and 24-H), 3.75 (d, 1 H, *J* = 13 Hz, 21-H), 3.5 (d, 1 H, *J* = 13 Hz, 21-H), 2.05 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 1.2 (s, 6 H, 26-Me and 27-Me), 1.1 (s, 3 H), 1.05 (s, 6 H), 1.0 (s, 3 H), 0.8 (s, 3 H, 30-Me)], and mass [*m/e* 556 (M$^+$), 541 (base), 523, 496, 481, 463, 439, 436, 423, 421, 403, 383, and 367] spectra were in accord with structure 6. Anal. Calcd for $C_{34}H_{52}O_6$: C, 73.47; H, 9.48. Found: C, 73.38; H, 9.35.

Hispidone Diene (9). To a solution of hispidone (5, 80 mg) in glacial acetic acid (10 mL) was added mercuric acetate (155 mg), and the mixture was left at room temperature for 48 h. The precipitated mercury acetate was removed by filtration and the filtrate was evaporated in vacuo. Purification of the residue by preparative TLC followed by crystallization from methanol yielded colorless tiny needless, mp 236–237 °C. The IR [(KBr) 3550, 3040, and 1705 cm^{-1}], UV [(MeOH) λ_{max} 231, 237, and 246 nm (ϵ 11 600, 12 300, and 7800)], and mass [*m/e* 470 (M$^+$), 452, 412, 398, 394, 381, 365, 337, 309, 295, 269, 257, and 244] spectra were in accord with structure 9. Anal. Calcd for $C_{30}H_{46}O_4$: C, 76.59; H, 9.78. Found: C, 76.60; H, 10.3.

Hispidone Acetonide (8). To a solution of hispidone (5, 100 mg) in dry acetone (12 mL) was added two drops of concentrated H_2SO_4, and the mixture was left at room temperature. The reaction, monitored by TLC, was complete after 6 h. The solvent was evaporated in vacuo and the residue was purified by preparative TLC followed by crystallization from methanol to yield colorless shining flakes, mp 185–187 °C, undepressed by admixture with a sample of 3-dehydrosapelin B acetonide prepared from sapelin B as described below. TLC comparsion of 8 with 3-dehydrosapelin B acetonide, performed with various solvent systems, displayed identical R_f values and the IR spectra were virtually susperimposable. The mass [*m/e* 513 (M$^+$), 498, 454, 440, 422, 381, 367, 363, 297, 245, 113 (base), 59, and 58] spectrum was in accord with structure 8. Anal. Calcd for $C_{33}H_{52}O_4$: C, 77.3; H, 10.2. Found: C, 77.0; H, 10.4.

Sapelin B Acetonide (7). To a solution of sapelin B (103 mg) in dry acetone (12 mL) was added anhydrous $CuSO_4$ (225 mg) and the mixture was left, under TLC control, at room temperature for 72 h (under identical conditions hispidone (5) was recovered unchanged). Filtration followed by evaporation of the solvent in vacuo yielded a residue which was crystallized from aqueous methanol as colorless needles whose melting point and IR spectrum were in accord with the literature data.[6]

3-Dehydrosapelin B Acetonide. To a stirred solution of sapelin B acetonide (7, 100 mg) in acetone (30 mL) at 0 °C was added dropwise a cold solution of Jones reagent until the orange color persisted. After workup, the residue (TLC pure) was crystallized from methanol as colorless shining flakes, mp 185–187 °C (lit.[8] mp 179–182 °C), identical in all respects with hispidone acetonide (8).

Bourjotinolone A (2). This substance, crystallized from isopropyl ether, had mp 167–168 °C, (lit.[3] mp 176 °C) and $[\alpha]^{25}_D$ −30.3° (c 1.575, $CHCl_3$; lit.[3] −34°). The IR [(KBr) 3330 1700, 1380, 1365, and 828 cm^{-1}], ^{1}H NMR [($CDCl_3$) 5.3 (m, 1 H, 7-H), 4.05 (m, 1 H, 23-H), 3.95 (~d, 1 H, *J* = 11.5 Hz, 21-H), 3.4 (~d, 1 H, *J* = 11.5 Hz, 21-H), 2.9 (d, 1 H, *J* = 9 Hz, 24-H), 1.3 (s, 6 H, 26-Me and 27-Me), 1.1 (s, 3 H), 1.05 (s, 9 H), 0.8 (s, 3 H, 30-Me)], and mass [*m/e* 472 (M$^+$), 457, 454, 439, 425, 421, 396, 381 (base), 367, 363, 311, 299, and 297] spectra were in accord with structure 2. Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.2; H, 10.2. Found: C, 76.02; H, 9.96.

