A New Access to Homoerythrina Alkaloids

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Summary: A new spiroannulation reaction based on a "one-pot", tandem alkylation–Michael addition sequence of 2-tetralone has been developed. The combination of this process with an intramolecular Schmidt rearrangement of an azido ketone allows an efficient access to the Homoerythrina skeleton.

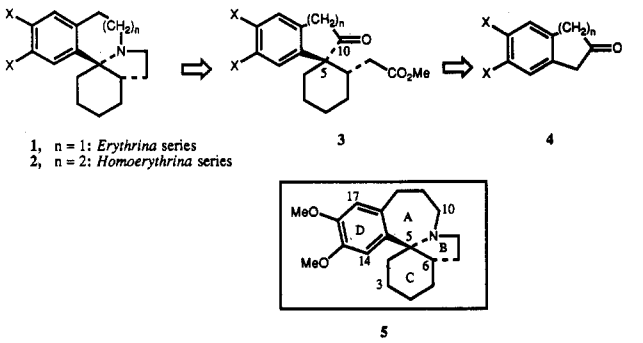
In contrast to the homologous series of *Erythrina* alkaloids,[1] and the related *Cephalotaxus* alkaloids,[2] the Homoerythrina bases have been largely neglected from both synthetic and pharmacological standpoints.[3]

The recent report that a strong molluscicidal activity is associated with some Homoerythrina alkaloids[4] prompted us to start a synthetic program toward these relatively underdeveloped systems. It appeared to us to be highly desirable to design a new, easily tunable strategy, in order to elaborate either Homoerythrina or *Erythrina* derivatives. Herein we report a novel, concise solution to this problem, culminating in the preparation of (±)-3-demethoxy-1,2-dihydrocomosidine (**5**).[5]

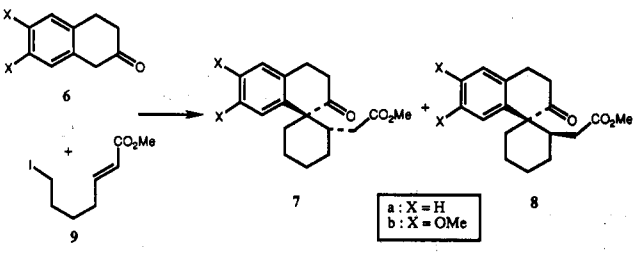
The central features of this approach are as follows: (i) a new spiroannulation reaction based on a tandem alkylation–Michael addition of 2-tetralone derivatives **4** ($n = 2$), allowing an efficient access to the spiro keto esters **3** ($n = 2$) in a stereoselective manner, and (ii) the construction of the AB ring system by a regioselective nitrogen insertion into the C5–C10 bond of azido ketones derived from keto esters **3** ($n = 2$), by means of a recently described intramolecular Schmidt reaction.[6,7]

On condensation of the sodium enolate of 2-tetralone (**6a**), generated with NaH, with the iodo ester **9**[8] (THF, 20 °C, 12 h), the desired spiro ester was obtained in 68% yield as an equimolar mixture of diastereomers **7a** and **8a**. However, when sodium hydride was replaced by cesium carbonate[9] (DMF, 20 °C, 12 h) *only* the adduct **7a**[10] was isolated in 66% yield, along with a trace amount of dialkylated product **10**. It should be noted that **10** was

Scheme I



Scheme II



obtained as the major product when a large excess of iodide **9** was used.

The stereochemical assignments of compounds **7a** and **8a** were supported by ^{1}H NMR, revealing a large NOE enhancement between the H-6 and H-14 for the spiro adduct **7a**. Such a phenomenon is absent in **8a**.

This finding showed unambiguously that the aromatic ring and the acetate appendage are in a *trans* diequatorial arrangement in compound **7a**.

The mechanism of this spiroannulation should be postulated as involving the initial alkylation of the tetralone enolate, followed by the intramolecular Michael addition of the resulting keto ester.[11] The obtention of the dialkylated product **10** corroborates such a mechanism. Furthermore, treatment of tetralone (**6a**) with the *tert*-butyl ester **12** using phase-transfer conditions (nBu$_4$N HSO$_4$, KOH 50%, CH_2Cl_2, 20 °C, 6 h) led to the monoalkylated derivative **13** in a modest yield. The latter

(1) For recent reviews of the *Erythrina* alkaloids, see: Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Brossi, Ed.; Academic Press: New York, 1981; Vol XVIII, Chapter 1; Manske, R. H. F. In *Alkaloids*; Academic Press: New York, 1967, Vol X, Chapter 12.

