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A SHORT BIOMIMETIC SYNTHESIS OF THE ISOQUINOLINE AND THE NAPHTHALENE MOIETIES OF ANCISTROCLADUS ALKALOIDS FROM COMMON ß-POLYCARBONYL PRECURSORS

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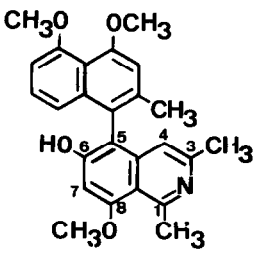
Summary: The diketones (**8**) and (**11**), key intermediates for an biogenetically modelled synthesis of the ancistrocladus alkaloids, were each prepared in one step only, and transformed into the isoquinoline and naphthalene moieties of (**1**) and (**2**).

The spasmolytically active lianas of the genera Ancistrocladus and Triphyophyllum contain a group of structurally and biogenetically unique isoquinoline alkaloids[1], two representatives of which are ancistrocladeine (**1**)[2] and tetradehydro triphyophylline (**2**)[3]. The unusual substitution pattern of these alkaloids does not fit in the known biosynthetic scheme of isoquinoline formation from aromatic aminoacids like tyrosine, applicable to all the numerous isoquinoline alkaloids investigated so far. The methylgroup at C-3 and the naphthalene substituent at C-5 or C-7, as well as the oxygen function at C-8 strongly point to a hitherto unprecedented biogenetic pathway to isoquinoline alkaloids from acetate via ß-polyketones.



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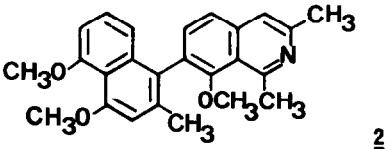

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We have recently been able to demonstrate the chemical plausibility of the polyketide character of the ancistrocladus alkaloids by facile cyclization of selectively protected ß-pentaketones, which had been obtained by mild ozonolysis of dihydroindanes[4]. We now wish to describe a drastically shortened way to such ß-pentaketones, as a valuable device for a short biogenetically modelled synthesis of the naphthyl isoquinoline alkaloids.

Double condensation of diesters like (3) and (16) with acetone seemed to be a promising strategy for building up β-pentaketone derived intermediates (7) and (10) very rationally in one step only. However, in contrast to the successful synthesis of heptaketones by a similar twofold reaction of dilithio acetylacetone[5], we could not find detectable amounts of (7) or its cyclization product (8) in the reaction of diester (3) with different enolates of acetone (4, M = K, Na, or Li). The apparent difficulties - the relatively weak reactivity of acetone monoanions, which demands high reaction temperatures where decomposition already occurs, as well as the tendency of acetone to undergo selfcondensation - could be overcome by using the dianion of acetone (5), a highly nucleophilic reagent recently described[6].

