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The Total Synthesis of (±)-*cis*- and *trans*-Trikentrin A

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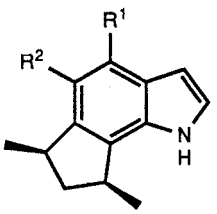
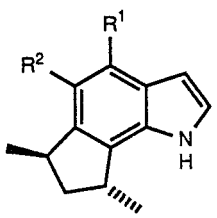
Abstract

The synthesis of the title compounds, which are novel cyclopent[*g*]indoles isolated from a marine sponge *Trikentrion flabelliforme*, is described. An aryl radical cyclization and a 1,5-electrocyclic reaction of a nitrene are key steps in formation of the two five-membered rings.

In a preliminary communication[1] the synthesis of (±)-*cis*-trikentrin A (1), one of a series of five novel biologically active indoles (1)–(5) recently isolated from a marine sponge, *Trikentrion flabelliforme*,[2] was reported. The full details of its preparation and the extension of the synthesis to the *trans* isomer (3) are now described.



	R^1	R^2
(1)	Et	H
(2)	H	but-1-enyl



	R^1	R^2
(3)	Et	H
(4)	H	but-1-enyl
(5)	but-1-enyl	H

Results and Discussion

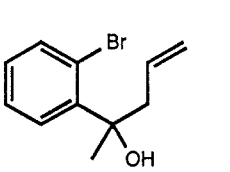
The series of metabolites (1)–(5) all contain a dimethylcyclopentene moiety fused to an indole ring. The potential utility of an aryl radical cyclization in the preparation of the indan system present in these compounds attracted attention since, despite considerable mechanistic study,[3,4] no carbocyclic examples had been applied to the synthesis of natural products.

Reaction of allylmagnesium bromide with *o*-bromoacetophenone gave the radical precursor (6) in 75% yield. Treatment of the aryl bromide (6) in benzene

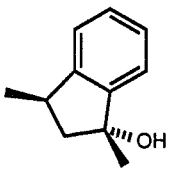
[1] MacLeod, J. K., and Monahan, L. C., *Tetrahedron Lett.*, 1988, **29**, 391.
[2] Capon, R. J., MacLeod, J. K., and Scammells, P. J., *Tetrahedron*, 1986, **42**, 6545.
[3] Giese, B., 'Radicals in Organic Synthesis' (Pergamon Press: Oxford 1986).
[4] Abeywickrema, A. N., and Beckwith, A. L. J., *J. Chem. Soc., Chem. Commun.*, 1986, 464.

0004-9425/90/020329$03.00

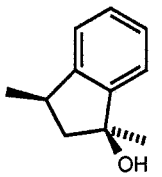
at reflux with tributyltin hydride under 'infinite dilution' conditions led to an approximately 50 : 50 mixture of diastereomeric 1,3-dimethylindanols (7a,b). These are the products of '*exo*' ring closure,[3] and there was no evidence of the six-membered ring which would occur from '*endo*' cyclization. Only traces (<2%) of the monosubstituted benzene resulting from direct reduction of the aryl bromide were detected. The indanols could be separated by careful column chromatography but this was generally accompanied by the ready elimination of water. Thus a direct procedure to the *cis* indan involved formation of the dimethylindene (8) from the diastereomeric mixture of (7a,b) by acid treatment and subsequent hydrogenation. This yielded 1,3-dimethylindan (9a) in 82% yield from (6) with the expected *cis* isomer predominating (>9 : 1 *cis/trans*). The literature[5] suggested that direct hydrogenolysis of the benzylic alcohols



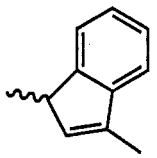
(6)



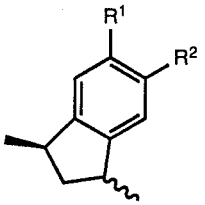
(7a)



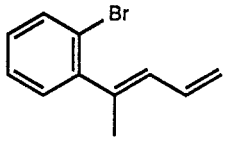
(7b)



(8)



(a) *cis*
(b) *trans*



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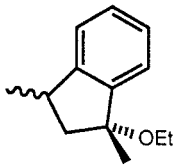
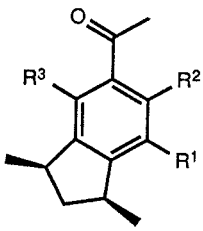
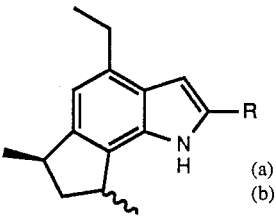


(11)

