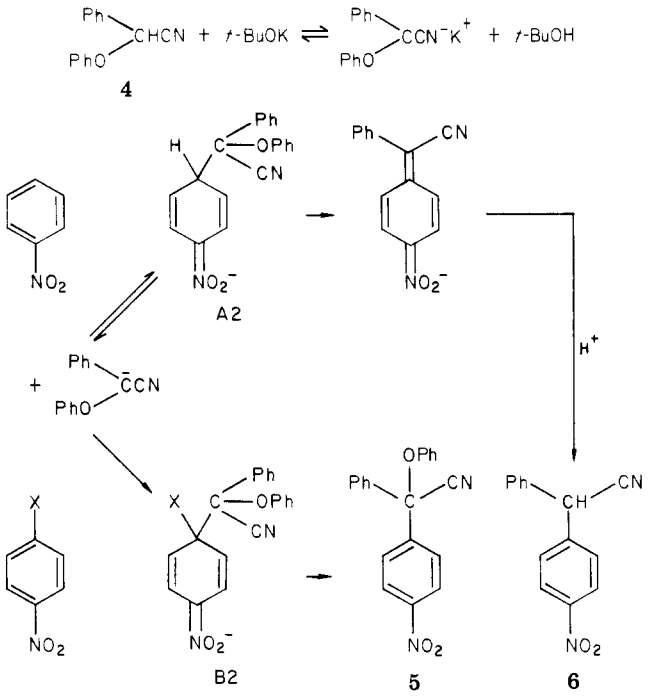
Scheme II[a]



	X	t-BuOK/4 ratio	yield, % 5	6
1	F	1.0	54	10
2	F	2.0	36	30
3	F	4.0	trace	50
4	Cl	1.0	56	8
5	Cl	2.0	24	45

[a] Tertiary carbanions replace hydrogen only para to the nitro group.[4] The procedure was identical to that applied for the reaction between 1 and 4-fluoronitrobenzene. Yields were determined after separation of the products by column chromatography.

out in the presence of an excess of NaOH in Me_2SO results in the substitution of both hydrogen and fluorine. Therefore, this reaction was used for studies of the competition.

The rates of the formation of σ complexes A1 and B1 and the conversion B1 → **2** do not depend on the presence of excessive base. On the other hand, the transformation of A1 into **3** should be accelerated if it proceeds via β-elimination and should not be if it involves the hydride shift. Hence, if the vicarious substitution of hydrogen proceeds via the hydride shift, the product ratio **2**/**3** should not be influenced by an excessive base; on the contrary, if it proceeds via β-elimination, an excess of base should favor the formation of **3**. The results shown in Scheme I lead to the conclusion that the reaction proceeds via β-elimination.

The same conclusion could be derived from the intermolecular competition of the substitution of hydrogen and halogen in nitrobenzene and 4-halonitrobenzene with tertiary carbanion of phenoxyphenylacetonitrile (**4**). (Scheme II). Here the tendency for substitution of halogen is more pronounced than in the case in Scheme I, but when the base concentration is high enough the substitution of hydrogen in nitrobenzene occurs exclusively.

The results shown in Schemes I and II allow one to exclude the hydride shift and accept the β-elimination as the way of transformation of σ complexes A into the products of the vicarious substitution. So far the differentiation between E2 and E1cB eliminations cannot be perceived.

The results shown in Schemes I and II evidence also reversibility of the formation of σ complexes A. Indeed, taking into account that the rate of the replacement of halogen by carbanions is not influenced by bases, the fact that an excess of base, via acceleration of the conversion of σ complexes A1 and A2 changes the reaction course shows that these complexes are formed in fast and reversible process.

The same conclusion can be drawn from the value of the isotope effect. Since the formation of σ complex A is not the rate-limiting step, the isotope effect is thermodynamic in its nature—the presence of deuterium instead of hydrogen atom shifts the equilibrium to the side of the σ complex, and, in consequence, deuterium is substituted somewhat faster than hydrogen. The absence of the primary isotope effect is, in our opinion, due to the nonsymmetric transition state of the β-elimination step.

The detailed results of further studies on the mechanism of this reaction will be published later.

