Pergamon

Tetrahedron Letters, Vol. 37, No. 36, pp. 6611-6614, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01412-8

Construction of the Quaternary C-7 Centre of Akuammiline Alkaloids. Synthesis of 3,4-Secoakuammilan Derivatives

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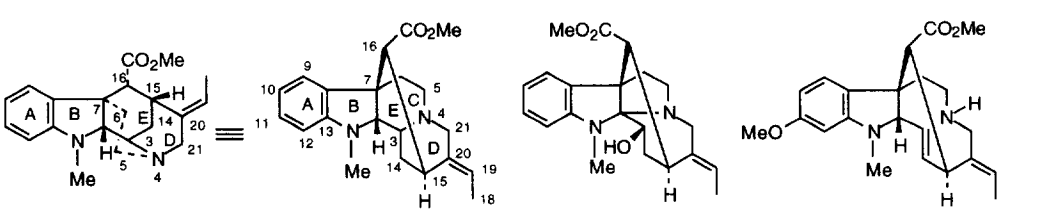
Abstract: The first synthesis of 3,4-secoakuammilan derivatives is reported, the key step being the formation of the quaternary C-7 centre by Pummerer cyclization of tetrahydrocarbazole sulfoxide **4**.

The akuammiline-type alkaloids[1] (*e.g.* cathafoline, Figure 1) constitute a subgroup of Corynanthean indole alkaloids[2] characterized by the existence of a C_7-C_{16} bond[3] and, consequently, by the presence of a quaternary, highly congested, carbon centre at C-7. Although these alkaloids have received some attention from the synthetic standpoint, the efforts in this field have not so far succeeded in the synthesis of natural products. Thus, attempts to construct the quaternary centre at C-7 of the akuammiline alkaloids either by closure of the E ring from appropriately substituted C/D ring-cleaved indolo[2,3-*a*]quinolizidines (bond formed C_7-C_{16}; biomimetic approach)[4] or by closure of the C ring from tetracyclic 6,7-seco derivatives[5] have resulted in failure.[6]

The latter unsuccessful results suggested that the generation of the crucial quaternary C-7 centre by formation of C_6-C_7 bond would be more easily accomplished by cyclization on the indole 3-position from more flexible, less crowded, tricyclic 3,4-seco intermediates. This approach could also constitute a synthetic entry to the alkaloids that possess the 3,4-secoakuammilan skeleton, such as those of the echitamine series

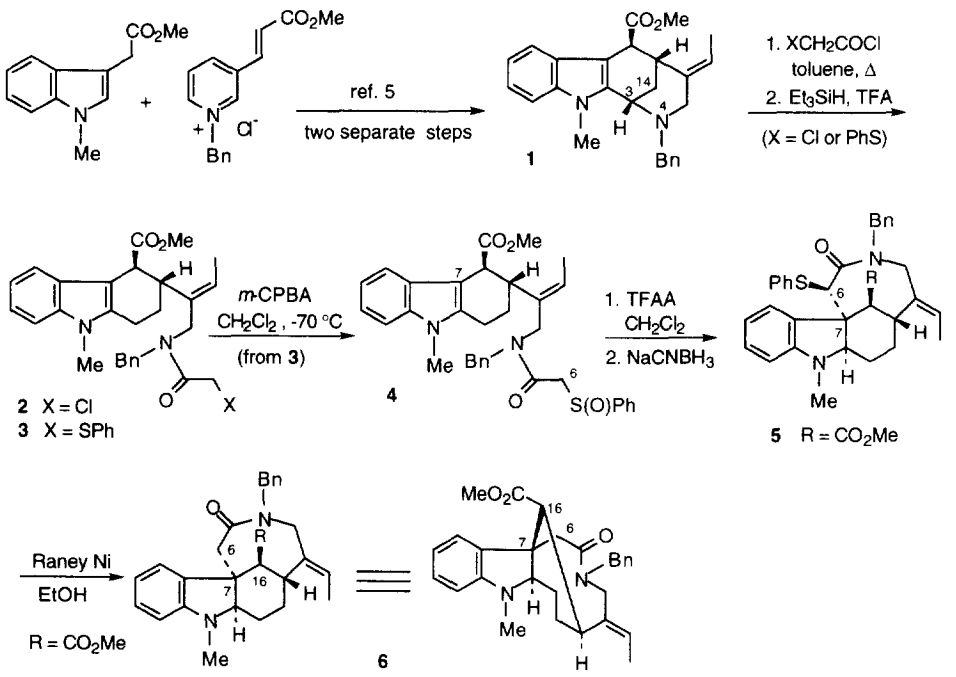


Cathafoline (Akuammiline series) | Deformocorymine (Echitamine series) | 3,4-Seco-3,14-dehydrocabucraline

Figure 1

(2,4-cyclo-3,4-secoakuammilan) or the tetracyclic alkaloid 3,4-seco-3,14-dehydrocabucraline.[7] With this aim, in a previous work[8] we studied the photocyclization of tricyclic chloroacetamide **2** (Scheme 1); however, contrary to our synthetic interest, cyclization occurred on the indole 4-position to give a tetracyclic ten-membered lactam embodying an unnatural ring system.

