molecular structures of the monopentafulvene 9[15] and 1,5-cyclooctanedione[22] are very similar. In 8, there is considerable distortion in the ring methylenes with bond angles ranging from 113° for C6-C7-C8 to 116° for C2-C3-C4. Similar ring methylene distortions are found in 9 and in 1,5-cyclooctanedione but are smaller by approximately 2°.

The X-ray structure of the *cis*-3,7-substituted-bicyclo-[3.3.0]octane difulvene[23] shows an increased intramolecular distance between the electrophilic carbons of the pentafulvene chromophores compared to 8 and exhibits a much smaller hypochromic effect.

Monopentafulvenes are known to undergo reductive intermolecular coupling in low yields when treated with metals such as Mg and Na(Hg),[6] and with sodium *N,N*-dimethylnaphthylamine.[24] It was hoped that selected dipentafulvenes would undergo facile intramolecular reductive coupling to form novel metallocene compounds. Ideal candidates included dipentafulvenes 8 and 10 because the crystal structures showed the cyclopentadienyl rings and exocyclic π-systems to be proximate, and upon intramolecular coupling, two new five-membered rings would be formed. Intramolecular reductive couplings were attempted on dipentafulvenes 5, 6, 8, and 10 but were unsuccessful. Instead, a black polymer coated the surface of the metal and no coupling product was isolated or an inseparable mixture of products resulted.

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Supplementary Material Available: ^{13}C NMR spectra of compounds 8, 10, and 12 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(22) Miller, R. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1527.
(23) Fronczek, F. R.; Cronan, J. M., Jr.; McLaughlin, M. L. *Acta Crystallogr.* **1990**, *C46*, 1176.
(24) Oku, A.; Yoshida, M.; Matsumoto, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 524.
(25) Freiesleben, W. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 396.
(26) Olah, G. A.; Prakash, G. K. S.; Liong, G. *J. Org. Chem.* **1977**, *42*, 661.

Diastereoselective Synthesis of *all-cis*-Perhydropyrrolo[3,2,1-*hi*]indol-7-one. A Building Block for the Synthesis of D-Norpandolane-Type Alkaloids

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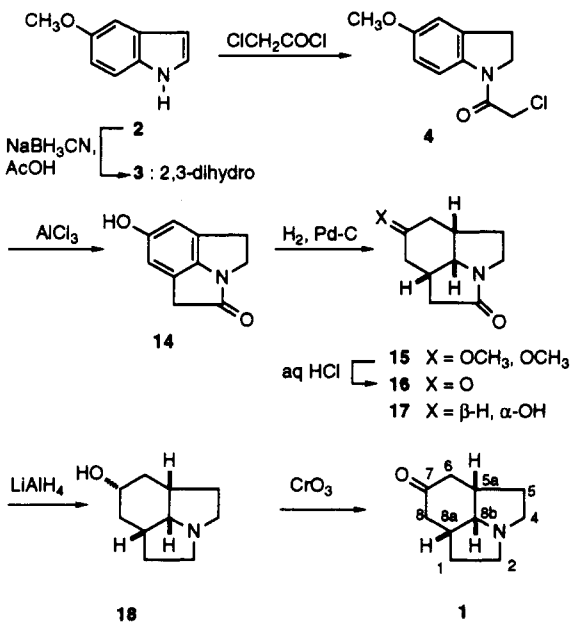
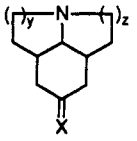
Azatricyclic systems Ia (hexahydrojulolidine) and Ib (hexahydrolilolidine) have been subject of intense synthetic interest because they constitute substructures of *Lycopodium*,[1] *Aspidosperma*,[2] and some *Amaryllidaceae*[3] alkaloids, respectively. Several total syntheses of the former two groups of these alkaloids use functionalized derivatives of Ia or Ib as synthetic precursors.[1,2] However, the lower homologue system Ic has received little synthetic attention.[4] This tricyclic ring system incorporates the characteristic CDE ring moiety of pentacyclic D-norpandolane-type alkaloids,[5] which are a group of indole alkaloids with a rather unusual skeletal type having the piperidine D ring present in *Aspidosperma* alkaloids contracted to a pyrrolidine.

