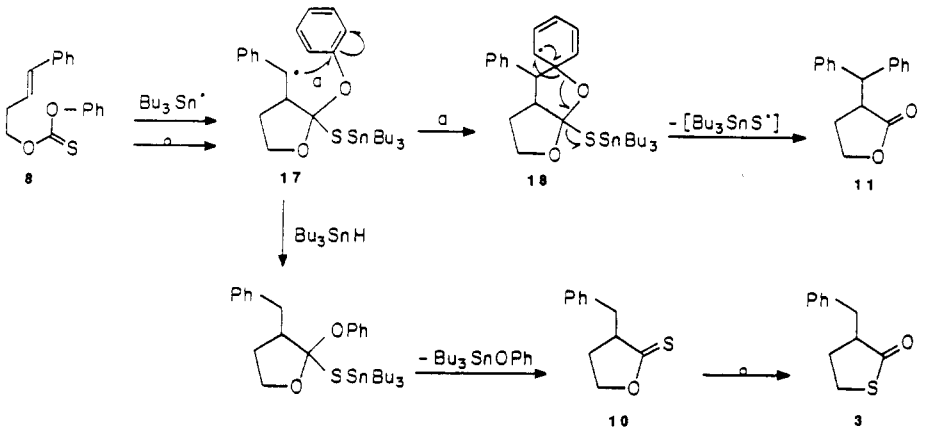
Scheme III



analyses of the crude product of both reactions indicated that the thionolactone was formed during the reaction and not on hydrolytic workup as observed[6] in the cyclization of dithiocarbonate **1** to thiololactone **3** and dithiolactone **4**.

In contrast the thionocarbamate **7** failed to cyclize under the above-mentioned conditions. It seems that due to the stabilization power of the nitrogen atom[8] the triheterosubstituted radical **13** (Y = pyrrolidine) is not sufficiently reactive to maintain a viable chain reaction through addition to the double bond. Barton and McCombie have previously noted that a steroidal thiocarbamate did not undergo the stannane-induced deoxygenation.[4a] Although *O*-phenyl thionocarbonate **8** underwent the expected cyclization the reaction was found to be far more complex, giving a mixture of thiolactones **3** and **10** and lactone **11**.[9] When the reaction was repeated in toluene only **3** and **11** were obtained. This demonstrates that **11** was not formed via attack of the cyclized radical **17** on the solvent benzene. We propose a mechanism involving the intramolecular addition of the radical **17** onto the phenolic ring to give the spirohydroaromatic system **18**. Rearomatization with concommitant elimination of $Bu_3SnS^{\bullet}$ leads to formation of α-diphenylmethyl γ-lactone **11** (Scheme III). A part of the thionolactone **10** resulting from "normal cyclization" (cf. Scheme II) isomerized to the thiololactone **3** in boiling benzene while in boiling toluene this isomerization was complete.

We conclude that the intramolecular addition of a radical centered on a triheterosubstituted carbon atom (e.g. A, R = alk-3-enyl, Y = SMe or Im) to a suitably positioned double bond is favored over other possible competing processes like β-fission and hydrogen atom abstraction. These triheterosubstituted carbon radicals are synthetic equivalents to alkoxy carbonyl radicals. The former are effective intermediates in the synthesis of thionolactones under mild nonpolar conditions in the same way as the latter are in the synthesis of lactones (cf. eq 1; see ref 3). The rapid cyclization of free radicals of type A having a multiple bond in the side chain R may interfere with planned reactions involving fragmented radicals B.[10] We are currently investigating the scope and limitations of these and related free radical cyclization reactions.

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(8) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.

(9) **11**: NMR (270 MHz, CD_2Cl_2) δ 2.01–2.11 (m, 1 H, C*H*HCH$_2$O), 2.29–2.41 (m, 1 H, C*H*HCH$_2$O), 3.38–3.48 (dt, J = 6.8 Hz, 9.1 Hz, 1 H, CHC=O), 3.93–4.01 (dt, J = 4.0 Hz, 8.7 Hz, 1 H, C*H*HO), 4.08–4.18 (dt, J = 7.2 Hz, 8.7 Hz, 1 H, CH*H*O), 4.46 (d, J = 6.8 Hz, 1 H, Ph_2CH), 7.16–7.44 (m, 10 H); IR (film) 3028, 2912, 1766 vs (C=O), 1601, 1153, 1027 cm^{-1}; mass spectrum, m/e (relative intensity) 252 (M^+, 4), 167 (PhCHPh, 100), 165 (31), 115 (23), 91 (25), 77 (28); exact mass calcd for $C_{17}H_{16}O_2$ m/e 252.1150, found m/e 252.1158. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.97; H, 6.29.