We present here the first synthetic construction of the 3,4-secoakuammilan skeleton. The key step was an electrophilic cyclization on the indole 3-position of a thionium ion generated by Pummerer rearrangement[9] of a tricyclic amido sulfoxide, with formation of an eight-membered ring lactam.[10] The required sulfoxide **4** was prepared as outlined in Scheme 1, from the known tetracycle **1**,[5] taking advantage of the easy cleavage of the C_3-N_4 bond in isogramine-type systems.[11] Thus, treatment of **1** with (phenylsulfinyl)acetyl chloride followed by reduction of the resulting dihydrocarbazole with triethylsilane in the presence of trifluoroacetic acid gave tetrahydrocarbazole **3**[12] (62% overall yield[13]), which was then chemoselectively oxidized at the sulfur atom with *m*-CPBA to give sulfoxide **4**[14] (72% yield) as a mixture of stereoisomers.



Scheme 1

Pummerer rearrangement of amido sulfoxide **4** was carried out under the usual conditions (TFAA in dichloromethane at 0 °C for 10 min). When the presumed acyloxy sulfide intermediate was refluxed in dichloromethane for 6 h and the crude mixture was treated with sodium cyanoborohydride to reduce the α-methyleneindoline double bond, the desired tetracyclic lactam **5**[15] was isolated in 23% yield as a single diastereoisomer. Variable amounts of sulfide **3**, coming from the reduction of the intermediate thionium ion,

were also obtained. Finally, desulfurization of **5** with Raney nickel (W-2) in ethanol gave tetracycle **6**[16] in 80% yield.

Inspection of the ^{1}H- and ^{13}C-NMR spectra of lactam **5** allowed the unambiguous elucidation of its structure with the aid of 2D-NMR techniques (^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY). That cyclization had occurred on the indole 3-position was clearly established by the observation of a quaternary carbon at δ52.5 in the ^{13}C-NMR spectrum and by HMBC correlations of 6-H with C-2 and C-7, and 16-H with C-2, C-6 and C-7. The relative configuration of C-2 was inferred from the chemical shift of this carbon (δ69.2)[17] and from the observation of a NOESY cross peak between 2-H and 6-H that would not exist in the opposite configuration. A similar spectroscopic analysis from **6** was in complete agreement with the above structural assignment.

The strategy developed here provides a solution for the construction of the quaternary C-7 centre of akuammiline alkaloids that might be applicable to the synthesis of alkaloids of this group.

Acknowledgment. Financial support from the DGICYT, Spain (project PB94-0214) is gratefully acknowledged. Thanks are also due to the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya, for Grant SGR95-0428.