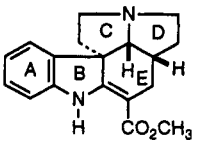
We report here a short, diastereoselective synthesis of the all-cis isomer 1 of ketone Id, which is potentially a key intermediate for the synthesis of the alkaloid deethylibophyllidine.[6,7]

Scheme I





Ia X = H, H; y = z = 2
b X = H, H; y = 1; z = 2
c X = H, H; y = z = 1
d X = O; y = z = 1

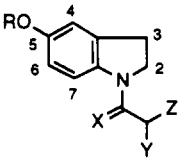


Deethylibophyllidine

(1) (a) MacLean, D. B. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 241-298. (b) Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185-240.
(2) Overman, L. E.; Sworin, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 275-307.
(3) Martin, S. F., In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1987; Vol. 30, pp 251-376.
(4) (a) For the synthesis of Ic, see: Mandell, L.; Piper, J. U.; Singh, K. P. *J. Org. Chem.* **1963**, *28*, 3440. (b) For processes leading to this tricyclic ring system: Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397.
(5) Cordell, G. A. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4. The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; pp 467-537. See also: Khuong-Huu, F.; Cesario, M.; Guilhem, J.; Goutarel, R. *Tetrahedron* **1976**, *32*, 2539.
(6) (a) Kan, C.; Husson, H.-P.; Jacquemin, H.; Kan, S.-K.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 55. For previous synthesis of deethylibophyllidine, see: (b) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002. (c) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 88. (d) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553.
(7) Although it has been claimed[8a] that the alkaloid strychnochromine incorporates the tricyclic ring system Ic, recent work[8b] has demonstrated that it has a different skeletal type.

0022-3263/92/1957-2508$03.00/0

Table I. ^{13}C NMR Chemical Shifts of Indolines[a,b]



	R	X	Y	Z
4	CH_3	O	Cl	H
5	H	O	Cl	H
6	CH_3	O	OH	H
7	CH_3	O	H	H
8	CH_3	O	SCH_3	Cl
9	CH_3	O	SCH_3	H
10	CH_3	O	$SOCH_3$	H
11	CH_3	O	SCH_3	SCH_3
12	CH_3	H, H	OEt	OEt
13	CH_3	H, H	SCH_3	SCH_3

compd	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	R	C=X	CH	Y, Z
3	47.5	30.1	131.1	111.4	153.5	112.0	110.0	145.4	55.6			
4	47.7	27.9	132.9	110.5	156.8	112.0	117.9	136.1	55.4	163.3	42.8	
5[c]	47.4	27.8	133.8	112.4	154.7	113.5	117.2	135.3		163.4	43.9	
6[c]	45.8	28.0	133.6	112.0	156.7	112.1	116.7	136.9	55.6	170.0	61.2	
7	49.3	28.4	133.4	111.3	156.9	112.4	118.0	138.5	56.0	168.7	24.2	
9	47.8	27.8	132.8	110.5	156.4	111.8	117.4	136.6	55.3	166.0	37.0	15.2
10	48.4	27.5	133.2	110.5	156.7	111.7	117.4	135.6	55.2	161.4	58.8	38.9
11	47.8	28.0	133.0	110.8	156.7	111.9	117.8	136.5	55.4	164.5	55.4	12.1
12	54.0	26.8	131.1	112.0	152.8	111.6	107.0	147.0	55.8	55.1	101.7	62.2[d]
13	54.7	28.7	131.1	111.7	153.0	112.1	106.8	146.4	55.9	55.6	53.5	12.2

[a] In ppm relative to TMS. [b] In $CDCl_3$ solution. [c] In DMSO-d_6 solution. [d] δ 15.1 (OCH_2CH_3).

Although ketone **Id** has three stereogenic centers, its symmetry reduces the possible number of stereoisomers to two meso and two enantiomeric forms, of which only the symmetric all-cis isomer **1** is suitable for our purpose. The synthesis of **1** was effected as outlined in Scheme I. The key step was the closure of the pyrrolidine ring by formation of C_1–C_{8a} bond from an appropriately substituted indoline, the remaining steps simply implying the adjustment of the oxidation level. However, one of these steps, namely the hydrogenation of the benzene ring, was crucial from the stereochemical standpoint because it allowed the control of the cis relative configuration between the three stereocenters.