(10) An example has been reported by Clive: Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 980.

Total Synthesis of (±)-Meloscine and (±)-Epimeloscine[1]

Summary: Total syntheses of the *Melodinus* alkaloids (±)-meloscine and (±)-epimeloscine are reported. These are the first reported total syntheses of members of this structurally unique alkaloid class.

Sir: The *Melodinus* alkaloids, isolated from the New Caledonian plant *Melodinus scandens* Forst., are structurally unique by virtue of incorporating a quinoline moiety within the *Aspidosperma* alkaloid skeleton.[2-4] These alkaloids, e.g. **2–4**, are believed to arise by oxidative rearrangement of 18,19-dehydrotabersonine (**1**), see Scheme I.[2] Although initial efforts to demonstrate this conversion in the laboratory were unsuccessful,[5] significant

(1) Part 20 in the series Synthesis Applications of Cationic Aza-Cope Rearrangements. For part 19, see: Overman, L. E.; Wild, H. *Tetrahedron Lett.*, in press.

(2) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886.

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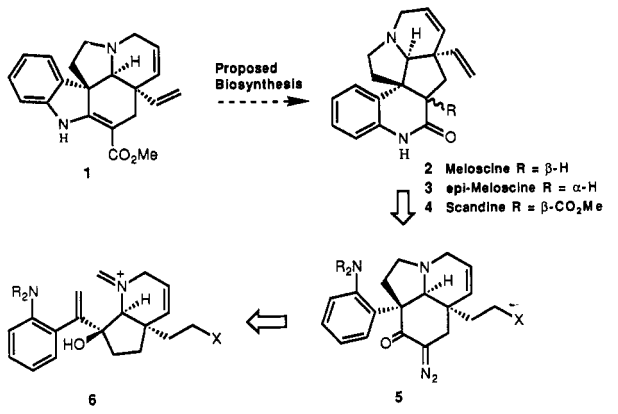
(4) Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett.* **1970**, 3395.

0022-3263/89/1954-1236$01.50/0

Scheme I

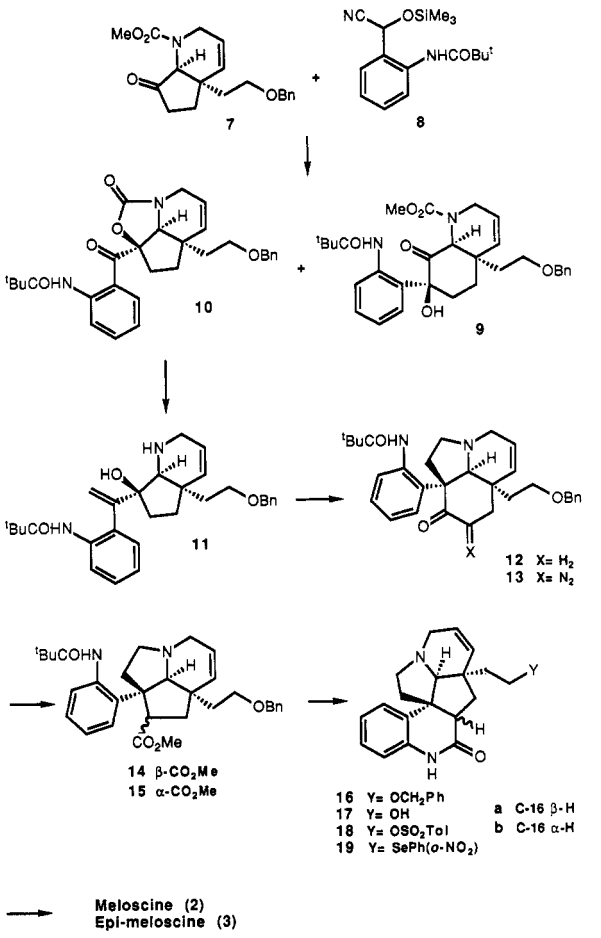


progress toward this aim has recently been reported.[6,7] Notably, the natural *Melodinus* alkaloids (+)-meloscine (**2**), and (+)-scandine (**4**) have been obtained by Hugel and Lévy from **1**.[7] These conversions, although nicely mimicing in part the proposed biotransformation, proceed in low (ca. 2%) overall efficiency.[7] In this communication we report the *first* total syntheses of members of the *Melodinus* alkaloid class. Our strategy, outlined in Scheme I, visualized Wolff ring-contraction of **5** to access the melodinus ring system. The key 9a-arylhydrolilolidine intermediate **5** was envisaged to arise by tandem cationic aza-Cope rearrangement–Mannich cyclization of formaldiminium ion intermediate **6**.[1]

