An Efficient Approach to the Basic Skeleton of the *cis*-Trikentrins

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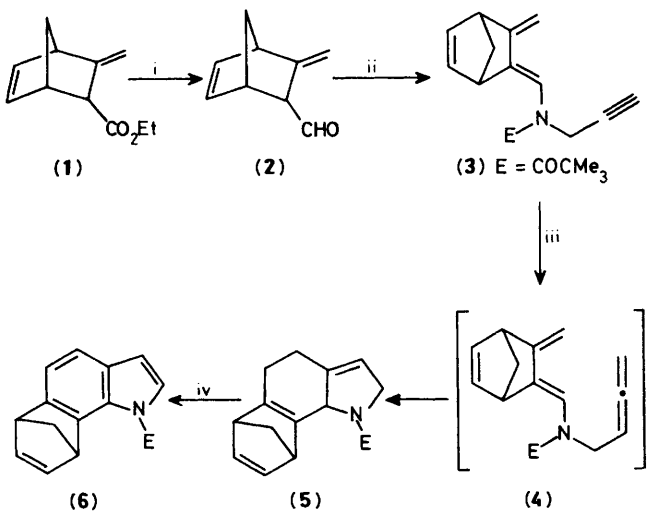
An efficient approach to a novel tricyclic indole, the basic skeleton of *cis*-trikentrins (**10**), utilizing an allene intramolecular Diels–Alder reaction of a 2,3-disubstituted allenic dienamide (**4**), is described.

Recently, a series of the *cis*-trikentrins has been isolated from the marine sponge *Trikentrion flabelliforme*.[1] A characteristic of the structure of this unusual class of indole alkaloids is a *cis*- or *trans*-dimethylcyclopentene system, which possesses a fused indole nucleus, and the lack of substitution at the 3-position on the indole nucleus. Moreover, these compounds have attracted interest because of their antimicrobial activity.

A recent report on the synthesis of (±)-*cis*-trikentrin A[1] by an aryl radical cyclization prompts us to report results of our independent study. Here, we report a new and efficient synthesis of the basic tricyclic indole skeleton of *cis*-trikentrins (**10**), based on our recently reported indole synthesis *via* the intramolecular Diels–Alder reaction of the 2,3-disubstituted allenic dienamide (**4**).[2]

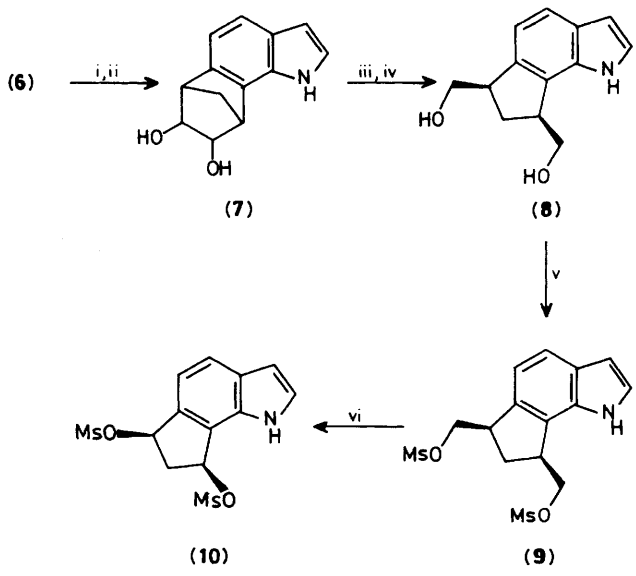
The key intermediate, the tetracyclic indole (**6**), was prepared as shown in Scheme 1. The bicyclic ester (**1**)[3] was converted into the aldehyde (**2**)† by $LiAlH_4$ reduction and pyridinium chlorochromate (PCC) oxidation in 78% yield. The requisite prop-2-ynyl dienamide (**3**),† a precursor of (**4**), was easily prepared according to Oppolzer's method[4] from (**2**) in 45% yield. When (**3**) was treated with HCHO, Pr^i_2NH, and CuBr (cat. amount) in refluxing 1,4-dioxane (homologative allenylation),[5] the resulting allene (**4**) was found to undergo immediately an intramolecular Diels–Alder reaction under these conditions, directly giving the adduct (**5**)† as a colourless crystalline solid in 73% yield. Treatment of (**5**) with chloranil in refluxing toluene provided (**6**)† as white crystals in 58% yield.