After considerable experimentation, the key cyclization was accomplished in 20% yield by Friedel–Crafts alkylation of 1-(chloroacetyl)indoline **4**[9] which, in turn, was prepared in 95% yield from 5-methoxyindoline (**3**).[10] Under the drastic reaction conditions (high temperature for a short time), concomitant demethylation of the methoxy group occurred to give the tricyclic phenol **14**. Also, part of the starting material was recovered as the corresponding phenol **5**. Attempts to induce the cyclization by other procedures were unsuccessful, probably due to the strain of the resulting rigid oxindole system. Thus, attempted cyclization via a radical species generated either by photolysis or by tributyltin hydride treatment of **4** failed: only alcohol **6**[11] and acetamide **7**,[12] respectively,

Table II. ^{13}C NMR Chemical Shifts of *all-cis*-Perhydropyrrolo[3,2,1-*hi*]indoles[a,b]

compd	C-1	C-2	C-4	C-5	C-5a	C-6	C-7	C-8	C-8a	C-8b
15	37.8	172.7	43.5	33.5	31.6	31.9	99.7[c]	32.8	32.5	62.8
16	39.5	175.7	41.3	32.1	34.2	40.3	209.9	41.0	29.6	61.6
17	37.9	172.8	44.1	33.3	32.8	35.7	66.9	37.2	34.2	62.4
18	36.4	52.1	52.1	36.4	35.2	38.4	67.6	38.4	35.2	64.9
1	32.1	53.3	53.3	32.1	35.9	40.5	212.6	40.5	35.9	64.9

[a] In ppm relative to TMS. [b] In $CDCl_3$ solution. [c] δ 47.3 and 47.8 (OMe).

were obtained. Attempted cyclizations via a thionium ion intermediate also failed: both treatment of α-chloro sulfide **8**[13] with $SnCl_4$ and Pummerer rearrangement of sulfoxide **10**[11,15] led to bis(methylthio)acetamide **11**[11,16] as the only isolable product, and reaction of dithioacetal **13**[11,17] with dimethyl(methylthio)sulfonium fluoroborate[18] did not result in the desired cyclization either. The ^{13}C NMR chemical shifts of indolines **3–7** and **9–13** are given in Table I.

Catalytic hydrogenation of **14** over palladium on charcoal took place smoothly (rt, 1 atm), probably due to the release of strain associated to the process, to give a mixture

(8) (a) Angenot, L.; Coune, C.; Quetin-Leclercq, J.; Tavernier, D. *Phytochemistry* **1988**, *27*, 595. (b) Quetin-Leclercq, J.; Angenot, L.; Dupont, L.; Dideberg, O.; Warin, R.; Delaude, C.; Coune, C. *Tetrahedron Lett.* **1991**, *32*, 4295.

(9) This procedure has been employed for the cyclization of the demethoxy analog: Naruto, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1972**, *20*, 2163.

(10) Indoline **3** was prepared from indole **2** in 78% yield by the Gribble method: Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859. For an alternate procedure, see: Achenbach, H.; Raffelsberger, B.; Addae-Mensah, I. *Liebigs Ann. Chem.* **1982**, 830.

(11) This compound gave satisfactory elemental analysis. For the ^{13}C NMR data, see Table I.

(12) Hunt, R. R.; Rickard, R. L. *J. Chem. Soc. C* **1966**, 344.

(13) Compound **8** was prepared by acylation of **3** with chloro(methylthio)acetyl chloride.[14]

(14) Tamura, Y.; Uenishi, J.; Maeda, H.; Choi, H.; Ishibashi, H. *Synthesis* **1981**, 534.

(15) Sulfoxide **10** was prepared by acylation of **3** with (methylthio)-acetyl chloride (86%) followed by oxidation of the resulting sulfide **9** with *m*-chloroperbenzoic acid (70%).

(16) The formation of dithioacetals from sulfoxides under Pummerer conditions, by way of a thionium ion intermediate, has been previously reported: (a) Harris, T. D.; Boekelheide, V. *J. Org. Chem.* **1976**, *41*, 2770. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.

(17) Dithioacetal **13** was prepared by alkylation of **3** with bromoacetaldehyde diethyl acetal (95%) followed by reaction of the resulting acetal **12** with methanethiol in the presence of BF_3·Et_2O (70%).