Previous studies from these laboratories indicated that the allylic alcohol functionality of key intermediate **6** could be developed by combining a bicyclic ketone and a styrenyl nucleophile.[8] Thus, the *cis*-hexahydro-7*H*-1-pyridin-7-one **7** (see Scheme II) became our initial target. This intermediate was assembled on a preparative scale in 13 steps and 11% overall yields from readily available ethyl 2-oxocyclopentaneacetate[9] by using the general approach[8b] employed in our earlier *Aspidosperma* alkaloid synthesis.[10]

Coupling of the hydropyrindinone **7** with the dianion of trimethylsilyl cyanohydrin **8**[8a] under *carefully* controlled conditions provides, in high yield, the desired tricyclic carbamate **10** as a single stereoisomer. Optimum results were obtained when addition of ketone **7** to a THF solution of the dianion was conducted at −70 °C. Quenching at this temperature with sufficient 3 M HCl/MeOH to bring the pH to 6.5 prior to base hydrolysis of the crude isolate (LiOH in MeOH/H_2O, 0 °C) then afforded **10** in 76% yield. Deviation from these conditions led to considerable (15–60%) formation of the unwanted hydroquinolone **9**, which presumably arises by α-ketol rearrangement of a pyrindinol precursor.[11] Olefination of **10** (excess $Ph_3P{=}CH_2$, 23 °C) followed by selective hydrolysis of the cyclic

Scheme II



carbamate (excess KOH in EtOH/H_2O at 130 °C) gave the desired aza-Cope rearrangement precursor **11** in 78% yield.

Treatment of pyrindinol **11** with paraformaldehyde (3 equiv) and camphorsulfonic acid (0.9 equiv) in refluxing benzene for 3–5 h occasioned aza-Cope–Mannich rearrangement to afford the crucial tricyclic ketone **12** in 82% yield as a colorless solid (mp 120–120.5 °C). After a number of initial attempts to effect ring contraction of **12** met with failure, we found that the α-diazo ketone **13** could be prepared from **12** in near quantitative yield if diazo transfer from 2,4,6-triisopropylbenzenesulfonyl azide was carried out under phase-transfer conditions.[12] Subsequent irradiation of **13** (in 20:1 Et_2O/MeOH, 450-W Vycor-filtered Hanovia lamp, 18 min, 23 °C) produced two epimeric ring-contracted esters in a ratio of 4:1 and in excellent overall yield (95%) from ketone **12**. Treatment of either of the esters **14** or **15** with a large excess of KOH (ca. 700 equiv) in EtOH/H_2O (6:1) at 0 °C followed by slow warming to 150 °C over a 24-h period gave the desired pentacyclic amides **16a** and **16b** in 95% yield and a ratio of ca. 10:1, respectively.[13]

Elaboration of the major pentacyclic amide **16a** to (±)-meloscine (**2**) was straightforward. Debenzylation of **16a** with Na/NH_3 (−70 °C for 10 s) followed by tosylation of the resultant alcohol **17a** (TsCl, pyridine–$CHCl_3$, 23 °C, 16 h) afforded the primary tosylate **18a** in 96% yield after purification. Formation of the selenide **19a** was effected

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(10) All intermediates were fully characterized by ^{1}NMR, ^{13}C NMR, IR, and mass spectrometric analyses (see supplementary material). Elemental composition was determined for each intermediate by high resolution MS or combustion analysis. Unless otherwise indicated, yields refer to purified product isolated after chromatography on silica gel.

(11) NMR analysis indicates that the initial observable adduct is a mixture of the pyrindinol benzylic silyl cyanohydrin and cyanohydrin. The successful workup was designed to favor cyclization of the hydroxy carbamate grouping prior to cleavage of the cyanohydrin.