	R^1	R^2
(9)	H	H
(12)	Ac	H
(14)	CH(OH)Me	H
(15)	Et	H
(16)	Et	CHO
(17)	Et	$CH{=}C(N_3)CO_2Et$

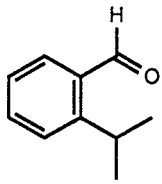


	R^1	R^2	R^3
(13A)	NO_2	H	H
(13B)	H	H	NO_2
(13C)	H	NO_2	H

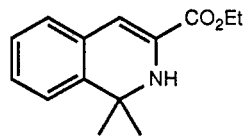


(a) *cis*
(b) *trans*

(18) R = CO_2Et
(21) R = CO_2H



(19)



(20)

[5] For example, Rylander, P., 'Catalytic Hydrogenation in Organic Syntheses' (Academic Press: New York 1979).

(7a,b) should proceed with inversion of stereochemistry in the presence of palladium on charcoal, and with retention of stereochemistry when Raney nickel was used as catalyst. Reduction of pure samples of either diastereomer with Pd/C in a variety of solvents (chloroform, ethanol, hexane) gave predominantly the *cis* indan (9a), as did an initial attempt at reduction with W4 Raney nickel. This was presumably due to a facile elimination of water prior to reduction, possibly catalysed by traces of acid. Indeed, the reduction of the *trans*-dimethyl-substituted alcohol (7b), with the slightly alkaline W7 Raney nickel, gave predominantly the *trans* indan (9b) (>9 : 1 *trans/cis*) in 92% yield.

Unfortunately the radical cyclization (6) → (7) gave rather inconsistent yields particularly when carried out on a multigram scale. In those attempts which resulted in poor yield a considerable amount of polymeric material was recovered. The most likely explanation appears to be that elimination of water was occurring prior to cyclization, to give the diene (10), or its geometrical isomer, leading to subsequent polymerization. Removal of the tin residues produced in the reaction was also difficult and alternative methods of carrying out the cyclization were investigated. The use of a catalytic amount of tributyltin halide with sodium cyanoborohydride to perform an *in situ* reduction to the corresponding tin hydride has been reported.[6] This method inherently produces the desired low concentration of tributyltin hydride to promote cyclization over direct reduction of the debrominated starting material and reduces drastically the amount of tin residues to be removed at the end of the reaction. However, this created other difficulties in the present example because of a displacement reaction between solvent and the benzylic hydroxy group. When ethanol was used as solvent a mixture of the two diastereomeric ethyl ethers (11) was obtained in addition to the expected alcohols (7). Lowering the reaction temperature did not avoid this reaction. Changing to aprotic solvents, for example acetonitrile, resulted in production of the indans (9), presumably through hydroxy displacement by hydride ion. It was found that the best method for the radical cyclization involved the use of infinite dilution conditions at approximately 70°C in benzene, with the potassium fluoride method of workup, which has been previously described.[7]

The remainder of the synthesis was carried out by using the same procedures for both the *cis* and *trans* series.

Acetylation of (9) with acetyl chloride in dichloromethane, with aluminium chloride as Lewis acid, led to the 5-acetyl-1,3-dimethylindan (12) regiospecifically (85%) as had been previously established[8] for the *trans* compound. It was expected that the electron-withdrawing acetyl function would help direct nitration to give the nitroindan (13A) which could be used to introduce the nitrogen functionality of the indole ring. In fact a mixture of all three possible isomeric mononitrated indans (13A–C) was obtained on treatment of the acetyl compound (12a) with a mixture of concentrated nitric and sulfuric acids. The major isomer resulted from substitution *ortho* to the acetyl group (A/B/C 1 : 1 : 5). Clearly the steric bulk of the dimethylcyclopentene ring influenced the regioselectivity, necessitating a different strategy for elaborating the indole

[6] Stork, G., and Sher, P. M., *J. Am. Chem. Soc.*, 1986, **108**, 303.
[7] Stork, G., and Baine, N. H., *J. Am. Chem. Soc.*, 1982, **104**, 2321.
[8] Jackson, W. R., and Jennings, W. B., *J. Chem. Soc. B*, 1969, 1223.