Scheme 1. *Reagents and conditions*: i, $LiAlH_4$, ether, 0 °C to room temp., then PCC, CH_2Cl_2, room temp., 78%; ii, prop-2-ynylamine, molecular sieves 4Å, toluene, room temp., then Me_3CCOCl, *N*,*N*-diethylaniline, toluene, room temp., 45%; iii, HCHO, Pr^i_2NH, CuBr (cat. amount), 1,4-dioxane, 101 °C, 73%; iv, chloranil, toluene, 110 °C, 58%.

† All new compounds gave satisfactory analytical and spectral data. (**6**); m.p. 84—85 °C; i.r., ν_{max} ($CHCl_3$) 1695 cm^{-1}; ^1H n.m.r., δ($CDCl_3$) 7.55 (d, *J* 4.2 Hz, 1H), 7.39—6.77 (m, 4H), 6.53 (d, *J* 4.2 Hz, 1H), 4.60 (br.s, 1H), 3.95 (br.s, 1H), 2.25 (tm, *J* 1.5 Hz, 2H), 1.52 (s, 9H); u.v., λ_{max} (MeOH) 314 (log ε 3.63), 278 (sh, log ε 3.80), 241 (sh, log ε 4.11) and 229 nm (sh, log ε 4.16); *m/z*, M^+ 265. (**10**); i.r., ν_{max} ($CHCl_3$) 3410 cm^{-1}; ^1H n.m.r., δ($CDCl_3$) 8.07 (br.s, 1H), 7.50 (d, *J* 8.0 Hz, 1H), 7.15 (dd, *J* 3.2 and 2.5 Hz, 1H), 7.00 (dd, *J* 8.0 and 0.4 Hz, 1H), 6.56 (dd, *J* 3.2 and 2.1 Hz, 1H), 3.47 (m, 1H), 3.24 (m, 1H), 2.62 (dt, *J* 12.4 and 7.6 Hz, 1H), 1.51 (d, *J* 6.9 Hz, 3H), 1.37 (d, *J* 6.8 Hz, 3H), 1.33 (dt, *J* 12.4 and 8.7 Hz, 1H); u.v., λ_{max} (MeOH) 268 (log ε 4.11) and 220 nm (log ε 4.87); *m/z* ($C_{13}H_{15}N$), calc. 185.1204, found 185.1203.

The conversion of (**6**) to (**10**) was achieved by oxidative cleavage of the nonconjugated double bond and reductive removal of two oxygen atoms (Scheme 2). Treatment of (**6**) with OsO_4 (cat. amount) and 4-methylmorphine-*N*-oxide (NMO), followed by alkaline hydrolysis with KOH, afforded the diol (**7**)† in 71% yield. Periodate oxidation of (**7**) gave the dialdehyde, which was converted into the diol (**8**)† by successive reduction using di-isobutylaluminium hydride (DIBAL-H) in 50% yield. The diol (**8**) was transformed into the dimesylate (**9**)† according to a general procedure in 84% yield. Treatment of (**9**) with activated Zn dust and NaI in refluxing dimethoxyethane (DME) by Fujimoto's method[6] gave (**10**)† as a colourless oil in 65% yield. Compound (**10**) exhibited spectroscopic properties very similar to those of the natural *cis*-trikentrins.[1]



Scheme 2. *Reagents and conditions*: i, OsO_4 (cat. amount), NMO, 1,4-dioxane/H_2O, room temp., 75%; ii, KOH, MeOH/H_2O, room temp., 94%; iii, $NaIO_4$, tetrahydrofuran (THF)/H_2O, room temp.; iv, DIBAL-H, benzene, 0 °C, 50% in 2 steps; v, MsCl (Ms = $MeSO_2$), NEt_3, CH_2Cl_2, 0 °C, 84%; vi, activated Zn dust, NaI, DME, 85 °C, 65%.

The method described appears to provide a general synthetic route to *cis*-trikentrins, and is capable of being used in the preparation of natural products, as well as biologically interesting analogues. Extension of this methodology to the synthesis of natural *cis*-trikentrins is currently under investigation.

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