(12) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

(13) This interesting transformation is believed to proceed via hydrolysis of an initially formed pentacyclic imide. Warming the reaction mixture too rapidly results in simple hydrolysis of the ester to the tetracyclic acid derivative of **14**, which is not converted to **16** under these conditions.

in 58% efficiency (90% yield based on consumed starting material) by treatment of **18a** with excess *o*-nitrophenyl selenocyanate and $NaBH_4$ (EtOH, 23 °C, 20 h).[14] Oxidation of **19a** (*m*-chloroperoxybenzoic acid, -70 °C, CH_2Cl_2) followed by addition of Me_2S and Et_3N and simple warming to room temperature provided (±)-meloscine (**2**) in 81% yield as a colorless solid, mp 220-222 °C (Et_2O). Spectral (500-MHz ^1H NMR, ^{13}C NMR) properties of this material were consistent with those reported[2,15] and synthetic (±)-**2** was indistinguishable (by TLC comparisons) from an authentic sample of (+)-meloscine kindly provided by Professor J. Lévy. Repetition of this sequence with the minor pentacyclic diastereomer **16b** afforded (±)-epimeloscine (**3**)[2,15] in 43% overall yield from **16b**.

In summary, the *first* total syntheses of the structurally unusual *Melodinus* alkaloids, (±)-meloscine and (±)-epimeloscine, were accomplished by a highly stereocontrolled sequence. These syntheses provide further demonstration of the utility of tandem cationic aza-Cope rearrangement-Mannich cyclization reactions as key elements of alkaloid synthesis design.[1]

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Supplementary Material Available: Experimental procedures for preparing **10** and **16** as well as full characterization data for **7** and **10-19** (12 pages). Ordering information is given on any current masthead page.

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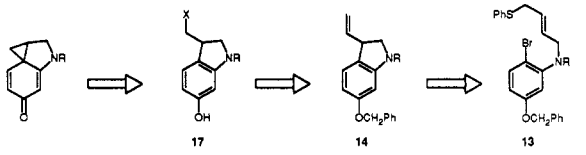
Total Synthesis of (±)-*N*-(Phenylsulfonyl)- and (±)-*N*-(*tert*-Butyloxycarbonyl)-CI, (±)-CI-CDPI$_1$, and (±)-CI-CDPI$_2$: CC-1065 Functional Analogues Incorporating the Parent 1,2,7,7a-Tetrahydrocycloprop[1,2-*c*]indol-4-one (CI) Left-Hand Subunit

Summary: The total synthesis of (±)-*N*-(phenylsulfonyl)- and (±)-*N*-(*tert*-butyloxycarbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [(±)-*N*-(phenylsulfonyl)-CI (**7**) and (±)-*N*-BOC-CI (**8**)] and its incorporation into the total synthesis of (±)-CI-CDPI$_1$ (**5**) and (±)-CI-CDPI$_2$ (**6**), minimum potent pharmacophores of the antitumor antibiotic CC-1065, are detailed.

Sir: (+)-CC-1065 (**1**, NSC-298223)[1] possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity. The site and mechanism of the (+)-CC-1065 antitumor activity has been related to its irreversible, covalent alkylation of sequence-selective B-DNA minor groove sites [5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′] and proceeds by acid-catalyzed, 3′-adenine N-3 alkylation of the electrophilic cyclopropane present in the left-hand subunit (CPI) of (+)-CC-1065.[2] In contrast to initial conclusions,[2-4] recent investigations have demonstrated that the sequence-selective DNA binding properties and antitumor activity of (+)-CC-1065 are embodied in the CPI left-hand subunit albeit at a substantially reduced potency (ca. 10000×).[5] Thus, the definition of the structural and functional features of the CC-1065 CPI left-hand subunit that contribute to its sequence-selective B-DNA minor groove binding properties, cytotoxic activity, and intrinsic antitumor activity has become important to the understanding of the properties of the agents.[6-9] Herein we detail the total synthesis of *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [*N*-(phenylsulfonyl)-CI (**7**) and *N*-BOC-CI (**8**)] constituting stable derivatives of the parent spirocyclic cyclopropylcyclohexadienone ring system of the CC-1065 left-hand subunit,[10] describe initial studies of their comparative properties versus the stable N^2-(phenylsulfonyl)-CPI (**3**) and N^2-BOC-CPI (**4**), and detail the incorporation of this parent CI left-hand subunit into the total synthesis of two functional analogues of CC-1065: (±)-CI-CDPI$_1$ (**5**) and (±)-CI-CDPI$_2$ (**6**),[11] constituting

Scheme I



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