ring system. An ethyl substituent would direct substitution *ortho* and would therefore be expected to work in conjunction with the steric effect already observed, to give 5,6-disubstitution of the indan nucleus. Therefore, since the two-carbon substituent required in the final products was a simple ethyl group, reduction of (12) was carried out at this stage. The transformation was accomplished in two steps by established procedures—sodium borohydride reduction to the benzylic alcohol (14) and its subsequent hydrogenolysis to give the 5-ethylindan (15) in 79% overall yield. Formylation of (15), which is a trialkylated benzene, proceeded readily with dichloromethyl methyl ether and titanium tetrachloride in dichloromethane at 0°C[9] to give a single regioisomer, 6-ethyl-1,3-dimethylindan-5-carbaldehyde (16) in 74% distilled yield. The indole ring was then elaborated by using the method first proposed by Hemetsberger *et al.*[10] and recently by Moody.[11] Thus the aldehyde (16) was condensed with ethyl azidoacetate in sodium ethoxide at −5°C. Some problems were encountered in carrying out this condensation, problems which may be due to steric hindrance at the reaction site as has been previously reported,[12] but it could be accomplished in good yield by using a large excess of freshly prepared azidoacetate.[13] The unsaturated azide (17) was thermolysed in toluene at reflux for 2 h, a procedure which resulted in electrocyclization of the intermediate nitrene to give the indole ester (18). There was no evidence of the alternative insertion into the adjacent alkyl substituent to give an isoquinoline derivative as has been reported for the benzaldehyde (19) to give the heterocycle (20).[14] Under these conditions the isoquinoline formation is a minor pathway for an isopropyl substituent (35%), while for a methyl substituent only indole formation is observed. From our result it appears that an ethyl substituent is not sufficient to promote the triplet nitrene or radical processes thought to be responsible for formation of the six-membered ring.

The final steps of the synthesis involved the removal of the carboxylic ester substituent from the 2-position of the indole. The ester (18) was readily hydrolysed to the corresponding acid (21) by heating to reflux in an aqueous dioxan solution of potassium hydroxide. Exhaustive extraction of an acidified solution gave the acid in 74% yield. A variety of methods exist for the decarboxylation of indole-2-carboxylic acids, but they do not seem to have very general applicability[11,15] and lead to variable yields. However, the acids (21a,b) were readily decarboxylated under flash vacuum pyrolysis conditions to give, respectively, (±)-*cis*- and *trans*-trikentrin A (1) and (3). The n.m.r. and mass spectra of the synthetic materials were identical to those obtained for the natural compounds.

Experimental

^1H and ^{13}C n.m.r. spectra were recorded on either a Varian XL200 or a JEOL FX200 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal calibrant. Mass spectra were obtained with a VG 7070F instrument at 70 eV by using the direct insertion probe.

[9] Rieche, A., Gross, H., and Höft, E., *Chem. Ber.*, 1960, **93**, 88.
[10] Hemetsberger, H., Knittel, D., and Weidmann, H., *Monatsh. Chem.*, 1970, **101**, 161.
[11] Moody, C. J., *J. Chem. Soc., Perkin Trans. 1*, 1984, 2895.
[12] Moody, C. J., and Ward, J. G., *J. Chem. Soc., Perkin Trans. 1*, 1984, 2895.
[13] Forster, M. O., and Fierz, H. E., *J. Chem. Soc.*, 1908, **93**, 76.
[14] Hickey, D. M. B., Moody, C. J., and Rees, C. W., *J. Chem. Soc., Chem. Commun.*, 1982, 3.
[15] Piers, E., and Brown, R. K., *Can. J. Chem.*, 1962, **40**, 559.

Flash chromatography was performed on Merck Kieselgel 60 (0·04–0·063 mm) while other column chromatography was performed by using Ajax Chemicals silica gel (0·07–0·15 mm). Gas chromatography was carried out by using a 2% OV17-packed column in a Varian 3400 instrument. Medium-pressure liquid chromatography (m.p.l.c.) was performed by using a Merck prepacked Li Chroprep Si 60 (40–63 μm) size B column, and compounds were detected in the eluate by means of a Waters R403 differential refractometer.

Ether was dried by distillation from the ketyl derived from sodium and benzophenone, and dichloromethane was dried by distillation from calcium hydride.

2-(2-Bromophenyl)pent-4-en-2-ol (6)

