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The Total Synthesis of (±)-*cis*-Trikentrin B *via* Allene Intramolecular Cycloaddition

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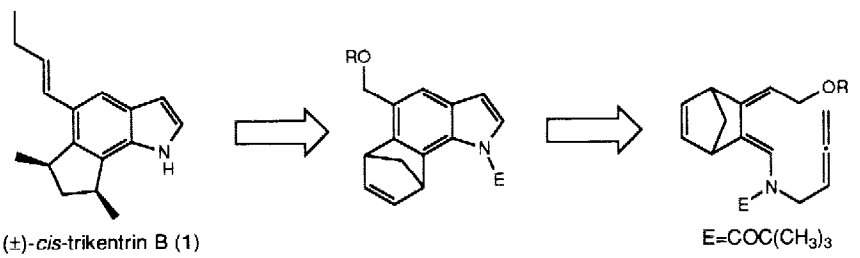
Summary: The first total synthesis of (±)-*cis*-trikentrin B (**1**) based on a new indole synthesis *via* the intramolecular Diels-Alder reaction of 1,2,3-trisubstituted allenic dienamide (**8**) is described.

The trikentrins, isolated from the marine sponge *Trikentrion flabelliforme* by Capon and co-workers in 1986,[1] are unusual class of indole alkaloids. Their unique structural characteristics and antimicrobial activity have been attracted interest in their biogenesis and medicinal chemistry, providing a focus for intense synthetic interest. The recent total synthesis of (±)-*cis*-trikentrin A *via* an aryl radical cyclization[2] is the only total synthesis of trikentrins to date. As part of our program of research on the allene intramolecular cycloaddition reaction[3], we herein report the first total synthesis of (±)-*cis*-trikentrin B (**1**) based on our independent study of a new indole synthesis *via* the intramolecular Diels-Alder reaction of 1,2,3-trisubstituted allenic dienamide (**8**)[4] as outlined retrosynthetically in Scheme I. Natural **1** is a minor component of the trikentrins, and its dry weight yield from the sponge is very low (0.007%). Moreover, the natural **1** was only obtained as a two component mixture with *iso*-*trans*-trikentrin B.

Scheme I

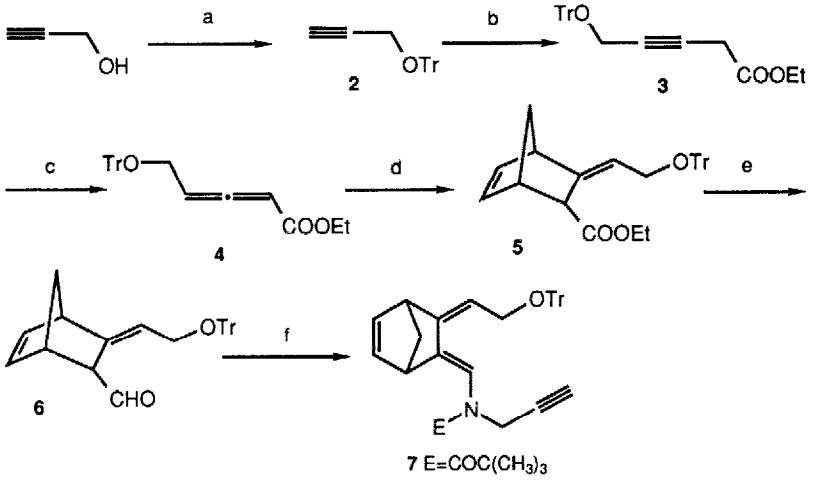


(±)-*cis*-trikentrin B (1) E=COC(CH$_3$)$_3$

This paper is dedicated to Professor Haruaki Yajima on this occasion of his retirement from Kyoto University in March 1989.

The propargyl dienamide (**7**), a precursor of the allenic dienamide (**8**), was prepared as shown in Scheme II. The propargyl ether (**2**) was converted into the allenic ester (**4**) by Layton's method[5] followed by base catalyzed isomerization. The intermolecular Diels-Alder reaction of **4** with cyclopentadiene in refluxing benzene afforded the bicyclic ester (**5**).[6] The ester **5** was converted into the bicyclic aldehyde (**6**) by lithium aluminum hydride reduction and pyridinium chlorochromate(PCC) oxidation. The propargyl dienamide (**7**) was easily prepared according to Oppolzer's method[7] from **6**.