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Registry No. **1**, 7205-98-3; 1 anion, 87013-25-0; **4**, 32121-27-0; **4** anion, 87013-26-1; D, 7782-39-0; nitrobenzene, 98-95-3; 4-fluoronitrobenzene, 350-46-9; 4-chloronitrobenzene, 100-00-5; 4-nitrobenzenediazonium tetrafluoroborate, 456-27-9; nitrobenzene-*4-d*, 13122-36-6.

Mieczysław Mąkosza,* Tomasz Glinka
Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw, Poland
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Total Syntheses of (±)-Mesembrine, (±)-Joubertinamine, and (±)-*N*-Demethylmesembrenone

Summary: The syntheses of three members of the sceletium alkaloid family are developed from a common synthon, leading to short, high-yielding stereorational routes to (±)-mesembrine, (±)-joubertinamine, and (±)-*N*-demethylmesembrenone. The latter is synthesized for the first time and allows its previously postulated role in providing the complex racemic alkaloid channaine to be examined. The sequence of reactions employed in obtaining the above alkaloids represents new synthetic methodology that is likely to be generally useful in providing an efficient entry into complex molecules containing a cis-2,3-fused pyrrolidine nucleus.

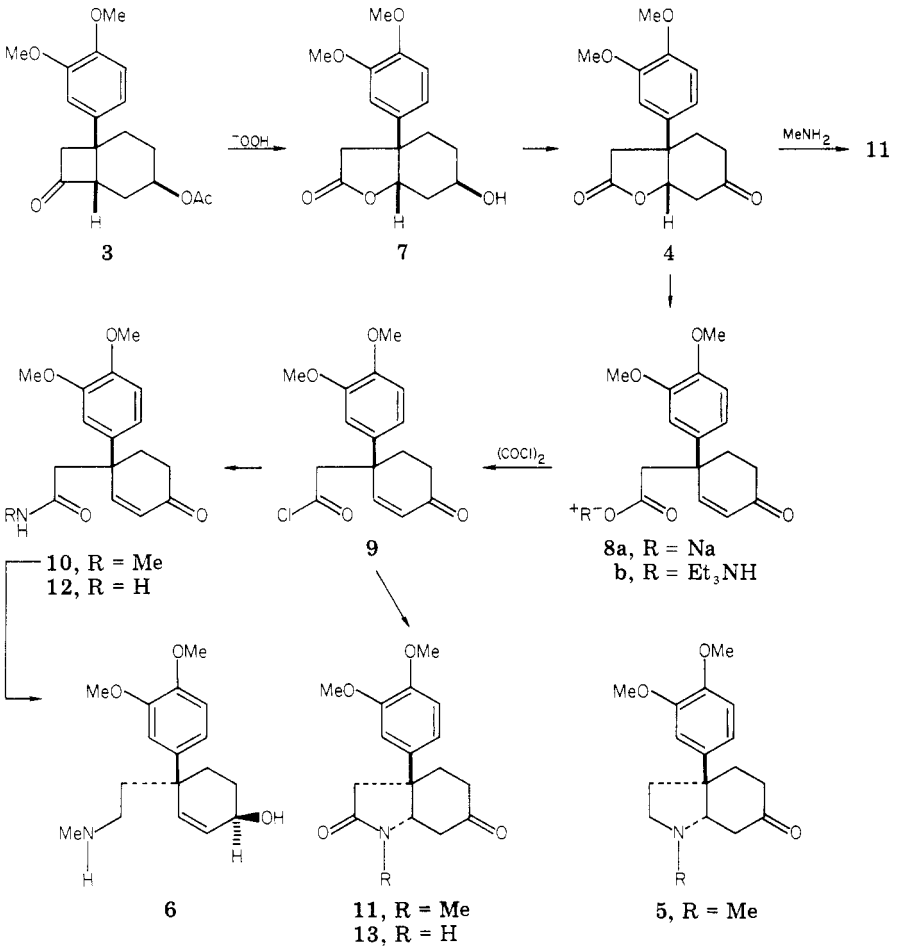
Sir: We have described recently a general synthetic route to the octahydroindole alkaloids of the mesembrine family and related bases of the joubertiamine type.[1] This synthesis had as its cornerstone the formation of a cis bicyclo[4.2.0]octanone and a controlled unidirectional aza-ring expansion of the latter to the octahydroindolone nucleus. Herein is described an alternative approach that has improved flexibility over the modified Beckman rearrangement utilized previously.