Allyl bromide (7·26 g, 60 mmol) in dry ether (20 ml) was added to a stirred suspension of magnesium (2·25 g, 60 mmol) in dry ether (4 ml) at a rate sufficient to maintain gentle reflux. After the addition was complete, the mixture was heated to reflux for a further 45 min and was then allowed to cool. A solution of *o*-bromoacetophenone (6 g, 30 mmol) in dry ether (20 ml) was added dropwise and the mixture was then heated to reflux temperature for a further 45 min. The reaction mixture was poured onto iced water (50 ml), and dilute sulfuric acid (20 ml, 10% solution) was added. The organic layer was separated and the aqueous layer was extracted with ether (2×50 ml). The combined organic fractions were dried ($MgSO_4$), the solvent was removed in vacuum, and the residue distilled to give the *title compound* (5·25 g, 75%) as a clear *oil*, b.p. 118°C/0·06 mmHg (Found: C, 55·1; H, 5·3; Br, 33·4. $C_{11}H_{13}BrO$ requires C, 54·8; H, 5·5; Br, 33·2%). ^1H n.m.r. δ 7·60, dd, J 7·9, 1·8 Hz, 1H; 7·44, dd, J 7·9, 1·4 Hz, 1H; 7·15, ddd, J 7·9, 7·3, 1·4 Hz, 1H; 6·94, ddd, J 7·9, 7·3, 1·8 Hz, 1H; 5·45, m, 1H; 4·96, m, 2H; 3·15, dd, J 14·0, 8·2 Hz, 1H; 2·78, br, 1H; 2·54, dd, J 14·0, 8·2 Hz, 1H; 1·60, s, 3H. ^{13}C n.m.r. δ 145·4 (q), 134·9, 133·5, 128·4, 128·2, 127·3, 119·9 (q), 119·0, 74·6, 45·0, 27·2. M.s. *m/z* (relative intensity) 242 and 240 (M, <1%), 225 (60), 223 (65), 201 (97), 199 (100), 185 (26), 183 (28), 145 (15), 144 (51), 143 (32), 43 (71).

cis-*1,3-Dimethylindan (9a)*

A solution of the aryl bromide (6) (2·4 g, 10 mmol) and azobisisobutyronitrile (100 mg) in benzene (200 ml) was degassed and kept under an atmosphere of nitrogen. The solution was heated to 70°C and a solution of tributyltin hydride (3·2 g, *c.* 11 mmol) in benzene (20 ml) was added dropwise. The reaction was monitored by t.l.c. or g.l.c. and when it was complete the benzene was removed by distillation. The residue was dissolved in ether (50 ml), saturated potassium fluoride (50 ml) was added, and the mixture was stirred vigorously for 2 h. Th precipitated tin salts were then removed by filtration through Celite, the ether layer was separated, and the solvent was removed by distillation. The resulting mixture of diastereomeric 1,3-dimethylindan-1-ols (7) was then dissolved in chloroform (50 ml), 10% Pd/C (75 mg) was added, and the mixture was hydrogenated at ambient pressure and temperature. The reduction was complete after 16 h. The catalyst was removed by filtration through Celite, and the solvent was removed by distillation to give a clear oil (1·19 g, 82%) which contained >90% *cis*-1,3-dimethylindan, the remainder being the *trans* isomer (confirmed by comparison of ^1H n.m.r. spectrum with literature data[16]). This was used without further purification.

trans-*1,3-Dimethylindan (9b)*

The radical cyclization was carried out in the same manner as for the *cis* isomer, but separation of the diastereomeric indanols was achieved by m.p.l.c. with ethyl acetate/hexane (15 : 85) as eluent before the reduction step. The 1,3-dimethylindan-1-ol (7b) (240 mg, 15 mmol) was then dissolved in ethanol (15 ml), and W7 Raney nickel[17] (3·3 ml of settled material, *c.* 2 g) was added. The mixture was hydrogenated at ambient temperature and pressure, and after complete reduction the catalyst was removed by filtration through Celite and washed with methanol. The ethanol solution was then poured into hexane (30 ml), and

[16] Cracey, D. E. F., Jackson, W. R., Jennings, W. B., Rennison, S. C., and Spratt, R., *J. Chem. Soc. B*, 1969, 1210.
[17] Billica, H. R., and Adkins, H., *Org. Synth.*, Coll. Vol. 3, 176.

the mixture was washed with water (3×30 ml). The organic fraction was dried ($MgSO_4$), and the solvent was removed by distillation to give a clear oil (220 mg, 92%) which contained >95% *trans*-1,3-dimethylindan (9b), the remainder being the *cis* isomer (confirmed by comparison of ^1H n.m.r. spectrum with literature data[16]).

Following Descriptions

The following details are for the synthesis of the *cis* series of compounds. Similar procedures on a smaller scale were used for the preparation of the isomeric *trans* compounds. Elemental analyses or accurate mass measurements (where traces of solvent were difficult to remove from recrystallized compounds) were obtained for the *cis* compounds. Mass spectra were identical for both the *cis* and *trans* isomers.