Scheme II



Reagents and Conditions: (a) $TrCl/NEt_3/CH_2Cl_2$/room temperature/overnight (94%); (b) n-BuLi/THF/-78°C/30 min; $BF_3{\cdot}OEt_2$/-78°C to -20°C; $N_2CHCOOEt$/-20°C/1 h (43%); (c) $NEt_3/CHCl_3$/room temperature/7 h(quant.); (d) cyclopentadiene/benzene/80°C/3 h (93%); (e)$LiAlH_4$/THF/0°C/1 h; PCC/CH_2Cl_2/30 min (78%); (f) propargylamine/4-A sieves/ether/3 h; NaH/DME/-18°C/10 min; $(CH_3)_3CCOCl$/-18°C to room temperature (45%).

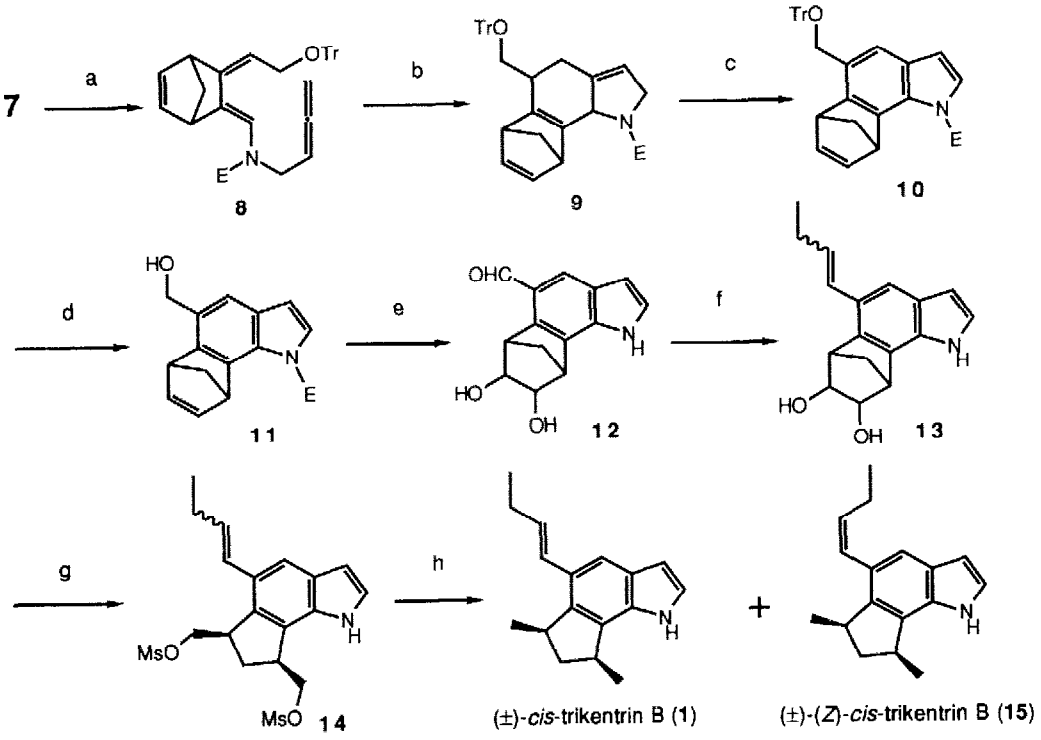
Preparation of key intermediate, the tetracyclic indole (**10**) followed the route in Scheme III. Treatment of **7** with formaldehyde (35% solution in water), diisopropylamine and CuBr (catalytic amount)[8] gave the allenic dienamide (**8**). When **8** was heated in toluene at 160°C, the intramolecular Diels-Alder reaction proceeded, to give the adduct (**9**). Dehydrogenation of **9** with chloranil in refluxing toluene provided **10** in satisfactory yield as white crystals.

The conversion of **10** into **1** was achieved by initial introduction of the butenyl group by a Wittig reaction followed by selective oxidative cleavage of the nonconjugated double bond, and reductive removal of two oxygen atoms. Detritylation of **10** using 10-camphorsulfonic acid (CSA) afforded the alcohol(**11**). Compound **11**, when treated with PCC, was transformed into the

corresponding aldehyde, which was submitted for OsO_4 oxidation and alkaline hydrolysis to afford the diol (**12**). Wittig olefination of **12** with $Ph_3P{=}CHCH_2CH_3$ provided **13** as an E/Z isomeric mixture (approximately E/Z ratio = 2:1). Further oxidative cleavage of the 1,2-diol function of **13** with sodium periodate, gave rise to the corresponding cis-dialdehyde, which was readily transformed into the cis-dimesylate (**14**) by diisobutylaluminum hydride reduction and mesylation according to general procedures.