Bourjotinolone A Monoacetate (3). This was prepared from pyridine–acetic anhydride at room temperature overnight and crystallized from pentane as colorless tiny rods, mp 145–146 °C (lit.[3] mp 148 °C), $[\alpha]^{25}_D$ −50° (*c* 1.035, $CHCl_3$; lit.[3] −107°). The IR [(KBr) 3500, 1730, 1706, and 1239 cm^{-1}], ^{1}H NMR [($CDCl_3$) 5.35 (m, 1 H, H-7), 5.1 (m, 1 H, 23-H), 3.95 (~d, 1 H, *J* = 11 Hz, 21-H), 3.55 (~d, 1 H, *J* = 11 Hz, 21-H), 3.2 (d, 1 H, *J* = 9 Hz, 24-H), 2.05 (s, 3 H, OAc), 1.2 (s, 6 H, 26-Me and 27-Me), 1.15 (s,

(8) Chan, W. R.; Taylor, D. R.; Yee, T. H. *J. Chem. Soc. C* **1971**, 2662.

3 H), 1.1 (s, 6 H), 1.05 (s, 3 H), 0.8 (s, 3 H, 30-Me)], and mass [m/e 514 (M^+), 499, 481, 455, 454, 439, 421, 396, 381 (base), 367, 363, 311, 299, and 297] spectra were in accord with structure **3**. Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.7; H, 9.8. Found: C, 74.8; H, 10.0.

Bourjotinolone A Diene (10). This was prepared according to the procedure followed for hispidone diene (**9**). The diene, crystallized from aqueous methanol, had mp 153–155 °C. The UV [(MeOH) λ_{max} 231, 237, and 246 nm (ϵ 14 700, 15 900, and 10 200)] and mass [m/e 470 (M^+), 452 (base), 437, 434, 423, 410, 409, 394, 381, 365, 337, 309, 295, and 269] spectra were in accord with structure **10**.

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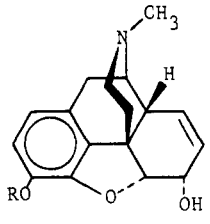
Registry No. **1**, 73891-71-1; **2**, 6985-35-9; **3**, 6985-36-0; **4**, 26790-94-3; **5**, 73891-72-2; **6**, 73891-73-3; **7**, 26808-11-7; **8**, 33573-55-6; **9**, 73891-74-4; **10**, 73891-75-5.

Communications

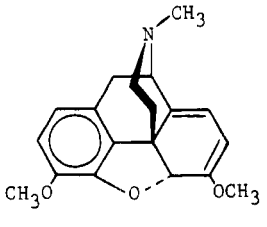
Synthetic Opium Alkaloids and Derivatives. A Short Total Synthesis of (±)-Dihydrothebainone, (±)-Dihydrocodeinone, and (±)-Nordihydrocodeinone as an Approach to a Practical Synthesis of Morphine, Codeine, and Congeners

Summary: Racemic dihydrothebainone (**19**), nordihydrocodeinone (**21**), and dihydrocodeinone (**22**) were synthesized in high overall yield from 3-methoxyphenethylamine (**4**), via the key intermediate (±)-1-bromonordihydrothebainone (**18**); the route utilized unprotected phenolic intermediates, involved directed Grewe-type cyclization, and, for **21** and **22**, exploited novel oxide bridge closure in the N-nor series.

Sir: Natural (−)-codeine (**1**) continues to occupy a position of central importance among the medically valuable derivatives of the opium poppy as the most frequently prescribed analgesic–antitussive agent worldwide. Since the first total synthesis[1] of (−)-codeine (**1**) and (−)-morphine (**2**), other successful routes,[2-8] including Grewe-type[4-6] and biomimetic approaches,[7,8] have appeared. However, a practical total synthesis of these drugs has remained elusive. These and continuing efforts,[9] together with possible shortages,[10,11] underscore the desirability of securing a route which could render licit production of medical



1: R = CH_3
2: R = H



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opiates independent of the natural and sole commercial source of these drugs. Since the reports[4,5] that Grewe-type electrophilic cyclization of (±)-1-benzylhexahydroisoquinoline **9** afforded a 3% yield of the codeine precursor dihydrothebainone (**19**) (with isomeric **20** as the vastly predominant cyclization product), several groups have attempted to utilize this approach to codeine by introduction of a blocking substituent at the 6-position of the benzyl moiety in order to direct cyclization to the desired dihydrothebainone oxygenation pattern. Studies utilizing a methyl substituent were successful in this regard; however, such an approach must also employ a readily removable group to be of value in synthesis of codeine and congeners, of course not the case in the methyl series.[12] Substitution of bromine for methyl, unsuccessful heretofore,[12b,13,14] would be ideal since transformation of 4-hydroxymorphinans such as **19** to **22** (with the oxide bridge closed as in codeine) first involves bromination at C-1 of the morphinan system and later removal of the C-1 bromine atom by hydrogenolysis.[15] Recent work[16] describing conversion of (−)-dihydrothebainone [(−)-**19**] to (−)-codeine (**1**) (68% overall) via (−)-dihydrocodeinone [(−)-**22**] and to (−)-thebaine (**3**) (an important minor opium alkaloid) in somewhat higher yield renders any totally synthetic ap-

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