5-Acetyl-1,3-dimethylindan (12)

Acetyl chloride (0·82 g), 10·5 mmol) was dissolved in dichloromethane (10 ml), and added dropwise to a suspension of aluminium chloride (1·17 g, 8·75 mmol) in dichloromethane (10 ml) which had been cooled to 0°C.[8] The mixture was stirred for 30 min under an atmosphere of nitrogen, after which time a homogeneous solution was formed. The 1,3-dimethylindan (9a) (1·02 g, 7 mmol) was then added dropwise as a solution in dichloromethane (10 ml), and the resulting orange solution was stirred at 0°C for a further 30 min. The reaction mixture was then poured onto ice/hydrochloric acid which gave a clear solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2×30 ml). The combined organic extracts were dried ($MgSO_4$), the solvent was removed in vacuum, and the residue was purified by bulb-to-bulb distillation to give the corresponding *acetylated compound* (12a) (1·12 g, 85%), b.p. 132–137°C/2·5 mmHg (lit.[8]* 152–153°C/12 mmHg) (Found: $M^{+\bullet}$, 188·120. $C_{13}H_{16}O$ requires $M^{+\bullet}$, 188·120). *cis*: ^1H n.m.r. δ 7·83, d, J 8·0 Hz, 1H; 7·77, s, 1H; 7·25, d, J 8·0 Hz, 1H; 3·1, m, 2H; 2·59, s, 3H; 2·55, m, 1H; 1·35, d, J 6·8 Hz, 3H; 1·33, d, J 6·7 Hz, 3H; 1·3–1·4, 1H, m (obscured). ^{13}C n.m.r. δ 198·2 (q), 154·3 (q) 149·0 (q), 135·7 (q), 127·1, 122·7, 122·5, 44·8, 38·2, 37·7, 26·6, 19·1, 18·9. *trans*: ^1H n.m.r. δ 7·70, m, 2H; 7·17 d, J 7·7 Hz, 1H; 3·23, m, 2H; 2·52, s, 3H; 1·87, t, J 6·8 Hz, 2H; 1·19, d, J 7·6 Hz, 3H; 1·18, d, J 7·6 Hz, 3H. ^{13}C n.m.r. δ 198·2 (q), 154·2 (q), 148·8 (q), 135·8(q), 127·2, 123·3, 123·2, 42·7, 37·6, 37·2, 29·6, 20·3, 20·1. M.s. *m/z* (relative intensity) 188 (M, 35%), 173 (100), 145 (22), 128 (12), 115 (11).

1-(1,3-Dimethylindan-5-yl)ethanol (14)

The acetylindan (12a) (940 mg, 5 mmol) was dissolved in methanol (15 ml), and the solution was cooled to 0°C. Sodium borohydride (210 mg, 5·5 mmol) was added in portions, and the reaction mixture was stirred for 2 h with cooling. A solution of sodium dihydrogen phosphate (10%, 20 ml) was added, and stirring was continued for a further 30 min. Water (10 ml) and dichloromethane (30 ml) were added, and the organic fraction was separated. The aqueous fraction was reextracted with dichloromethane (2×30 ml), the combined organic fractions were dried ($MgSO_4$), and the solvent was removed in vacuum to give the *title compound* (14a) (790 mg, 83%), b.p. 83–86°C/0·07 mmHg (Found: C, 81·7; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·6%). *cis*: ^1H n.m.r. δ 7·0–7·25, m, 3H; 4·88, q, J 6·5 Hz, 1H; 3·10, m, 2H; 2·50, dt, J 12·1, 7·1 Hz, 1H; 1·49, d, J 6·5 Hz, 3H; 1·31, d, J 6·6 Hz, 3H; 1·30, d, J 6·6 Hz, 3H; 1·3–1·4, m, 1H (obscured); ^{13}C n.m.r. δ 148·9 (q), 148·0 (q), 144·0 (q), 123·6, 123·5,[A]† 122·8, 119·9, 70·7, 70·6,[A] 45·2, 38·1, 37·9, 25·2, 25·1,[A] 19·4 (two coincident signals). *trans*: ^1H n.m.r. δ 7·0–7·25, m, 3H; 4·86, m, 1H; 3·23, m, 2H; 1·89 t, J 6·7 Hz, 2H; 1·49, d, J 6·3 Hz, 3H; 1·24 and 1·23, d, J 7·0 Hz, 3H (separate signals for diastereomers); 1·22, d, J 7·1 Hz, 3H; ^{13}C n.m.r. δ 148·74 (q), 147·78 (q), 144·2 (q), 123·7, 123·3, 120·4, 120·4,[A] 70·6, 43·2, 37·6, 37·3, 25·1, 25·0, 20·5 (two coincident signals). M.s. *m/z* (relative intensity) 190 (M, 35%), 175 (100), 145 (23), 131 (28), 105 (55), 91 (29).

* *trans* Compound.

† Additional signals due to diastereomer are identified by a superscript A.