Finally, transformation of **14** into (±)-cis-trikentrin B (**1**) was accomplished by Fujimoto's method.[9] Compound **14**, when treated with activated Zn dust

Scheme III



Reagents and Conditions: (a) HCHO/i-Pr_2NH/CuBr/1,4-dioxane/101°C/5h (79%); (b) toluene/160°C/2 h (74%); (c) chloranil/toluene/110°C(54%) ; (d) CSA/MeOH/THF/room temperature/10 h (90%); (e) PCC/CH_2Cl_2/room temperature; OsO_4/NMO/1,4-dioxane/H_2O/10 h/room temperature; NaOH/MeOH/H_2O /room temperature/5 min (60% crude yield); (f) $Ph_3P{=}CHCH_2CH_3$/THF/0°C to room temperature (60%); (g) $NaIO_4$/THF/H_2O/room temperature/5 h; DIBAH/ toluene/-78°C/30 min; MsCl/NEt_3/CH_2Cl_2/0°C/30 min (58%); (h) activated Zn/NaI/DME/85°C/20 h (87%).

and sodium iodide in refluxing 1,2-dimethoxyethane, was transformed into a mixture of **1** and its geometrical isomer, (±)-(Z)-cis-trikentrin B (**15**)[10] (colorless oil, 87% yield, approximately E/Z ratio = 2:1), which was separated by pre-packed column chromatography on silica gel. Purity of **1**[11] was determined by capillary GC to be over 95%.

The synthetic compound, a mixture of **1** and **15** was evaluated for their antimicrobial activity. It possesses growth inhibitory activity particularly against the Gram positive bacteria, whereas it exhibits essentially no antimicrobial activity against the Gram negative bacteria.[12]

In summary, the first total synthesis of **1**, which is unattainable in pure form from natural source, has been achieved via our new indole synthesis. Thus, our pathway to **1** has demonstrated the utility of a new indole synthesis for preparation of natural polyalkylated indoles.

References and Notes

1. Capon, R. J.; Macleod, J. K.; Scammells, P. J. Tetrahedron, **1986**, 42, 6545.
2. Macleod, J. K.; Monahan, L. C. Tetrahedron Lett., **1988**, 29, 391.
3. Yasukouchi, T.; Kanematsu, K. J. Chem. Soc., Chem. Commun., **1989**, 953.
4. (a) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. Tetrahedron Lett., **1986**, 27, 1837. (b) Idem., ibid., **1987**, 28, 5895.
5. Hooz, J.; Layton, R. B. Can. J. Chem. **1972**, 50, 1105.
6. (a) Gras, J. L. J. Chem. Res. (s), **1982**, 300. (b) Gandhi, R. P.; Ishar, M. P. S.; Wali, A. J. Chem. Soc., Chem. Commun., **1988**, 1074.
7. Oppolzer, O.; Bieber, L.; Francotte, E. Tetrahedron Lett., **1979**, 981.
8. Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. J. Chem. Soc., Chem. Commun., **1979**, 859.
9. Fujimoto, Y.; Tatsuno, T. Tetrahedron Lett., **1976**, 3325.
10. The ^{1}H NMR spectrum of **15** (270 MHz, $CDCl_3$) displays a 11-Hz coupling between the olefinic protons on the (Z)-butenyl group.
11. Data for the synthetic **1**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.92 (bs, 1H), 7.60 (s, 1H), 7.13 (dd, J = 3.3, 2.4 Hz, 1H), 6.59 (dm, J = 16 Hz, 1H), 6.52 (dd, J = 3.3, 2.0 Hz, 1H), 6.17 (dt, J = 16, 6.4 Hz, 1H), 3.56-3.42 (m, 2H), 2.70 (dt, J = 13, 9.1 Hz, 1H), 2.33-2.20 (m, 2H), 1.54 (dt, J = 13, 2.4 Hz 1H), 1.44 (d, J = 7.3 Hz 3H), 1.34 (d, J = 6.9 Hz, 3H), 1.11 (t, J = 7.4 Hz 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 140.6 (s), 131.9 (s), 131.0 (d), 129.1 (s), 127.7 (s), 127.4 (s), 127.4 (d), 123.7 (d), 115.6 (d), 103.1 (d), 41.8 (t), 38.4 (d), 37.0 (d), 26.3 (t), 24.2 (q), 22.5 (q), 14.0 (q); IR ($CHCl_3$) 3460, 2930 cm^{-1}; MS m/z 239 (M^+); high resolution MS calcd for $C_{17}H_{21}N$ 239.1673, found 239.1674.
12. We are grateful to Pharmaceuticals Research Center, Kanebo, LTD. for evaluation of antimicrobial activity.

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