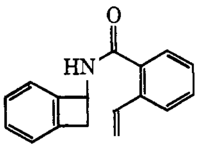
## The Total Synthesis of *dl*-Chelidonine[1]

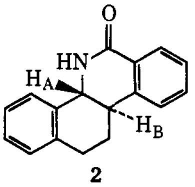
*Sir:*

*d*-Chelidonine, the main alkaloid of *Chelidonium majus*, was first isolated in 1839.[2] Its constitution and relative configuration, as depicted in **12**, R = CH$_3$, have been derived on the basis of extensive chemical[3] and spectroscopic[4] evidence. Either enantiomer,[5] as well as the racemic mixture,[6] can be obtained from different plants of the family *Papaveraceae*. *l*-Norchelidonine (**12**, R = H) is also known to occur in nature.[5b,7] We now wish to report the first total syntheses of *dl*-norchelidonine and *dl*-chelidonine (diphylline), the key step of which exploits a general scheme recently presented for the formation of new heterocyclic systems.[8]

In the search for a simple stereoselective approach to the chelidonine framework,[9] the amide **1**[10,11] was heated in boiling bromobenzene for 16 hr to give the trans fused compound **2**[9–11] (mp 210–211°; nmr $J_{AB}$ = 12.5 Hz; 90%). By contrast, thermolysis of the more flexible urethane **3**[10,11] afforded the desired cis fused product **4**[10,11] (mp 135–137°; nmr $J_{AB}$ = 6 Hz; 78%).



**1**



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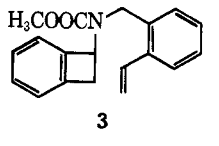

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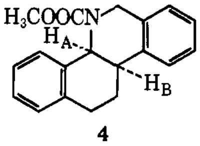
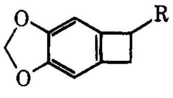
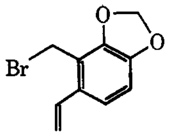


**4**

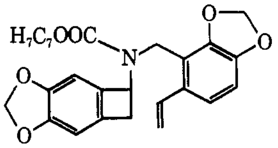
The two building blocks **5d** and **6** required for this synthesis of chelidonine were easily obtained as follows. Basic hydrolysis of the known nitrile **5a**[12] yielded the carboxylic acid **5b**[10,11] (mp 144–148°), which, on Curtius degradation, followed by reaction of the crude isocyanate **5c** with benzyl alcohol at 25° for 3 days, furnished the urethane **5d**[10,11] (mp 170–172°; 47%). In analogy to described procedures the known 2,3-methylenedioxybenzaldehyde[13] was converted[14] to 1,2,3,4-tetrahydro-7,8-methylenedioxyisoquinoline[10,11] (mp (HCl) 235–240°; 62%), which by successive Hofmann and von Braun degradations[15] afforded the benzyl bromide **6**[10,11] (mp 85–86°, 45%).



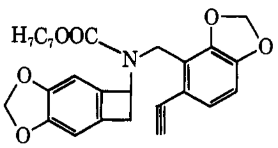
**5a**, R = CN
**b**, R = COOH
**c**, R = N=C=O
**d**, R = NHCOOC$_7$H$_7$



**6**



**7**



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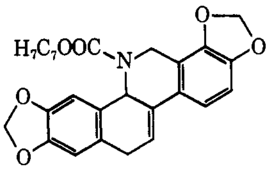
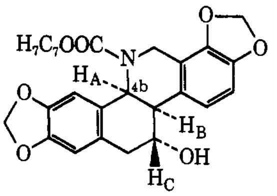
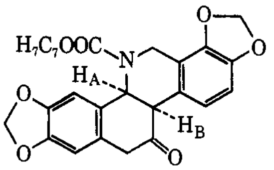