5-Ethyl-1,3-dimethylindan (15)

The alcohol (14a) (760 mg, 4 mmol) was dissolved in chloroform (15 ml), 10% palladium on charcoal (70 mg) was added, and the mixture was hydrogenated at ambient temperature and pressure. After 16 h the reduction was complete, and the catalyst was removed by filtration through Celite. The solvent was removed by distillation, and the residue purified by bulb-to-bulb distillation to give the *title compound* (15a) as a clear oil (670 mg, 96%), b.p. 83–86°C/0·07 mmHg (Found: C, 89·6; H, 10·3. $C_{13}H_{18}$ requires C, 89·6; H, 10·4%). *cis*: ^{1}H n.m.r. δ 7·0–7·15, m, 3H; 2·95–3·15, m, 2H; 2·64, q, *J* 7·6 Hz, 2H; 2·47, dt, *J* 11·9, 6·8 Hz, 1H; 1·32, d, *J* 6·8 Hz, 3H; 1·28, d, *J* 6·8 Hz, 3H; 1·24, t, *J* 7·7 Hz, 3H; 1·2–1·4, m, 1H (obscured). ^{13}C n.m.r. δ 148·6 (q), 145·8 (q), 142·3 (q), 125·8, 122·6, 122·3, 45·3, 38·0, 37·7, 28·8, 19·4, 19·3, 15·8. *trans*: ^{1}H n.m.r. δ 7·0–7·17, m. 3H; 3·24, m, 2H; 2·63, q, *J* 7·6 Hz, 2H; 1·88, t, *J* 6·7 Hz, 2H; 1·24, t, *J* 7·6 Hz, 3H; 1·23, d, *J* 6·7 Hz, 3H; 1·22, d, *J* 6·7 Hz, 3H. ^{13}C n.m.r. δ 146·5 (q), 145·7 (q), 142·4 (q), 126·0, 123·2, 122·8, 43·3, 37·6, 37·3, 28·8, 20·6, 20·6, 15·8. M.s. *m/z* (relative intensity) 174 (M, 33%), 159 (100), 145 (47), 131 (24).

6-Ethyl-1,3-dimethylindan-5-carbaldehyde (16)

The ethylindan (15a) (610 mg, 3·5 mmol) was dissolved in dichloromethane (25 ml), and the solution was cooled to 0°C. Titanium tetrachloride (995 mg, 5·25 mmol) was added dropwise, and then dichloromethyl methyl ether (600 mg, 5·25 mmol) in dichloromethane (10 ml) was added rapidly, a treatment which resulted in a marked colour change from orange to deep purple. The reaction mixture was stirred for 15 min, and quenched by the addition of water (40 ml) which gave a yellow solution. The organic fraction was separated, and the aqueous fraction was then extracted with dichloromethane (2×40 ml). The combined organic fractions were dried ($MgSO_4$), the solvent was removed, and the residue was purified by bulb-to-bulb distillation to give the *title compound* (16a) (520 mg, 74%), b.p. 115–117°C/0·07 mmHg (Found: C, 83·0; H, 9·0. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%). *cis*: ^{1}H n.m.r. δ 10·20, s, 1H; 7·56, s, 1H; 6·99, s, 1H; 2·8–3·2, m, 2H; 2·96, q, *J* 7·3 Hz, 2H; 2·44, dt, *J* 12·0, 7·1 Hz, 1H; 1·25, d, *J* 7·1 Hz, 3H; 1·24, d, *J* 7·1 Hz, 3H; 1·17, t, *J* 7·3 Hz, 3H; 1·2–1·3, m, 1H (obscured). ^{13}C n.m.r. δ 192·04, 155·43 (q), 146·93 (q), 146·08 (q), 132·16 (q), 125·41, 124·59, 44·91, 38·55, 37·99, 25·78, 19·25, 18·93, 16·79. *trans*: ^{1}H n.m.r. δ 10·24, s, 1H; 7·08, s, 1H; 3·2–3·4, m, 2H; 3·02, q, *J* 7·5 Hz, 2H; 1·90, t, *J* 6·8 Hz, 2H; 1·25, t, *J* 7·5 Hz, 3H; 1·24, d, *J* 7·5 Hz, 6H. ^{13}C n.m.r. δ 192·1, 155·4 (q), 146·9 (q), 146·2 (q), 132·4 (q), 126·2, 125·1, 42·9, 38·0, 37·1, 25·8, 20·6, 20·2, 16·7. M.s. *m/z* (relative intensity) 202 (M, 22%), 187 (41), 174 (27), 173 (27), 159 (72), 145 (40), 131 (33), 129 (24), 128 (22), 115 (23), 91 (24).