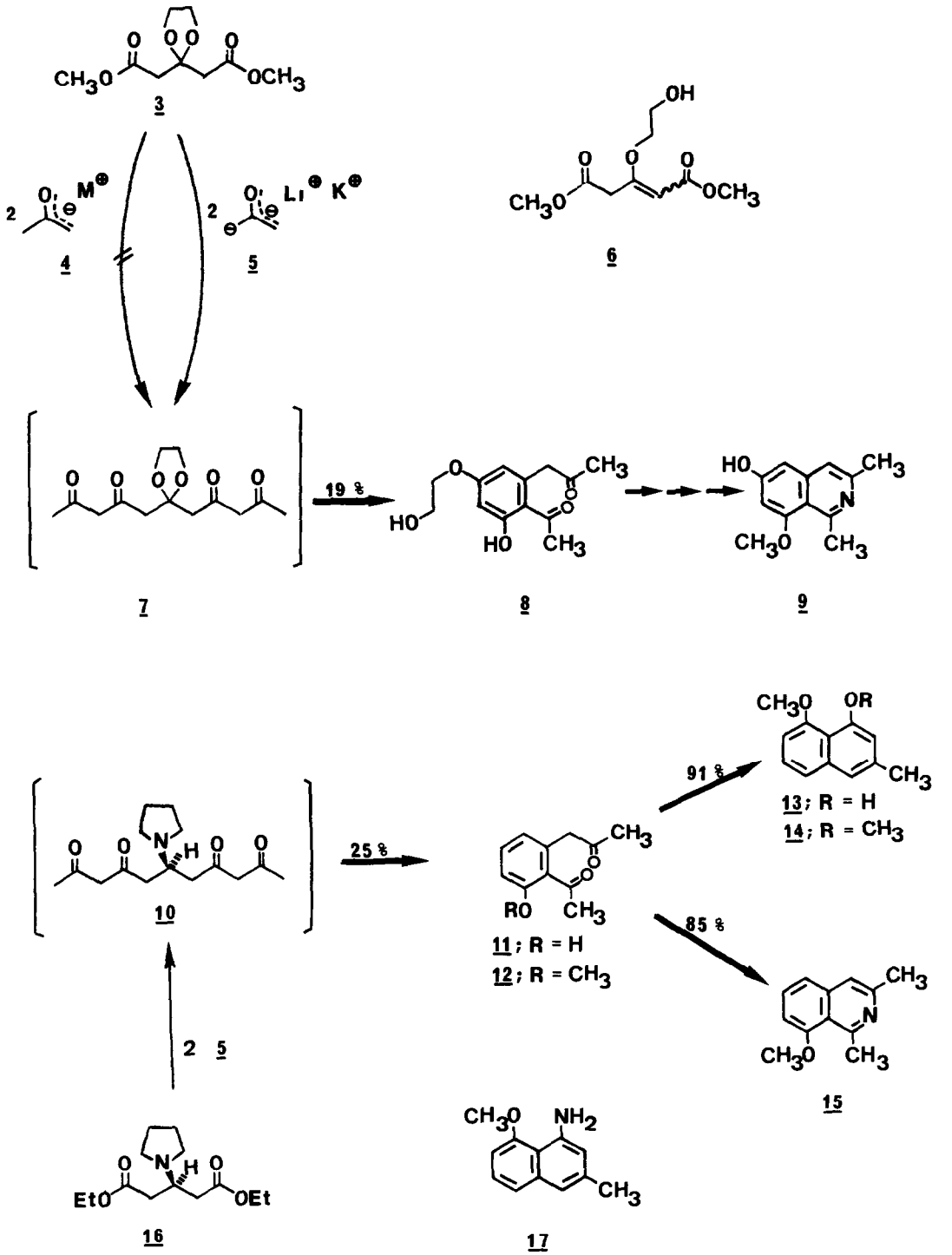
Thus, lithio potassio acetone smoothly reacted at -35° C with diester (3) to give the pentaketone monoketal (7) in situ, which evaded isolation under these conditions, but cyclized directly to the aromatic diketone (8)[7]. Besides this desired product, we found considerable amounts (22 %) of the oily diester (6)[8]; arising from base catalyzed ring opening of the strained ethylene ketal. This side reaction could not completely be suppressed by using six membered ring ketals.

For the synthesis of the aromatic compounds (11) - (15), which lack the oxygenfunction at the "central" C-atom, we condensed dianion (5) with diester (16) and thus obtained diketone (11) through the intermediate (10). Considering the fact that (8) and (11) are accessible now in only one step each, the achieved yields are very satisfactory.

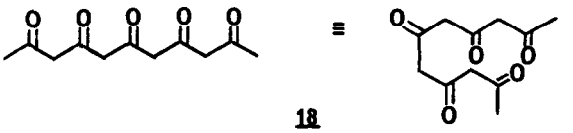
We have already described the facile conversion of (8) into the isoquinoline (9), and of (11) into the naphthalene (14), the two molecular moieties of ancistrocladeine (1)[4]. Now naphthalene monomethylether (13) - the partial structure of some ancistrocladus alkaloids, but also occurring free in tropical heartwood[9] - can be synthesized by aldol condensation (0.4 M KOH/MeOH, 25° C) of methylether (12) (mp = 54° C)[8] in excellent yields. This constitutes the first biomimetic synthesis of (13)[10].

From the same key intermediate (12), the "deoxygenated" isoquinoline moiety (15)[11] of (2) can easily be prepared by reaction with conc. ammonia in MeOH at 25° C (dec. of hydrobromide $>260^{\circ}$ C)[8]. The formation of aminonaphthalene (17)[12] (14 %, mp of acetamide = 152° C)[8] can be suppressed by running the reaction in aqueous NH_4Cl solution, instead.