(18) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

of tricyclic amido acetal **15**, amido ketone **16**, and amido alcohol **17**, all of them having the required all-cis relative configuration at the fused carbons. The ratio acetal **15**/ketone **16** was variable depending on the run, but the overall yield for these two compounds was approximately 60%. The unexpected formation of acetal **15** can be accounted for by considering that trace amounts of $PdCl_2$ may be present as an impurity in the catalyst.[19] When the above crude reaction mixture was directly submitted to acid hydrolysis, a mixture of ketone **16** and alcohol **17** (approximate ratio 4:1) was obtained in 70% overall yield from phenol **14**. Although tricycles **15**, **16**, and **17** could be separated and characterized, this is unnecessary from the synthetic standpoint since lithium aluminum hydride reduction of the **16** + **17** mixture gives rise to a single amino alcohol **18** in 94% yield. Finally, Jones oxidation of **18** afforded the target amino ketone **1** in 72% yield.

The ^{13}C NMR chemical shifts of perhydropyrrolo[3,2,1-*hi*]indoles **15**–**18** and **1** are given in Table II. These data are clear evidence of the symmetry of **18** and **1**. The relative configuration of these compounds was deduced from the multiplicity and coupling constants of H-8b in the ^1H NMR spectra. In all cases the signal attributable to this proton appears as a triplet with a J value between 4.5 and 7.0 Hz, which implies an equatorial disposition with respect to the cyclohexane ring. Consequently, the nitrogen substituent is axial and both octahydroindole moieties must necessarily be cis.

Experimental Section

General. Unless otherwise noted, ^1H NMR spectra were recorded at 200 MHz. All ^{13}C NMR spectra were recorded at 50.3 MHz. TLC was performed using as developing solvent the one indicated as eluant for column chromatography, and the spots were visualized with iodoplatinate reagent. Microanalyses were performed by Centro de Investigación y Desarrollo (C.S.I.C.), Barcelona.

1-(Chloroacetyl)-5-methoxyindoline (4). A solution of chloroacetyl chloride (1.53 g, 13.5 mmol) in $CHCl_3$ (15 mL) was added dropwise under N_2 to a stirred mixture of 5-methoxyindoline (**3**)[10] (1.35 g, 9.1 mmol) and anhydrous K_2CO_3 (2.9 g) in $CHCl_3$ (30 mL). After the mixture was stirred at room temperature for 90 min, H_2O was added, and the resulting mixture was stirred for 20 min. The organic layer was separated, and the aqueous phase was extracted with $CHCl_3$. Evaporation of the combined dried organic extracts afforded 1.9 g (95%) of chloroacetamide **4** as a white solid: mp 143–144 °C (CH_3CN–H_2O); IR ($CHCl_3$) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (t, J = 8.3 Hz, 3-CH_2), 3.77 (s, OMe), 4.12 (s, $COCH_2$), 4.12 (t, J = 8.3 Hz, 2-CH_2), 6.73 (d, J = 9.1 Hz, H-6), 6.75 (s, H-4), 8.11 (d, J = 9.1 Hz, H-7); ^{13}C NMR Table I. Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.32; Cl, 15.74; N, 6.20. Found: C, 58.58; H, 5.42; Cl, 15.77; N, 6.10.

7-Hydroxy-4,5-dihydro-1*H*-pyrrolo[3,2,1-*hi*]indol-2-one (14). A mixture of **4** (600 mg, 2.66 mmol) and freshly sublimed $AlCl_3$ (1.41 g, 10.6 mmol) was heated at 360–370 °C on a sand bath for 2–4 min under N_2. After the mixture was cooled, ice–water, 5% aqueous HCl, and $CHCl_3$ were added to the resulting brown solid, and the mixture was filtered. The two phases were separated, and the aqueous layer was extracted with $CHCl_3$ (6 × 20 mL). The combined organic extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (SiO_2, 1:1 CH_2Cl_2–AcOEt) to give starting material **4** (100 mg), phenol **5** (153 mg), and tricycle **14** (96 mg, 20%).

5: mp 200–201 °C (CH_2Cl_2–MeOH); IR (KBr) 3370, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.06 (t, J = 8.3 Hz, 3-CH_2), 4.05 (t, J = 8.3 Hz, 2-CH_2), 4.42 (s, $COCH_2$), 6.55 (d, J = 8.8 Hz, H-6), 6.65 (s, H-4), 7.83 (d, J = 8.8 Hz, H-7), 9.23 (s, OH); ^{13}C NMR, Table I. Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.73; H, 4.72; N, 6.61. Found: C, 56.37; H, 4.64; N, 6.37.