*Ethyl 6,7-(1,3-Dimethyltrimethylene)-4-ethylindole-2-carboxylate (18)**

The formylindan (16a) (400 mg, 2 mmol) and ethyl azidoacetate (2·8 g, 20 mmol) were dissolved in ethanol (2 ml), and added dropwise to a stirred solution of sodium (460 mg, 20 mmol) in ethanol (20 ml) between −10 and 0°C. The reaction mixture was stirred for a further 1 h after addition was complete, and then allowed to warm to room temperature. Water (25 ml) was added, and the solution was then extracted with dichloromethane (3×30 ml). The combined organic fraction was dried ($MgSO_4$), and the solvent was removed in vacuum to give the crude azide (17a) which was used without further purification. [I.r. (*cis*) (17a) 2120 cm^{-1}, (*trans*) (17b) 2120 cm^{-1}.] The crude azide (560 mg, 1·8 mmol) was dissolved in toluene, and was heated to reflux for 1·5 h. The solvent was removed to yield the *title ester* (18a) which was recrystallized from cyclohexane (490 mg, 86% from formyl compound), m.p. 85–87°C (Found: $M^{+\bullet}$, 285·1728. $C_{18}H_{23}NO_2$ requires $M^{+\bullet}$, 285·1729). *cis*: ^{1}H n.m.r. δ 8·6–8·7, br s, 1H; 7·27, d, *J* 1·8 Hz, 1H; 6·84, s, 1H; 4·39, q, *J* 7·0 Hz, 2H; 3·42, m, 1H; 3·20, m, 1H; 2·91, q, *J* 7·5 Hz, 2H; 2·61, m, 1H; 1·49, d, *J* 6·9 Hz, 3H; 1·41, t, *J* 7·0 Hz, 3H; 1·35, d, *J* 6·9 Hz, 3H; 1·33, t, *J* 7·5 Hz, 3H; 1·2–1·5, m, 1H (obscured). ^{13}C n.m.r. δ 162·2 (q) 146·5 (q), 137·1 (q), 133·9 (q), 127·4 (q), 126·4 (q), 126·3 (q), 115·4, 107·7,

* Best name for indexing purposes: ethyl 4-ethyl-6,8-dimethyl-1,6,7,8-tetrahydrocyclopent[*g*]-indole-2-carboxylate.

60·8, 44·2, 39·2, 37·1, 26·3, 21·0, 20·8, 15·0, 14·4. *trans*: ^{1}H n.m.r. δ 8·7, br, 1H; 7·27, d, J 1·8 Hz, 1H; 6·84, s, 1H; 4·39, q, J 7·2 Hz, 2H; 3·45, m, 2H; 2·91, q, J 7·6 Hz, 2H. ^{13}C n.m.r. δ 162·0 (q), 146·0 (q), 137·1 (q), 133·7 (q), 127·8 (q), 126·4 (q), 126·3 (q), 115·2, 107·9, 60·8, 43·6, 38·1, 36·0, 26·2, 20·5, 19·9, 15·0, 14·4. M.s. *m/z* (relative intensity) 285 (M, 100%), 270 (49), 224 (60).

*6,7-(Dimethyltrimethylene)-4-ethylindole-2-carboxylic Acid (21)**

The ester (18a) (142 mg, 0·5 mmol) was added to sodium hydroxide solution (25%, 5 ml), and dioxan was added until complete solution was achieved. The mixture was then heated at reflux for 2 h. The solution was cooled, water (10 ml) was added, and the mixture was extracted with dichloromethane (2×10 ml) then made acidic by addition of dilute hydrochloric acid. The acidic solution was extracted exhaustively with dichloromethane (5×15 ml), the combined organic fraction was dried, and the solvent was removed in vacuum to give the *title acid* (21a) as a white solid which was recrystallized from methanol (95 mg, 74%), m.p. 220–224°C (dec.) (Found: $M^{+\bullet}$, 257·1428. $C_{16}H_{19}NO_2$ requires $M^{+\bullet}$, 257·1415). *cis*: ^{1}H n.m.r. δ 8·75, br s, 1H; 7·46, d, J 2·0 Hz, 1H; 6·87, s, 1H; 3·46, m, 1H; 3·22, m, 1H; 2·95, q, J 7·7 Hz, 2H; 2·65, dt, J 12·6, 7·7 Hz, 1H; 1·52, d, J 6·8 Hz, 3H; 1·37, d, J 7·5 Hz, 3H; 1·36 t, J 7·7 Hz, 3H; 1·3, m, 1H (obscured). ^{13}C n.m.r. δ 166·7 (q), 147·3 (q), 137·4 (q), 134·5 (q), 127·5 (q), 126·6 (q), 125·1 (q), 115·5, 110·0, 44·2, 39·3, 37·1, 26·3, 21·0, 20·9, 15·0. *trans*: ^{1}H n.m.r. δ 8·74, br s, 1H; 7·44, d, J 1·9 Hz, 1H; 6·86, s, 1H; 3·45, m, 2H; 2·93, q, J 7·6 Hz, 2H; 2·0, m, 2H; 1·34, t, J 7·6 Hz, 3H; 1·32, d, J 7·0 Hz, 3H; 1·25, d, J 7·0 Hz, 3H. ^{13}C n.m.r. δ 166·6 (q), 146·9 (q), 137·5 (q), 134·3 (q), 127·9 (q), 127·7 (q), 126·4 (q), 115·6, 110·2, 43·6, 38·3, 36·0, 26·3, 20·5, 19·9, 15·0. M.s. *m/z* (relative intensity) 257 (M, 83%), 242 (100), 228 (17), 224 (92), 210 (15).