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12. **3** (3:1 mixture of rotamers): ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.65 (d, J = 6.8 Hz, 3H, 18-H), 1.86 (m, 2 H, 14-H), 2.84 (m, 2H, 3-H), 3.33 (m, 1H, 15-H), 3.61 (s, 3H, OMe), 3.68 (s, 5H, NMe, 6-H), 3.90 (m, 2H, 16-H, 21-H), 4.60 (m, 2H, CH_2Ph), 5.45 (q, J = 6.8 Hz, 1H, 19-H), 7.05-7.60 (m, 14H); ^{13}C-NMR ($CDCl_3$, 75 MHz) 12.8 (C-18), 22.1 (C-3), 26.8 (C-14), 29.1 (NMe), 36.4 (C-6), 38.8 (C-15), 43.8 (C-16), 47.4 (C-21), 48.8 (CH_2Ph), 51.8 (OMe), 105.9 (C-7), 108.7 (C-12), 117.4 (C-9), 119.3 (C-10), 120.3, 121.0 (C-11, C-19), 125.5 (C-8), 133.5 (C-20), 135.4 (C-2), 136.9 (C-13), 169.7, 174.7 (CO).
13. All yields are from material purified by column chromatography. All new compounds gave satisfactory spectral, analytical and/or HMRS data.
14. **4** (mixture of stereoisomers at sulfur): mp 78-80 °C (hexane-ether); ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.57 (m, 3H, 18-H), 1.84 (m, 2H, 14-H), 2.82 (m, 2H, 3-H), 3.28 (ddd, J = 11, 10, and 1.9 Hz, 1 H, 15-H), 3.60 (s, 3H, OMe), 3.67 (s, 3H, NMe), 3.70-4.20 (m, 5H, 21-H, 16-H, 6-H), 4.50 (m, 2H, CH_2Ph), 5.14 (m, 1H, 19-H), 7.05-7.70 (m, 14H); ^{13}C-NMR ($CDCl_3$, 75 MHz, major stereoisomer) 12.9 (C-18), 22.1 (C-3), 26.8 (C-14), 29.1 (NMe), 38.8 (C-15), 43.7 (C-16), 47.3 (C-21), 48.8 (CH_2Ph), 51.9 (OMe), 61.2 (C-6), 105.9 (C-7), 108.9 (C-12), 117.5 (C-9), 119.4 (C-10), 121.1, 124.5 (C-11, C-19), 125.5 (C-8), 133.0 (C-20), 135.4 (C-2), 136.6 (C-13), 165.4, 174.6 (CO).
15. **5**: ^{1}H-NMR ($CDCl_3$, 500 MHz) 1.55 (m, 1H, 14-H), 1.65 (d, J = 6.5 Hz, 3H, 18-H), 1.80 (m, 1H, 14-H), 2.22 (m, 1H, 3-H), 2.40 (m, 1H, 3-H), 2.84 (s, 3H, NMe), 3.01 (s, 1H, 16-H), 3.13 (s, 3H, OMe), 3.24 (d, J = 15.5 Hz, 1H, 21-H), 3.49 (dd, J = 9.5 and 10 Hz, 1H, 15-H), 3.79 (d, J = 15 Hz, 1H, CH_2Ph), 3.91 (dd, J = 8 and 10 Hz, 1H, 2-H), 4.30 (d, J = 15.5 Hz, 1H, 21-H), 4.34 (s, 1H, 6-H), 5.42 (q, J = 6.5 Hz, 1H, 19-H), 5.62 (d, J = 15 Hz, 1H, CH_2Ph), 6.42 (d, J = 8 Hz, 1H, 12-H), 6.64 (dd, J = 7 and 7.5 Hz, 1H, 10-H), 7.10-7.30 (m, 11H, Ph, 11-H), 7.65 (dd, J = 7.5 and 1 Hz, 1H, 9-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) 13.2 (C-18), 21.3 (C-14), 24.2 (C-3), 33.1 (C-15), 34.3 (NMe), 48.2 (CH_2Ph), 49.0 (C-16), 51.5 (C-21), 51.6 (OMe), 52.5 (C-7), 62.3 (C-6), 69.2 (C-2), 106.3 (C-12), 117.0 (C-10), 127.3-130.5 (complex signal), 131.5 (C-8), 135.5 (C-20), 153.0 (C-13), 170.4, 174.7 (CO).
16. **6**: ^{1}H-NMR ($CDCl_3$, 500 MHz) 1.02 (m, 1H, 14-H), 1.65 (d, J = 7 Hz, 3H, 18-H), 1.77 (m, 1H, 3-H), 2.04 (m, 1H, 14-H), 2.14 (m, 1H, 3-H), 2.72 (s, 3H, NMe), 2.79 (d, J = 13.5 Hz, 1H, 6-H), 3.02 (s, 1H, 16-H), 3.08 (s, 3H, OMe), 3.20 (t, J = 8.5 Hz, 1H, 15-H), 3.28 (d, J = 16 Hz, 1H, 21-H), 3.31 (d, J = 13.5 Hz, 1H, 6-H), 3.52 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.73 (t, J = 7.5 Hz, 1H, 2-H), 4.37 (d, J = 16 Hz, 1H, 21-H), 5.34 (d, J = 14.5 Hz, 1H, CH_2Ph), 5.37 (q, J = 7 Hz, 1H, 19-H), 6.36 (d, J = 8 Hz, 1H, 12-H), 6.51 (dd, J = 7 and 8 Hz, 1H, 10-H), 6.88 (d, J = 7 Hz, 1H, 9-H), 7.00 (dd, J = 7 and 8 Hz, 1H, 11-H), 7.20-7.30 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$, 75 MHz) 13.5 (C-18), 22.7 (C-14), 22.8 (C-3), 33.2 (C-15), 33.6 (NMe), 46.6 (CH_2Ph), 47.5 (C-7), 50.3 (C-6), 51.3 (C-16), 51.6 (OMe), 52.6 (C-21), 65.4 (C-2), 106.8 (C-12), 116.5 (C-10), 123.1 (C-9), 126.9 (C-19), 127.4 (C-11), 128.4, 128.6 (Ph), 134.7 (C-8), 136.4 (Ph), 137.0 (C-20), 151.4 (C-13), 170.4, 174.9 (CO).
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(*Received in UK* 26 *June* 1996; *accepted* 19 *July* 1996)