(2) For a recent review of the *Cephalotaxus* alkaloids, see: Hudlicky, T.; Kwart, L. D.; Reed, J. W. In. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed., Wiley: New York, 1987, Vol V, Chapter 5.

(3) For a recent reviews of the Homoerythrina alkaloids, see: Bick, R. I.; C. Panichanun, S. In. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed., Springer Verlag: New York, 1990, Vol VII, Chapter 1.

(4) Aladesanmi, A. J.; Adewunmi, C. O.; Kelley, C. J.; Leary, J. D.; Bischoff, T. A.; Zhang, X.; Snyder, J. K. *Phytochem.*, **1988**, *27*, 3789–3792.

(5) Langlois, N.; Das, B. C.; Potier, P.; Lacombe, L. *Bull. Soc. Chim. Fr* **1970**, 3535.

(6) For consistency, the numbering system used throughout this paper is the one of Homoerythrina alkaloids.

(7) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.*, **1992**, *57*, 1635–1637. Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.*, **1991**, *113*, 8965–8966. Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.*, **1992**, *33*, 5291–5294.

(8) Methyl (*E*)-7-iodo-2-heptenoate **9** was prepared from 2-hydroxytetrahydropyran by adapatation of known procedures. Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381–1396.

(9) Potassium carbonate was found to be ineffective in this transformation, leading mainly to the dialkylated product **10**, along with spiro compound **7a** (25% yield).

(10) **7a**: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.47 (d, J = 7.97 Hz, 1H), 7.20 (m, 3H), 3.49 (s, 3H), 3.10 (m, 2H), 2.86 (ddd, J = 13.1, 10.6, 7.2 Hz, 1H), 2.45 (m, 2H), 2.24 (dd, J = 15.4, 10.0 Hz, 1H), 2.20 (m, 1H), 2.04 (broad d, J = 14.1 Hz, 1H), 1.94 (dd, J = 15.4, 3.2 Hz, 1H), 1.75 (m, 4H), 1.58 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8 (C), 173.4 (C), 142.9 (C), 136.4 (C), 127.9 (CH), 127.1 (CH), 126.6 (CH), 126.3 (CH), 54.5 (C), 51.1 (CH_3), 41.6 (CH), 39.5 (CH_2), 38.5 (CH_2), 36.3 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 25.7 (CH_2), 21.9 (CH_2); IR (neat, cm^{-1}) 1730, 1700, 1440; MS (EI, 70 eV) m/e 286 (M^+, 100), 254 (59), 197 (12), 169 (27), 159 (63), 128 (49), 91 (32), 59 (9). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.39; H, 7.89.

(11) A competition experiment conducted by treatment of tetralone **6a** with 1-iodo-5-hexene (2 equiv) and methyl crotonate (2 equiv) in the presence of cesium carbonate led exclusively to a mixture of mono- and dihexenyltetralone derivatives.

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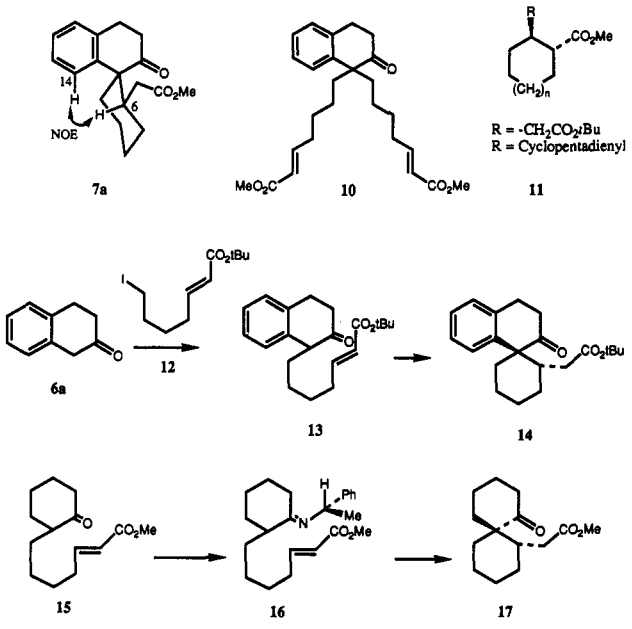
Scheme III