(±)-*Trikentrin A*

The acid (21) was sublimed under a vacuum of 0·003 mmHg through a furnace tube (silica, 15 by 1·5 cm) maintained at approximately 600°C. The product was collected in a trap cooled by liquid nitrogen. The individual racemic *cis* and *trans* products gave spectra (^{1}H, ^{13}C n.m.r., m.s.) identical with those of the natural products (1) and (3) respectively.[2]

Nitration of 5-Acetyl-1,3-dimethylindan (12a)

The acetylindan (12a) (96 mg, 0·5 mmol) was added to concentrated sulfuric acid (0·2 ml) which had been cooled to 0°C. A cooled mixture of concentrated sulfuric and nitric acids (2 : 3) (0·1 ml) was added dropwise,[18] and the resulting solution was stirred, with cooling, for a further 10 min. Ice was then added while the solution was stirred vigorously, and the mixture was allowed to warm to room temperature. Dichloromethane (5 ml) and water (5 ml) were added, the organic layer was separated, and the aqueous layer was reextracted

Table 1. Radical cyclizations (6) → (7a,b)

Solvent	Reaction temp., conditions	Time (h)	Yield (%)
Ethanol	reflux	1·75	65
Methanol	reflux	15	42
Methanol	room temp., irradiated[A]	1·5	20
Butanol	reflux	0·5	10
Acetonitrile	reflux	1·5	27
Acetonitrile	room temp., irradiated[A]	1·5	70
Tetrahydrofuran	reflux	48	20
Pentane	room temp., irradiated[A]	30	55[B]

[A] By using a medium-pressure mercury lamp with a Pyrex filter.
[B] Based on reacted (*c.* 50%) material.

* 4-Ethyl-6,8-dimethyl-1,6,7,8-tetrahydrocyclopent[*g*]indole-2-carboxylic acid.

[18] Corson, B. B., and Hazer, R. K., *Org. Synth.*, Coll. Vol. 2, 434.

with dichloromethane (2×8 ml); the combined organic fractions were dried ($MgSO_4$), and the solvent removed in vacuum to yield a mixture of isomeric nitroindans (13A–C) (90 mg, 77%). The ratio of isomers was shown by ^1H n.m.r. spectrometry to be 1 : 1 : 5 for A : B : C.

General Procedure for Radical Cyclization by Using a Catalytic Amount of Tributyltin hydride

Sodium cyanoborohydride (170 mg, 2·5 mmol) was dissolved in solvent (10 ml), and tributyltin chloride (82 mg, 0·25 mmol) was added. The mixture was stirred at room temperature, and a solution of the aryl bromide (6) (600 mg, 2·5 mmol) and azobisisobutyronitrile (10 mg) in solvent (2 ml) was added. The reaction mixture was then heated or irradiated as indicated in Table 1, and followed by t.l.c. When the starting material could no longer be detected, the solvent was distilled off, and the residue was dissolved in ether (10 ml). A saturated solution of potassium fluoride (10 ml) was added, and the two-phase mixture was stirred vigorously for 2–3 h. It was then cooled and filtered through Celite; the organic portion was separated, dried ($MgSO_4$), and the solvent was removed by distillation. The crude mixture of products [indanols, indene, and product derived from substitution by the solvent] was dissolved in chloroform, palladium on charcoal (20 mg) was added, and the solution was stirred at room temperature under a hydrogen atmosphere. The resulting mixture of *cis* and *trans* indans (7a,b) was isolated in the yields indicated in Table 1.

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