14: mp 238–239 °C (AcOEt–EtOH) (lit.[20] mp 229–230 °C dec); IR (KBr) 3150, 1680, 1670, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.42 (t, J = 7.8 Hz, 5-CH_2), 3.67 (s, 1-CH_2), 3.88 (t, J = 7.8 Hz, 4-CH_2), 6.47 and 6.50 (2s, 1 H each, ArH), 8.83 (s, OH); ^{13}C NMR (DMSO-d_6) δ 34.0 (C-5), 43.4, 44.6 (C-1 and C-4), 111.0 (C-6 and C-8), 119.2, 121.7 (C-8a and C-5a), 146.4 (C-8b), 155.2 (C-7), 171.5 (C-2). Anal. Calcd for $C_{10}H_9NO_2 \cdot H_2O$: C, 62.16; H, 5.79; N, 7.24. Found: C, 62.56; H, 6.10; N, 6.85.

Hydrogenation of Phenol 14. To a solution of **14** (520 mg, 2.97 mmol) in MeOH (55 mL) was added 10% palladium on carbon (120 mg). The mixture was shaken under hydrogen at atmospheric pressure for 24 h, the catalyst was removed by filtration, and the filtrate was evaporated. The resulting oil was dissolved in MeOH (5 mL) and 4 N aqueous HCl (11 mL), and the solution was stirred at room temperature for 6 h and extracted with CH_2Cl_2. After the solution was dried, the solvent was removed, and the remaining oil was flash chromatographed (SiO_2, 10:10:1 AcOEt–CH_2Cl_2–EtOH) to give 297 mg (56%) of keto amide **16** and 75 mg (14%) of hydroxy amide **17**.

(5a*RS*,8a*RS*,8b*RS*)-1,4,5,5a,6,8,8a,8b-Octahydropyrrolo[3,2,1-*hi*]indole-2,7-dione (16): IR (film) 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, 1 H), 2.0–2.5 (m, 6 H), 2.61 (m, H-8a), 2.9–3.1 (m, 3 H), 3.85 (ddd, J = 12.5, 8.0, 5.6 Hz, H-4), 4.21 (t, J = 7.0 Hz, H-8b); ^{13}C NMR, Table II. Anal. Calcd for $C_{10}H_{13}NO_2 \cdot H_2O$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.60; H, 7.36; N, 6.70.

(5a*RS*,7*SR*,8a*RS*,8b*RS*)-7-Hydroxy-4,5,5a,6,7,8,8a,8b-octahydro-1*H*-pyrrolo[3,2,1-*hi*]indol-2-one (17): mp 139–140 °C (AcOEt–EtOH); IR (KBr) 3320, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (q, J = 12 Hz, H-6ax), 1.06 (q, J = 12 Hz, H-8ax), 1.91 (dddd, J = 12, 6.5, 3.3, 3 Hz, H-6eq), 1.93 (m, H-5ax and H-8eq), 2.17 (d, J = 15.5 Hz, H-1ax), 2.23 (m, H-5a), 2.31 (m, H-5eq), 2.51 (m, H-8a), 2.94 (dd, J = 15.5, 6.5 Hz, H-1eq), 3.22 (t, J = 11 Hz, H-4ax), 3.39 (ddd, J = 11.5, 11, 7.5 Hz, H-4eq), 3.54 (tt, J = 11.5, 3.5 Hz, H-7ax), 3.88 (t, J = 5.5 Hz, H-8b); ^{13}C NMR, Table II. Anal. Calcd for $C_{10}H_{15}NO_2 \cdot {}^1/_3H_2O$: C, 64.14; H, 8.38; N, 7.47. Found: C, 64.08, H, 8.16; N, 7.23.

When the reaction mixture was flash chromatographed (SiO_2, 1:1 AcOEt–CH_2Cl_2) before the hydrolytic treatment, besides compounds **16** and **17**, ketal **15** was obtained: ^1H NMR: δ 1.1 (m, 2 H), 1.8–2.3 (m, 6 H), 2.51 (sext, J = 6.5 Hz, H-8a), 2.93 (dd, J = 15, 6.5 Hz, H-1α), 3.16 and 3.20 (2s, 2 OCH_3), 3.20 (masked, H-4α), 3.36 (m, H-4β), 3.98 (t, J = 4.5 Hz, H-8b); ^{13}C NMR, Table II.

