Total Synthesis of (±)-Chaenorhine

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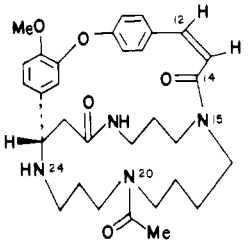
Chaenorhine (**1**; derived from *chaenorhinum origanifolium*),



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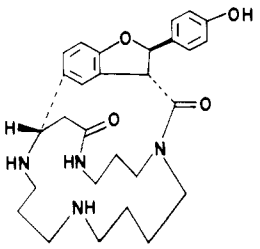

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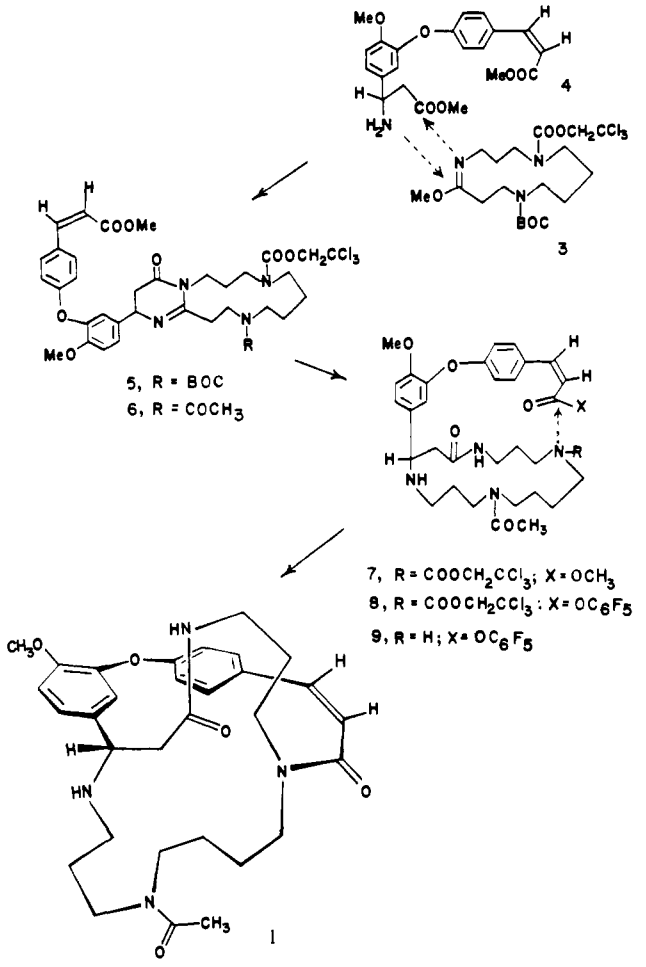
a member of the polyamine family of alkaloids, was isolated and characterized in the laboratories of Schmidt and Hesse.[1] Incorporating units corresponding to spermine and *p*-hydroxycinnamic acid, it is related to other naturally occurring macrocyclic polyamine lactams such as the hypotensive agent ephedradine A (**2**).[1c,2] An unusual feature common to both dilactams **1** and **2** is the bicyclic, cavity-like structure in which a 17-membered ring containing the spermine portion of the molecule is fused to a second large-ring system carrying the aromatic residue.

We now report the total synthesis of (±)-chaenorhine by a pathway involving successive ring expansions of smaller lactam systems.[3-5] The type of convergent synthesis used in forming chaenorhine suggests a general rationale for the formation of cryptate molecules in which there can be an unsymmetrical distribution of heteroatoms.[15]

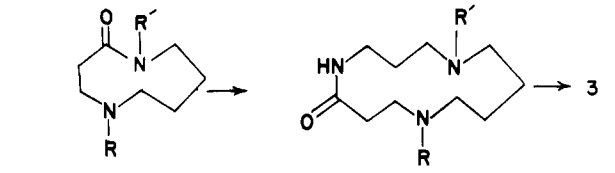
The synthesis is summarized in Scheme I showing the use of two key fragments, the 13-membered imino ether **3** and the substituted β-amino ester **4**. Coupling of these components to form **5** would be followed by reductive ring opening leading to **9**, the monocyclic precursor of chaenorhine. In addition to the projected macrocyclization of **9** to **1**, special problems in the synthesis appeared to involve the differentiation of the three secondary amino groups of the polyamine ring at N-15, N-20, and N-24 and the preservation of cis stereochemistry in the double bond at the 12-position.