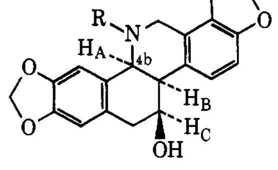
**9**



**10**



**11**



**12**

Condensation of the two components **5d** and **6** was accomplished by conversion of the former to its sodium salt with 1.2 mol of sodium hydride in *N*,*N*-dimethylformamide at 0°, followed by addition of 1.0 mol of the bromide **6** and 0.15 mol of sodium iodide and subsequent stirring of the mixture at 25° for 16 hr to form the oily styrene **7**[11,16] (77%). Bromination of **7** with

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(1) Presented in part at the IUPAC Symposium on Cycloaddition Reactions, Munich, Germany, Sept 7–10, 1970.

(2) J. M. Probst, *Ann. Pharm.*, **29**, 113 (1839).

(3) F. von Bruchhausen and H. W. Bersch, *Ber.*, **63**, 2520 (1930); **64**, 947 (1931); E. Späth and F. Kuffner, *ibid.*, **64**, 370 (1931).

(4) H. W. Bersch, *Arch. Pharm.*, **291**, 491 (1958); F. Šantavý, M. Horák, M. Maturová, and J. Brabenec, *Collect. Czech. Chem. Commun.*, **25**, 1344 (1960); E. Seoane, *An. Real. Soc. Espan. Fis. Quim., Ser. B*, **61**, 755 (1965).

(5) (a) J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.*, **22**, 279 (1957); (b) **24**, 3141 (1959).

(6) J. O. Schlotterbeck and H. C. Watkins, *Ber.*, **35**, 7 (1902), J. Slavík, L. Slavíková, and J. Brabenec, *Collect. Czech. Chem. Commun.*, **30**, 3697 (1965); L. Slavíková, *ibid.*, **33**, 635 (1968).

(7) J. Slavík, *ibid.*, **24**, 3601 (1959).

(8) W. Oppolzer, *J. Amer. Chem. Soc.*, **93**, 3833 (1971).

(9) For a different approach to hexahydrobenz[*c*]phenanthridines, see I. Ninomiya, T. Naito, and T. Mori, *Tetrahedron Lett.*, 3643 (1969).

(10) Elemental analytical data in excellent accord with theory were obtained for this substance.

(11) The ir and nmr spectra were in agreement with the assigned structure.

(12) E. F. Jenny and K. Schenker, Swiss Patent 485,647 (1970).

(13) C. Wilkinson, R. L. Metcalf, and T. R. Fukuto, *J. Agr. Food Chem.*, **14**, 73 (1966).

(14) W. J. Gensler, K. T. Shamasundar, and S. Marburg, *J. Org. Chem.*, **33**, 2861 (1968).

(15) J. von Braun, *Ber.*, **50**, 45 (1917).

(16) Satisfactory high-resolution mass spectra were obtained, using a CEC-21-110 B spectrometer.