Besides the demonstration of efficient synthetic methodology, there is other motivation to prepare (±)-*N*-demethylmesembrenone. In pursuing isolation and structural studies of alkaloids of the *Sceletium* family, characteri-

(1) Jeffs, P. W.; Cortese, N.A.; Wolfram, J. *J. Org. Chem.* **1972**, *47*, 3881.

0022-3263/83/1948-3861$01.50/0

Scheme I



zation of the alkaloid channaine (1) has provided a base that represents not only a unique skeletal type but also contains an architecture that is considerably more complex than is extant in other member alkaloids of this family.[2] The racemic nature of channaine has prompted the suggestion that this compound may be an artifact, originating from (±)-*N*-demethylmesembrenone (2). Consequently, a synthesis of 2 was important not only in its own right but also as a means of examining the validity of the proposed origin of channaine.

Consideration of various synthetic routes to 2 suggested that oxa-ring expansion of an appropriately substituted bicyclo[4.2.0]octanone, cf. 3, to the keto lactone 4 would provide an attractive intermediate that could be elaborated to *Sceletium* bases of both the joubertiamine and mesembrine ring systems. The versatility of this approach is illustrated by short, high-yield syntheses of (±)-mesembrine (5),[3] (±)-joubertinamine (6),[4,5] and (±)-*N*-demethylmesembrenone (2).[8]

The dimethoxyphenyl-substituted cyclobutanone 3, obtained as previously described,[1] on reaction with 30% alkaline hydrogen peroxide (2.5 equiv) afforded the hydroxy lactone 7 in quantitative yield (Scheme I). Oxidation of 7 to the keto lactone 4 proceeded in 86% yield with pyridinium chlorochromate. The transformation of the keto lactone to the cis octahydroindolone 11 (R = Me) was accomplished by refluxing in ethanolic methylamine for 12 h. The success of this reaction contrasted with a similar attempt at ammonolysis of 4 with ethanolic ammonia at 25 °C that led to quantitative recovery of starting material. The synthesis of 11 (R = Me) constitutes a formal total synthesis of (±)-mesembrine since it has been converted previously in two steps to the alkaloid.[9]

Elimination of the β-keto lactone could be achieved with nonnucleophilic bases such as sodium hydride–benzene, or, more conveniently, with triethylamine in refluxing methanol, to afford the cyclohexenone carboxylate salts 8a or 8b, respectively, and ultimately provided direct access through the acid chloride 9 to several variants of the mesembrane and secomesembrane ring systems. The utility of this approach was demonstrated by a synthesis of (±)-jourbertinamine (6). Reaction of the lactone 4 with ethanolic triethylamine and treatment of the resulting salt 8b with oxalyl chloride in benzene gave a quantitative

(2) Abou-Donia, A.; Jeffs, P. W.; McPhail, A. T.; Miller, R. W. *J. Chem. Soc., Chem. Commun.* **1978**, 1078.

(3) For recent synthesis of (±)-mesembrine and related bases, see: Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. Keck, G. E.; Webb, R. R. *Ibid.* **1982**, *47*, 1302. Takano, S.; Imamura, Y.; Osawara, K. *Chem. Lett.* **1981**, 1385. Sanchez, I. H.; Tallabs, F. R. *Ibid.* **1981**, 891. Pearson, A. J.; Richards, I. C.; Gardner, D. V. *J. Chem. Soc., Chem. Commun.* **1982**, 807.

(4) The stereochemistry of the hydroxyl function has remained undefined in spite of a reported synthesis of joubertinamine.[5] The 6β-configuration inferred from ^{1}H NMR data[6] has been confirmed by relating it to mesembranol by a series of stereochemically unambiguous steps.[7]

(5) Psotta, K.; Wiechers, A. *Tetrahedron* **1979**, *35*, 255.