The condensation of lithio potassio acetone (5) with the diesters (3) and (16) - to our knowledge the first application of this potent reagent in natural product synthesis - provides a novel, very short way to natural naphthalenes and isoquinolines. At the same time, the reaction sequences (stressed arrows) demonstrate a plausible biogenetic scheme for the formation of the naphthyl iso-


3
4
5
6
7
8
9
19 %
10
11 ; R = H
12 ; R = CH3
13 ; R = H
14 ; R = CH3
15
16
17
25 %
91 %
85 %
2 5

quinoline alkaloids in vivo with the unprotected β-pentaketone (**18**) as a possible intermediate.



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Acknowledgements

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References and Notes

1) T.R. Govindachari and P.C. Parthasarathy; Heterocycles 7, 661 (1977).

2) J.P. Foucher, J.L. Pousset, A. Cavé, and R.R. Paris; Plantes méd. phytothér. 9, 26 (1975).

3) M. Lavault and J. Bruneton; C.R. Acad. Sc. Paris C, 287, 129 (1978).

4) G. Bringmann; Angew. Chem., Int. Ed. Engl. 21 (1982), in press.

5) T.M. Harris, A.D. Webb, C.M. Harris, P.J. Wittek, and T.P. Murray; J. Am. Chem. Soc., 98, 6065 (1976).

6) J.S. Hubbard and T.M. Harris; J. Am. Chem. Soc. 102, 2110 (1980).

7) Identical in all respects with the diketone obtained after ozonolysis of an appropriate dihydroindane by subsequent cyclization on silica gel, see ref. 4).

8) All new compounds have been completely characterized by analytical and spectroscopic methods; NMR ($CDCl_3$) and IR (CCl_4) data are given for:

(**6**): δ = 2.65 (1 H, br), 3.68 (3 H, s), 3.73 (3 H, s), 3.87 (2 H, d, J = 4.4 Hz), 3.89 (2 H, s), 3.99 (2 H, d, J = 4.4 Hz), 5.23 (1 H, s) ppm; $\tilde{\nu}$ = 3500, 1735, 1705, 1625 cm^{-1}.

(**12**): δ = 2.17 (3H, s), 2.51 (3 H, s), 3.77 (2 H, s), 3.84 (3 H, s), 6.73 (1 H, d, J = 7.6 Hz), 6.87 (1 H, d, J = 8.3 Hz), 7.29 (1 H, dd, J≈ 8 Hz) ppm; $\tilde{\nu}$ = 1720, 1685 cm^{-1}.

(**15**): δ = 2.61 (3 H, s), 3.09 (3 H, s), 3.96 (3 H, s), 6.80 (1 H, d, J = 7.8 Hz), 7.23 (1 H, J = 7.8 Hz), 7.25 (1 H, s), 7.48 (1 H, t, J = 7.8 Hz) ppm; $\tilde{\nu}$ = 1620, 1560 cm^{-1}.

(**17**): δ = 2.35 (3 H, s), 3.94 (3 H, s), 5.1 (2 H, br), 6.42 (1 H, d, J = 1.5 Hz), 6.61 (1 H, dd, J = 3.0 Hz, J = 5.7 Hz), 6.90 (1 H, d, partially resolved), 7.2 (2 H, m) ppm; $\tilde{\nu}$ = 3500, 3395 cm^{-1}.

9) G.S. Sidhu, A.V.B. Sankaram, and S. Mahmood Ali; Indian J. Chem. 6, 681 (1968)

10) Naphthalene (**13**) has been prepared in low yield (ca. 2.5 %) by total synthesis (B.O Hanford and W.B. Whalley; J. Chem. Soc. 1963, 3896), as well as by degradation of musizin (C.J. Covell, F.E. King, and J.W.W. Morgan; ibid. 1961, 703).

11) An isoquinoline, to which structure (**15**) was assigned from UV-data only, had previously been obtained in traces in the synthesis of the corresponding 6-methoxy isomer: W. Zieliński; Synthesis 1980, 70.

12) The position of the aminogroup was unequivocally demonstrated by hydrolysis of its diazonium salt to naphthol (**13**) in 72 % yield.

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