1.1 mol of bromine in dichloromethane at −12° and subsequent treatment of the reaction mixture with 2.4 mol of potassium *tert*-butoxide and 8 mol of 1,5-diazabicyclo[5.4.0]undec-5-ene in hexamethylphosphoramide at 25° for 20 hr afforded the liquid acetylene **8**[11,16] (30%). The latter rearranged smoothly in *o*-xylene at 120° within 1 hr to the crystalline tetrahydrobenz[*c*]phenanthridine **9**[10,11] (mp 137–140°; 73%). Hydroboration of **9** with an excess of diborane in tetrahydrofuran at 25° for 1 hr, followed by oxidation of the adduct with hydrogen peroxide, produced in 68% yield a 1:1 mixture of the alcohol **10**[10,11] (mp 171–172°; nmr $J_{AB}$ = 6 Hz, $J_{BC}$ = 4 Hz) and its C-4b epimer[10,11] (mp 177–182°), which were separated by chromatography on silica gel. Jones oxidation[17] of the cis-fused alcohol **10** at 0° for 3 min gave the ketone **11**[10,11] (mp 172–173°; nmr $J_{AB}$ = 2.5 Hz; 32%). Reduction of **11** with sodium borohydride in methanol–dioxane (1:1) at 0° for 1 hr proceeded stereospecifically to form exclusively the desired cis,cis alcohol **12**, R = $COOC_7H_7$[10,11] (mp 214–217°), which after hydrogenolysis of the benzyloxycarbonyl group (Pd/C, ethanol) afforded *dl*-norchelidonine **12**, R = H[11,16] (mp 212–217°; nmr $J_{AB}$ = 3.5 Hz, $J_{BC}$ = 2 Hz; 90%). The synthetic *dl*-norchelidonine, which exhibited the same uv, ir ($CH_2Cl_2$), nmr, and mass spectra and identical chromatographic behavior as the natural levorotatory alkaloid, furnished upon N-methylation[7] *dl*-chelidonine (**12**, R = $CH_3$), mp 217–218°, after crystallization from ethanol. The synthetic and natural *dl*-chelidonine showed no depression of their melting points upon admixture and displayed identical ir spectra (KBr) and chromatographic properties. Further modifications of this scheme to provide complete control of stereochemistry are planned.

**Acknowledgment.** We wish to thank Professor J. Slavík for generous samples of natural *l*-norchelidonine and *dl*-chelidonine.

(17) C. D. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

**W. Oppolzer, K. Keller**
*Pharmaceutical Chemical Laboratories, Sandoz Ltd.*
*4002 Basle, Switzerland*

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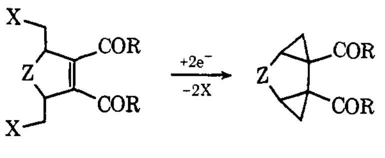
## Reductive Bis Alkylation and Its Use in the Synthesis of σ-Homobenzene Derivatives[1]

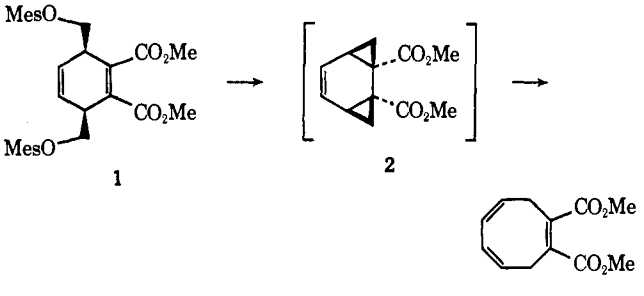
*Sir:*

We have examined the reductive bis alkylation of 1,2-biscarbonyl-substituted ethylenes (eq 1) as an entry into the σ-homobenzene group of compounds with the following results.



(1)

The reaction of **1** with 2 equiv of lithium naphthalenide at −78° in tetrahydrofuran afforded on work-up a 60% yield of dimethyl 1,4,6-cyclooctatriene-1,2-dicarboxylate (**3**). Diester **3** was identified[2] by its nmr (δ 3.17 (4 H, d, $J_{34}$ = 7 Hz, =$CHCH_2$), 3.93 (6 H, s, $OCH_3$), 5.8 (2 H, $ABX_2$ pattern, $J_{AB}$ = 10 Hz, $J_{AX}$ = 7 Hz, CH=*CH*$CH_2$), 6.25 (2 H, d, $J_{45}$ = 10 Hz, *CH*=$CHCH_2$)), and conversion to cyclooctene-1,2-dicarboxylic acid[3] by sequential hydrogenation and saponification. In agreement with the mechanism proposed in eq 1, reductive bis alkylation of the dihydro derivative of **1**, **4**, afforded a material, δ 0.5 (2 H, ABX pattern, $J_{AB}$ = 4.5 Hz, $J_{AX}$ = 4.5 Hz), 0.8–2.2 (8 H, complex m), 3.6 (6 H, s, $OCH_3$), assigned structure **5**.[4]