Formation of the imino ether **3** containing the polyamine unit was carried out along the lines of our earlier celacinnine synthesis[4] and started with the nine-membered amino lactam **10**[5] (Scheme II). This was converted to the BOC derivative **11** ($(BOC)_2O$/CH_2Cl_2/25 °C) (99%) and then alkylated with 3-(*N*-bromopropyl)phthalimide (NaH/DMF/25 °C) to form **12** (75%). Removal of the phthalimido protecting group (H_2NNH_2/EtOH/reflux) provided the amino lactam **13** (93%), which was then converted to the 13-membered lactam **14** by refluxing in 2,4-lutidine,[6] followed by reaction with 2,2,2-trichloroethyl chloroformate (Et_3N/CH_2Cl_2/25 °C) to form **15**. The overall yield of **15** from **13** was 42%. The last step in this sequence involved treatment of **15** with Meerwein's reagent (Me_3O^+, BF_4^-/CH_2Cl_2/25 °C) and then aqueous $NaHCO_3$ to yield **3** (91%), normally used directly, without purification, for the subsequent coupling step.

Scheme I

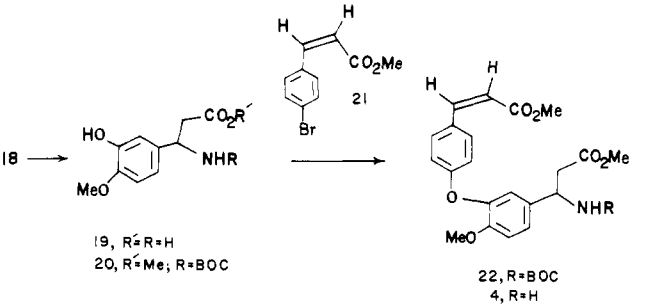


Scheme II



10, R = H; R′ = H
11, R = BOC; R′ = H
12, R = BOC; R′ = $(CH_2)_3$NPhth
13, R = BOC; R′ = $(CH_2)_3NH_2$
16, R = H; R′ = $(CH_2)_3NH_2$[6]
14, R = BOC; R′ = H
15, R = BOC; R′ = $CO_2CH_2CCl_3$
17, R = R′ = H[6]

Scheme III



19, R′ = R = H
20, R′ = Me; R = BOC
22, R = BOC
4, R = H

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(6) This transamidation reaction required more vigorous conditions than did the conversion of the unprotected amino lactam **16** to the 13-membered lactam **17** (1 N NaOH, 50 °C). The corresponding reaction in our celacinnine synthesis[4] also took place under much milder conditions. We thank Dr. K. Maruoka (Nagoya University) for an authentic sample of **17**.

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Component **4**, containing the aromatic residue, was prepared by the sequence outlined in Scheme III. The reaction of isovanillin (**18**) with NH_4OAc and malonic acid (*n*-BuOH/reflux) furnished the β-amino acid **19**[7] (64%), which was then esterified (MeOH/HCl/0 °C) and protected (BOC_2O/dioxane/H_2O/25 °C) to yield the phenolic intermediate **20** (99%). The copper phenoxide derived from **20** (NaH/py, CuCl) was coupled with methyl *cis*-*p*-bromocinnamate (**21**)[8] in refluxing pyridine forming the diaryl ether **22** (61%).[9] Removal of the BOC group (BF_3·Et_2O/HOAc/CH_2Cl_2/0 °C)[10] took place (90%) without isomerization of the double bond, yielding the required β-amino ester **4**.

The coupling of the amino ester **4** with the imino ether **3**[4,11] was achieved by heating the two reactants in chlorobenzene (115 °C/9 h) to form the bicyclic 4-oxotetrahydropyrimidine **5** (25%) along with the trans isomer (6%).[12] Selective introduction of the acetyl group at N-20 was then accomplished (80%) by removal of the BOC group (BF_3·OEt_2/CH_2Cl_2/0 °C)[10] followed by reaction with acetyl chloride (DMAP/CH_2Cl_2/25 °C).[13] The bicyclic product **6** was opened to the 17-membered lactam **7** under the conditions developed earlier[4,5] ($NaBH_3CN$/AcOH/50 °C) (95%).