(5a*R*,7*r*,8a*S*,8b*s*)-1,2,4,5,5a,6,7,8,8a,8b-Decahydropyrrolo[3,2,1-*hi*]indol-7-ol (18). To a solution of the crude mixture of lactams **16** and **17** (374 mg, 2.1 mmol) in anhydrous THF (30 mL) was added $LiAlH_4$ (304 mg, 8 mmol) under N_2. The mixture was refluxed for 6 h. After the mixture was cooled, water and a saturated solution of sodium potassium tartrate (30 mL) were slowly added. The aqueous phase was separated and extracted with THF (4 × 20 mL). Evaporation of the combined dried organic extracts gave **18** as an oil (330 mg, 94%), which was used without further purification in the next step. An analytical sample was obtained by column chromatography (Al_2O_3, neutral, 4:1 Et_2O–MeOH): IR (film) 3370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (q, J = 12 Hz, H-6ax and H-8ax), 1.78 (dd, J = 12, 5 Hz, H-1ax and H-5ax), 1.93 (m, H-5a and H-8a), 2.24 (dt, J = 12, 3.5 Hz, H-6eq and H-8eq), 2.25 (m, H-1eq and H-5eq), 2.49 (ddd, J = 12, 8.8, 5 Hz, H-2ax and H-4ax), 3.08 (ddd, J = 12, 6, 0.5 Hz, H-2eq and H-4eq), 3.48 (t, J = 6 Hz, H-8b), 3.55 (tt, J = 12, 3.5 Hz, H-7ax); ^{13}C NMR, Table II. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.82; H, 10.25. Found: C, 71.52; H, 10.48.

(5a*R*,8a*S*,8b*s*)-2,4,5,5a,6,8,8a,8b-Octahydro-1*H*-pyrrolo[3,2,1-*hi*]indol-7-one (1). 1.23 M Jones reagent (2.05 mL, 2.55 mmol) was added at 0 °C to a stirred solution of alcohol **18** (140 mg, 0.84 mmol) in acetone (5 mL), and the mixture was stirred at 25 °C for 45 min. Addition of 10% aqueous $NaHSO_3$ solution (15 mL) and 4 N aqueous NaOH (12 mL), followed by extraction with Et_2O, left an oil, which was chromatographed (Al_2O_3, 4:1 Et_2O–EtOH) to give ketone **1** (100 mg, 72%): IR (film) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 and 1.96 (2 dddd, J = 13.0, 6.5, 6.5, 6.5 Hz, 1- and 5-CH_2), 2.22 (dd, J = 17.5, 8 Hz, H-6α and H-8α), 2.41

(19) Camps, P.; Ortuño, R. M.; Serratosa, F. *Tetrahedron Lett.* **1978**, 3159.

(20) Okuno, Y.; Kawamori, M.; Hirao, K.-I.; Yonemitsu, O. *Chem. Pharm. Bull.* **1975**, *23*, 2584.

(dd, J = 17.5, 6 Hz, H-6β and H-8β), 2.56 (apparent br. sext, J = 6.5 Hz, H-5a and H-8a), 2.71 (ddd, J = 11.0, 6.5, 6.5 Hz, H-2α and H-4α), 3.11 (ddd, J = 11.0, 6.0, 5.5 Hz, H-2β and H-4β), 3.75 (t, J = 6.8, H-8b); ^{13}C NMR, Table II; MS (m/z, relative intensity) 166 (M^+ + 1, 10), 165 (M^+, 61), 164 (41), 106 (28), 96 (100), 82 (84). Anal. Calcd for $C_{10}H_{15}NO \cdot {}^1/_2H_2O$: C, 68.92; H, 9.18; N, 8.04. Found: C, 68.86; H, 9.23; N, 8.02.

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Erythro Selective Additions of Tetra-*n*-butylammonium Enolates of 2-Oxetanones to Aldehydes: Application to Tetrahydrofuran Synthesis

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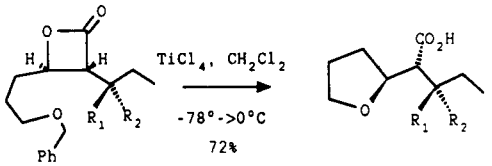
We have shown that 2-oxetanones bearing a 3-(benzyloxy)propyl substituent at the 4-position rearrange upon Lewis acid treatment to give α-substituted tetrahydrofuranacetic acids.[1,2] These intramolecular β cleavage reactions have been shown to proceed with complete inversion of stereochemistry,[1] giving highest product yields with titanium tetrachloride mediation.