**1** **2** **3**

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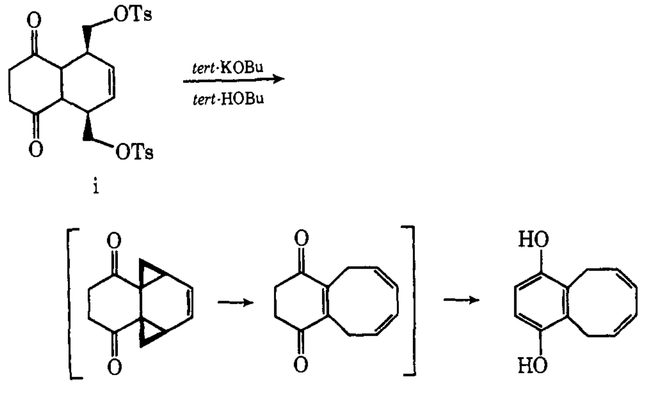
(1) We distinguish between saturated and unsaturated valence tautomers by the prefixes σ and π, respectively.

(2) All new compounds mentioned have afforded appropriate elemental and spectral (nmr, ir, uv, mass spectral) analysis: **1**, mp 90–92°; nmr ($CDCl_3$) δ 3.02 (6 H, s), 3.6 (2 H, br), 3.8 (6 H, s), 4.35 (4 H, d, *J* = 5 Hz), 5.97 (2 H, d, *J* = 3 Hz); ir ($CHCl_3$) 5.8, 7.35, 8.5 μ; **4**, mp 89–91°; nmr ($CDCl_3$) δ 1.9 (4 H, br), 3.02, (8 H, 6 H, s superimposed on 2 H m), 3.8 (6 H, s), 4.3 (4 H, ABX pattern); ir (KBr) 5.75, 5.8 (sh), 7.4, 8.5 μ; **6**, mp 116–116.5°; nmr ($CDCl_3$) δ 0.2–1.0 (2 H, complex m), 1.2–1.6 (2 H, complex m), 1.53 (18 H, s), 3.09 (6 H, s), 3.4 (2 H, br), 4.0–4.8 (4 H, ABX pattern); ir (KBr) 5.8 (sh), 5.85, 7.4, 8.5, 8.6 μ; **9**, nmr ($CDCl_3$) δ −0.41 (1 H, m), 0.04 (1 H, m), 0.7–1.0 (2 H, m), 1.2–1.9 (3 H, m), 1.34 (9 H, s), 1.41 (9 H, s), 2.07 (3 H, s); ir (neat) 5.85 μ; **10**, mp 100.2–100.5° dec; nmr ($CDCl_3$) δ 0.0–0.7 (4 H, m), 1.0–1.9 (4 H, m), 1.41 (9 H, s), 1.45 (9 H, s), 2.5 (1 H, br), 2.98 (3 H, s), 4.6 (2 H, ABX pattern); ir (KBr) 5.8, 5.85 (sh), 7.4, 8.6 μ; i, mp 136–138° dec; nmr ($CDCl_3$) δ 2.44 (6 H, s), 2.3–3.1 (8 H, m), 4.1 (4 H, m), 5.60 (2 H, br), 7.2–7.9 (8 H, $A_2B_2$ pattern); ir (KBr) 5.82, 7.4, 8.5 μ; product from i, mp 183–185°; nmr (DMSO-$d_6$) δ 3.5 (4 H, d, *J* = 4 Hz), 5.6–5.85 (4 H, br), 6.5 (2 H, s), 8.0 (2 H, br s, exchanges with $D_2O$); ir (KBr) 2.9 μ.

(3) J. Sicher, F. Sipos, and J. Jonas, *Collect. Czech. Chem. Commun.*, 26, 262 (1961).

(4) A similar bis alkylation–ring expansion sequence under more usual alkylation conditions is observed when i is treated with potassium *tert*-butoxide.



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