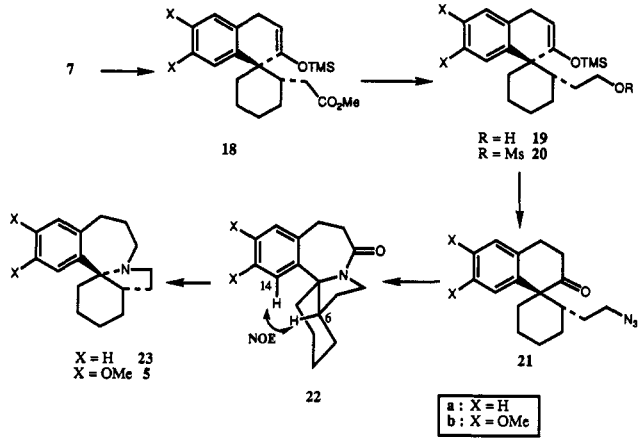
could be cyclized by means of *t*BuOK in THF into spiro derivative **14**. This result further probes a mechanism in which the alkylation step takes place first, followed by the intramolecular Michael addition. This is in striking contrast with the previously reported behavior of cyclopentadienyl anions or lithium ester enolates toward iodide **9** and homologs. Indeed, these more basic nucleophiles react according to a mechanism in which the Michael addition takes place first, followed by an intramolecular alkylation of the resulting enolate, to give compounds of type **11**.[12]

At first glance the formation of the single stereomer **7a** during the spiroannulation, when cesium carbonate is used as base, might reflect a thermodynamic control during the key Michael addition, through a retro-Michael process;[13] however, we were unable to detect evidence of such an equilibration by treating an equimolar mixture of adducts **7a** and **8a** with cesium carbonate (DMF, 22 °C, 24 h). Therefore, the stereochemical course of the present spiroannulation is more likely the result of a kinetic control, possibly directed by the chelation of the ester group of the heptenoate appendage by the cesium counterion of the tetralone enolate.

It is noteworthy that a similar stereochemical finding is observed during the spiroannulation of the keto ester **15**. Indeed this intramolecular Michael addition reaction, which proceeds through imine **16**, led to the *single* adduct **17**.[14]

In a similar fashion, condensation of 6,7-dimethoxy-2-tetralone[15] **6b** with iodide **9** (3 equiv of Cs_2CO_3, DMF, 20 °C) gave spiro compound **7b** in 48% yield as a single isomer. It should be noted that the sodium enolate of **6b** reacted with iodo ester **9** to give **7b** in low yield.

Scheme IV



With keto esters **7a,b** in hand, we then turned our attention to the preparation of the azido ketones **21**, the requisite substrates for the crucial Schmidt rearrangement.[7] All attempts at ketalization of the keto group of **7a** led either to unchanged starting materials or extensive decomposition; however, trimethylsilyl triflate smoothly converted **7a** into enol ether **18a** (3 equiv of TMSOTf, CH_2Cl_2, Et_2N, 20 °C, 48 h). Lithium aluminum hydride reduction of **18a**, followed by treatment with methanesulfonyl chloride, proceeded uneventually to give mesylate **20a**. Finally, sodium azide displacement of the mesylate group occurred with concomitant cleavage of the trimethylsilyl enol ether to provide the desired azido ketone **21a** in an overall yield of 53% from **7a**. The same reaction sequence, starting with the dimethoxy spiro ketone **7b**, afforded azido ketone **21b** in an overall yield of 51%.

We next examined the nitrogen insertion by the intramolecular Schmidt rearrangement.[7] In the event, treatment of compound **21a** with TFA (CH_2Cl_2, 20 °C, 6 h), led to the *single* lactam **22a**[16] in 81% yield. The structural assignment of the latter compound rests on ^1H and ^{13}C NMR data, including COSY and CH correlation spectra.