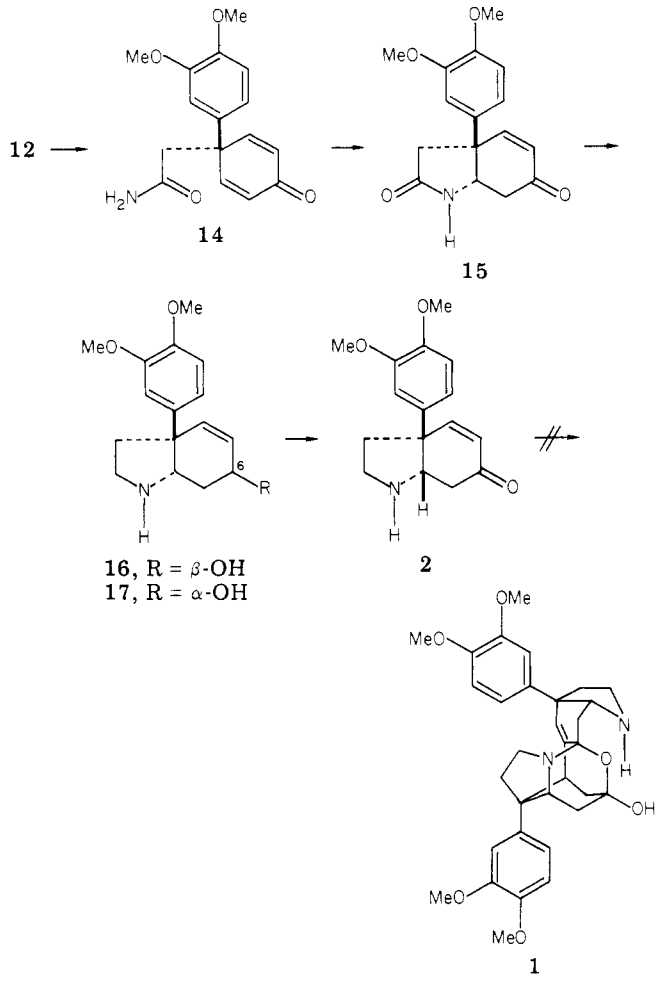
(6) Jeffs, P. W.; Capps, T. M.; Redfearn, R. *J. Org. Chem.* **1982**, 47, 3611.

(7) Jeffs, P. W.; Redfearn, R., unpublished observation.

(8) *N*-Demethylmesembrenone has not as yet been isolated as a naturally occurring base. Isolation of the closely related alkaloids, *N*-demethylmesembrenol (Kruger, P. E. J.; Arndt, R. R. *J. S. Afr. Chem. Inst.* **1971**, *24*, 235) and (±)-*N*-formyl-*N*-demethylmesembrenone (Karle, J. M. *Acta Crystallogr., Sect. B* **1977**, *B33*, 185) from *S. strictum* in which channaine also occurs suggests that *N*-demethylmesembrenone is likely to occur in this plant.

(9) Oh-Ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 299. Wijnberg, J. B. P. A; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579.

Scheme II



conversion to the acid chloride **9**. Transformation of **9** to the keto amide **10** was accomplished with 2.2 equiv of methylamine in methanol at 25 °C. Contrastingly, when **9** was reacted in the presences of excess methylamine in methanol at room temperature, 2-oxomesembrine (**11**) was obtained directly. Although the conversion of **10** to jourbertinamine required only the requisite reduction of the amide and enone functions, preferably in the latter case with appropriate stereochemical control,[6] the accomplishment of these seemingly trivial transformations was achieved only after considerable experimentation. Ultimately the conversion of **10** to (±)-joubertinamine (**6**) was achieved in 65% yield by a carefully controlled reduction with excess $LiAlH_4$ in THF at 0–10 °C for 2 h and 25 °C for 70 h. Increasing the temperature of this reaction led only to products that arise from reductive cleavage of the ethanamide side chain. The overall yield of (±)-joubertinamine from **3** by this route is 17%.