With the intention of broadening the scope of this finding, we wanted to know if these ring-opening reactions could be applied to structures such as 1 (see Scheme I) in which a secondary alcohol group is β to the carbonyl moiety. We envisioned a two-step sequence from the enolate 3 of aldol reaction followed by intramolecular lactone ring opening as a means of targeting the derivatives 2. With appropriate choice of aldehyde, application of this strategy to the construction of tetrahydrofuran rings bearing multiple side-chain asymmetry, a feature common to a number of biologically active natural products,[3] might be possible.



1a R_1=OH, R_2=H
1b R_1=H, R_2=OH

2a R_1=OH, R_2=H
2b R_1=H, R_2=OH

Given the stereospecific nature of the intramolecular ring-opening step, it follows that all three stereocenters in the tetrahydrofurans 2 would ultimately be decided by the stereochemistry of the aldol addition, which in turn should be controlled by the enolate counterion.[4] Earlier work[1] had shown that enolate 3 could be generated as a stable tetraalkylammonium salt by fluoride treatment of the α-silyl species 4.[5] Aldol additions of tetraalkylammonium enolates, typically generated from silyl enol ethers,[6] have been documented.[7] However, studies to date have largely been limited to the use of acyclic analogues and ring systems larger than four.[8] Our first priority, therefore, was to demonstrate the feasibility of the proposed aldol reaction.

Scheme I

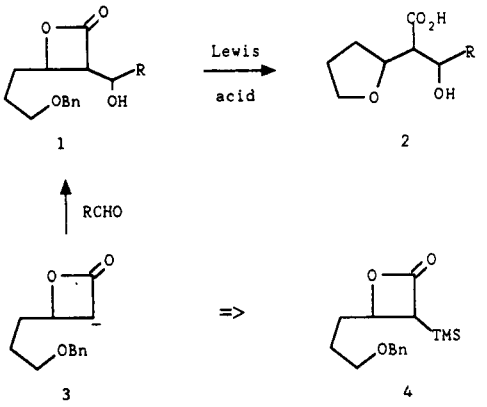


Table I. Results of Fluoride-Initiated Aldol Reactions of Lactones 4-6

entry	lactone	R^2	A/B[a]	no.	yield[b] (%)
1	5	Ph	88:12	7/8	79
2	6	Ph	85:15	9/10	81
3	5	Et	63:37	11/12	88[c]
4	5	^{i}Pr	96:4	13/14	85
5	5	^{i}Pr	62:38[d]	13/14	57
6	5	furyl	77:23	15/16	71
7	4	Et	55:45	1a/1b	72

[a] The ratio of erythro to threo isomer for each reaction was determined by ^{1}H NMR integration of the β-H signals of the crude product mixture. [b] Values refer to combined isolated yields of both stereoisomers. [c] Estimated yield. See Experimental Section. [d] Reaction carried out by rapid addition of 5 to the aldehyde/Bu_4NF mixture.

Results and Discussion

For this study, the structurally simpler silyl lactones 5 and 6 were prepared,[9] in addition to the required lactone 4,[10] and reacted with a series of aldehydes in the presence of Bu_4NF (see Table I). Although initial attempts proved disappointing, optimum yields were eventually obtained by slow addition of the silyl lactone to a mixture of aldehyde and stoichiometric fluoride in THF at −78 °C. Under these conditions, proton exchange between the generated enolate and its silyl precursor, which had plagued us in an earlier study,[1] could be avoided. Rapid addition of the lactone resulted in the formation of complex byproducts as well as decreased stereoselectivity (see entry 5).

(1) Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829.
(2) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991.
(3) For examples, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, K. *Tetrahedron Lett.* **1987**, *28*, 5861.
(4) For recent review articles on this topic, see: (a) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177.
(5) For a related use of this strategy, see: Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.
(6) For exceptions to this generalization, see ref 5 and: Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887.
(7) (a) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (b) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (c) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932.
(8) For the one exception to this, see ref 7c.
(9) For the preparation of 5 and 6, see: Brady, W. T.; Saidi, K. *J. Org. Chem.* **1979**, *44*, 733.
(10) For the preparation of this lactone, see: Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573.

0022-3263/92/1957-2511$03.00/0