The presence of only one methylene group bearing a nitrogen atom in the ^{13}C NMR (DEPT) spectrum of lactam **22a** unambiguously demonstrates the regioselectivity of the rearrangement. Evidence for the relative stereochemistry depicted in structure **22a** came from the strong NOE enhancement between H-6 and the aromatic proton H-14. We should note that the stereochemistry of the Schmidt product **22a** confirms the stereochemical assignment proposed for the parent spiro keto ester **7a**.

In a similar fashion, azido ketone **21b**[17] was converted into **22b** in 85% yield (neat TFA, 30 °C, 1 h). LAH reduction (THF, 20 °C, 18 h) of **22a** afforded smoothly the tetracyclic base **23** in 92% yield. Similarly, **22b** gave (±)-3-demethoxy-1,2-dihydrocomosidine **5**[18] (95% yield).

The methods outlined herein should be flexible enough to synthesize a large variety of Homoerythrina alkaloids;

(12) Stille, J. R.; Grubbs, R. H. *J. Org. Chem.* **1989**, *54*, 434–444. Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723–1726. Recently, sulfur and nitrogen nucleophiles have been reported to undergo similar tandem $S_{N}2'$–Michael reactions with **9** and homologs, in which the alkylation step occurred first: Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *54*, 1727–1733.

(13) According to MMX calculation, compound **7a** is predicted to be 2.4 kcal mol^{-1} more stable than diastereomer **8a**.

(14) d'Angelo, J.; Ferroud, C.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1989**, *30*, 6511–6514.

(15) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129–130.

(16) **22a**: mp 124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 1H), 7.22 (m, 3H), 3.82 (ddd, *J* = 12.7, 9.1, 1.9 Hz, 1H), 3.61 (m, 1H), 3.53 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.98 (ddd, *J* = 17.4, 5.2, 3.9 Hz, 1H), 2.94 (m, 1H), 2.74 (ddd, *J* = 15.5, 5.1, 4.7 Hz, 1H), 2.48 (m, 2H), 2.10 (m, 2H), 1.88 (m, 3H), 1.61 (m, 3H), 0.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9 (C), 140.4, (C), 139.7 (C), 130.6 (CH), 127.7 (CH), 127.6 (CH), 126.1 (CH), 66.5 (C), 46.5 (CH_2), 43.1 (CH), 36.2 (CH_2), 35.3 (CH_2), 30.3 (CH_2), 27.0 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 20.7 (CH_2); IR (neat, cm^{-1}) 1592; HRMS (EI, 70 eV) calcd for $C_{17}H_{21}NO$ (M^+) 255.1623, found 255.1624.

(17) Azido ketone **21b** should be carefully purified in order to get reproducible results in this transformation.

moreover, an extension of this methodology to the preparation of *Erythrina* alkaloids, starting from 2-indanone derivatives **4** (n = 1), is currently under investigation in our laboratory.

(18) **5**: ^{1}H NMR (400 MHz, acetone-d_6) δ 6.97 (s, 1H), 6.65 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.16 (ddd, J = 14.16, 10.62, 3.16 Hz, 1H), 3.01 (m, 2H), 2.79 (m, 4H), 2.56 (m, 1H), 2.22 (broad d, J = 13.6 Hz, 1H), 1.83 (broad q, J = 12.5 Hz, 1H), 1.70–1.50 (m, 6H), 1.43–1.25 (m, 2H); ^{13}C NMR (50 MHz, C_6D_6) δ 148.2 (2C), 140.3 (C), 135.3 (C), 117.0 (CH), 114.3 (CH), 67.6 (C), 56.9 (CH_3), 56.1 (CH_3), 48.7 ($2CH_2$), 43.3 (CH), 37.8 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 28.2 (CH_2), 26.5 (CH_2), 25.7 (CH_2), 22.7 (CH_2); IR (neat, cm^{-1}) 2928, 2852, 1606, 1582, 1511, 1460, 1442.

Acknowledgment. The authors acknowledge J. Mahuteau for her assistance in carrying out NMR studies.

Supplementary Material Available: Experimental procedures and spectral data, including ^{1}H and ^{13}C NMR data of compounds **7a,b**, **8a**, **21a,b**, **22a,b**, **23**, and **5** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.