While the foregoing synthesis of (±)-mesembrine and (±)-joubertinamine provided the basis for a synthetic plan for (±)-*N*-demethylmesembrenone, two additional aspects required examination. Namely, a method for introduction of unsaturation represented by the 4,5-double bond and an effective procedure for the formation of the secondary γ-lactam were required. In the latter situation, the previous failure to effect the direct transposition of the keto lactone (**4**) to the corresponding secondary lactam with ammonia led us to examine a stepwise procedure for this transformation. In the event, conversion of **4** to the intermediate **9** and subsequent reaction of the latter with ammonia provided the amide **12**. Intramolecular Michael addition of the amide anion derived from **12** and LDA in DMF at 25 °C gave quantitative cyclization to the model cis octahydroindolone **13**. Following this success, introduction of the required unsaturation into the carbocyclic ring system was effected by oxidation of the enone amide **12** to the symmetrical dienone **14** with DDQ (Scheme II). Cyclization of the dienone with LDA–DMF afforded the γ-lactam **15**, which was reduced with $LiAlH_4$ to give a 80:20 mixture of the two epimeric *N*-demethylmesembrenols **16** and **17**. In view of the postulated origin of channaine,[2] it appeared desirable to generate *N*-demethylmesembrenone under neutral conditions. Attempts to effect this conversion by oxidation of **16** and **17** with activated MnO_2 in a range of solvents was unsuccessful. Fortunately, oxidation of mixture of the two allylic alcohols proceeded smoothly with pyridinium chlorochromate in CH_2Cl_2 to give (±)-*N*-demethylmesembrenone (**2**) in 95% yield.

Having successfully completed these syntheses, we now wished to test the biosynthetic hypothesis discussed above. If channaine is indeed an artifact, it should by produced in an acid- or base-catalyzed self-condensation of *N*-demethylmesembrenone. However, all attempts to effect this conversion were unsuccessful. In particular, (±)-*N*-demethylmesembrenone was recovered unchanged from 3 N HCl following basification, also from exposure to 2 N NaOH, and on elution from basic alumina. Since the foregoing conditions were generally representative, or in some cases more drastic than those used in the isolation of channaine from *S. strictum*, we reluctantly conclude that (±)-channaine should be considered as a natural product until further evidence is obtained to indicate otherwise.

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Registry No. (±)-**2**, 81255-05-2; (±)-**3**, 87014-17-3; (±)-**4**, 87014-19-5; (±)-**5**, 6023-73-0; (±)-**6**, 71357-60-3; (±)-**7**, 87014-18-4; (±)-**8a**, 87014-20-8; (±)-**8b**, 87014-22-0; (±)-**9**, 87014-23-1; (±)-**10**, 87014-24-2; (±)-**11** (R = Me), 21104-34-7; (±)-**12**, 87014-25-3; (±)-**13**, 87014-26-4; (±)-**14**, 87014-27-5; (±)-**15**, 87039-28-9; (±)-**16**, 87068-15-3; (±)-**17**, 87068-16-4; methylamine, 74-89-5.

* Address correspondence to Smith, Kline, and French Laboratories, Philadelphia, PA 19101.

Peter W. Jeffs,* Richard Redfearn
Joachim Wolfram
P. M. Gross Chemical Laboratory
Duke University
Durham, North Carolina 27706
Received April 21, 1983

Total Synthesis of the Lipid-Altering and Antiatherosclerotic Furochromone Khellin. The Furoic Acid Route to Highly Functionalized Benzofurans

Summary: 3-Furoic acid is converted to enaminone diester **8**, which undergoes Dieckmann cyclization to yield the highly functionalized benzofuran **9**. Methylation, Baeyer–Villager oxidation (CHO → OH) and conversion of the resulting hydroxy ester **10** to khellinone constitutes a formal synthesis of khellin.

Sir: Khellin (**1**) is one of several furochromones that can be isolated from *Ammi visnaga L.*, a perennial herbaceous plant that grows wild in many Eastern Mediterranean countries.[1] As early as 2270 B.C. the Egyptians were using

(1) Späth, E.; Gruber, W. *Chem. Ber.* **1938**, *71*, 106.

0022-3263/83/1948-3863$01.50/0