The last phase of the synthesis required activation of the carboxylate at C-14. This was accomplished by hydrolysis of the methyl ester **7** (dilute NaOH/THF/MeOH/55 °C) followed by esterification with pentafluorophenol (DCC/THF/25 °C) yielding **8**. Removal of the 2,2,2-trichloroethoxycarbonyl group at N-15 and cyclization of the resulting amino ester to chaenorhine (**1**) was achieved by treatment of **8** with Zn/HOAc at 25 °C (12 h), filtration and evaporation of excess HOAc in vacuo, and then slow addition of the resulting diamino ester **9** (diacetate) in dioxane to a solution of DMAP (1 equiv) in pyridine (14 h/95 °C) (22% conversion of **7** to **1**).[14] The synthetic material was identical in all respects (TLC, 500-MHz NMR, MS, IR) with an authentic sample of natural (*S*)-(+)-chaenorhine kindly supplied by Professor M. Hesse, the University of Zurich. We are continuing our work on the synthesis of macrocyclic polyamine alkaloids, including ephedradine A (**2**).[15]

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Supplementary Material Available: ^1H NMR, infrared, and mass spectral and elemental analytical data, physical constants, and purification procedures for key intermediates (10 pages). Ordering information is given on any current masthead page.

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(8) *cis*-Methyl-*p*-bromocinnamate (**21**) was prepared starting from the methyl ester of *p*-bromophenylalanine hydrochloride (Dornow, A.; Winter, G. *Chem. Ber.* **1951**, *84*, 307). Esterification (CH_3OH, HCl) and diazotization (isoamyl nitrite) was followed by treatment with BF_3·Et_2O and DCC in CH_2Cl_2 according to the following procedure: Takamura, N.; Mizoguchi, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 299.
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(11) For earlier work on the reactions of β-amino esters and β-lactams with imino ethers see: (a) Takahata, H.; Tomoguchi, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1981**, *29*, 2526 and references contained therein. (b) Bormann, D. *Chem. Ber.* **1970**, *103*, 1797. In our experience, β-lactams give better yields in this coupling reaction. As yet we have not found an efficient route for the preparation of the β-lactam equivalent of **4**.
(12) Some isomerization of the cis double bond to the trans form took place at this stage. The cis/trans mixture (inseparable by liquid chromatography on silica gel) was carried through to the final cyclization step.
(13) Introduction of the acetyl group prior to the formation of the imino ether **3** was not feasible because of the sensitivity of the $NCOCH_3$ group to Meerwein's reagent. Hanessian, S. *Tetrahedron Lett.* **1967**, 1549.
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(15) Our approach to the synthesis of ephedradine A (**2**) involves the coupling of a suitable β-amino ester or β-lactam component with the imino ether **3**.

Argon Matrix Isolation of Bis(trifluoromethyl)oxirene, Perfluoromethylethyloxirene, and Their Isomeric Ketocarbenes

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Oxirenes represent the simplest and most elusive 4 n–π heterocycles, and although the search for them began over a century ago,[1] all attempts to isolate them have been unsuccessful to date.[2-5] Evidence for their transient existence was obtained in 1968 in the photochemical Wolff rearrangement of α-diazo ketones,[6] and since then they have been shown to occur as reactive intermediates in several other reactions.[7,8] Efforts for the isolation of their ring-opened isomers, the α-keto carbenes, have been more rewarding, and since 1968 several of them have been isolated in low-temperature matrices and identified by ESR spectroscopy.[9-12] However, attempts to observe their IR spectrum have failed to date.[3,4]

Ab initio MO calculations predict oxirene to be thermodynamically less stable than its ring-opened isomer, formylmethylene, and the ring-opening process to feature insufficient activation energy to kinetically stabilize the ring structure.[13] The ground state of formylmethylene is predicted to be a triplet with a small T_0–S_1 energy separation.[14]

Substituents and especially electron-withdrawing groups could enhance the ring stability of substituted oxirenes to the point that they might become stabilizable by low-temperature matrix isolation techniques as has been found to be the case with thiirenes.[8]

Consequently, we have carried out a detailed study of the low-temperature argon matrix photolysis of hexafluoro-3-diazo-2-butanone, **1**, octafluoro-2-diazo-3-pentanone, **2**, and octafluoro-3-diazo-2-pentanone, **3**, and report here the isolation of bis(trifluoromethyl)oxirene and perfluoromethylethyloxirene along with their corresponding ketocarbenes.

Photolysis of **1**[12,15] with λ >335 nm light resulted in the slow disappearance of the original IR spectrum and the appearance of the spectrum of bis(trifluoromethyl)ketene with significant absorptions at 2192 (s), 1420 (s), 1340 (s), 1310 (m), 1305 (w), 1300 (w), 1245 (w), 1188 (vs), 1180 (s), 1170 (s), 1165 (m), 1155 (m), 992 (m), 988 (m), 728 (w), 550 (w), 535 (w), and 450 (w) cm^{-1}, in agreement with the published spectrum.[16] In addition,

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